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A magnetically-driven robotic soft-tethered capsule platform for minimally invasive colonoscopy

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SUMMARY

1. INTRODUCTION

1.1. Epidemiology

Colo-Rectal Cancer (CRC) is a major cause of morbidity and mortality; with about 18 million new cases diagnosed in 2018 it is one of the malignancy with the higher incidence worldwide. The development of colorectal adenocarcinoma usually follows a stepwise process, in which a progressive activation of oncogenes and deactivation of oncosuppressors (APC, K-RAS, p-53) is observed, leading to the transformation of adenomatous lesions into invasive adenocarcinomas, passing through different stages of dysplasia. This process usually takes several years. More rarely, a more rapid progression to invasive carcinoma has been described, involving mismatch repair methylation [1].

5-year survival rate for CRC is strictly dependent on the stage of the disease being 100% when adenomas are excised, 94% when CRC is diagnosed at an early stage, decreasing to 11% in case of metastatic disease. Therefore early diagnosis and in particular the possibility to identify premalignant lesions (i.e. adenomas or early CRC) is a key point for an effective treatment of the disease (Fig. 1) [2, 3].

The finding of colonic adenomas during screening colonoscopies is relatively frequent, it is estimated that in approximately 19.4% of procedures any type of polyp is found, in 6.4% of cases an advanced benign adenoma is identified, and in 0.6% of cases a diagnosis of CRC is made.

The high frequency of the disease and the possibility of treatment at an early stage are characteristics for which colorectal cancer could benefit from screening programs, in fact screening on asymptomatic patients could identify premalignant or very early malignant lesions that could benefit from local removal that is burdened by much lower morbidity and mortality than surgical treatment, or discover CRC at an early stage, when the oncological prognosis is more favorable.

Indeed CRC screening programs have been shown to reduce both incidence and mortality for colon and rectal cancer as reported in several randomized controlled trials [4-6].

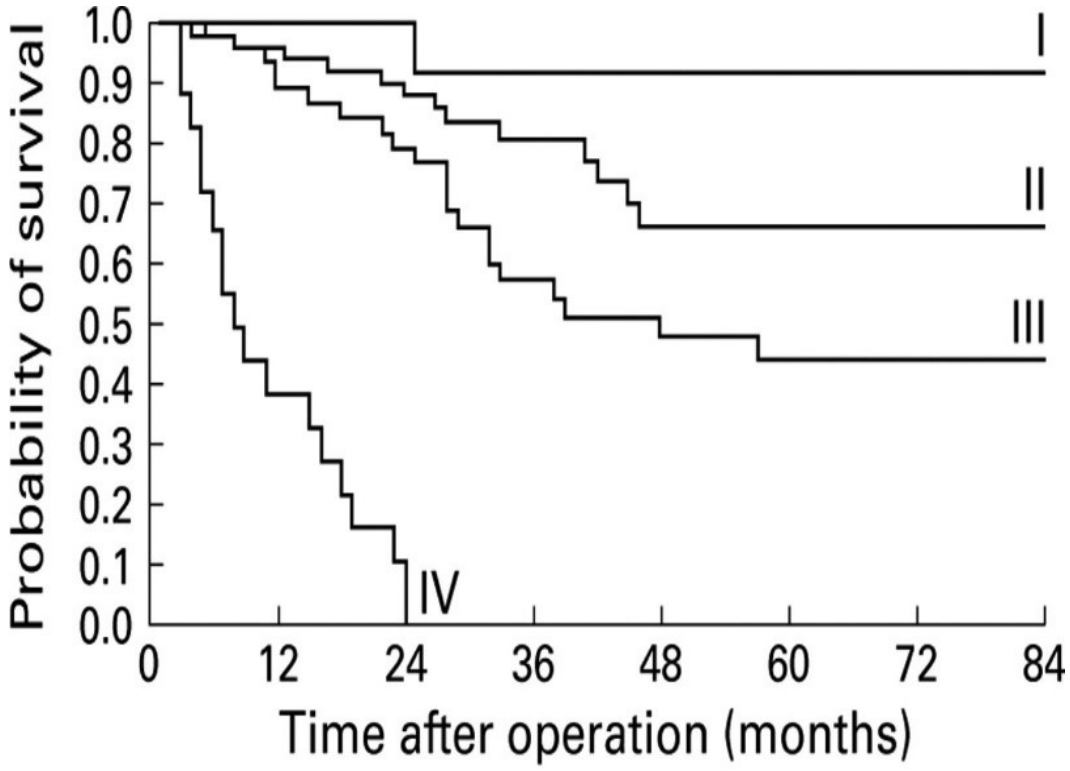


Figure 1: colorectal cancer survival curves

1.2. Screening of CRC

Currently, there are four main techniques for CRC diagnosis and screening: (I) fecal occult blood test.; (II) sigmoidoscopy; and (III) computed tomography (CT)-scan or virtual colonoscopy; (IV) flexible colonoscopy

I Fecal occult blood test (FOBT)

Research of occult fecal blood is based on the principle that a consistent part of CRC may loose traces of blood that can be identified on stools. Several blood tests are available for CRC screening with a slight variability as reguard effectiveness and accuracy among the tests. Fecal immunochemical test directly measures hemoglobin in the stool and is performed on a single sample of stool from the patient. Guaiac-based fecal occult blood test identifies hemoglobin from

a peroxidase reaction that turns a guaiac reagent-impregnated paper to blue and it is usually performed on 3 consecutive bowel evacuations. Finally multitarget stool DNA testing is a composite of tests that associates with an immunochemical assay for hemoglobin a molecular assays DNA mutations associated with colorectal neoplasia.

Fecal test have shown a sensitivity varying from 74 to 92% and a specificity of about 90% in the identification of CRC, but accuracy is much lower for the identification of premalignant lesions with a sensitivity of about 20% for adenomas > 10 mm and an much lower for smaller lesions [9, 10]. The inability in identifying premalignant lesion is the major drawback of this kind of test whose main advantages are a low invasiveness (no bowel preparation is required and there aren't risks associated to the procedure) and low costs. In order to improve accuracy FOBT are usually performed annually. Nevertheless screening programs based on FOBT have shown to reduce CRC mortality by 16%, according to a Cochrane meta-analysis [11]

II Sigmoidoscopy

Sigmoidoscopy consists in the exploration of the rectum and a variable tract of sigmoid colon with a flexible endoscope. It can identify malignant and premalignant lesion in the explored bowel. It is more comfortable than a complete colonoscopy with lower risks (procedural complication like perforation or bleeding requiring transfusion are less than 0,002%), it does not require sedation or bowel preparation but it does not allow the exploration of a considerable tract of large bowel, as less than 1/3 of colorectal cancers arise from the rectosigmoid tract [12].

Randomized controlled clinical trials demonstrate that screening programs based on sigmoidoscopy may reduce the mortality for CRC from 22% to 31 and the incidence from 18 to 23 [4 - 6].

III Virtual colonoscopy

Virtual colonoscopy refers to virtual reconstruction in two or three dimention of the bowel lumen after a thin-slice CT. Virtual colonoscopy has shown a high sensitivity and specificity for colorectal lesion grater than 10 mm (85 and 88% respectively), but its sensitivity falls to 55% for polips grater than 6 mm and is not able to identify lesions smaller than 6 mm [9 - 10]. If any kind of lesion is identified a flexible colonoscopy is needed. With respect of flexible colonoscopy carries a lower risk of complications like bowel perforation or bleeding but require bowel preparation, colon and rectal insufflation in order to distend the bowel and its accuracy drop off for small lesions and flat polyps. Moreover the patient is subject to radiationobtaining multiple, thin-slice CT data and using computers to construct images of the bowel mucosa in two and three dimensions, with other enhancements to assist in interpretation. Thus, due to these drawbacks together with the high costs of the procedure and the long procedural times, virtual colonoscopy plays a limited role in screening for colorectal cancer [10].

IV Flexible colonoscopy

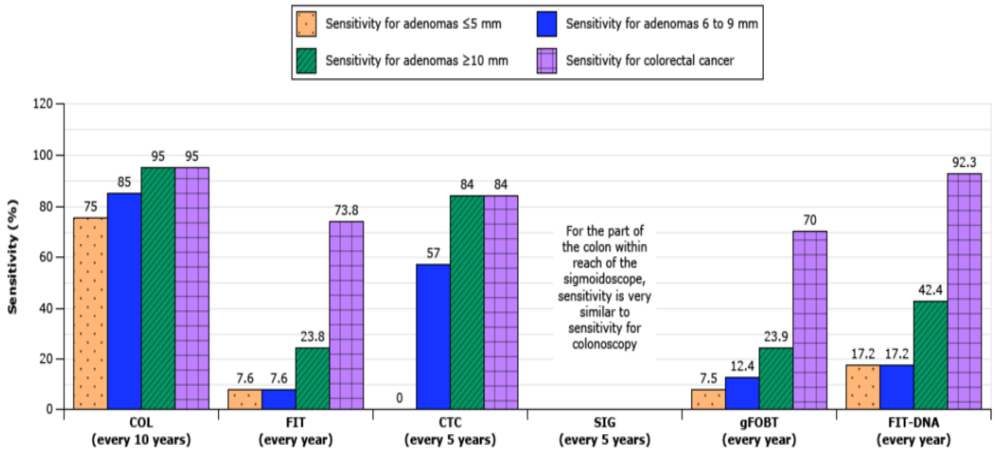
Conventional colonoscopy is considered the gold standard in the exploration of the large bowel thanks to the fact that it can visualize with high definition cameras bowel wall and, at the same time, perform diagnostic or therapeutic procedures like biopsies or polypectomies. It can identify premalignant colorectal lesion and perform local excision with a lower morbidity and mortality rate than surgical resection, thus reducing incidence and mortality. Many reports show a sensitivity grater than 95% for colorectal cancer lesions grater than 10 mm and a sensitivity of about 85 and 75% for polyps of 6-9 mm and less than 6 mm in diameter respectively [9, 10].

Although no randomized trials evaluating the efficacy of flexible colonoscopy in CRC screening are available, many reports suggest that it may reduce incidence and mortality for CRC up to 80% [13 - 17].

Major disadvantages of this technique are the need of bowel cleasing, it frequently cause significant discomfort or pain so that intravenous sedation, analgesia or even general anaesthesia are needed

and carries on a relatively high risk of complications like bowel perforation with an average risk up to 0,5/1000 and bleeding with an average risk of 2,6/1000, even if these complications are mainly related to operative maneuvers, primarily polypectomies, being size of the lesion and proximal location the major risk factors [18, 19]. Another disadvantage of flexible colonoscopy is that its accuracy depends on operator skills. A meta-analysis by van Rijin et al. reported an adenoma miss rate up to 26% for small polyps (1–5 mm) [20]. It is thought that missed adenoma may justify at least 50% of all interval carcinomas defined as a cancer diagnosed between two screening colonoscopies [21]. As a consequence high attention has been payed in order to define quality standards for colonoscopies, as adenoma detection rate has been shown to be inversely correlated with the incidence of colorectal cancer [22]. Despite these disadvantages, colonoscopy is considered the gold standard in the management of any benign colorectal lesion as the alternative of surgical resection has higher mortality, morbidity and costs [22, 23]. Even if no randomized trials have directly compared different screening programs on CRC incidence or mortality, data on the accuracy of flexible colonoscopy and cost-benefits analysis often led to recommend flexible endoscopy every 10 ears and yearly fecal occult blood test research as first level screening test, but many reports highlights that compared with no screening, all screening stratagies are more cost-effective [24, 25].

Nevertheless, owing to pain and discomfort often associated to flexible endoscopy, acceptance to screening programs is often limited with adherence rate at most 60%, thus many efforts have been spent to develop minimally invasive endoscopic devices that may overcame these drawbacks and the development of endoscopic capsules seemed to be attractive alternative to flexible endoscopy [26].



Test specificity	86	96.4	88	87	92.5	89.8
Colorectal cancer deaths averted per 1000 40-year-olds (n)*	22 to 24	20 to 23	16 to 24	16 to 21	20 to 23	21 to 24

Figure 2 sensitivity and specificity of colorectal cancer screening modalities

2. CAPSULE ENDOSCOPY

Endoscopic capsule has been designed nearly 20 years ago with the main purpose of exploring the small bowel. Nowadays, after 20 years of development, multiple endoscopic capsules are available with different specific exploration fields. They are all plastic capsule with length and diameter ranging from 26 to 31 mm and 11 to 13 mm respectively (Fig 3). They are equipped with a single or double camera with a field of view ranging from 140 to 360° and different capabilities of frame storing, ranging from 2 to 20 frames/sand depending on its specific aims (being maximum in devices designed to explore upper GI) (Tab 1) [27].

Figure 3 available endoscopic capsules

Table 1 available endoscopic capsule features

	PillCam SB2	EndoCapsule	CapsoCam SV-1	MIRO	OMON
Manufacturer	Given Imaging, Israel	Olympus, Japan	CapsoVision, USA	IntroMedic, Korea	Chongqing Jinshan, China
Battery life (h)	8 – 11	8	15	9 – 11	8
Dimensions (mm)	26 x 11	26 x 11	31 x 11.3	10.8 x 24	13 x 27.9
Field of view (°)	156	145	360	150	140
Image storing speed (frames/s)	2	2	20	2 – 3	2 - 15

All currently available capsules are characterized by passive advancement system by means of bowel peristalsis so they have to be swallowed after specific bowel preparation. For patients unable to swallow or for children special device are able to deliver the capsule directly in stomach or duodenum.

Obscure gastrointestinal bleeding is the main indication for capsule endoscopy [28]. Its use is recommended in case of obscure gastrointestinal bleeding in emodinamically stable patients when previous negative esophagogastroduodenoscopy (EGDS) and colonoscopy have been performed [29]. Diagnostic yields in case of obscure gastrointestinal bleeding is reported being about 67% and it rise up to 90% in case of overt bleeding. These results are comparable with the ones reached with double baloon enteroscoy [30, 31].

Capsule endoscopy can be a well tolerted tool to explore small bowel in patients with ereditary poliposis (Familiar Adenomatous Poliposis, Lynch syndrome, Peutz Jager syndrome). Literature report a sensitivity in identifying small bowel tumors of about 80% with major limits in the exmination of proximal duodenum [32 -34].

