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Doctoral Dissertation
Doctoral Program in Bioengineering and Medical-Surgical Sciences (36th Cycle)

Towards autonomous robotic surgical system: Robot for Endoscopic Dissection

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* * * * * *

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Giacomo Lo Secco
Turin, April 20, 2024

Summary

Within the doctoral topic “Autonomous Robotic Surgical System”, I worked on the development of an endoscopic plug-in capsule able to diagnose and treat early digestive tumor. To achieve the result, the support of Professor Alberto Arezzo and the engineering team of the Sant'Anna University in Pisa was crucial.

Introduction: digestive tract tumors represent a challenge for the national healthcare system. They are burdened by high mortality and morbidity rates and lead to increased healthcare cost. In Italy, we registered over 60,000 new cases per year of colon, rectal, stomach and esophagus cancers. Screening programs allow early diagnosis of the tumor and consequently a less invasive treatment compared to more advanced one. Investments in prevention improve patients’ quality of life and reduces healthcare cost. Endoscopic Submucosal Dissection (ESD) is a procedure that allows *en bloc* endoluminal excision of early lesions of the gastrointestinal tract but is burdened by a high rate of complications. The most feared, perforation, which is reported with a rate of up to 10%, and bleeding, rate about 9%. Furthermore, the procedure is described by the operators as complex, uncomfortable, with high average time, approximately 95 minutes for lesions between 3-4 cm. It is due by the inability to manipulate, to perform traction and suturing with available endoscopic instruments. Transanal Endoscopic Microsurgery (TEM) compared to ESD is a surgical technique. However, it could be performed only on the distal 15-20 cm of the rectum due to the size and rigidity of the platform.

Methods: the aim of this PhD work is to overcome the limits of both TEM and ESD by developing a new master-slave system, miniaturized, and flexible platform that allows endoluminal resections in all sections that can be explored with common endoscopes. The experimental phase began with the settlement of a multidisciplinary team involving surgeons and engineer. Then the team studied the relevant literature to establish the foundations from which to start in terms of geometry and the required forces.

Our research work addresses several key challenges in the development of a robotic surgical system, focusing on communication, miniaturization, hardware/software integration, and design optimization.

The main non-technical issue was facilitating collaboration between surgeons and engineers. We initially faced difficulties due to different problem-solving approaches and terminologies. However, through multiple meetings and open discussions, the team learned to adopt and share each other's perspectives, leading to effective teamwork. The first technical challenge was miniaturizing the robotic arms while maintaining sufficient force for surgical tasks. The soft pneumatic arms were the best we were able to test in terms of optimized force interaction with tissue.

Results: the prototype capsule is 30mm in length, an external diameter of 23mm, the soft arms could reach a bending angle of 90° with a pressure inside the arm of 1,5 bar, able to develop a pulling force of 1N and a lifting force of 1,4N. The platform is composed by the plug-in capsule, the processor unit and the double controller, one for each arm, Geomagic.

This research highlights the interdisciplinary collaboration and technical innovation needed to meet the challenges of robotic surgical system development.

Conclusions: at the conclusion of the study, a functional prototype was created and tested on phantom and ex-vivo models, successfully performing basic tasks

such as reaching a target, pulling/pushing, and collecting tissue samples, demonstrating the platform's potential for future clinical applications.

Acknowledgment

And I would like to acknowledge Professor Alberto Arezzo and Professor Gastone Ciuti for their consistent support, Xuyang Ren and Yu Huan, without their brilliance and dedication the project would not have reached this level of development

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I Introduction

1.1 Epidemiology:

Digestive tract tumors represent a challenge for the national healthcare system. They are burdened by high mortality and morbidity rates and lead to increased healthcare cost. In Italy, we registered over 60,000 new cases per year of colon, rectal, stomach and oesophagus cancers[1].

Screening programs allow early diagnosis of the tumor and consequently a less invasive treatment compared to more advanced one. Investments in prevention improve patients' quality of life and reduces healthcare cost.

Colorectal cancer (CRC) stands as one of the most frequently diagnosed malignancies globally, afflicting both genders indiscriminately. It manifests primarily in the colon or rectum, often originating from precancerous polyps. CRC's etiology is multifactorial, involving genetic predispositions, lifestyle determinants, and environmental factors. Various variables contribute to CRC's development: advancing age, familial history of CRC or colorectal polyps, inflammatory bowel diseases, sedentary lifestyles, obesity, smoking, alcohol consumption, and diets variables[2, 3].

The incidence of CRC exhibits geographical disparities, with higher rates prevalent in developed nations compared to their developing counterparts. Globally, the World Health Organization (WHO) estimates approximately 1.9 million new cases of CRC annually, positioning it as the third most common cancer worldwide. Developed regions, such as North America, Europe, and Australia, reach the highest rank in terms of incidence[1].

Esophageal Cancer arises from the epithelial cells lining the oesophagus, the conduit facilitating the passage of food and liquids to the stomach. There are two principal histological subtypes: oesophageal squamous cell carcinoma (ESCC) and

oesophageal adenocarcinoma (EAC), each associated with distinct risk factors and epidemiological patterns. The risk factors for oesophageal cancer vary contingent upon its histological subtype. ESCC correlates strongly with tobacco smoking, alcohol consumption, dietary deficiencies, hot beverage consumption, exposure to carcinogens, and socioeconomic determinants. Conversely, EAC is linked to gastroesophageal reflux disease (GERD), obesity, hiatal hernia, Barrett's oesophagus, tobacco smoking, and dietary factors[4].

Oesophageal cancer ranks among the leading causes of cancer-related mortalities globally, characterized by pronounced geographic and demographic heterogeneity in its incidence. ESCC predominates in regions marked by high rates of tobacco and alcohol consumption, notably parts of Asia, Africa, and South America. Conversely, EAC exhibits higher prevalence in Western nations, particularly among individuals afflicted with GERD, obesity, and Barrett's oesophagus[5].

Gastric cancer represents a substantial global health burden, particularly prevalent in Eastern Asia, Eastern Europe, and select regions of South America. Gastric cancer ranks as the fifth most prevalent cancer worldwide and the third leading cause of cancer-related mortality. Its incidence demonstrates wide geographical variance, with zenithal rates observed in Eastern Asia and Eastern Europe. Conversely, its incidence remains relatively subdued in Western nations, albeit retaining substantial public health significance[6].

Many factors contribute to gastric cancer development, encompassing Helicobacter pylori (H. pylori) infection, dietary habits, smoking, obesity, familial predispositions, genetic mutations, and prior gastric surgeries[7].

1.2 Screening program

CRC screening programs play a pivotal role in mitigating its incidence and mortality rates. Common screening methodologies comprise fecal occult blood tests, colonoscopies, sigmoidoscopies, and stool DNA tests. Early detection through screening facilitates the identification and removal of precancerous polyps or incipient tumors, substantially enhancing prognosis and survival rates[8]. Additionally, lifestyle adjustments such as adopting healthy dietary habits, engaging in regular physical exercise, maintaining optimal body weight, and

abstaining from tobacco and excessive alcohol consumption can attenuate the global risk[9].

Unlike CRC, a universally accepted screening program for oesophageal cancer is not available. Diagnosis frequently occurs at advanced stages, impeding prognosis and therapeutic options. Nonetheless, efforts aimed at preventing oesophageal cancer center on modifiable risk factors such as tobacco, alcohol, obesity, dietary habits, GERD and Barrett's esophagus treatment[10].

Regions characterized by heightened gastric cancer prevalence have instituted population-based screening initiatives targeting precancerous lesions and early-stage tumors. Common screening modalities include upper gastrointestinal endoscopies, serum biomarker tests, and stool-based tests for H. pylori. Additionally, primary prevention efforts focus on H. pylori eradication, dietary modifications, smoking cessation, and the promotion of healthy lifestyle behaviors[11].

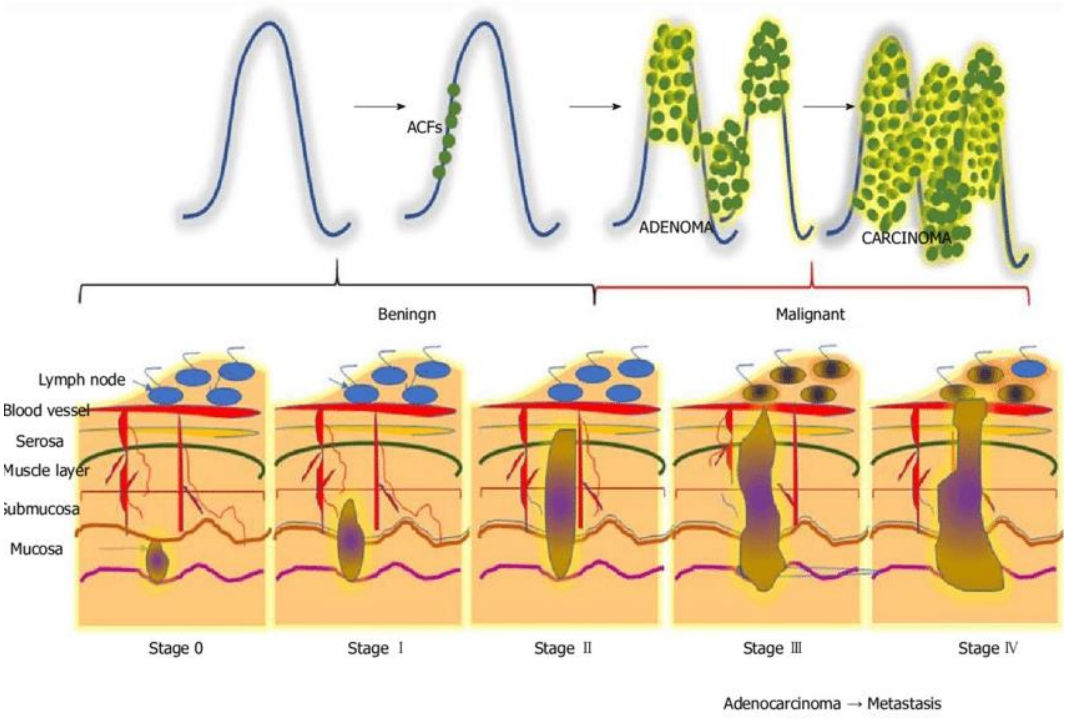


FIGURE 1 - DIFFERENT STAGES DURING THE PROGRESSION OF COLORECTAL CARCINOGENESIS

In figure 1 it is reported a schematic view of cancer progression from precancerous lesions to metastatic carcinoma: Stage 0: The cancerous cells grow within the inner lining of the mucosa; Stage I: The cancerous cells grow throughout the mucosa and submucosa. The cancerous growth invades into the muscular layer of the colon; Stage II: The cancerous growth penetrates through the wall of the colon without spreading to neighbouring tissues or lymph nodes; Stage III: The cancer penetrates