In the field of celiac disease the use of capsule endoscopy is recommended in cases of complicated or nonresponsive celiac disease (persisting abdominal pain, adenocarcinoma surveillance, overt bleeding etc.) being able to detect possible cause of complication like tumors, ulcerations, strictures in 60% of cases [35]. Moreover it can be useful in serum negative patients with villous atrophy [36].

Finally capsule endoscopy can be indicated in case of suspected Crohn's disease after negative EGDS and colonoscopy, in absence of obstructive symptoms, with a diagnostic yeald of about 60% [37].

There are not absolute contraindications for capsule endoscopy, but its use in patients with suspected strictures, fistulas or motility disorders have to be tailored because in these patients capsule can be retained in up to 5% of the cases. A patency capsule made of dissolvable material can be used before endoscopy in order to test bowel progression.

Capsule endoscopy could be a minimally invasive technique even for for the exploration of the large bowel, but when compared with flexible colonoscopy showed a relatively low accuracy; its sensitivity was less than 65% for polyps > 6 mm and it was able to identify only 75% of CRC discovered by colonoscopy [38]. As a consequence until now videocapsule colonoscopy is not recommended as screening strategy for CRC [39].

The major drawback of currently available capsules is the absence of active movement ability. Mainly in gastrointestinal tracts reached by flexible endoscopy (i.e. colon and upper GI), where capsule low invasiveness would be useful in screening programs, passive progression unavoidably lower the accuracy in exploration of bowel wall with respect to traditional endoscopy. Moreover passive advancement would not allow any kind of therapeutic action in case of detection of lesions amenable of endoscopic treatment. So robotic technologies have been applied to capsule models to develop locomotion systems in order to allow autonomous movement capabilities. A "front-wheel" approach for active and smooth navigation in the colon should limit stress forces on the bowel wall and, as a consequence, the pain related to flexible endoscopy as it is mainly due to the

stretch of the wall on his mesentery (especially noticeable on sigmoid tract and splenic and hepatic flexures) which is the consequence of the fact that to advance the endoscope it is necessary to push it from its proximal end.

3. ROBOTIC CAPSULES

The development of miniaturised robotic technology offered the possibility to integrate in capsules many primary functionalities that should interact to each other, first of all the capability of active locomotion.

Main modules making up a robotic capsule are: a) locomotion; b) vision; c) localization; d) telemetry; e) powering.

Nowadays investigational available robotic capsule contain some but not all these modules, mainly for the difficulty in integrate them in a such confined area. In all capsules the informations recorded by single modules are sent, by cable or wireless, to an external platform where are integrated ad available on a human-machine interface by which the operator can control capsule functionalities. In the following chapters an update of the state of the art of single components is performed.

3.1. Locomotion

Absence of active locomotion of currently available capsules is the major limitation. Many effort have been spent in order to provide endoscopic devices of active locomotion. Two main kind of locomotion have been developed: internal locomotion (progression mechanism is miniaturized and integrated inside the device) and external locomotion (the capsule is linked, usually magnetically linked, to an external robot that provide movements).

Internal locomotion: many different effectors are described in literature. A submarine-like system was developed for underwater navigation in the stomach. The capsule is provided by four independent propellers placed on the back of the device. This capsule is driven from an external joystick and has been tested in vivo in a porcine stomach filled with water [40, 41] (Fig. 4).

Figure 4 submarine-like capsule locomotion system

Another possible mechanism for navigation in a water filled stomach is a flagellar swimming mechanism [42]. A wired device with indipendent water jets system has been also designed to allow 3D underwater locomotion in the stomach [43].

Other propellers have been developed for progression of capsule along bowel wall non requiring water immersion. Scuola Superiore Sant'Anna tested a worm-like mechanism consisting in cycles of pneumatic extentions and retractions associated to anchoring devices on the top and on the back of the tool (Fig 5) [44].

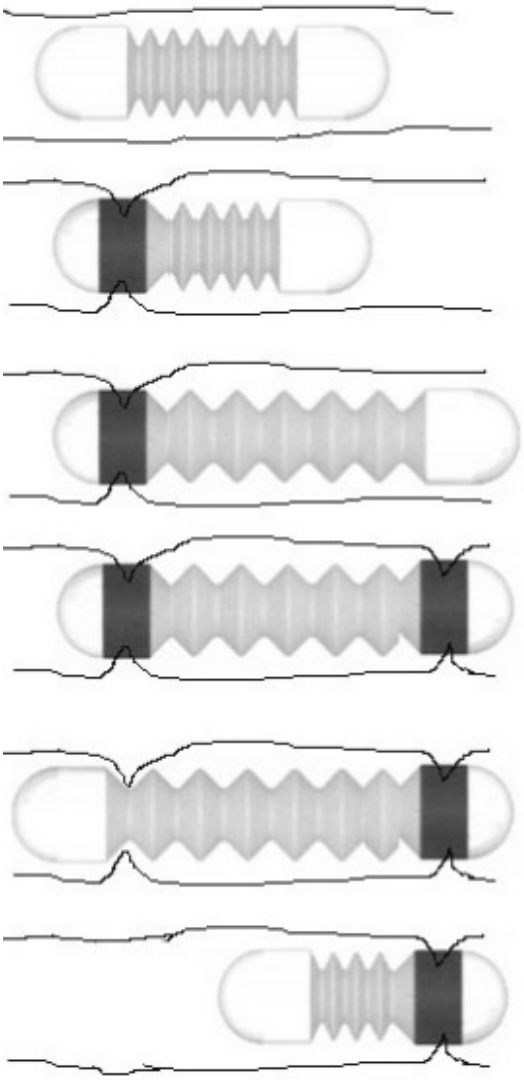


Figure 5 worm-like capsule locomotion system

Kim et al developed a conceptually similar locomotive mechanism consisting in compression and extension cycles on a shape memory alloy combined with the presence of anchoring needles [45] (Fig 6).

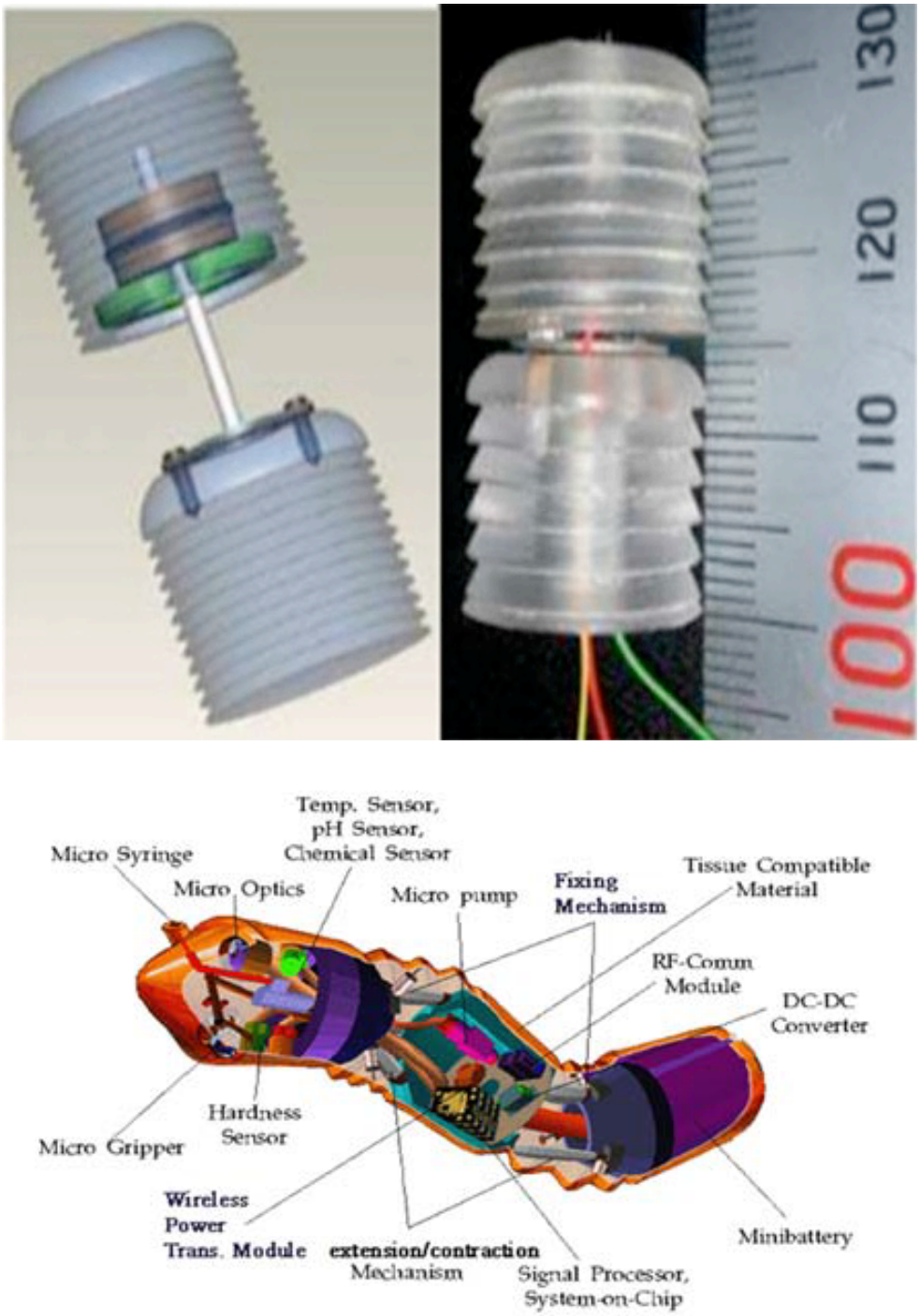


Figure 6 worm-like capsule locomotion system

This mechanism was than developed by many institution and has been tested in vivo on sigmoid porcine racts demonstrating effective progression.

Another mechanism uses six shape memory alloy units mimicking cilia extension [46]. Another one propose a system of multiple legs moving from the top to the back of the capsule in close

contact with bowel wall [47]. Park et al. tested a model where a single motor moves eight treads on the surface of the capsule that acting on bowel mucosa allow propulsion of the device [48]. Other bio-inspired mechanism have been proposed by The BioRobotics Institute of the Scuola Superiore Sant'Anna (Italy). Many prototypes with variable numbers of motorised legs have been tested [49, 50]. These solutions demonstrated a stable ancorage to the mucosa and a valid control of the movement in the space (Fig. 7).

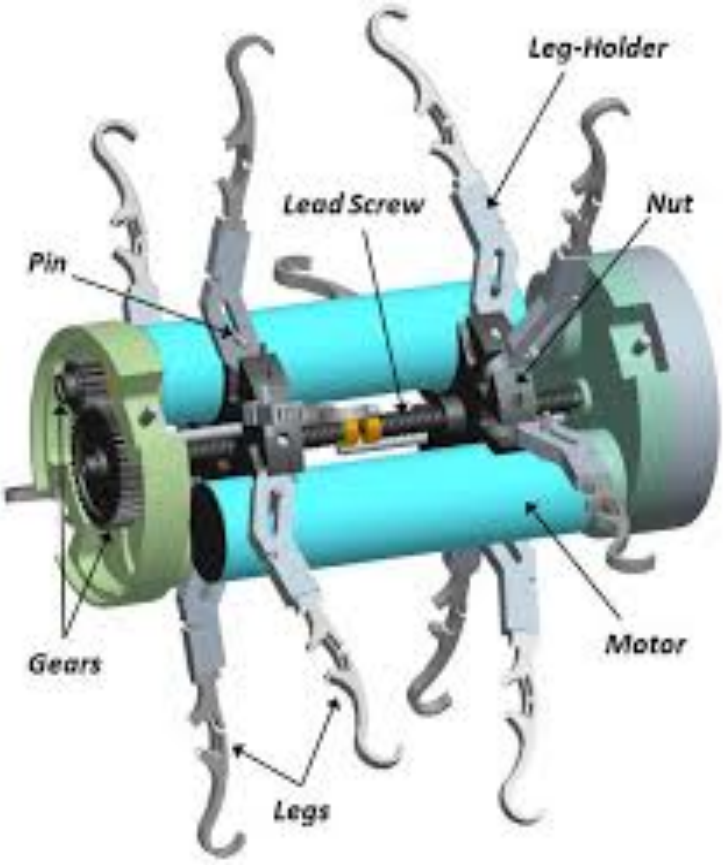


Figure 7 capsule locomotion system using robotic legs

Internal locomotion can be a promising technique, mainly because the possibility of limited distension of bowel, but the need to integrate in a limited space all the technological components, above all propellers actuators and high-capacity bacteries, brought to the creation of prototipes too large to be enployed.

External locomotion: in order to overcome this problem capsules carrying on permanent magnets or piezoelectric materials, magnetically linked to an external magnet have been designed. Active locomotion is allowed by movements of one or more external magnet or magnetizable materials generating magnetic field gradients. In this way the capsule is free from actuators and bacteries and the integration of the components is easier. Starting from the 2001 several patent applications for magnetically controlled devices were filed [51 – 55].

In 2006 Carpi et al. developed a wireless endoscopic capsule composed by a magnetized shell maneuvered by two handheld external permanent magnets and experimented this technology on ex vivo models [56]. With a similar technology given imaging reported the first in vivo navigation of a capsule carrying on permanent magnets in the stomach by means of an external handheld magnet in the stomach during the "Nanobased Capsule-Endoscopy with Molecular Imaging and Optical Biopsy (NEMO) project" [57]. Otha et al. reported a similar technology involving two external permanent magnet [58]. A clinical study involving healthy volounteers using the same technology called Magnetic Maneuverable Capsule (MMC) has been than conducted [59]. These tests showed good results in terms of sensitivity when compared with standard endoscopy, nowadays two wireless magnetic capsules moved by externale handheld magnet are available (the OMOM Controllable Capsule System and the MircroCam Navi MC1000-WM), but handheld magnet navigation resulted very little intuitive on several trials [60 - 63].

To overcome this drawback robotic technology has been introducted in order to move external magnetic fields with robotic arms. Different platforms have been proposed.

From 2009 Ciuti et al. developed a platform composed by a six degrees-of-freedom (DOF) robotic arm with a cilindrical permanent magnet as end effector, polarized on a sagittal section (Fig. 8) [64]. Capsule prototype are wired or wireless capsules incorporating camera, microcontroller and magnets. Magnetically linked capsule is polarized by means of a coronal section. Robotic arm is able to move around the patient generating translation movements (forward and backward), rotation on a plane of the capsule around its axis and, by means of the rotation of the external

magnets, upward and downward tilting movement. The operator uses a joystick to navigate the capsule on the basis of the visual feedback because joystick movements refer to a subjective reference system with respect to the capsule, thanks to an internal algorithm [65].