through layers of muscle into the serosa, the layer of visceral peritoneum. The cancer begins to spread to the lymph nodes; Stage IV: A tumour nodule forms in the tissue surrounding the colon, cancer cells appear within the lymph nodes, and the cancer begins to metastasize[12].

1.3 Endoscopic study of the oesophagus, stomach, colon, and rectum

Colonoscopy and oesophagogastroduodenoscopy (EGD) are endoscopic procedures utilized in the screening, diagnosis, and management of gastrointestinal (GI) cancers.

Colonoscopy plays a central role in the screening and prevention programs of CRC, offering direct visualization of the entire colon and rectum. Screening guidelines advocate for the implementation of colonoscopy as a primary screening modality for average-risk individuals beginning at the age of 50, with subsequent surveillance intervals determined by the findings and patient risk factors. Moreover, colonoscopy is recommended for high-risk populations, including those with a family history of CRC, inflammatory bowel disease, or hereditary colorectal cancer syndromes[8, 14].

Numerous studies have demonstrated the efficacy of colonoscopy in reducing CRC incidence and mortality through the detection and removal of precancerous polyps (adenomas) and early-stage tumors. The adenoma detection rate (ADR), defined as the proportion of colonoscopies in which one or more adenomas are detected, serves as a key quality metric for colonoscopy effectiveness. High ADRs have been associated with lower rates of interval CRC, highlighting the importance of thorough mucosal inspection during the procedure. Recent advancements in colonoscopy technology have further enhanced its diagnostic capabilities and safety profile[13, 14]. High-definition imaging, narrow-band imaging (NBI), and chromoendoscopy techniques enable improved visualization of mucosal abnormalities and subtle lesions, thereby enhancing adenoma detection rates. Additionally, the incorporation of adjunctive tools such as cap-assisted colonoscopy, water exchange techniques, and advanced endoscopic resection modalities (e.g., endoscopic mucosal resection, endoscopic submucosal dissection) has expanded the therapeutic armamentarium for managing complex lesions[14, 15].

EGD serves as the primary diagnostic modality for evaluating upper gastrointestinal pathology, encompassing the esophagus, stomach, and duodenum. While not routinely employed as a population-based screening test for cancer, EGD is indicated in specific clinical scenarios, such as the investigation of dysphagia, gastroesophageal reflux disease (GERD), upper gastrointestinal bleeding, unexplained anemia, or suspicion of gastric malignancy based on alarm symptoms (e.g., dysphagia, unintentional weight loss, persistent vomiting).

EGD facilitates the visualization and biopsy of suspicious lesions within the upper gastrointestinal tract, aiding in the diagnosis and staging of esophageal, gastric, and duodenal neoplasms. Furthermore, therapeutic interventions such as endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), and stent placement can be performed during EGD for palliative or curative purposes in select cases[16, 17].

In addition to diagnostic evaluation, EGD plays a crucial role in surveillance and monitoring of patients with known or suspected upper gastrointestinal malignancies. Serial endoscopic examinations enable the assessment of treatment response, detection of recurrent or metachronous tumors, and implementation of adjunctive interventions as deemed necessary. Surveillance intervals are tailored to individual patient characteristics, tumor histology, and treatment modalities received[16, 18].

Colonoscopy and EGD serve as integral components of therapeutic endoscopy. Endoscopic resection techniques, including polypectomy, EMR, and ESD, enable en bloc or piecemeal removal of localized lesions offering minimally invasive alternatives to surgical resection in selected patients with early-stage gastrointestinal neoplasms.

In advanced or metastatic gastrointestinal cancers, colonoscopy and EGD are employed for palliative interventions aimed at relieving symptoms, optimizing quality of life, and prolonging survival. Palliative endoscopic procedures may include stent placement to alleviate malignant obstruction, endoscopic hemostasis for bleeding lesions, or endoscopic tumor ablation techniques (e.g., photodynamic therapy, radiofrequency ablation) for local tumor control[19, 20].

1.4 History of the robotics in surgery

The integration of robotics into surgical practice represents a transformative milestone in the field of medicine. Over the past few decades, surgical robots have revolutionized the way complex surgical procedures are performed, offering enhanced precision, dexterity, and visualization capabilities. This report provides a comprehensive overview of the evolution of robotic surgery, highlighting key milestones, technological advancements, and clinical applications.

The inception of robotic surgery can be traced back to the late 20th century, with the development of the first robotic systems aimed at assisting surgeons in performing minimally invasive procedures. In 1985, the PUMA 560, a robotic system designed by Victor Scheinman, was utilized for the first time in a neurosurgical biopsy. This groundbreaking achievement laid the groundwork for subsequent advancements in robotic-assisted surgery[21].

One of the most significant milestones in the history of robotic surgery occurred in 2000 with the introduction of the da Vinci Surgical System by Intuitive Surgical. The da Vinci system, comprising robotic arms controlled by a surgeon console, offered unparalleled precision and maneuverability in minimally invasive procedures. Its launch marked the beginning of a new era in surgical technology, with the system quickly gaining widespread adoption across various surgical specialties[22, 23].

Since its introduction, the da Vinci Surgical System has been utilized in a wide range of surgical procedures, including urology, gynecology, general surgery, cardiothoracic surgery, and orthopedics. Prostatectomy was among the first procedures to be performed using the da Vinci system, followed by hysterectomy, cholecystectomy, and colorectal surgery. The system's versatility and adaptability have led to its widespread acceptance as a standard tool in the surgical armamentarium[22].

Over the years, the da Vinci Surgical System has undergone several iterations and technological enhancements aimed at improving its functionality and performance. These advancements include the introduction of high-definition 3D imaging, improved ergonomics, enhanced software capabilities, and the integration of advanced instruments such as fluorescence imaging and staplers. Additionally, newer generations of robotic platforms, such as the da Vinci Xi and da Vinci SP systems, have been developed to address specific surgical needs and expand the scope of robotic surgery.

The history of robots in surgery is characterized by remarkable technological advancements and transformative innovations that have revolutionized surgical practice. From the pioneering efforts of early developers to the widespread adoption of robotic systems in modern operating rooms, the journey of robotic surgery reflects a commitment to improving patient care, enhancing surgical outcomes, and pushing the boundaries of medical technology[23].

1.5 State of the art in colorectal endoscopic surgery: TEM and ESD

Endoscopic Submucosal Dissection (ESD) is a procedure that allows *en bloc* endoluminal excision of early lesions of the gastrointestinal tract but is burdened by a high rate of complications. The most feared, perforation, which is reported with a rate of up to 10%, and bleeding, rate about 9%. Furthermore, the procedure is described by the operators as complex, uncomfortable, with high average time, approximately 95 minutes for lesions between 3-4 cm. It is due by the inability to manipulate, to perform traction and suturing with available endoscopic instruments[24].

Transanal Endoscopic Microsurgery (TEM) compared to ESD is a surgical technique. It is performed with common surgical laparoscopic instruments; however, it could be performed only on the distal 15 cm of the rectum due to the size and rigidity of the platform[25].

II Robotics in Endoscopy and the third space endoscopy

Endoscopy originated as a diagnostic tool for gastrointestinal pathologies. Over time, endoscopes have advanced, enabling operators to undertake various tasks such as biopsies, haemostasis, polypectomies, and complex therapeutic procedures. Conventional endoscopic procedures typically occur within the natural lumen of the gastrointestinal tract, constituting what is known as first-space endoscopy. However, in the past two decades, there has been a concerted effort among endoscopic innovators to explore the peritoneal cavity or second space through a technique called natural orifice transluminal endoscopic surgery (NOTES). In NOTES, access to the peritoneal cavity (second space) is achieved endoscopically through one of the body's natural orifices[26].

In 2004, Kalloo et al. pioneered a transgastric peritoneoscopy for liver biopsy in an animal model, involving the penetration of the gastric wall for peritoneal access[27]. Subsequently, it was reported detailed appendectomy and cholecystectomy via NOTES in humans. NOTES offered potential benefits such as minimal scarring, shorter hospital stays, and reduced pain[28]. However, it faced significant challenges. Inadequate instruments for dissection and retraction, coupled with difficulties in securely closing and suturing entry points, heightened the risk of pneumoperitoneum and led to severe infectious complications like peritonitis and sepsis. Consequently, NOTES failed to gain traction in clinical practice and eventually waned[29].