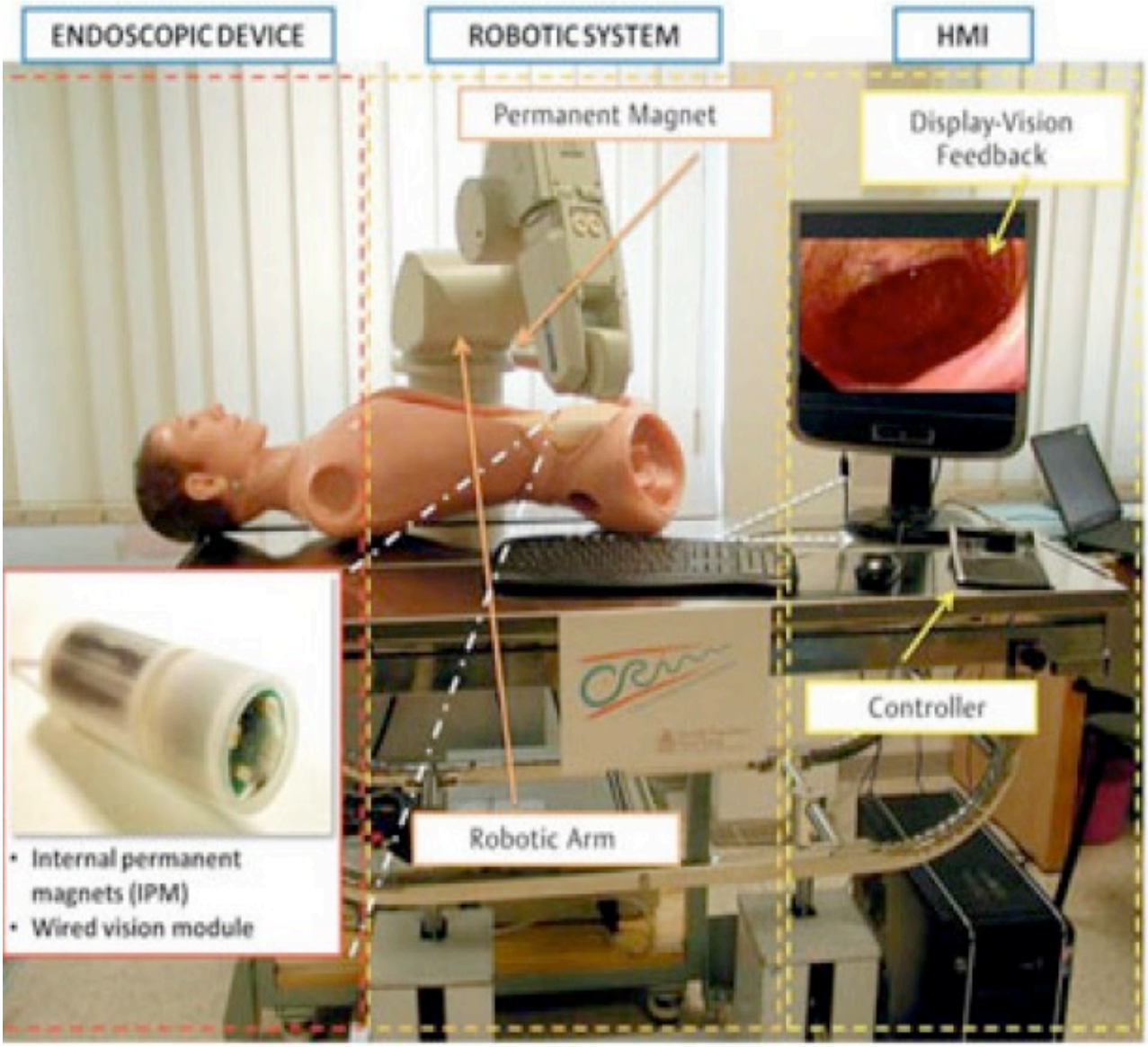


Figure 8 robotic magnetically driven robotic capsule platform

Mahoney et al. described a 6DOF robotic arm with a similar technology in 2013 [66] and Ankon Technologies created a clinically approved 5-DOF robotic arm holding a sferical magnet from upper GI capsule endoscopy [67]. A pilot study on healthy volounteers was conducted comparing this platform with standard endoscopy showing comparsable result in terms of accuracy [68].

A platform that moves two large permanent magnets in 2-DOF around a pivot point was developed by Carpi at al. from the commercially available Niobe system used to guide the tip of endovascular catheter for the treatment of cardiac arrithmias [69]. This system demonstrated high accuracy in orientation of wireless capsules in various cavities of porcine model but, because of the inability to create magnetic fields gradients, translation was not possible [70].

In order to minimize eventual risks related to interaction between robotic arm and patient, an active pressure sensing was proposed by Salerno et al. [71].

Another system able to create magnetic fields gradients consist in a electromagnetic coil system disposed externally to the patient [72, 73]. A capsule navigation technology that involves 12 external electromagnetic coils for a 5-DOF control was developed and demonstrated the feasibility of capsule navigation in water filled stomach of healthy volouteers [74, 75].

Magnetic resonance imaging (MRI) engine is a clinically available generator of magnetic fields with fixed direction. Kosa et al. described a prototipe of capsule with a flexible tail that hold miniature coil where alternative current can generate magnetic fields that, when inserted in MRI filed, generate oscillation of the tail and subsequent propulsion [76 - 79].

A similar swimming propulsion was developed by Morita et al. [80]. This capsule is composed by a tail that contains a permanent magnet and a head containing an electromagnet coil generating alternative magnetic field rerulting in oscillation of the tail and propulsion wosw direction is controlled by a joystick. This technology was successfully tested on dogs water filled stomach [81]. Othsuka et al. tested a similar swimming capsule propelling thanks to a fin in human stomach but it was not clear if adequate exploration was possible [82].

Finally rotational propulsion generated by a spiral structure in viscous or collapsed structures; rotation can be generated by a combination of internal motors, internal and external magnet. Some blind prototipes were developed and a prototipe holding a camera was tested on ex vivo porcine large bowel but rotational movement highly jaundiced imaging quality [83 – 89].

Vision modules able to detect intestinal lumen on the basis of light absence are under development and could be integrated in capsules, enabling autonomous progression interacting with robotc locomotion system.

Finally in the field of swallowing endoscopic capsules for exploration of small bowel, robotic technologies have been applied in order to add to the capsule the capability to stop and orientate, when needed, for lumen exploration or therapeutic activities. Zhou et al. proposed the use of magnetic forces to move parietal anchors that can hold the capsule to the mucosal layer [90]. Swain's group developed a prototype incorporating electrodes that can stimulate intestinal muscles whose contraction can stop capsule propulsion and some tests were performed on healthy volounteers [91, 92]. Another holding mechanism consisting in an extendable anchor moved by in internal motor was proposed by Woods et al. [93].

3.2. Vision

One of the most important tools, alongside with active locomotion, in order to achieve a platform with diagnostic and screening potentials, is the vision module. Currently available wireless capsules hold cameras with resolution of above 16 frames per second and up to 360 x 240 pixels [94, 95]. Wired cameras could hold high magnification cameras spatial resolution up to 320 x 320 pixels.

3D images can be reconstructed by multiple 2D images. Stereoscopic view, already available in laparoscopic technology, able to reconstruct 3D images, has been integrated in a wired magnetic capsula robotically drive in Endoo EU project.

Usually cameras are mounted on the top of the capsule but some of the currently available cameras hold multiple cameras [96]. Similar results can be obtained with microlens that can provide multiple images with a unique sensor even if the optimal configuration in not yet estabilished [97].

In order to achieve the best visualization of the lumen and of the gastrointestinal tract, owing to the limited space and the short optical focus, cameras with a wide field of view. It usually ranges between 140 and 170° but prototipes with fields of view up to 360° have been proposed [98].

Illumination is an essential tool and is provided by white light LED sources. Different technologies and cofiguration are available. Adaptive brighteness has been tested and its variation can be used to estimate the distance from bowel wall [99].

NBI is an imaging technique that filter blue and green light and enhance vessel architecture and glandular structure in biologic tissue and technology that enhance specific wavelenght ca be integrated in onboard cameras.

3.3. Localization

Spatial localization of the capsule is an adjunctive tool with useful implication. It can be helpful, integrating information provided by on-board cameras, to localize pathological findings or to restore the magnetic link when lost. Magnetic fields itself can be used to localize a magnetic object: multiple magnetic sensor outside the body can measure intensity and direction of capsule magnetic field and triangulate information for 3D reconstruction of spatial localization or magnetic sensors integrated in the capsula can measure magnetic fields generated by external landmarks sensor [100, 101]. In case of a robotic arm holding a permanent magnet, the external arm itself, endowed with a magnetic sensor, can be used to localize the capsule by moving in 3 fixed position in the space measuring magnetic forces and triangulating the information to localize the capsule and to indipendently restore the magnetic link if lost.

3.4. Telemetry

In case of wireless capsules every kind of information received by the capsule have to be transmitted to the robotic platform for elaboration. Radiofrequency is the most frequently use

modality even if transmission of low frequences requires large electronic components. Many efforts have been spent to develop new transceiver and antennas [102 – 105].

3.5. Powering

Power alimentation is a great challenge in wireless capsule because every adjunctive tool is a high consuming component. Nowadays available capsules have silver oxide button bacteries the provide a 15 h power supply but lithium bacteries are a promising solution [106, 107].

Wireless power supply using radiofrequency or magnetic fields have been developed with promising results [108, 109].

3.6. Irrigation and insufflation

Accurate visualization of gastrointestinal tract require distension of the lumen and adequate lens and mucosal cleaning. As a consequence insufflation modules and irrigation modules have to be integrated in the capsule.

In order to reduce capsule dimensions and maintain high functionalities wired capsules have been proposed with the advantage that some components such as power supply, telemetry, insufflation and irrigation modules would be placed externally.

4. TOWARDS ENDOO PROJECT

Into this wide field of research, our research group had the purpose of developing an endoscopic robotically driven magnetic capsule with diagnostic and therapeutic capabilities, able to perform a minimally invasive and painless colonoscopy thanks to a “front-wheel” magnetic–driven approach for active and smooth navigation in the colon. This should limit the discomfort during colonoscopy as it is mainly due to the distension of the bowel and to the stretching of the wall of the intestine and the mesentery, due to the fact that the advancement of the distal end of the instrument is allowed only by the thrust exerted by the operator at the proximal end of the same and, at the level of each curvature of the viscera, is exerted directly on the walls of the colon and only indirectly at the tip of the instrument. The segments with the tightest curves and the stretches of bowel less anchored to the abdominal wall (the sigma, splenic flexure, and hepatic flexure) will therefore be those where the force exerted on the wall is greatest and where the procedure will be most painful.

4.1. The beginning of the project

The idea behind this project was developed inside the VECTOR project (Versatile Endoscopic Capsule for gastrointestinal TumOr Recognition and therapy) aimed to use knowledge in the field of biorobotics and microtechnology to develop robotic endoscopic capsules for early diagnosis and therapy of diseases of the gastrointestinal tract.

In the developed model the endoscopic capsule contains a magnetic dipole which moves thanks to the variation of an external magnetic field; the source of the external magnetic field is a permanent magnetic dipole. This creates, according to the polarization, a magnetic field whose lines of force exit from one pole and close in the other and whose intensity, and consequently the intensity of the force that can be generated, decreases with the square of the distance. The second magnetic dipole, connected to the endoscopic device, when placed in the magnetic field is subjected to two types of forces: one force is directed towards the first dipole and attracts the opposite poles; the second is a

torsion force that pushes the dipole to orient itself according to the polarization and the lines of force of the field. The translation of the outer magnet will produce a consequent translation of the inner magnet, then of the capsule, while a rotation will correspond a similar rotation of the inner magnet, the device will then make orientation movements in place.

In order to improve accuracy and reproducibility of capsule movements the external permanent magnet, that in many reports was maneuvered by hand by the operator, was anchored to a robotic arm with 6 degrees of freedom.

Thus a first wired capsule prototype was made, equipped with a 1.48T permanent magnet, an optical system and an operative channel. The idea of equipping the capsule with electromagnet coils was abandoned because the forces needed to advance the capsule would require too large components.

4.2. Manual vs robotic magnetic control platform

A progression test on an ex vivo swine large bowel shaped and fixed to a phantom simulating the abdominal cavity was performed in order to compare manual and robotic control of the external permanent magnet by means of the robotic arm.

The robotic control was provided by an external workstation from which the operator could guide the capsule in an intuitive way thanks to a peripheral device equipped with six degrees of freedom, thanks to a software for the real-time control of the movement to maneuver the robotic arm in the same number of degrees of freedom. The acquired images were transmitted to the external workstation and displayed on a screen in real time.

The manual control was instead obtained by directly gripping the external magnet and moving it on the abdominal surface.

The colon was inflated at a constant pressure of 2 mmHg and six targets were placed along the inner wall of the colon. 10 operators had to drive the capsule from the rectum to the splenic flexure both manually and with a robotic platform. The number of completed test, the time to complete the

test and the rate of identified target was recorded and compared. The results showed that the progression of the capsule until the splenic flexure was achieved in all the tests but the navigation controlled by the robotic platform allowed a shorter time to complete the test (201 sec vs 423 sec) and a higher rate of target detection (87% vs 37%).

A problem that emerged was that with the peripheral device used in the robotic control, the operator could find it difficult to predict the movement of the endoscopic device not knowing neither the position nor the orientation and relying only on the image displayed on the screen, this is because the commands of the peripheral device correspond directly to movements of the robotic arm and depending on the position of the capsule inside the bowel, the same command can correspond to both forward and backward movements and lateral translation. Efforts have therefore been directed towards the study of a system that can integrate feedback signals from position sensors integratedin the capsule with the image of the screen and with the commands of the peripheral to obtain a more intuitive control of the device, it has been tried to realize a navigation system in which the operator can guide the capsule as if he were inside it.

Then it was developed a system able to sense when the magnetic link between the external magnet and the embedded magnet was about to lose based on 3 axes hall sensors. It has been established that the optimal distance between the 2 magnets, for a good control of the capsule, was 15 cm.