In 2007, Sumiyama et al. introduced a novel technique known as submucosal endoscopy or intramural endoscopy with a mucosal flap safety valve. Leveraging the principles of endoscopic submucosal dissection (ESD), this approach accessed the submucosal space or "third space" and utilized it as a working plane while a mucosal flap prevented peritoneal leakage[30]. Pasricha et al. embraced this principle and demonstrated the feasibility of oesophageal myotomy in a porcine model[31]. The technique was further refined by Inoue et al., who performed the first human case

of endoscopic myotomy for achalasia in 2008, now recognized as peroral endoscopic myotomy (POEM). This marked the advent of third-space endoscopy, which rapidly disseminated worldwide[32].

The technique has evolved and is employed not only for treating achalasia but also for addressing various gastrointestinal disorders such as Zenker's diverticulum (ZD), gastroparesis, and the resection of submucosal tumors and early gastrointestinal cancers[33].

However, traditional endoscopic instruments have usually three degrees of freedom (forward/backward, bending, axial rotation), this limits complex procedures. There arose a need for an enhanced endoscope capable of overcoming these limitations, providing greater manoeuvrability, instrument triangulation, and optimal exposure of the operative field.

While robots have long been employed in industry, their introduction to the medical practice is relatively recent. In the 2000s, the concept of master-slave robots emerged in minimally invasive surgery, with the da Vinci platform pioneering surgical master-slave systems. Its superiority stemmed from its seven degrees of freedom, mirroring human wrist movements effectively[34].

This unique capability of the da Vinci system addressed the shortcomings of conventional endoscopy. Subsequently, the master-slave robotic concept was translated to the operative endoscopy, leading to the development of robotic endoscopic platforms. These platforms promise for improving the performance of complex therapeutic endoscopic procedures. The result will be a better user experience and training issue. Nowadays we have demonstrated the clinical safety and cost effectiveness of these devices which are gaining space in the clinical practice.

Traditional endoscopic instruments present many challenges for users performing complex endoscopic procedures. The major obstacles are the lack of triangulation, spatial orientation, and optimal tissue traction. This creates an almost insurmountable obstacle if the operator wishes to use the endoscope to perform basic surgical tasks such as dissection, retraction, and ligation.

The development of the third space endoscopy gave a great boost to development of robotic endoscopic applications. These new platforms can overcome the difficulties related with the absence of the triangulation and the lack of lifting forces. This new scenario offers exciting opportunities for endoscopists to perform

more complex endoscopic procedures with high ergonomics and dexterity and reduced complication rates[35].

In table 1 you will find the most relevant endoscopic robotic platform tested in last years[34, 36].

TABLE 1 - RESUME OF THE AVAILABLE ENDOSCOPIC ROBOTS

Device	Degree of Freedom	Outer Diameter (mm)	Clinical Trial		Clinical Approval
The direct drive endoscopic system (DDES)	7	22	EMR NOTES	Animal in vivo	None
Endosamurai	5	15	EFTR NOTES	Animal in vivo	None
Master and slave transluminal endoscopic robot (EndoMaster EASE)	10	N/A	ESD EFTR NOTES	Animal in vivo Human	None
Endoluminal Assistant for Surgical Endoscopy (EASE)	10	18	ESD	Animal in vivo	None
Endoscopic therapeutic robot system (ETRS)	N/A	N/A	ESD	Animal ex vivo	None
I^2 snake robotic platform	7	16	None	None	None
Flex robotic system	N/A	18	ESD EFTR NOTES	Animal in vivo Human	FDA and CE
Revolute joint-based auxiliary transluminal endoscopic robot (REXTER)	4	N/A	ESD	Animal ex vivo	None
Portable endoscopic tool handler (PETH)	2	N/A	ESD	Animal ex vivo	None
K-FLEX	14	17	ESD	Animal ex vivo	None
Endoluminal surgical system (ELS)	7	22	ESD	Animal ex vivo	None
Flexible Auxiliary Single-arm Transluminal Endoscopic Robot system (FASTER)	3	N/A	ESD	Animal in vivo	None

FIGURE 2 ENDOLUMINAL SURGICAL SYSTEM (ELS)

FIGURE 3 - ENDOMASTER

(b)

FIGURE 4 - ENDOSAMURAI

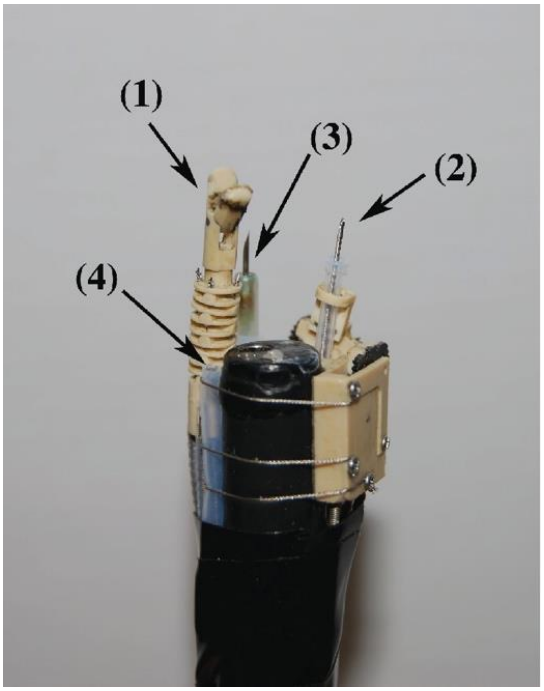


FIGURE 5 - ENDOSCOPIC THERAPEUTIC ROBOT SYSTEM (ETRS)

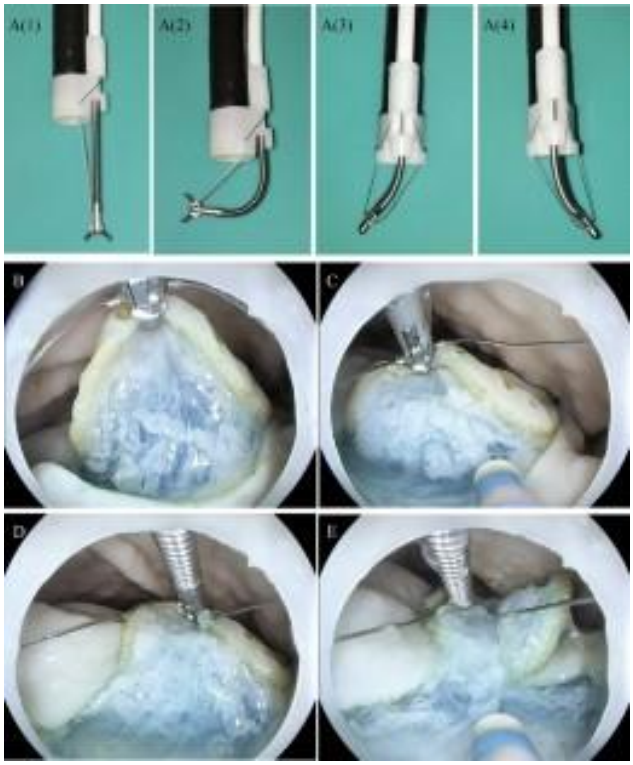


FIGURE 6 - FLEXIBLE AUXILIARY SINGLE-ARM TRANSLUMINAL ENDOSCOPIC ROBOT SYSTEM (FASTER)