4.3. Control interface

One of the objectives was then the realization of an interface that would make the management of the endoscopic device as intuitive as possible for the operator. To do this, it was necessary to develop a system that integrates the commands coming from the peripheral with the feedback coming from position sensors inside the capsule, so that the commands given by the operator directly correspond to the same number of movements of the endoscopic device.

With this aim, three interfaces for the control of a videocapsule have been developed and an ex vivo feasibility study has been carried out for a quantitative and qualitative comparison between them. quantitative and qualitative comparison between them (Fig. 9).

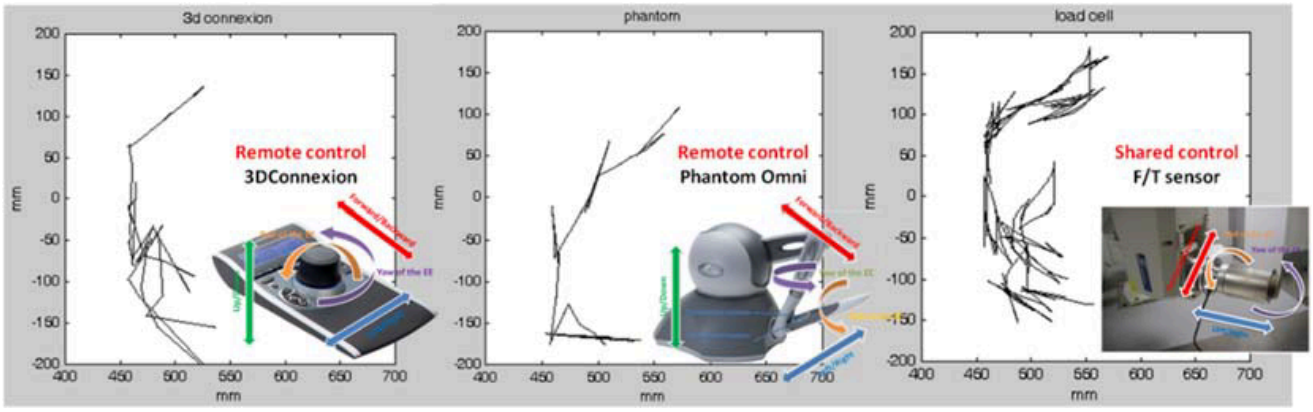


Figure 9 comparative fetures of three different interfaces

Of the interfaces realized for the study, two allow remote control while the third allows a shared manual and robotic control of the magnet external. As reguard the remote control, two peripherals have been realized: the first (3D Connection Space Pilot) consists of a control panel containing a knob with six degrees of freedom, the second (Phantom Omni) consists of an arm with three joints to which is still articulated a pen that is operated by the operator.

Both of these systems propose an intuitive control of the endoscopic device: a software integrates feedback from the capsule, the information about the position in space of the robotic arm and the external magnet and commands from the control station and transmits the commands to the robotic arm in such a way that the six degrees of freedom of the interface correspond bi-directionally to the possible movements of the capsule (forward, backward, left and right horizontal orientation, upward and downward orientation) independent of its position in space and of the anatomical location. The operator therefore could guide the capsule as if it was on board, relying almost exclusively on the endoscopic images endoscopic images. In Shared Control, instead, the operator imposes a translatory or rotatory directional pressure on a sensor positioned between the end of the

arm and the external magnet, which transmits the perceived command to the robotic mechanism that performs the movement. This system allows a very intuitive control, similar to the manual one, but the robotic assistance guarantees the stability of the external magnet and consequently a high precision of movement. To perform the comparison between the interfaces, ex vivo tests were conducted on 85 centimeters of pig colon, placed in a phantom model of the abdominal cavity; colored targets were placed on the inner surface of the colon in different positions and number at each test session. The objective of the study was to navigate the endoscopic capsule along the colon from the rectum to the mid-transverse, using and comparing all three interfaces and identifying and reporting the position and color of the targets each time they were displayed. For each interface, the execution time, the number of targets recognized, the number of times the link was lost, and an analysis of the trajectories performed by the robotic arm were recorded.

The tests demonstrated that the remote magnetic control with robotic assistance allows effective locomotion of the endoscopic capsule. The systems tested allowed good precision of movement both as regards the propulsion of the device, and as regards the orientation movements in space. In fact, with all three interfaces, all the doctors who carried out the tests have successfully completed the procedure by navigating the device from the rectum to the middle of the transverse colon. transverse colon. Analysis of the results showed that Shared Control allowed to perform the test in a shorter time and to identify a higher percentage of targets. However, the number of the losses of the magnetic link and the analysis of the robotic arm trajectories showed that the system controlled by the Phantom Omni interface ensures higher governability of the capsule, so we adopted this user for the platform [110].

4.4. Comparative tests

In order to define if the platform could be potentially competitive with flexible validate endoscopy, the a non-inferiorly study was conducted. 22 physicians performed a complete colonoscopy simulation both with the robotic platform and with a flexible colonoscope. Among them both

expert endoscopists and trainees were present The setting was an ex-vivo 80 kg pig large bowel segment tha was was inserted into a phantom simulating abdominal cavity and was fixed in order to simulate anatomical flexure of the colon. To ensure the stability of the system a layer of foam rubber (10 mm thick) covered by a sheet of Plexiglas was placed above the phantom simulating the abdominal wall. The colon was inflated with a constant pressure of 1 mmHg via an endoscopic insufflator (Surgiflator-40, WOM Word of Medicine AG, Germany). Along the inner surface of the bowel mucosa were placed some colored targets of about 5 mm in diameter. The position and the number of targets were different in each test (Fig. 10).

Figure 10 ex-vivo capsule navigation and target identification

All the operators were able to complete the colonoscopy both with the capsule and with the flexible colonoscope. In the capsule group the detection rate of the targets was 80.9%. In flexible colonoscopy group 85.8% of the targets have been identified with a non-statistically significative

difference (95% CI: 0.9% - 8.8%). A subgroups analysis showed that when only the expert endoscopist were considered, target detection rate was 74.2% with the robotic platform vs 83.9 % with flexible endoscopy, with a difference statistically significant (P = 0.002) while in the trainees group there was no difference in accuracy between the two techniques (87.6%). It is interesting to note that if detection rate during capsule endoscopy is compared, trainees were found to identify a higher percentage of targect with respect of expert endoscopist (87,6% vs 74,2%) with a statistically significant difference (P <0.0001). Capsule endoscopy required an average time of 556 sec ± 188 sec to complete the test, significantly higher that the time required with standard endoscope (194 sec ± 158 sec, P = 0.0001). No correlation was identified between the speed of the procedure and the number of pins identified.

Ex vivo comparative tests showed that capsule colonoscopy performed with the new platform is feasible in an ex-vivo model with a good diagnostic accuracy and a good acceptance by the operators. Anyway from these preliminary tests some drawbacks emerged, first of all the need to reduce capsule dimention and optimize some functionalities to be competitive in a clinical scenario.

5. THE ENDOO PROJECT

Promising preliminary results from capsule navigation tests led to focus our efforts to design a platform that could be really competitive with flexible endoscopy. The Endoo Project (Endoscopic versatile robotic guidance, diagnosis and therapy of magneticdriven soft-tethered endoluminal robots) grew up to finalize the research and complete the development of an integrated robotic platform for the navigation of a soft-tethered capsule able to perform painless colonoscopy with diagnostic and therapeutic capability. The project has been funded from the European Community's Horizon 2020 Framework Programme. The consortium was both academical and industrial with 2 medical partners (University of Torino and Edinburgh), 2 engineering partners (Scuola Superiore Sant'Anna di Pontedera, University College of London) and 2 industrial partners (Ekymed/Mediate and Ovesco Endoscopy).

As part of the Endoo project, comparative studies with flexible endoscopy have been performed with the goal of defining a product that could have all the features for clinical trials.

5.1. Endoo robotic system

The Endoo platform is composed of two main sub-modules: an external robotic driving platform (Fig. 11) and a soft-tethered capsule with diagnostic and therapeutic features (Figure 12) and relies on a modular robotic architecture aimed at assisting the surgeon during colonoscopic diagnosis and treatment.

The design of the entire robotic system is clinician-centered and it consists into a master-slave robotic architecture (Fig. 11A) and on an interactive (Figure 11B) control structure. Motions performed by the surgeon through an haptic serial control interface with 6 degrees of freedom (DoF; Geomagic TOUCH+, 3D Systems, Rock Hill, SC, USA, Fig. 11A) correspond to as many movements of an anthropomorphic robot, acting as the slave unit (i.e., the slave; COMAU Racer5-0.80 Aura, Fig. 11B) assembled onto a movable platform (Fig. 11C). An external permanent

magnet is attached to the end of the robotic arm with an embedded independent DoF (Fig. 11D), and thanks to the magnetic link, drives the capsule (Fig. 11E and 12) and controls its orientation (Fig. 11A).

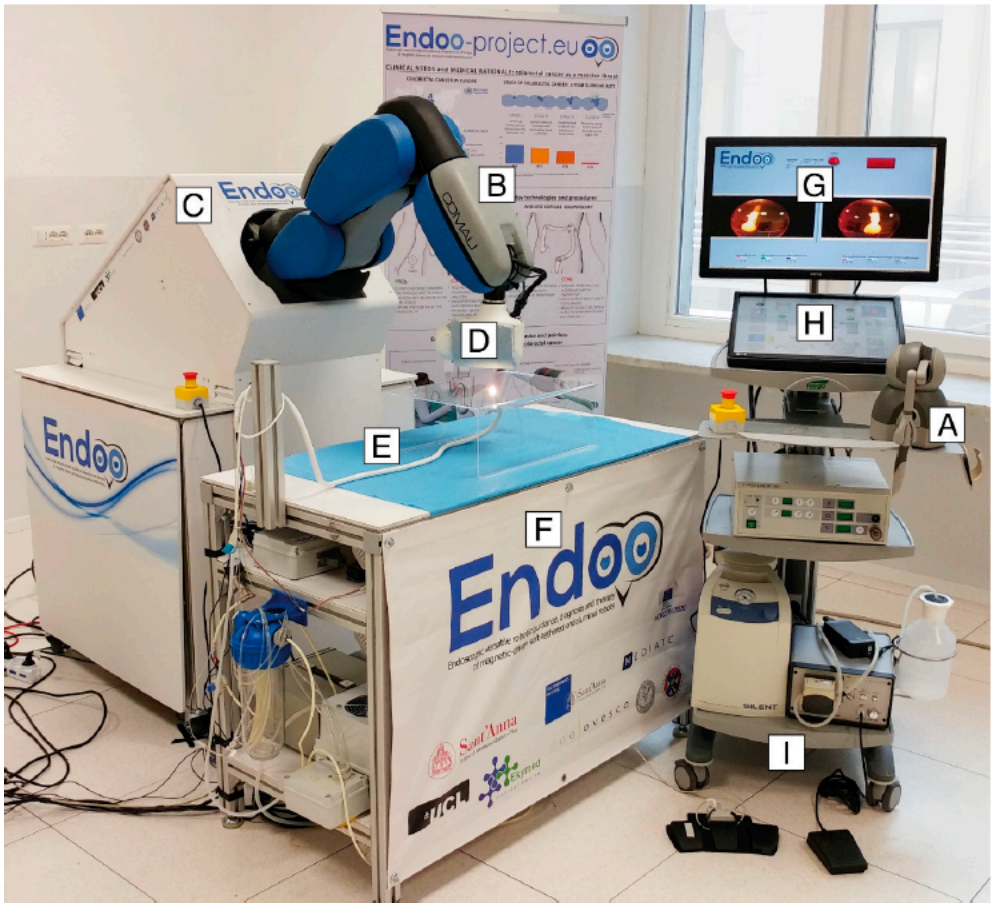


Figure 11 The Endoo robotic colonoscopy system: (A) haptic interface (joystick), (B) collaborative robot, (C) movable platform, (D) external permanent magnet, (E) capsule, (F) localization system, (G–H) graphical user interface, and (I) pumps and foot pedals. (G–I) The medical workstation.

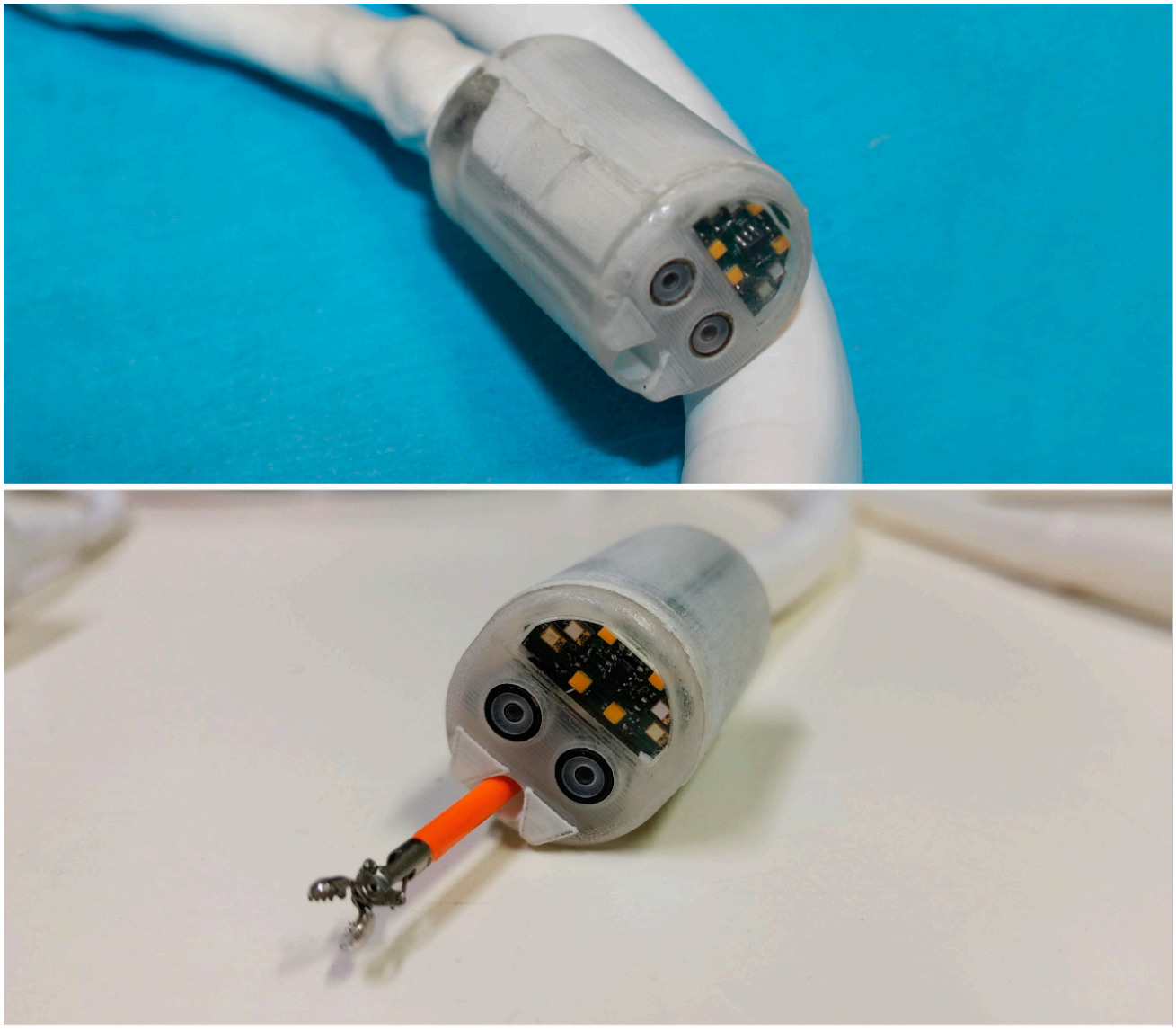


Figure 12 soft tethered robotic capsule

The Endoo capsule has been designed in order to guarantee exactly the same functionalities and high-grade standards of traditional colonoscopes, but with the aim of decreasing the overall invasiveness of the colonoscopic treatment, thanks to a “front-wheel” navigation strategy and to the soft-tether functional design. The Endoo soft-tethered capsule, with a total length of 160 cm, matches with commercial surgical tools and typical colonoscopy procedures. The capsule integrates two custom-made wide-angle lenses with 170° field-of-view (FoV) and 3 to 100 mm depth-of-focus (DoF) capabilities; images coming from the lenses are acquired through two high-