FIGURE 7 - FLEX ROBOTIC

FIGURE 8 – FLEX ROBOTIC PLATFORM

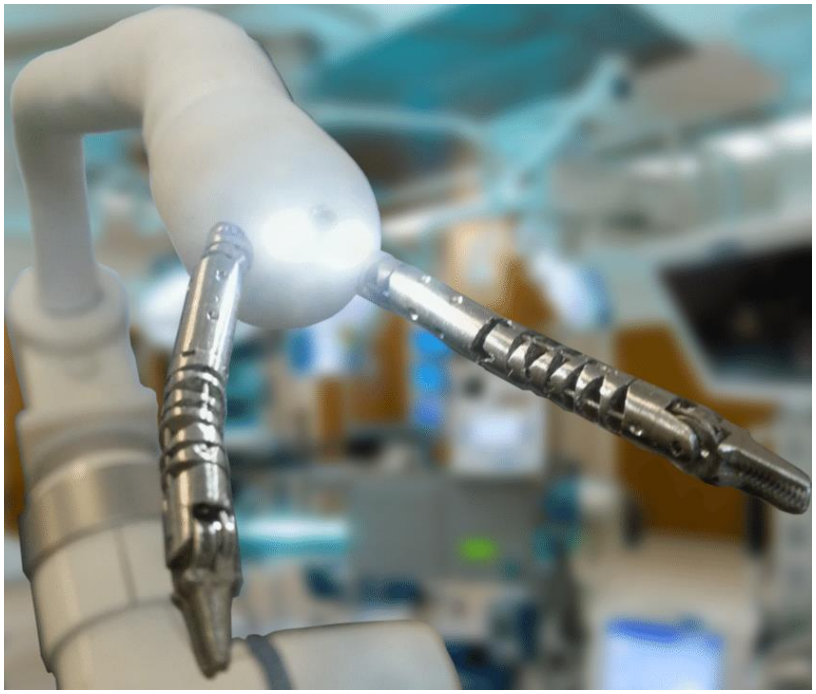


FIGURE 9 - I2 SNAKE

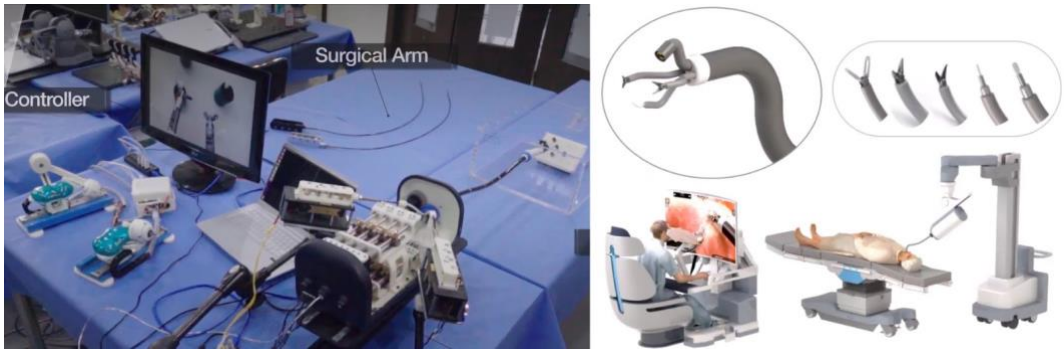


FIGURE 10 - K-FLEX

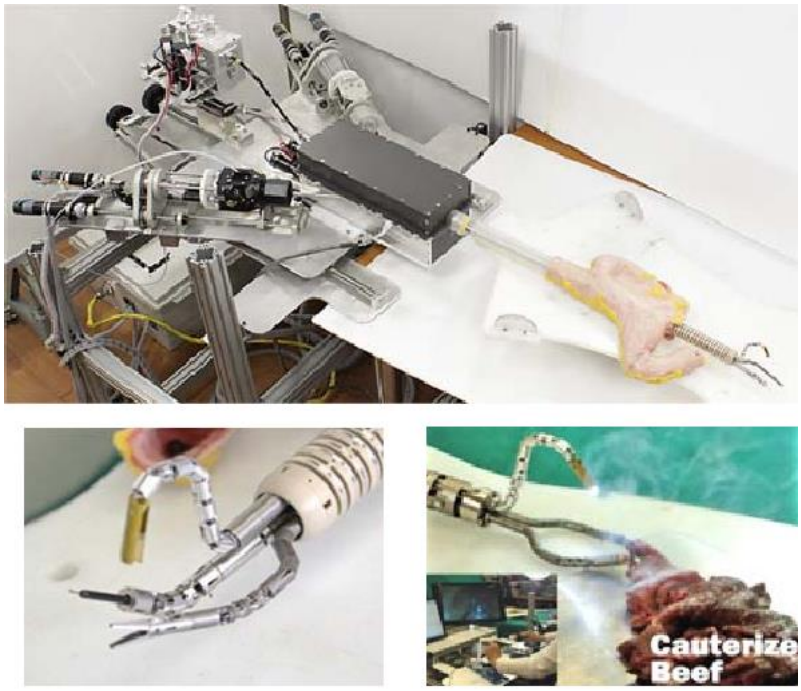


FIGURE 11 - PORTABLE ENDOSCOPIC TOOL HANDLER (PETH)

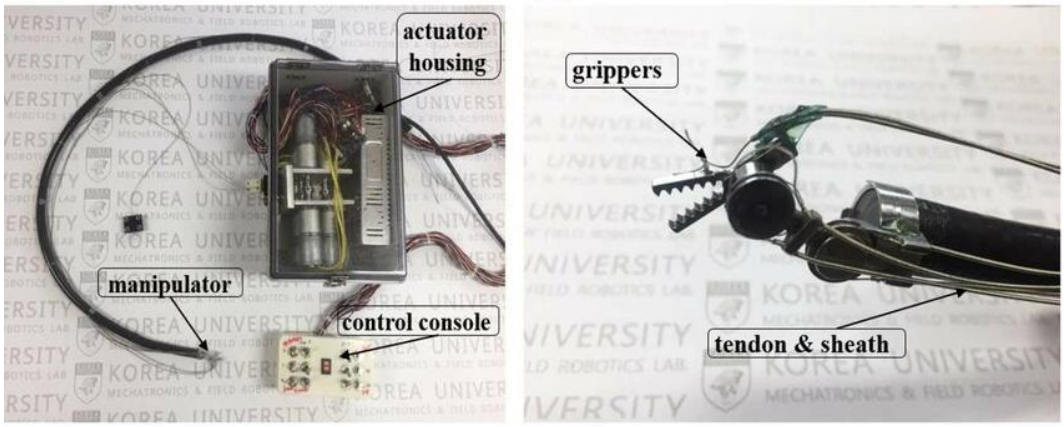


FIGURE 12 - REVOLUTE JOINT-BASED AUXILIARY TRANSLUMINAL ENDOSCOPIC ROBOT (REXTER)

III ROBOT FOR ENDOSCOPIC DISSECTION: THE RED PROJEC

3.1 The beginning

Three surgical techniques are commonly employed for the treatment of early gastrointestinal (GI) cancer. Endoscopic Mucosal Resection (EMR) and Endoscopic Submucosal Dissection (ESD) are flexible endoscopic methods suitable for mucosal lesion of the GI tract reachable by common endoscopes. On the other side, Trans anal Endoscopic Microsurgery (TEM) represents a surgical technique and specifically targets lesions in the rectum. The rigidity of this platform prevents it from crossing the rectum-sigmoidal junction. While TEM adheres to surgical principles such as tissue traction, enabling precise dissection, current endoscopic instruments generally lack the manoeuvrability required for surgical tasks like manipulation, dissection, and suturing.

To overcome these limitations, the aim of the RED project is to develop a miniature robotic capsule designed to be plugged-in to a conventional flexible endoscope for the surgical dissection of early neoplasms in the GI tract. This device comprises a cap body housing two robotic arms for manipulation and tissue dissection. Each arm offers three degrees of freedom, sufficient for the intended application. The advantages of using this robotic device include high operational accuracy, complete lesion removal, minimal endoscopic room requirements, avoidance of general anaesthesia for the patient, and significant reductions in hospitalization times and associated costs.

The project started with the evaluation of existing surgical instruments with robotic arms, including available endoscopic platforms that were still in the research phase. However, these technologies involved dedicated tools with high acquisition and operating costs. Consequently, we opted to develop a new robotic platform capable of utilizing a standard operating flexible endoscope with a maximum external diameter of 11.5mm. Typically, a robotic platform comprises various components, including the robot device, an outer box containing part of the robot control, a control PC, and a man-machine interface.

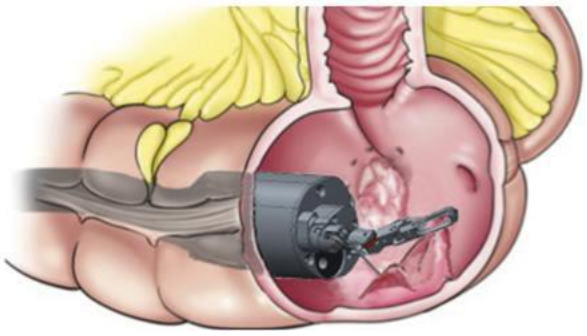


FIGURE 13 - ILLUSTRATION OF THE OPERATIVE CONFIGURATION OF RED

This new robotic platform, named RED (Robot for Endoscopic Dissection), was developed in collaboration with the Scuola Superiore Sant'Anna in Pisa. The first design was a hood at the tip of a standard endoscope, housing miniaturized commercial motors that drove two teleoperated robotic arms, a diathermic hook, and a gripper. While the endoscopist (surgeon A) positions the endoscope near the lesion, the operator (surgeon B) manipulates the robotic arms using a remote control.

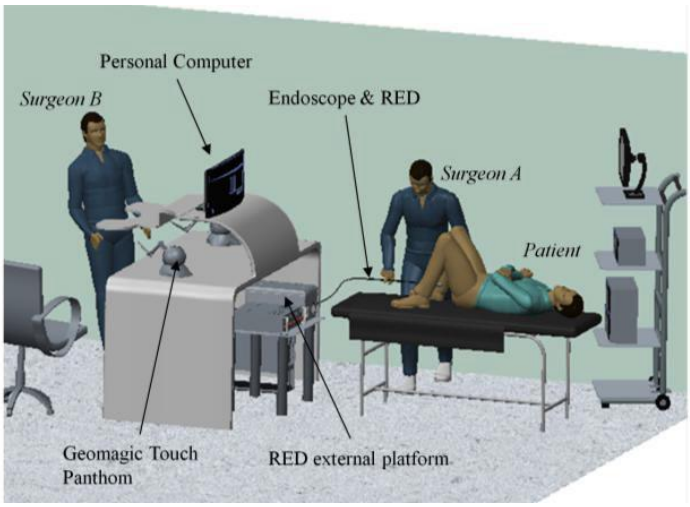


FIGURE 14 – ILLUSTRATION OF THE OPERATIVE ROOM

3.2 Determination of Force Parameters

Understanding the forces involved in typical surgical procedures is paramount for establishing the design criteria of new medical robotic devices whether standalone or integrated into standard endoscopes. During tissue manipulation for dissection, we had to investigate two primary forces: lifting and traction forces (Figure 15).

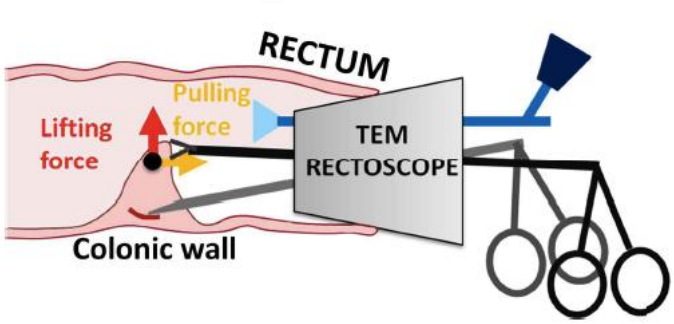


FIGURE 15 - ILLUSTRATION OF LIFTING AND PULLING FORCES DURING DISSECTION

At the very beginning of the RED project we conducted initial tests to assess the minimum force required for the gripper to perform dissection. Surgeons' exertion of lifting and pulling forces on rectal tissues were measured both ex-vivo and in-vivo. To replicate surgical conditions accurately, we adapted an endoscopic grasper commonly used for TEM, incorporating a force measurement tool developed by Ranzani et al [38].

The force measurement system, depicted in Figure 16, consists of two main components: one fixed near the surgical tool's handle and the other close to the rectoscope. The former constrains the tool's trajectory along the x (pulling) or z (lifting) axis and measures the force directly applied by the surgeon. A 6-degree-of-freedom (DoF) passively orientable arm supports the entire system, ensuring stability during measurements.

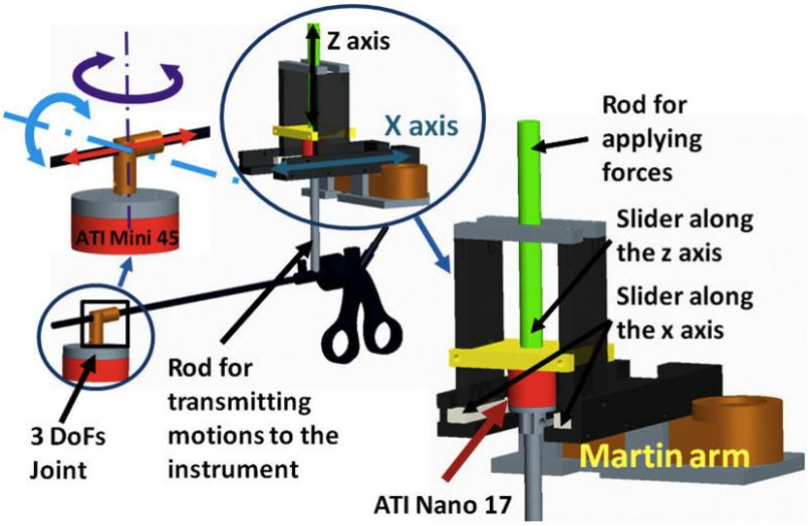


FIGURE 16 - ILLUSTRATION OF THE FORCE MEASUREMENT SYSTEM

The part near the rectoscope measures the reaction forces on the instrument caused by the fulcrum effect of the access trocar. It includes a tripod for positioning, a 6-axis F/T sensor, and a 3 DoF joint for guiding the instrument shaft.

Tests were conducted on both ex-vivo (porcine bowel in TEO training box) and in vivo (on ten domestic female pigs) specimens.

In both ex vivo and in vivo tests, surgeons used a 5mm Johan endoscopic instrument (Microfrance, St Aubin, France) to expose the endoluminal tissue. The procedure involved four phases, as outlined below (Figure 17).

1- Insertion of the laparoscopic tool through the rectoscope port.
2- Approaching the colorectal tissue with the grasper.
3- Lifting the endoluminal tissue until adequate exposure.
4- Pulling the endoluminal tissue along the desired direction.

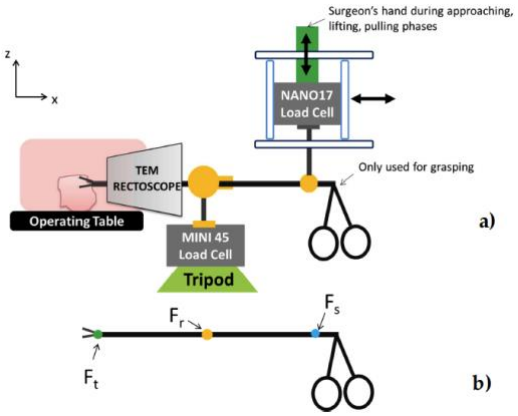


FIGURE 17 - ILLUSTRATION OF THE FORCE MEASUREMENT PHASE

3.3 Determination of Maximum External Dimensions

Before developing the robotic device, we needed to establish its maximum dimensions to ensure compatibility with the colon's anatomy. An analysis of colon's anatomy was conducted to understand the environment the device would operate. Geometric characteristics, including length, diameter, and angle of curvature, were extracted from previous studies and were used as the basis for the design[39]. We found that the overall mean diameter of the colon depends on the position of the patient, prone or supine, and it is significantly larger in the supine position compared to the prone position (mean diameter 4.29cm). On the other hand, all proximal colon segments exhibit a significant decrease in diameter when the patient lais on the prone position (cecum: $z = -3.19$, $p < 0.01$; ascending: $z = -2.36$, $p < 0.02$; transverse: $z = -2.03$, $p < 0.04$). Special attention was given to the splenic

flexure, a critical point for endoscope navigation, which was further evaluated using CAD software to assess available space.

3.4 First piezoelectric design

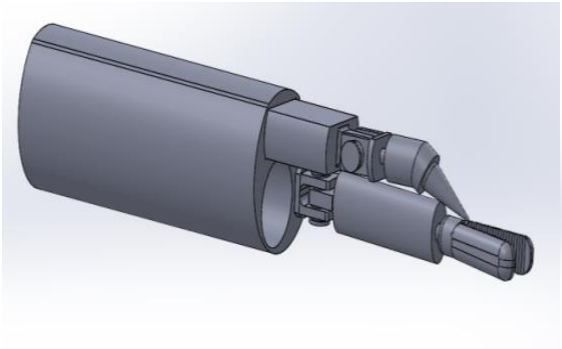


FIGURE 18 - CAD OF RED, SIDE VIEW

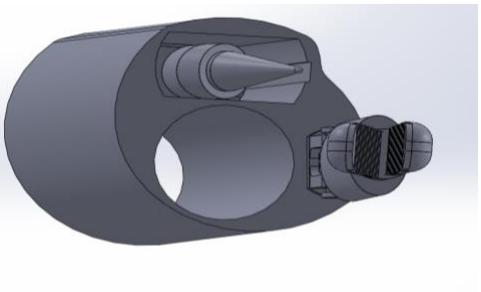


FIGURE 19 – CAD OF RED, FRONTAL VIEW

The first design regarded the capsule itself, we were able to register the forces applied by the arms but the project didn't reach the phantom test phase, and the platform was not equipped with a processor unit and controllers.

The early version design of the RED capsule was mainly made up of 3 components:

• *Hood*: system to be placed on the tip of a commercial endoscope (i.e. gastroscope and colonoscope). The paediatric colonoscope was used as the reference endoscope (from the datasheet the diameter is equal to 9.7 mm but in reality a diameter of 11.5 mm must be considered). The total dimensions of the cap was approximately 26mm in diameter and 50mm in length.

The goal was to reduce the external diameter of the hood to a minimum to lighten and reduce the entire structure.

Inside the hood there were two separate bases, containing the two robotic arms and the housing for the colonoscope. The sliding of the robotic arms was carried out with an external actuator and the movement mediated by cables. By separating the two bases of the arms, allowing independent sliding, the total degrees of freedom of the system are increased. This choice greatly facilitates the use of the cauterizer: this, having both degrees of freedom at the tip of the arm, during the "operation position", can also remain partly inside the cap and therefore vary the distance over which to act.

• *Arm-gripper:* the robotic arm had two degrees of freedom: pitch at the base and roll at the tip. Originally there was an onboard motor for the calliper roll (4mm motor diameter) and an external motor for the pitch.

This combination of motors was chosen because the gripper must exert greater force than the cauterizer (during a classic TEM procedure, the cauterizer can only cut the

tissue if it is under tension; tension also reduces perforation rates). With the pitch at the base of the arm it is possible to obtain a greater workspace, while with the roll at the tip, there is a lower loss of force, as the arm applying the force is smaller. As regards the forceps, we decided to use a classic fenestrated laparoscopic forceps with opening on one side only.

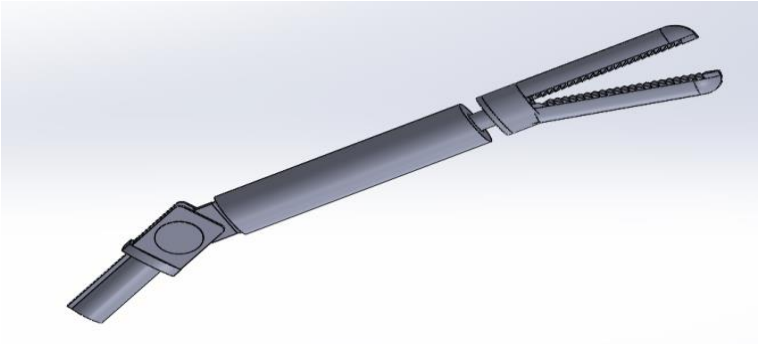


FIGURE 20 - CAD OF THE GRIPPER ARM OF THE FIRST PROTOTYPE

• *Arm-cauterizer*: the arm is characterized by two degrees of freedom (roll and pitch both located at the tip of the arm).

Two motors with a diameter of 4 mm each were integrated into the arm, that was the reason to place both degrees of freedom near the tip: the forces developed by these motors are not high, therefore reducing the length of the arm to a minimum of force application maximizes the force at the tip of the cauterizer.

The tip of the cautery is pre-curved as much as possible, always ensuring that the arm remains within the shape of the cap. A TEM's traditional cauterizer was used.