resolution 1080p CMOS sensors (for stereoscopic vision) and are transmitted to the main monitor dedicated to visualization, and used by the clinician for navigation. Illumination during the endoscopic procedure is enhanced by white LEDs and green/blue UV LEDs for NBI-like vision. The soft-tethered capsule integrates four fluidic channels: i) a 3.7 mm operating channel for suction, flushing and standard tools insertion, ii) two dedicated channels for colon insufflation and for cleaning and drying the lenses through two nozzles; and iii) a dedicated channel for water external flushing. In addition to the embedded permanent magnet, the capsule embeds two different sensors (i.e. a tri-axial hall effect sensor and an accelerometer) used for localization and closed-loop control during navigation; data coming from these sensors are used for monitoring the 5 degrees of freedom of the capsule (3 positions and 2 orientations, roll is not allowed).

Interactive forces between the magnetic end-effector of the robot and the external environment are monitored through a force/torque sensor (Mini45 Titanium, ATI Industrial Automation, Apex, NC, USA) in order to prevent harm to the patient (Fig. 11B). In addition, thanks to the integration of a sensorized skins, physically covering the anthropomorphic robot the Endoo platform guarantees a human-robot safe interaction (Fig. 11B) as required by the International Organization for Standardization/Technical Specifications (ISO/TS 15066:2016, i.e., a technical standard for collaborative robots) [112, 113].

The endoscopist can control the capsule in a master-slave paradigm, either using the teleoperation strategy with the joystick (Figures 13A) or performing adjustments and/or control of the motion trajectories with an hand-guidance strategy through the installed force/torque sensor (Fig. 13B).

In addition, a magnetic localization module is integrated into the operating table (Fig. 11F); it is aimed at localizing and mapping on-line the capsule pose during the entire treatment, elaborating information from the capsule sensors for guaranteeing the correct alignment and relative distance between the two magnetic units to avoid internal capsule-tissue high pressures.

Each of the functionalities of the Endoo robotic platform can be on-line monitored and controlled

by the endoscopist using a touch-screen graphical user interface, designed "ad-hoc" with a clinician-centered approach for the Endoo application and fully-adjustable according to the surgeon preferences. Monitors, joystick, pedals and pumps are integrated into a movable medical workstation that allows actuation and control of capsule's fluidic functionalities and data communication through the use of dedicated control units.

5.2. Capsule components

I lens irrigation (lens cleaning)

The lens cleaning module is activated from the medical workstation. The water flow of the Endoo platform has been measured to be 60 ml/min, which is comparable with the flow rate of commercially available colonsocopes (Olympus endoscope PCF-PH190I guarantee a 50 ml/min flow wile while Olympus endoscope CF-Q145I nozzles is equal to 70 ml/min respectively) (Figure 11).

II Insufflation

To test the insufflation capability, comparative tests with standard endoscope have been conducted. Following test have been performed:

- the capsule/endoscope was put into a bowl of water, then insufflation was started a qualitatively evaluation by phisitians have been done
- the tip of the capsule/ endoscope was put into a balloon and the insufflation capability was evaluated measuring boloon diameter after insufflation performance.
- the capsule/endoscope was put into an ex-vivo colon and insufflation pressure was measured by a probe inserted in the distal endo of the bowel.
- the tip of the capsule/endoscope and a pressure measurement tool was inserted into a glove and pressure of insufflation was measured in parallel

All the tests showed comparable insufflation pressures between standard endoscope and capsule

The measurement of the pressure during the tests has been performed using a SPER Scientific Manometer;

III Localization module

The localization module is a system that is able to identify the position and orientation of the capsule in the space, showing the coordinates of the position in the 3 axes with an error of about 1cm.

It consists of four main sub-modules: a current (DC) power supply, a transformer from direct current to alternating current (AC), a coil and three Hall effect sensors. It is based on the presence of 4 alternating magnetic fields placed under the table, so that the casule is subjected to a continuous magnetic field from the external magnet and 4 alternating magnetic from the underlying coils that work with different frequencies in order that the hall sensors, arranged on perpendicular planes inside the capsule, are able to identify the difference of the magnetic field produced from each coil independently. Collected data are analyzed by an algorithm which is able to identify the position and the orientation of the capsule.

After an initial calibration, in-vitro test were performed were the real position of the capsule was compared to the position identified by the system. After 100 measures an error of about 1cm emerged .

IV Polyp detection module

As polyp detection rate often is operator dependent, a useful tool would be an augmented reality module able to highlight endoluminal mucosal lesions.

Due to the large variety in the size, shape, color and textures of colon polyps, autonomous detections requires highly complex algorithms. A vision module based on a convolutional neural

network (CNN) framework has been conceived able to identify endoluminal polyps minimizing false detections.

Deep learning may be particularly useful in the development of this technology because huge iconographic databases of endoluminal colorectal lesions are available, facilitating the detection endoscopic images from visual modules.

CNNs include three different components: convolution, activation function and pooling operation layers (Fig 14).

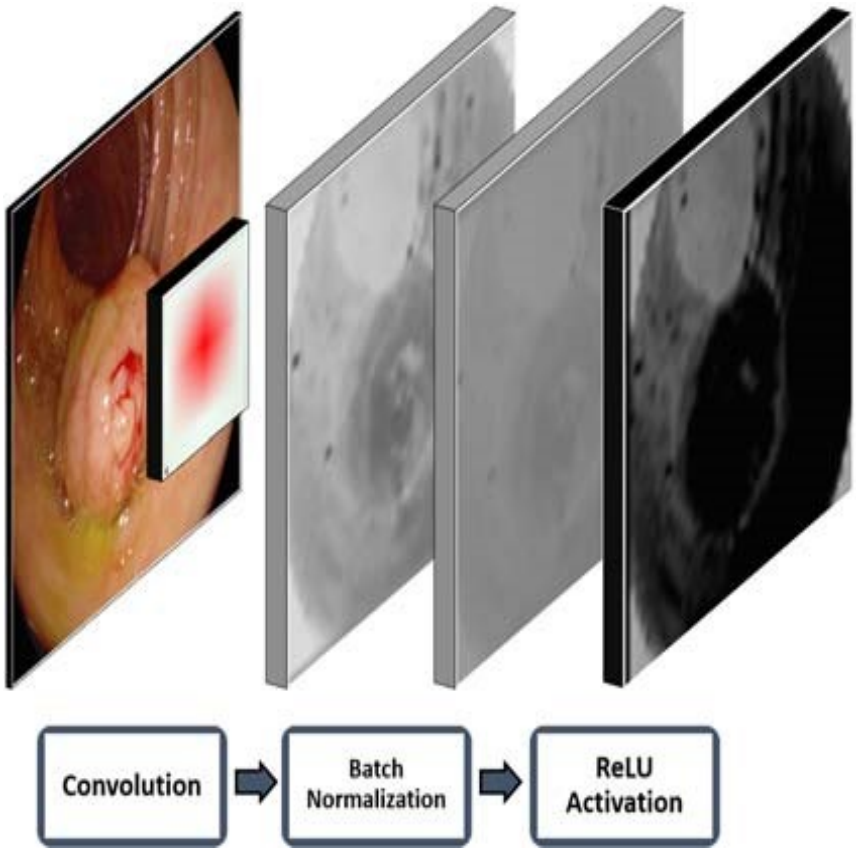


Figure 14 CNN's components

Six different convolution architectures have been tested for polyp detection and segmentation: AlexNet, GoogLeNet, VVG, and three version of the ResNets architecture with 50, 101 and 152 layers of depth.

Best detection rated was reached by FCN-VGG wich obtained a detection rate of 86% during in-vivo colonoscopies (Figure 15 and 16).

These are preliminary reports and efforts still need to be made to improve the technology, but visual modules for the recognition of colic polyps may be a useful tool to increase and standardize the accuracy of endoscopic procedures.

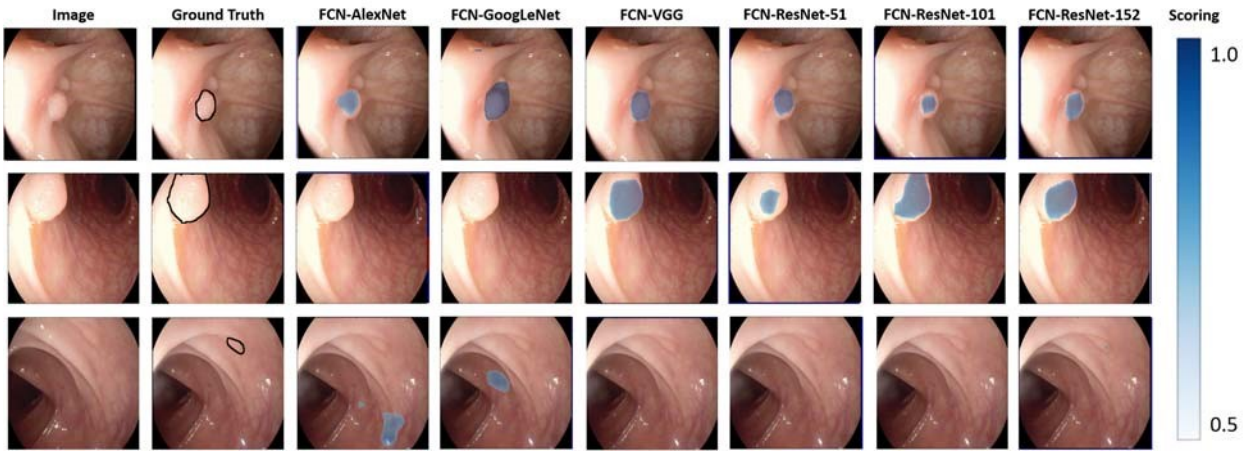


Figure 15 Example of three different scored segmentations produced by the six proposed FCN networks.

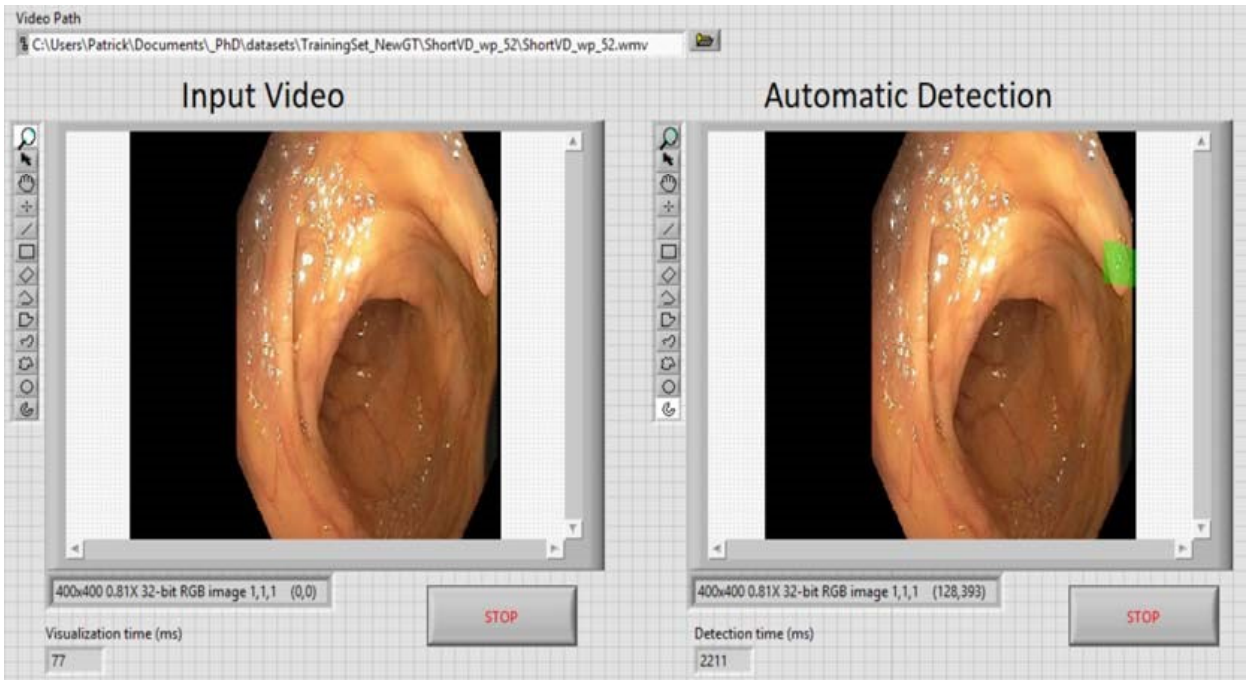


Figure 16 Front panel of automatic polyp segmentation software. On the right the polyp is highlighted