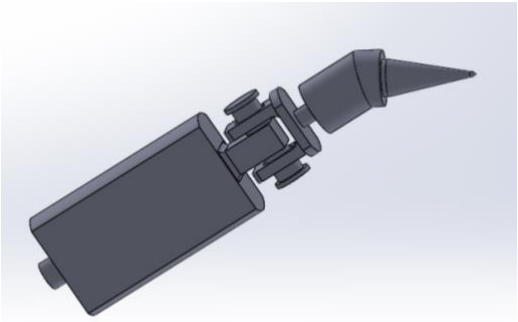


FIGURE 21 - CAD OF THE CAUTERY ARM OF THE FIRST PROTOTYPE

The configuration of the first RED capsule prototype is summarized below:

The one shown is just an example diagram to be better defined after choosing the motors, the internal actuation transfer mechanisms, and the right position of the arms. The structures of the arms and the cap will be made to minimize the overall dimensions, to obtain the smallest possible external diameter.

FIGURE 22 - PROTOTYPE OF THE FIRST RED DESIGN

FIGURE 23 - CAUTERY ARM MOVEMENTS

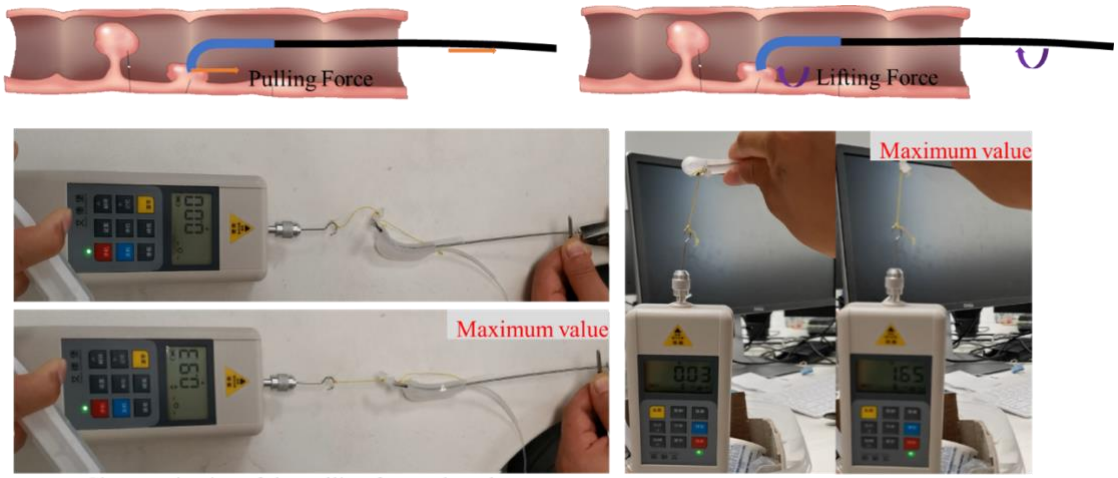
FIGURE 24 - GFRASPER ARM MOVEMENTS

IV Results

This study is based upon the previous RED project, in particular the geometry of the capsule and the analysis of the forces required to interact with tissues. Following this, a multidisciplinary team was established, involving two engineers who led the design and construction of a new prototype based on pneumatic arms. My role was to oversee the design phase, ensuring that the surgical needs were integrated, such as triangulation, minimum and maximum operating field distances, the orientation of the instruments, the manoeuvrability and user interface. I conducted practical tests at each step to verify the proper development of each component. I was also responsible for securing funding to finance the construction of the capsule by participating in the Proof of Concept (PoC) grant. Additionally, I handled the procurement of the components needed for the construction of the individual parts as they became necessary.
Initially, the tests were aimed at checking the functions of the single components, carried on a flat plane and playing on a rigid configuration, without the endoscope, assessing the feasibility of specific basic tasks. These tests were carried out both at the Sant'Anna School and at the MITIC laboratory of the University of Turin (UNITO). Afterward, we proceeded with the assembly of the capsule and performed tests on phantom models and ex-vivo models.
Except for the tests, the team worked remotely, holding weekly meetings on Webex to update each other on the engineering team's progress and to discuss surgical requirements. Examples of topics covered during these meetings included designing the robot arm's movement to reach a target, reducing the delay between command and execution, adjusting the bending angle of the robotic arm, refining the sliding movement of the two arms, and stabilizing the arm in a fixed position, locate the stop point of the rotation and forward and backward movements, adjusting the blind angles, set the speed of the back and forward movements, among other technical aspects.

4.1 Miniaturization:

The first important technical issue we had to face was miniaturizing the robotic arms while maintaining the ability to apply adequate lifting and pulling force.
The first prototype design was equipped with piezoelectric actuators, but we were not able to develop a sufficient traction on the tissue.
The new soft structure of the robotic arms reduced the diameter of the capsule by moving the actuator outside of it. The arms are made of a central body composed of silicone material with an external braided structure that shapes the arms under different inflation pressures. At this stage, the actuator is represented by a small compressor, which was placed outside the capsule, inside the control unit, and connected to the capsule through a thin tube. This tube allows air to flow, ensuring the correct pressure inside the arms. Each pressure value corresponds to a bending angle. Afterwards, the parameter relating to the force of interaction between arms and tissue was characterized, respecting the requirements of the surgical task. After that we were able to estimate the maximum length that the single arm could have with a maximum bending of 90 °. The target references for the manipulation forces were taken from the scientific previous publications[38]. A laboratory test was then carried out by deriving the "pulling" and "lifting" force of the fabric as indicated in Figure 25.



Characterization of the pulling force when the bending length is 30 mm

Characterization of the lifting force when the bending length is 30 mm

FIGURE 25 - PULLING AND LIFTING FORCE TEST ON THE SOFT ARMS

In table 2 are showed our results

TABLE 2 - CHARACTERISTIC OF THE NEW RED

Manipulator characteristic	Value
External diameter	23 mm from 26mm
Lenght	30 mm from 50mm
Bending angle	Max. 90°
Pressure to reach a bending angle 90°	1.5 bar
Lifting force target (*in-vivo*)	0.59 – 1.21 N [1]
Lifting force reached	**1.4 N**
Pulling force target (*in-vivo*)	0.18 – 1.09 N [1]
Pulling force reached	**1 N**

With this new configuration we were able to miniaturize the capsule from an external diameter of 26mm to 23mm. The length of the capsule from 50mm to 30mm. To characterize the performance of the operating instruments we carried out tests on the operating degree of freedom and the banding angle of the soft arms.

The new configuration of the arms could reach a bending angle of 90° with a pressure inside the arm of 1,5 bar, able to develop a pulling force of 1N and a lifting force of 1,4N.

Apart from the simple operating verification, a basic task test was conducted to target and pull a small ball with a ring.

The snapshots are illustrated in Figure 26.

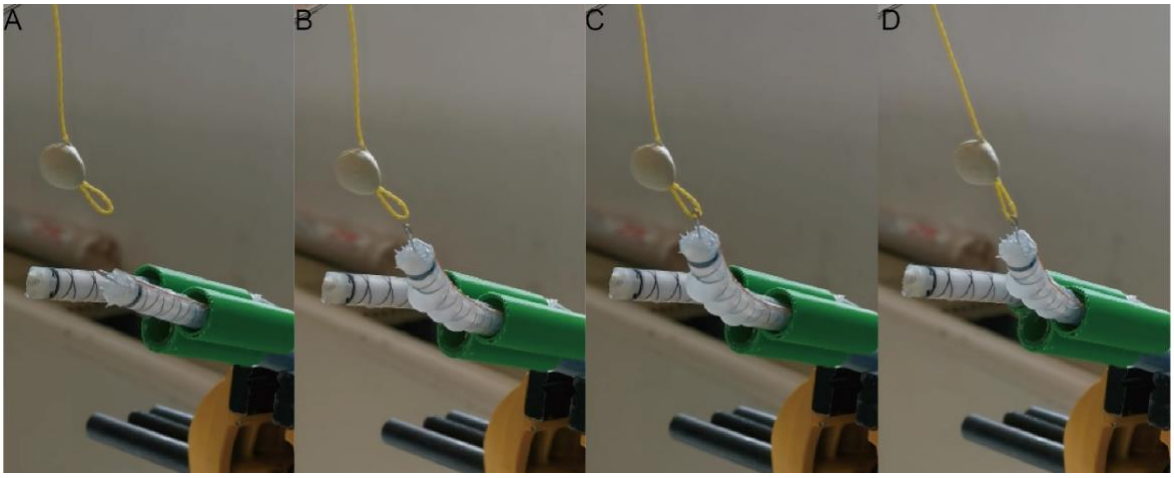


FIGURE 26 – A) SHOWS THE INITIAL STATE OF THE SOFT MODULE, THE SOFT MODULE APPROACHES THE TARGETED BALL IN FIGURE B), CATCHES THE TARGET IN FIGURE C), AND PULLS AWAY THE TARGET IN FIGURE D)

4.2 Hardware\software\actuators interface development:

In addition, for the final definition of the system architecture, a first software module was developed to allow communication between the master units and the central control system as in Figure 27

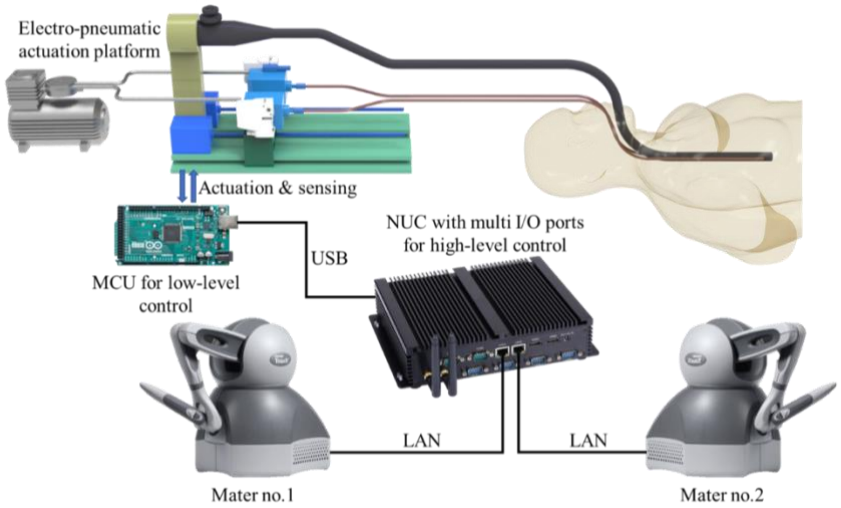


FIGURE 27 - ILLUSTRATION OF THE NEW RED PLATFORM COMMUNICATION UNITS

The data collected by the NUC (Next Unit of Computing) were processed in C ++ language and used to simulate the control of the system. In the initial software simulation, the actuation system was replicated with a simple LED mediated by a control unit for low-level data management, namely *Arduino UNO*. The system architecture is described and presented in Figure 28.

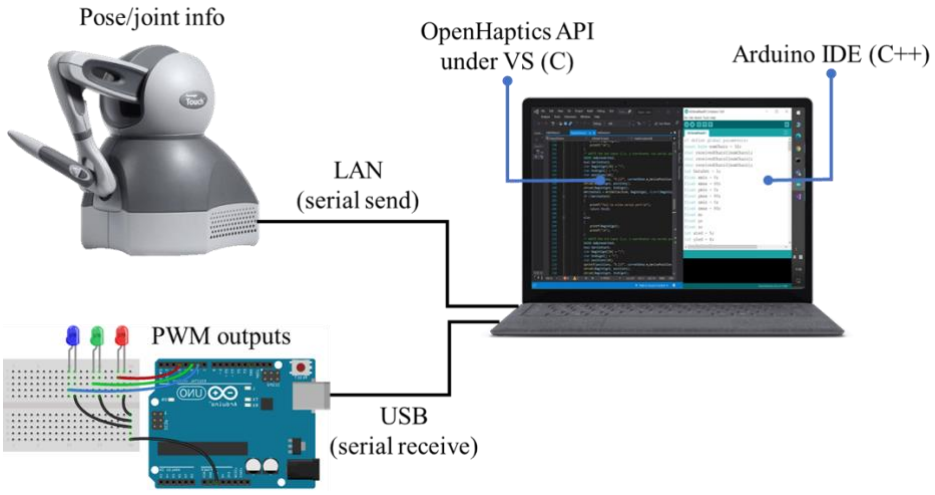


FIGURE 28 - SYSTEM ARCHITECTURE

4.3 Components collection during the COVID-19 pandemic era:

Once preliminary tests were performed and initial hardware and software architecture were established, we started to collect all components necessary to set up the prototype of the new RED.

The components were classified into categories of valve, motor and driver, soft module, air supply, controller, master device, and power supply. The collection started during the pandemic era, most of them came from China and it was very difficult and slow to obtain shipments.

In table 3 are reported all necessary components we had to collect.

TABLE 3 - LIST OF NECESSARY COMPONENTS

	PRODUCT	MODEL	Nr
VALVE	**[OPTION1]** Proportion valve (Festo) 4Connected cable of the valve (RS Component)	VPPI-5L-3-G18-1V1H-V1-S1D	2
		NEBU-M12G5-K-2.5-LE5	2
	[OPTION2] Pressure regulators (Camozzi)	K8P-0-E522-0	4
MOTOR and DRIVER	Motor4 sliding stage (MOBILEB)	Passo passo Nema17	4
	Rotation motor (MOBILEB)	Passo passo Nema17	4
	Motor coupler connector (MOBILEB)	NO415869 3-5mm	4
	Linear actuator (AMAZON)	12V 30N 30mm	2
	Step motor driver (MOBILEB)	TOOGOO TB6600	10
	optical cut-off switch (RS component)	194-4030	20
SOFT MODULE	Slicone Rubber (Smooth on)	Dragon skin 30 (0.9 kG)	4
AIR SUPPLY	PU air tube (RS Component)	917-2407	2
	Air compressor (AMAZON)	182-8736	2
CONTROLLER	NUC for High-level control	HUNSN I7 4500U 8G RAM 256 SSD	2
	MCU for Low-level control (RS Component)	715-4084	2
MASTER DEVICE	Haptic device (3D Systems)	Geomagic Touch Ethernet edition	2
POWER SUPPLY	Power adapter	10A 120w 12V	2
	Switching DC Power Supply	0-30V 0-5A	2

4.4 Geometric configuration according to maneuverability space and the point of maximum reachability in the bowel:

The prototype design consists of two similar pneumatic arms in terms of degrees of freedom and maneuverability space. As for the degrees of freedom, to guarantee the execution of the surgical task, each single arm was designed with 3 degrees of freedom, respectively 1) pull and push, 2) rotation around its axis, and 3) radial bending. Overall, we will have 6 degrees of freedom for each arm, plus the degree of freedom of gripping by means of the gripper integrated in the tip of one of the two arm. The other arm will be equipped with a hook for electrosurgery. These degrees of freedom, associated with the functional characteristics of the system (mainly the length of the manipulator itself), will ensure the movements necessary for the execution of the surgical task. The representation of the degrees of freedom is shown in Figure 29.

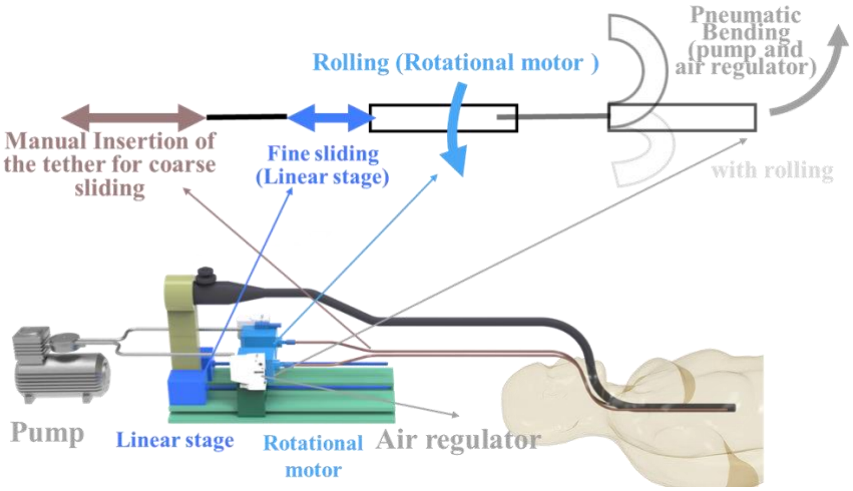


FIGURE 29 - REPRESENTATION OF THE DEGREES OF FREEDOM

To set the best geometric configuration of the prototype we started to calculate the maneuverability space of the manipulator. It should be noted that it was calculated considering the position of the two soft manipulators above and below the endoscope. The preliminary study aimed at calculating the point of maximum reachability which is reported in the two working configurations as shown in Figure 30.

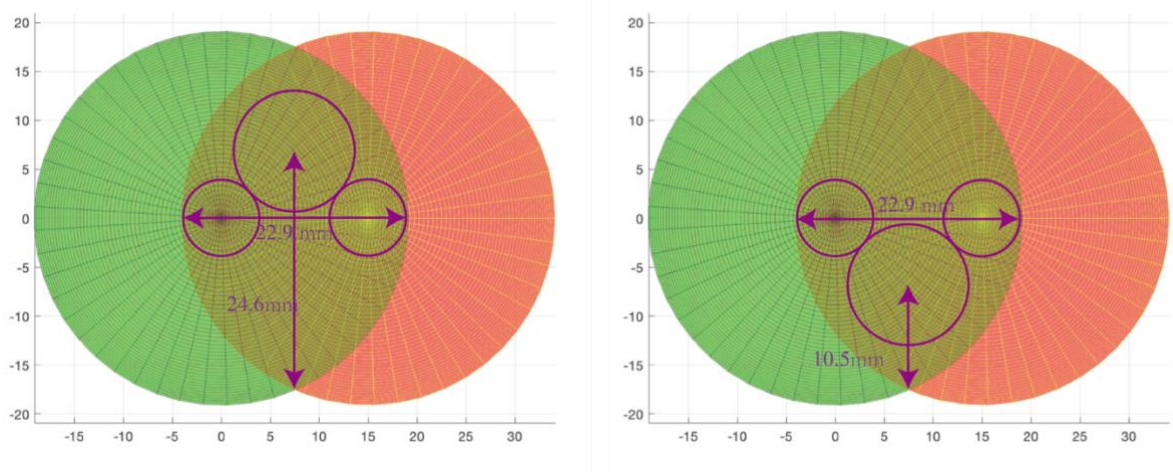


FIGURE 30 - TWO WORKING CONFIGURATIONS

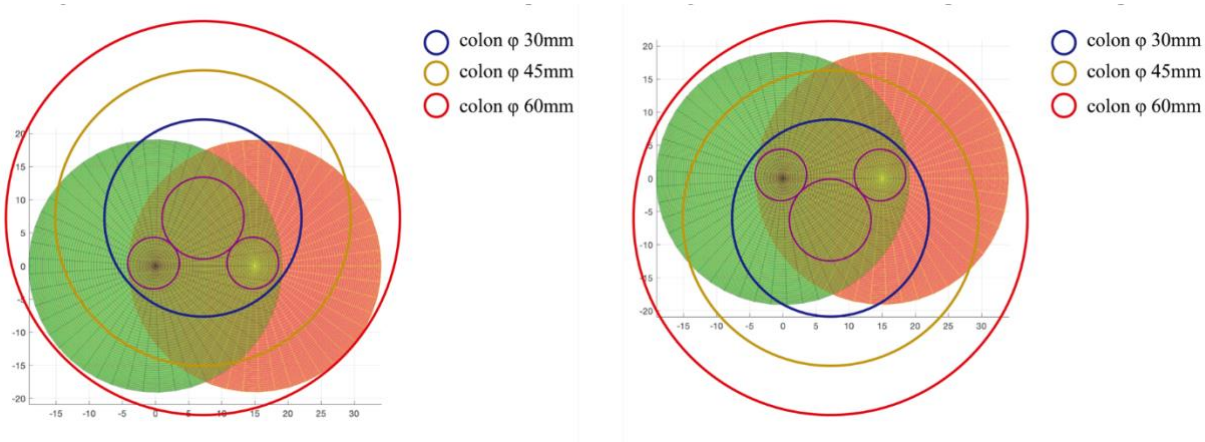


FIGURE 31 - WORKING SPACE IS PRESENTED WITH RESPECT TO THREE DIMENSIONS OF THE LARGE INTESTINE

In Figure 31 the working space is presented with respect to three dimensions of the large intestine, namely 30 mm, 45 mm, and 60 mm.