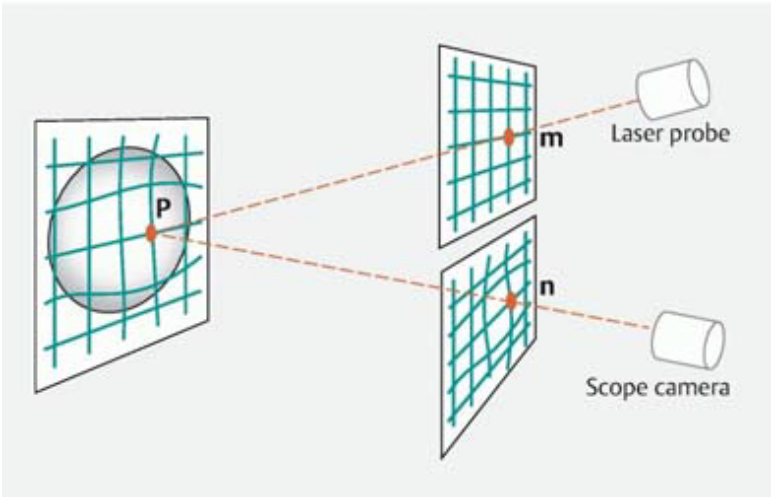
V 3D lumen mapping and reconstruction

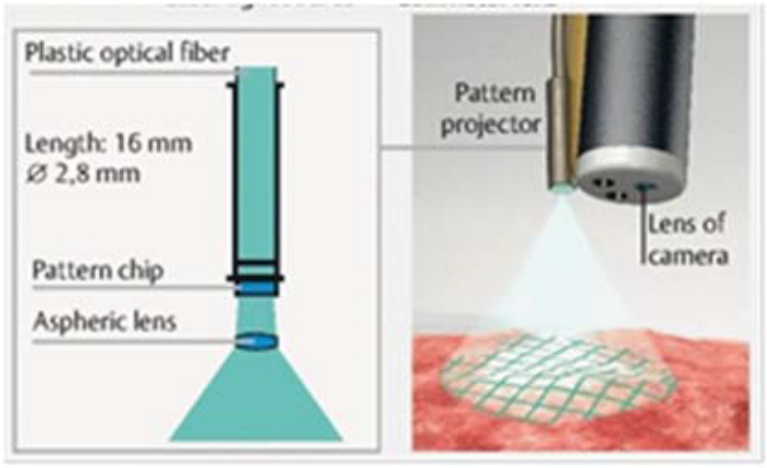
Algorithm have been produced with the goal of obtain three-dimensional reconstruction and recognition of the inner lumen of the bowel from the stereoscopic image module of the Endoo capsule.

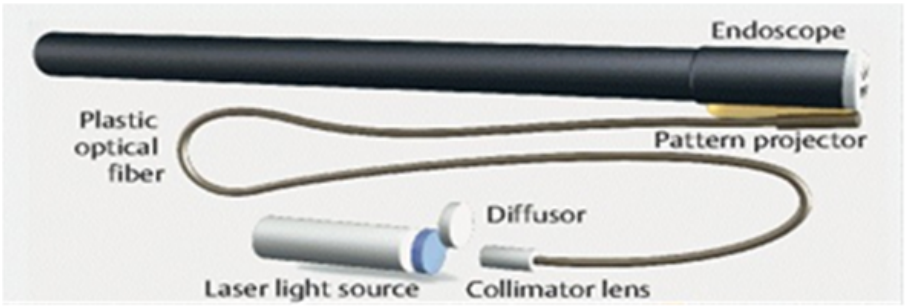
The three-dimensional structure of the colic lumen is reconstructed from the individual frames obtained during capsule navigation. The System is still under study, but may be an important tool for the development of autonomous navigation systems that can assist the operator during the procedure.

VI Laser grid measurement of digestive polyps

A software able to analyse polyp size has been designed as an accurate definition of endoluminal lesion size may affect subsequent therapeutic decisions. In order to test this new tool a colonoscopy was performed with an instrument equipped with a laser source that project a non-homogenous grid on the surface of the lesion. analysis of the deformation of the grid made It is than possible to estimate polyp size by analyzing grid deformation. A grid of known shape and size was projected from a probe on the tissue, subsequently corresponding points between the captured image and the projected pattern are matched using an algorithm. Being knowed the relative position of the camera and the projector, it was possible calculate the position in the space and the relative distance of all the grid points projected on the polyp (Fig. 17).







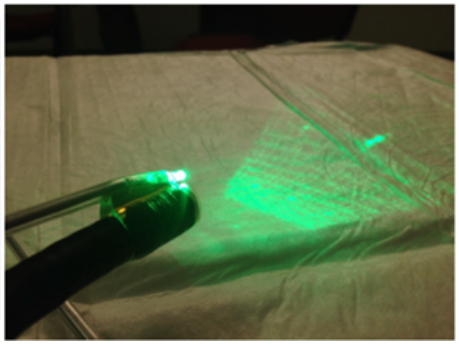


Figure 6 Basic functioning of the structured light probe.

In order to test the accuracy of the algorithm comparative test were performed., polyps of different size have been simulated in the inner surface of an ex-vivo model and their dimension has been estimated with traditional techniques (visual measuring, loop encirclement, biopsy forceps manipulation) and with the overmentioned software and results were compared (Fig. 18).

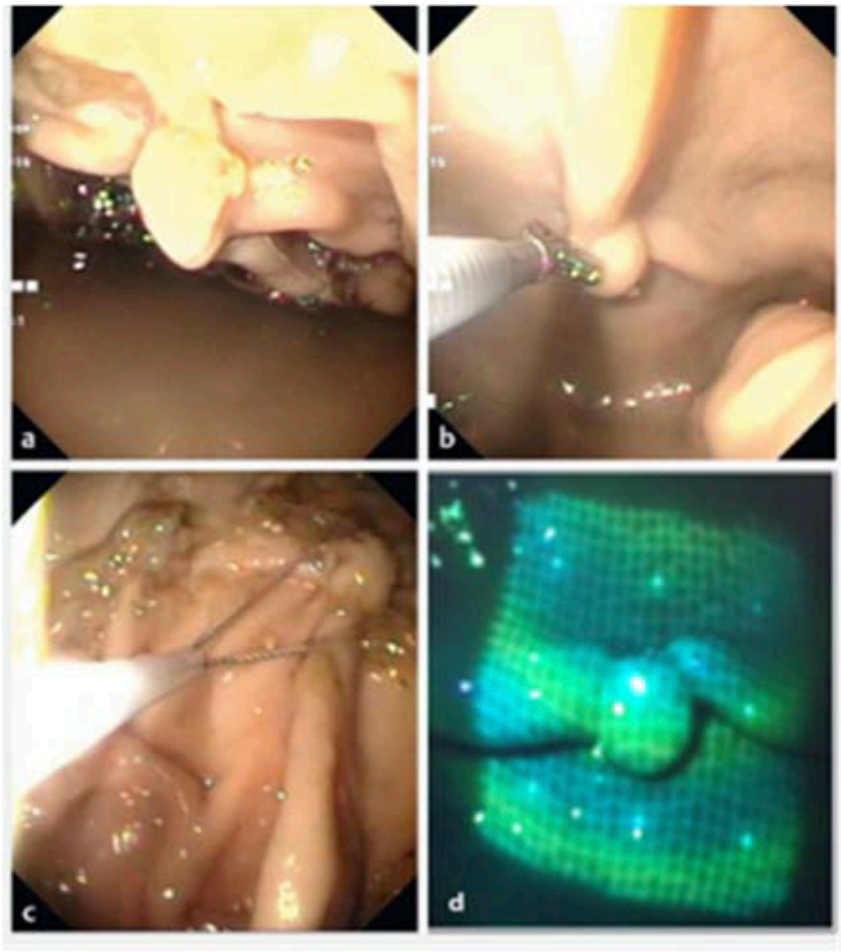


Figure 18 comparison of polyp dimention with traditional techniques (visual measuring, loop encirclement, biopsy forceps manipulation) and with laser grid measurement software

The proposed probe was able to reduce the average error in the measurement to 1.5 mm, IQR = 1.67 mm with a statistically significative difference with respect to the visual modality (P =0.002, 95%CI), without a significative difference towards forceps manipulation (P=0.81, 95%CI) or snare encirclement (P=0.99, 95%CI) but with the benefit of not occupying the operative channel. The average time to perform the measure was 54.75 seconds per polyp. It was significantly higher than with visual assessment but not significantly different than with other modalities. It is to be noted that software performance time was partly conditioned by lens cleaning problems. The software obtained good results in a quality assessment among operators.

These results demonstrated that the laser grid technology allows reliable and reproducible assessment of sample polyps and we were convinced to embed this technology into the Endoo capsule.

5.3. Endoo ex-vivo tests

In order to test Endoo functionalities and to compare Endoo platform with flexible endoscopy we performed ex-vivo tests using a custom-made abdominal simulator obtained through a forming process from CT scan of abdominal cavity, which was embedded with a fresh swine bowel, 100-120 cm long (Fig. 19).

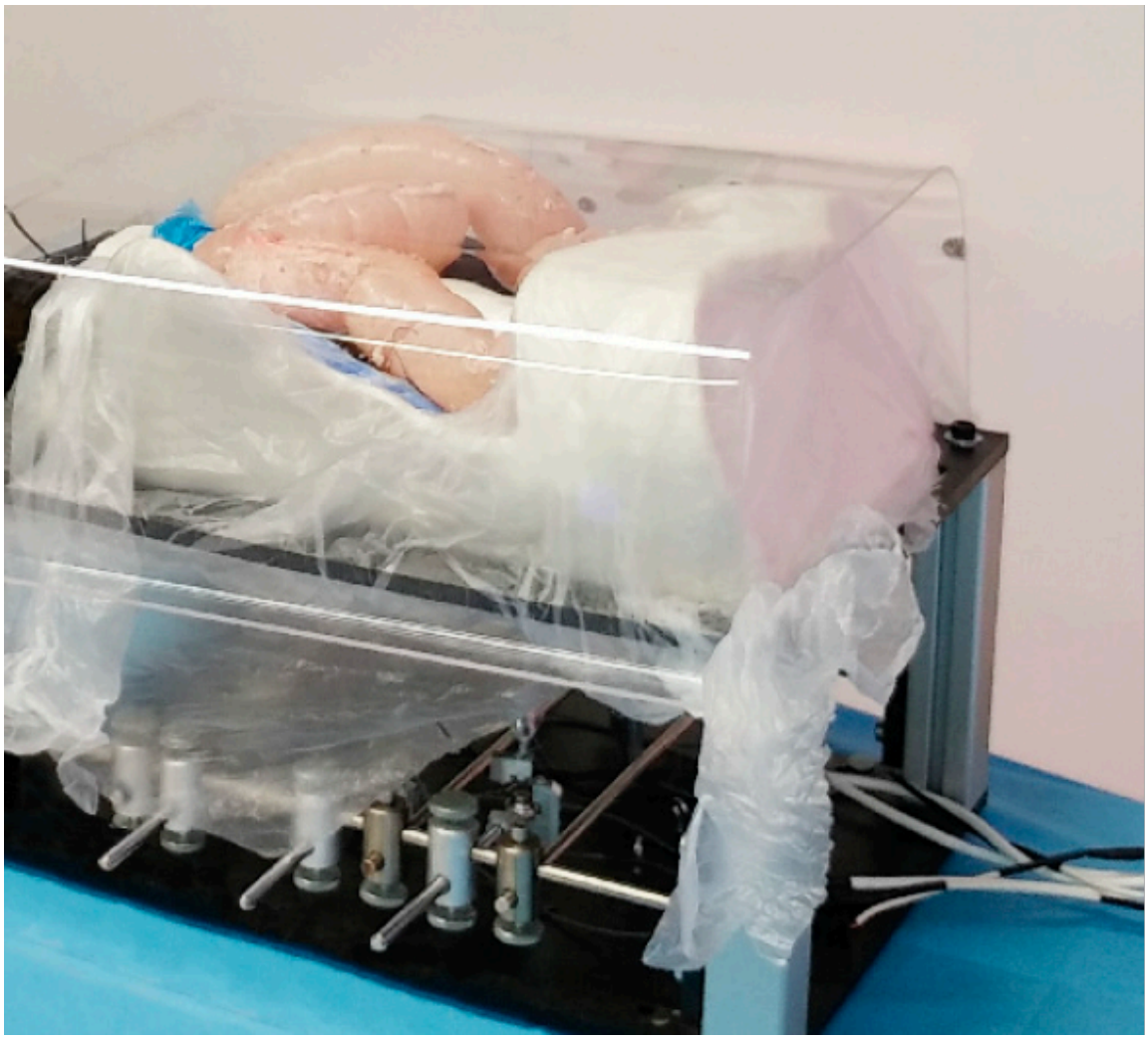


Figure 19 abdominal simulator

To test forces exerted on the bowel wall, the phantom integrated 6 mono-axial strain-gauge sensors (OMEGA LCL-005, OMEGA Engineering Inc., Karvina, Czech Republic) connected, through inextensible wires, to the colonic tracts. Sensors had the objective to register the forces along the colonic tract and were positioned simulating bowel mesentery from the rectum to the coecum as follows: S1 upper rectum, S2 mid-sigmoid tract, S3 splenic flexure; S4 mid-transverse colon; S5 hepatic flexure; S6 coecum (Fig. 20).

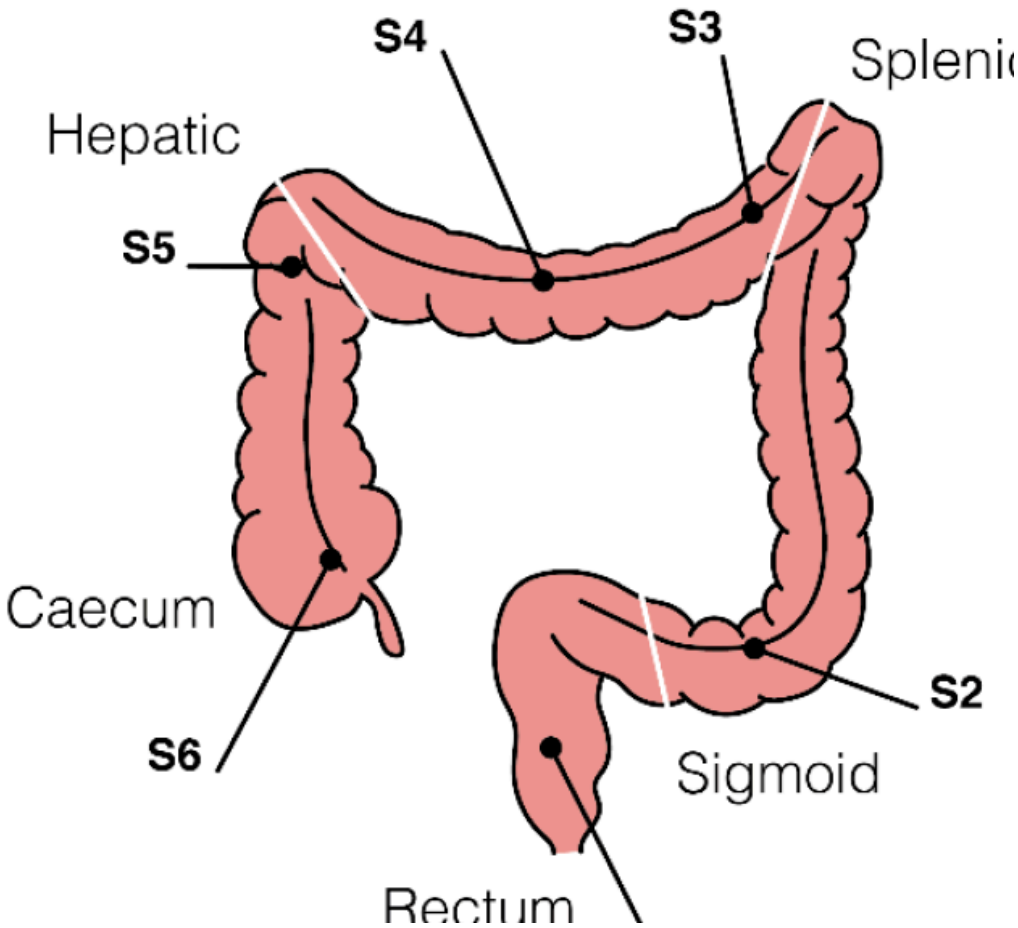


Figure 20 mono-axial strain-gauge sensors placement

When comparative tests were performed, the operators used PCF190 and Exera III, Olympus Endoscopy, Tokyo, Japan colonoscope to perform flexible endoscopy. Both expert endoscopist and trainees were involved in all the experimental setups that are summarized in table 2.

Table 2 Endoo ex-vivo test setups

Tests Category	Tests ID	Platforms	Experimental Condition	Sensorized Simulator	Participants (Expert)	Participants (Trainees)
Functionalities	Operating Channel	Endoo	Ex-vivo	NO	10	0
	Target Approach	Endoo	Ex-vivo	NO	10	0
	Lumen Progression	Endoo	Ex-vivo	NO	10	0
Endoo basic key functionalities	Interaction Forces	Endoo vs. Colonoscopy	Ex-vivo	YES	5	5
Comparative pre-compliance	Polyps Detection	Endoo vs. Colonoscopy	Ex-vivo	NO	5	5
Usability and comparative compliance	Colonoscopic Simulation	Endoo vs. Colonoscopy	Ex-vivo	NO	15 (15 procedures with Endoo—5 procedures with colonoscopes)	8 (6 procedures with Endoo—8 procedures with colonoscopes)

It is to be reported that Endoo is designed to be "one person technique", so during capsule endoscopy pushing and pulling meneuvers of the soft tether, when needed, was performed by the same operator involved in the test, and so was for the insertion of operating tools.

Following tests were performed:

I *Operative channel tests (FT&PC)*

The test consisted in the advancement of operative tools through the operative channel. A biopsy forceps, a snare for polypectomy and an endoscopic needle were used. These tools have been advanced and retracted in four different scenarios:

- advancement and retraction in straight position;
- advancement of tools up to the tip of the capsule, inversion and completion of the advancement of the tool;
- advancement of the tool after inversion completed;
- advancement of the tool when the capsule is in the coecum.

Ten expert endoscopists performed the test. During each test and in each scenario, succession rate was qualitatively evaluated by a questionnaire (1 – poor; 5 – excellent).

II *Target approach tests (FT&PC)*

The endoscopists had to approach endoluminal lesions with the most appropriate angle in order to perform resection (usually any lesion has to be placed at 6 o'clock in the visual field). The endoscopists had to advance the polypectomy snare and to catch the target.

The endoscopists had to perform the following actions:

- put a target in the visual field;
- For every action once the target has been visualized, the endoscopist will advance the operative tools in order to:
- catch the target with biopsy forceps;
- touch the target with the needle;
- catch the target with the snare.

Ten expert endoscopists performed the test. During each test and in each scenario, succession rate was qualitatively evaluated by a questionnaire to rate the stability of the platform (1 - poor stability; 5 - high stability).

III *Progression tests (FT&PC)*

The endoscopists had to drive the capsule from the sigmoid-descending junction to the splenic flexure and back, without losing it. In each trial, we measured:

- elapsed time to conclude the path;
- distance from start point in case of no incomplete test;
- number of magnetic link losses;
- number of magnetic losses in which the platform has not been able to restore magnetic link;

- the number of abnormal responses between capsule and phantom (*i.e.* tilting is no more possible because for the relative position of the robot, inverted response between capsule and phantom due to the inversion of reference axis).

Ten expert endoscopists performed the test.

IV *Interaction forces tests (IF)*

The endoscopists had to drive first the capsule from the rectum to the caecum and back, without losing it, then repeated it with a standard endoscope using the simulator equipped with sensors. Ten expert endoscopists performed the test. Data were both projected online and recorded to the subsequent data analysis.

Interaction forces have been calculated bothe during Endoo and during flexible endoscopic procedures and following data were registered: peak forces, cumulative forces during the whole endoscopic procedure, mean forces. Sensor were placed along the bowel tract as follows: S1, upper rectum; S2 mid-sigmoid colon; S3 and S4, splenic flexure and mid-transverse colon; S5 and S6, hepatic flexure and cecum. We thought that cumulative forces are the data that best represent from a physical point of view the interaction and consequently the pain generated during endoscopy; in fact, these factors are strictly related to momentum (mass and speed) and impulses exerted on the tissues during navigation. A non-parametric test (Wilcoxon rank sum test) was used to assess statistically significant differences between Endoo and flexible endoscopy.

V *Colonoscopy simulation tests (U&L)*

The endoscopists had to drive first the capsule from the rectum to the caecum and back, without losing it. Once the capsule reached the end point, the endoscopist retracted the wire in order to straighten it and he/she observed the capsule behavior. Results were compared with a standard endoscope.

In each trial, the following performance were measured:

- the elapsed time to conclude the path;
- the distance from anal verge in case of no completion of the test;
- the number of magnetic losses;
- the number of magnetic losses in which the platform was not able to restore magnetic link;
- the number of abnormal responses between capsule and phantom (*i.e.* tilting is no more possible because for the relative position of the robot, inverted response between capsule and phantom due to the inversion of reference axis). In each case, they registered the distance from the anal verge, the number of cases in which the endoscopist was not able to restore the connection and the orientation skills to do that in case of restored connection;
- the rate of losses of connection when straightening the wire.

Fifteen experts and six trainees performed the test with the Endoo platform, while five experts and eight trainees were involved in performing a conventional colonoscopy (overall, a total number of thirty-four procedures)Trainees received a 30 minutes educational and training session before performing the procedures. Expert endoscopists received a formal 15 minutes education and training session with the use of the capsule.

VI *Polyp detection test (U&L)*

Ten endoluminal lesions were created by stitches along each colonic model, each one of different shapes and dimensions (from 5 to 10 mm). Two of them at the sigmoid tract (at 6 and 12 o'clock); two at the descending colon (at 3 and 9 o'clock), two at the splenic flexure (at 6 and 12 o'clock), two at the hepatic flexure (at 3 and 9 o'clock) and two at the caecum (at 6 and 12 o'clock). Endoscopists had to drive the capsule through the colon from the starting point to the caecum and back, and he/she had to report each visualized target. For each test, polyp detection rate was registered.

Ten endoscopists performed the test, 5 experts and 5 trainees. The endoscopists had to drive first the capsule from the rectum to the caecum and back, without losing it, then repeated it with a standard endoscope.

5.4. Results

I *Operative channel tests (FT&PC)*

All clinicians rated as good (*i.e.* 3 – comparable with the state of the art) the functionality of the Endoo operative channel. Success rate was 100% when polypectomy snares, biopsy forceps and needles were advanced in every scenario.

II *Target approach tests (FT&PC)*

Target approach demonstrated 100% of success rate. Stability was rated with a score of 4.8/5.

III *Progression tests (FT&PC)*

The Endoo system showed a good and repeatable progression capability according to the qualitative and quantitative evaluation. Magnetic link was lost 5 times out of 10 procedures, but it was restored in 100% of the cases. Quantitative and qualitative results are reported in Table 3.

Table 3 progression tests

Participant #	Time (m:s)	Translation (feedbacks)	Tilting (feedbacks)	Loss of magnetic link	Ability to restore the magnetic link
Tester 1	3:15	Good and repeatable	Good and repeatable	0	-
Tester 2	4:10	Low magnetic	Good and repeatable	1	YES

		force, need to push the tether			
Tester 3	2:35	Repeatable but need to push the tether	Good control	0	-
Tester 4	3:20	Good and repeatable	Good yaw and pitch	1	YES
Tester 5	4:35	Good and repeatable	Poor controlling the right rotation.	0	-
Tester 6	3:34	Need to push the tether	Good and repeatable	0	-
Tester 7	2:52	Good and repeatable	Good and repeatable	0	-
Tester 8	6:45	Repeatable but need to push the tether	Good pitch control but yaw must to be improved	2	YES
Tester 9	5:12	Good, but need to push the tether	Good and repeatable	0	-
Tester 10	4:50	Need to push the tether	Good and repeatable	1	YES
Average value	**4:06**	**-**	**-**	**0.5**	**-**

IV Interaction forces test (IF)

As reported in figure 20 the forces measured by the sensorized platform during the endoscopy reached the higher peak values in the flexible endoscopy group compared with the Endoo group at the mid-sigmoid colon (S2) (1.89N vs. 1.05N), at the splenic flexure (S3) and mid-transverse colon (S4) (4.12N vs. 0.69N), and at the hepatic flexure (S5) and cecum (S6) (1.75N vs. 1.02N). The mean interaction forces were similar between the two groups in each bowel tract analyzed but the cumulative interaction forces were significantly higher during flexible than during Endoo colonoscopy at the splenic flexure (S3) and mid-transverse colon (S4) (16.53Ns vs. 1.67Ns, $p < 0.001$) and at the hepatic flexure (S5) and cecum (S6) (28.77Ns and 2.47Ns, $p = 0.005$).

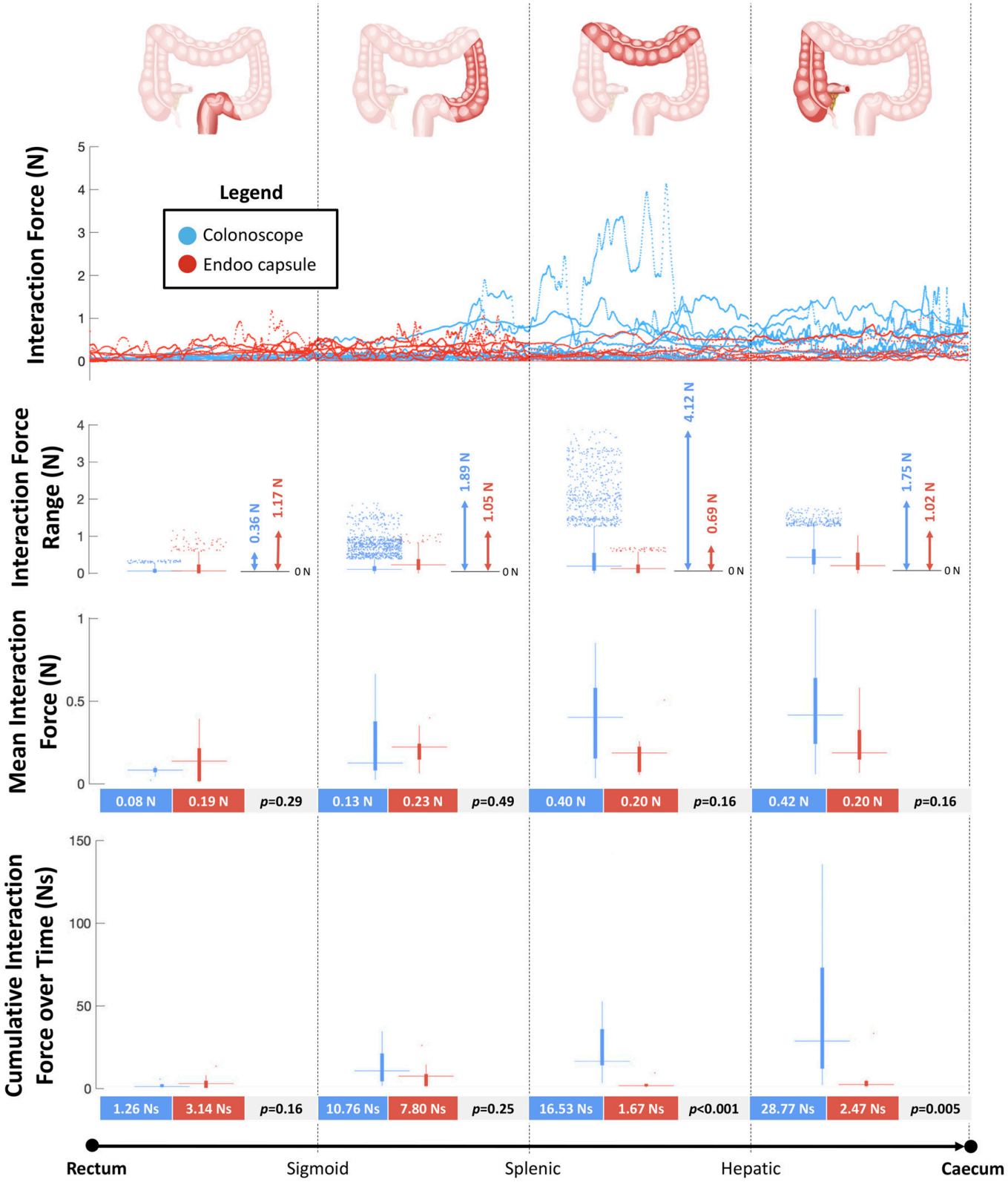


Figure 21 interaction forces

V Polyp detection test

Overall polyp detection rate was 91% with standard endoscopy and 87% with the Endoo system with a non statistically significative difference (p 0,16). The detection rate among the trainees was 86% by standard endoscopy and 88% by the Endoo system.

Quantitative results are reported in Table 4.

Table 4 polyp detection tests

Participant #	Expert /trainee	Tool	Polyps detected
Tester 1	Expert	Capsule	8
		Colonoscope	10
Tester 2	Expert	Capsule	9
		Colonoscope	10
Tester 3	Expert	Capsule	10
		Colonoscope	10
Tester 4	Expert	Capsule	7
		Colonoscope	10
Tester 5	Expert	Capsule	9
		Colonoscope	8
Tester 6	Trainee	Capsule	9
		Colonoscope	8
Tester 7	Trainee	Capsule	9
		Colonoscope	9
Tester 8	Trainee	Capsule	8
		Colonoscope	9
Tester 9	Trainee	Capsule	8
		Colonoscope	9
Tester 10	Trainee	Capsule	10
		Colonoscope	8

VI Colonoscopy simulation tests (U&L)

When colonoscopy simulation was performed with the Endoo system, the overall success rate (experts and trainees) was 67%, 53% when tests were performed by expert endoscopists, but 100% in the case of trainees. When colonoscopy simulation was performed with a standard endoscope, success rate was 100% (8 trials performed by trainees and 5 trials performed by expert users).

Overall (expert and trainees) average time in case of success with the Endoo system was 09:50 (from rectum to caecum) and 05:51 (from caecum to rectum); the average total time was 15:42. Whereas, overall average time in case of success with the flexible conventional colonoscope was 03:53 (from rectum to caecum) and 02:43 (from caecum to rectum); the average total time was 06:37.

The minimum overall time in case of the Endoo system was 06:30 (performed by an expert user), whereas the maximum overall time in case of the colonoscope (performed by a trainee) was 14:31. The average time for performing conventional colonoscopy by trainees, was 09:28, versus 17,58 with the Endoo system.

When magnetic link was lost, this was autonomously restored in 100% of cases. External manual pushing (with the proximity variable stiffness system activated) was requested and used by users in about 25% of the procedures (almost 80% of the times when the capsule was in the right colon).

Quantitative results are reported in Table 5 and summarized in figure 21

Figure 22 colonoscopy simulation tests

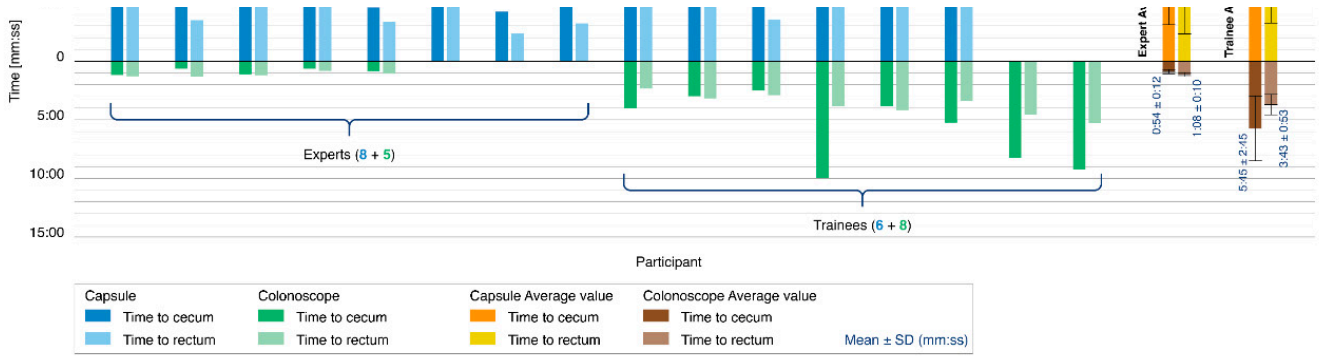


Table 5 colonoscopy simulation tests

Participant #	**Tool**	**Expert /trainee**	**Time to caecum (m:s)**	**Time to rectum (m:s)**	**Success**	**Distance if failure**	**n. of magn. loss**	**Ability to restore magnetic link**
1	Capsule	Expert (no training)	22:27	02:42	NO	Transvers colon	0	-
2	Capsule	Expert (no training)	17:24	12:50	NO	Hepatic flexure	2	YES
3	Capsule	Expert (no training)	11:20	05:00	NO	Hepatic flexure	1	YES

4	Capsule	Expert	06:14	06:39	NO	Hepatic flexure	0	-
5	Capsule	Expert (no training)	11:11	02:22	NO	Hepatic flexure	0	-
6	Capsule	Expert	09:14	03:30	NO	Hepatic flexure	1	YES
7	Capsule	Expert	10:23	04:54	NO	Hepatic flexure	2	YES
Average	**Capsule**	**Expert**	**12:36**	**5:25**	**NO**	**-**	**0.85**	**-**
8	Capsule	Expert	09:44	05:58	YES	-	1	YES
9	Capsule	Expert	07:34	03:30	YES	-	2	YES
10	Capsule	Expert	22:19	05:54	YES	-	2	YES
11	Capsule	Expert (no training)	12:17	12:07	YES	-	1	YES
12	Capsule	Expert	04:35	03:19	YES	-	1	YES
13	Capsule	Expert	05:03	04:58	YES	-	2	YES
14	Capsule	Expert	04:12	02:18	YES	-	0	-
15	Capsule	Expert	05:02	03:12	YES	-	1	YES
Average	**Capsule**	**Expert**	**08:50**	**05:09**	**YES**	**-**	**1.25**	**-**
16	Capsule	Trainee	10:10	14:10	YES	-	2	YES
17	Capsule	Trainee	15:00	05:03	YES	-	2	YES
18	Capsule	Trainee	15:20	03:35	YES	-	1	YES
19	Capsule	Trainee	07:15	08:16	YES	-	0	-
20	Capsule	Trainee	08:10	04:40	YES	-	1	YES
21	Capsule	Trainee	11:05	05:05	YES	-	2	YES
Average	**Capsule**	**Trainee**	**11:10**	**06:48**	**YES**	**-**	**1.33**	**-**
22	Scope	Expert	01:10	01:18	YES	-	-	-
23	Scope	Expert	00:40	01:20	YES	-	-	-
24	Scope	Expert	01:07	01:12	YES	-	-	-
25	Scope	Expert	00:42	00:50	YES	-	-	-
26	Scope	Expert	00:53	01:04	YES	-	-	-

Average	**Scope**	**Expert**	**00:54**	**01:08**	**YES**	**-**	**-**	**-**
27	Scope	Trainee	04:00	02:20	YES	-	-	-
28	Scope	Trainee	03:00	03:10	YES	-	-	-
29	Scope	Trainee	02:30	02:56	YES	-	-	-
30	Scope	Trainee	10:00	03:50	YES	-	-	-
31	Scope	Trainee	03:50	04:10	YES	-	-	-
32	Scope	Trainee	05:16	03:25	YES	-	-	-
33	Scope	Trainee	08:13	04:35	YES	-	-	-
34	Scope	Trainee	09:12	05:19	YES	-	-	-
Average	**Scope**	**Trainee**	**05:45**	**03:43**	**YES**	**-**	**-**	**-**

A brief summary of the aforementioned results comparing Endoo capsule endoscopy and flexible colonoscopy is displayed on table 6.

Table 6 comparative results

Test	Results		p	Conclusion
	Endoo	**Flexible colonoscopy**		
Operating Channel	3/5 (qualitative)*	3/5 (qualitative)*	/	Comparable
Target Approach	○ 100% success rate ○ 4,8/5 (qualitative)*	○ 100% success rate ○ 3/5 (qualitative)*	/	Endoo shows higher stability
Lumen Progression	5/10 loss of magnetic link, 100% restored	/	/	Good and repeatable (sometimes need to push the tether)
Interaction Forces (cumulative)	○ Splenic flexure - transverse: 1,67 Ns ○ Hepatic flexure - cecum: 2,47 Ns	○ Splenic flexure - transverse: 16,53 Ns ○ Hepatic flexure - cecum: 28,77 Ns	< 0,001 = 0,005	Endoo allows a softer endoscopy with lower stretching forces
Polyps Detection Rate	87%	91%	NS	Comparable
Colonoscopic Simulation	67% cecum achievement	100% cecum achievement	/	Endoo shows loss of maneuverability in the right colon (teather hindrance?)

* 1 – poor; 2 – inferior to flexible endoscopy; 3 – comparable to flexible endoscopy; 4 - superior to flexible endoscopy; 5 - excellent

6. FUTURE PERSPECTIVE

In order to test the feasibility, the safety and the accuracy of Endoo in the clinical practice a study protocol has been conceived and presented to the ethical committee. Selected and informed healthy patients will be asked to perform a screening colonoscopy both with Endoo platform and with flexible endoscopy and results will be compared.

They will be selected between subject performing colonoscopy that never perfomed colonoscopy before and without previous abdominal surgery in medical history. They will be asked to perform capsule complete colonoscopy with Endoo before performing complete colonoscopy with flexible intrument.

Inclusion criteria will be: age > 18 years, elective indication to endoscopy, ASA I or II. Exclusion criteria will be: previous abdominal surgery, previous colonoscopies, suspected stenosis, ferromagnetic protesis or devices, inplanted pacemakers or ICD, pregnancy, BMI > 35, suspected inflammatory bowel disease.

Subjects will sign an informed consent form that will allow experimental collection of relevant and anonymized effectiveness and safety data. Subjects may withdraw their consent to have the data collected at any time during their participation.

Primary endpoint will be:

- colonoscopy complection rate
- number of lesions eventually detected
- degree of discomfort of the patient

Secondary endpoints will be:

- time to complete the exam
- distance from the anal verge in case of no completion of the exam
- the number of magnetic losses in which the platform has not been able to restore magnetic link
- estimated dimension of the polyp eventually detected

- complication rate

Quality data (i.e. degree of discomfort) will be taken from a questionnaires submitted to patients where patients are asked to answer the following questions:

How would you define the procedure with Endoo?	✓ Satisfying ✓ Almost satisfying ✓ Unsatisfying
How would you define the procedure with standard colonoscope?	✓ Satisfying ✓ Almost satisfying ✓ Unsatisfying
Did you feel more comfortable during capsule endoscopy or flexible endoscopy?	✓ Endoo ✓ Flexible endoscopy
Would you accept to partecipate to a screening program where colonoscopy is performed with Endoo?	✓ Yes ✓ No

7. DISCUSSION AND CONCLUSION

The Endoo system demonstrated good results as regard single functionalities. All clinicians rated as good (*i.e.*, 3 – comparable with the state of the art) the functionality of the Endoo operative channel. In particular, the insertion of the instrument is fluid even if the tether is subjected to tight bending.

It is worth mentioning that robotic platform with magnetic link seems to ensure higher stability during operative maneuvers with respect to flexible conventional endoscopy as reported from a qualitative evaluation and from a subsequent survey among endoscopists.

Moreover, the Endoo platform showed a good and repeatable progression capability comparable with flexible conventional endoscopy according to the qualitative and quantitative evaluation. In general, the capability to control the tilting of the capsule is good and repeatable but the clinicians reported, as a qualitative feedback during the tests, the necessity to improve the control of the yaw angle of the capsule. The translation control is good, but it is necessary to help the advancement of the Endoo capsule pushing the tether from outside to generate a sufficient force that is composed by the contribution of the magnetic propulsion force and of the external manual pushing force.

Even if numerousness was too low to obtain statistical significance, it seems that Endoo system has, today, lower success rate compared to flexible endoscopy. However, it is worth noting that when performed by trainees, success rate of the Endoo was 100%, demonstrating better familiarity with the novel technology platform.

From survey between clinician, after completion of the tests, it emerges that most of the users (mainly expert users) referred a progressive loss of maneuverability as the capsule moved distant from the anal verge; after hepatic flexure maneuverability (*i.e.*, tilting and progression) became counterintuitive. Indeed, when reaching the caecum was not possible, hepatic flexure was the most common end site. Otherwise, in the left colon, capsule guidance was referred to be intuitive and the same rate of success was registered between expert endoscopists and trainees. It has been

supposed that the complexity in maneuvering the capsule in the right colon depends on the tether related friction that significantly increases with the complexity of the colon and number of colonic curves overtaken. In that case, proximity increased stiffness of the Endoo tether and manual pushing has to be performed. However, it has been demonstrated that it is possible to navigate the Endoo capsule to the caecum.

As regard polyp detection rate Endoo platform provides a very good polyp detection success rate that can reach almost 100% (success rate of the expert endoscopists with the conventional colonoscope) after a proper training and extended use of the Endoo platform.

Ultimately, data on the forces exerted on the colonic wall confirmed that magnetic guidance may allow to perform a softer procedure with lower stretching forces on bowel wall with respect to flexible endoscopy, leading to higher comfortability and therefore higher compliance by patients.

In conclusion, the Endoo system allowed to perform one of the first complete colonoscopies with a magnetically driven capsule, although tests were performed only in *ex-vivo* models. The navigation system seems to be very intuitive as trainees and expert endoscopists obtained comparable results.

Endoo maneuverability seems to be comparable with standard endoscopy when capsule movements are not hampered by the tether, while the longer the tether in inserted in the bowel the harder capsule progression and orientation is achieved.

Accuracy in the detection of endoluminal lesions is comparable between the Endoo system and standard flexible endoscopy. The same detection rate was reached between trainees and expert endoscopists with the Endoo platform and showed excellent stability during operative maneuvers; indeed, expert endoscopists generally reported that it was higher than flexible endoscope.

Moreover, capsule navigation seems to allow a smoother navigation as it registered much lower stretching forces than flexible endoscopy.

Efforts will be spent in order to implement further tether features to reduce friction; moreover, Endoo technology can be implemented in order to obtain semi-autonomous navigation thanks to lumen and polyp detection algorithms.

The data obtained so far seems to show that Endoo platform is ready to run comparative test on healthy humans. Endoo features may candidate magnetic capsule endoscopy as a potential substitute of conventional flexible endoscopy as diagnostic and therapeutic colonoscopy could be performed with the same accuracy and the same operative skills in a minimally invasive way without discomfort of the patients.

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