As can be seen from Figure 31, configuration 1 (left) allows reaching the lower part of the intestine with a diameter of 30 mm in the worst condition, that is, if the endoscope is on the diametrically opposite side of the lesion. However, this working condition is reasonably true in cases of operation in sections of reduced diameter, such as sections of the intestine of 30 mm, while we foresee the possibility of handling the endoscope, and therefore of the prototype constrained system, in the sections with a diameter greater to reach the lesion.

4.5 Controller and software configuration:

After many training sessions we were able to set the velocity of the movement of the arms, the extent of the banding angle of the single arm, and the stop point of the rotation and forward and backward movements of each arm.
We implemented the capsule with some visual markers on both arms, indicating the maximum and minor extension of the forward and backward linear movements, we set the "blind angle" of the rotational movements in a more comfort position (lateral for the knife), the speed of the back and forward movements to be comfortable for the operator.
We also tested many controllers' configurations to achieve the best user-friendly setting. At the end of the training and test sessions the prototype was able to reach a specific target on a flat plane playing on a rigid configuration (the endoscope fixed on the bench).
At the end of the PhD course, we succeeded in producing the first RED+ prototype. We were able to perform bench tests and ex-vivo tests, we demonstrated the feasibility of a soft arm architecture and the ability to apply the right force on the tissues. We achieved the software improvement and control assessment according to our needs.
Figure 32 shows the prototype assembled with a commercial endoscope, the control system, and the remote actuator.

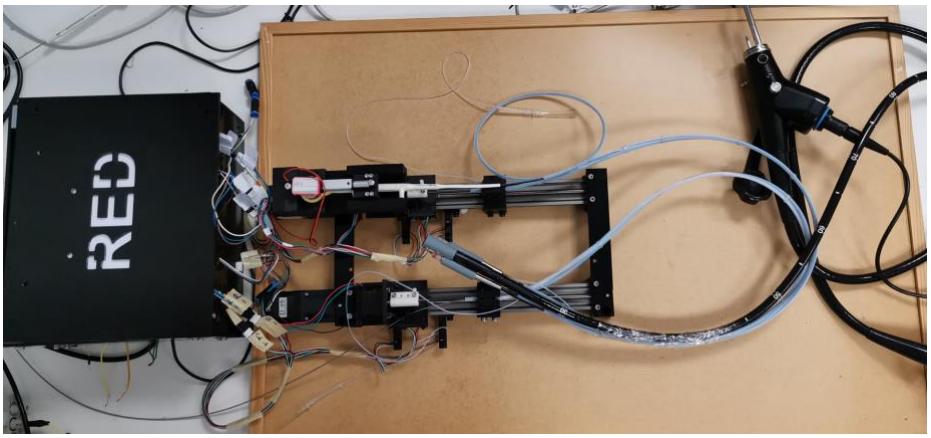


FIGURE 32 - RED+ ASSEMBLED WITH A COMMERCIAL ENDOSCOPE

The following pictures show the phases of the test performed in 3 different setting: (Figure 33) free manipulation; (Figure 35) manipulation inside a phantom; (Figures 34, 36) manipulation in ex-vivo platform.

FIGURE 33 - ON BENCH TEST ON FLAT PLANE

FIGURE 34 - EX VIVO TEST

FIGURE 35 - TEST ON PLASTIC MODEL

FIGURE 36 - EX VIVO TEST

All tests performed showed an excellent control experience in terms of precision, operator experience and comfort.

From the analysis of the characteristics of the various Phantoms available from Geomagic, it was decided to use the Touch model:

FIGURE 37 – CONTROLLER

To control the cautery arm the movements will be:

Sliding: move the pen along the red arrow indicated in the figure; the joint considered for the check will be the one underlined in blue.

FIGURE 38 - SLIDING MOVEMENT

Pitch: consider the joint circled in blue and to obtain the pitch move the pen with a wrist movement from top to bottom and vice versa.

FIGURE 39 - PITCH MOVEMENT

Roll: rotation of the base of the phantom

FIGURE 40 - ROLL MOVEMENT

To activate the cautery we used the button on the pen

FIGURE 41 - CAUTERY ACTIVATION

Activity 2: As regards the phantom dedicated to the gripper arm, modifications will be made to insert an opening and closing system.

In the following image, a traditional laparoscopic forceps has been attached (for example only) to give an idea of what the final system could look like:

To control the gripper arm the movements will be:

Sliding: same principle used for the phantom dedicated to the cautery arm.

FIGURE 42 - PITCH IN THE GRIPPER ARM

Pitch:

FIGURE 43 - FORCEPS CONTROL

Opening and closure of the forceps

V Discussion and conclusions

Since the screening program on gastrointestinal neoplasm gave a high rate of early diagnosis, we should find a new minimal invasive way to treat this early stage and precancerous lesion. The development of the third space endoscopy gave a big impulse in this direction.

Superficial gastrointestinal precancerous lesions and early cancer in the GI are commonly addressed through minimally invasive techniques: EMR, to treat precancerous benign lesions, and ESD to treat both benign lesions and early cancer, are the most used methods for this purpose. Similarly, in the rectum, TEM is preferred due to its advantages in lesion visualization, tissue manipulation, dissection, and suturing, resulting in lower margin positivity, less specimen fragmentation, and reduced long-term recurrence rates compared to ESD.

However, TEM is conditioned in its application to the distal part of the colon, usually from the anus to ~20cm, due to the rigidity of the platform. In contrast, EMR and ESD techniques, utilize a common endoscope and offer broader applicability for treating early lesions across the oesophagus, stomach, duodenum, and colon.

Once facing superficial lesions, we are constrained to achieve an "en-bloc" excision, posing risks of bowel perforation and higher local recurrence rates. Bridging the gap between TEM's advantages and the challenges posed by ESD in addressing early neoplastic lesions throughout the GI tract remains a significant anatomical and biomedical industrial challenge.

During the last decades many endoscopic master-slave systems have been produced, only few of them reached the approval, but none nowadays is available to treat lesion inside the lumen of the entire gastroenteric tract. On the other hand, the proposed solutions included mainly dedicated endoscopic platforms (most of them developed by industries already active in the field of endoscopy), research devices and articulated robots. All these proposals, regardless of their effectiveness, have in common the development of platforms specifically designed for this use, with significant purchasing and management costs.

The ideas to carry the ESD experience along the GI tract with the facilitation given by triangulation and the concept of plug-in device are well established. Nakadate et al[40] proposed a new plug-in robot and concluded that their system can safely

perform ESD in an *ex vivo* porcine stomach. Their conclusions suggest that even operators who have limited experience can use the system to perform ESD. Sang Hyun et al published a study describing how their platform, ROSE, can provide simple, effective, and safe multidirectional traction during ESD. They concluded that experienced endoscopists are satisfied, and novices could perform ESD safely and efciently[41]. Xiaoxiao et al underlined how the lack of effective countertraction contributes to the technical difficulties and adverse events during ESD, their auxiliary single-arm endoscopic robot-assisted learning plan reduces the technical difficulty and enhance the safety profile of ESD for novices[42].

The aim of this project is to carry the surgical TEM experience to perform dissections for early neoplastic lesions throughout the GI tract, overcoming its anatomical and technical limitations. Another fundamental aim is to develop a master-slave system, and in the future a standing alone robotic system, able to perform a surgical task inside the lumen. The platform is designed as a plug-in hood, compatible with all the commercial endoscopic instruments, reducing purchasing and management costs.

We want to achieve the ability to manipulate the tissue and apply the traction needed for a surgical dissection. This new robotic platform, developed in collaboration with the Scuola Superiore Sant'Anna (Pisa), is called RED+ (Robot for Endoscopic Dissection). This hood facilitates the movement of two teleoperated robotic arms. During the procedure, the endoscopist manoeuvres the endoscope in proximity to the lesion, while an operator remotely controls the robotic arms using a remote-control device.

We found that the main issue we had to overcome was to reach the right lifting and pulling forces to stretch tissue and perform the dissection. RED+ reached this goal by a pneumatic flex design of the arm. In this way we were able to reach the desired forces at this level of miniaturization, set an efficient user interface, and the capsule is able to navigate on tip of a commercial colonoscope.

RED+ is equipped with two different arms, that, in the non-operative configuration are incorporated inside the hood. Through a sliding movement both arms can reach the operative configuration, in which the bending movement of the arms makes possible to reach a lesion 3 cm far from the tip of the endoscope and guarantee the triangulation, tissue manipulation, traction and dissection of the tissue.

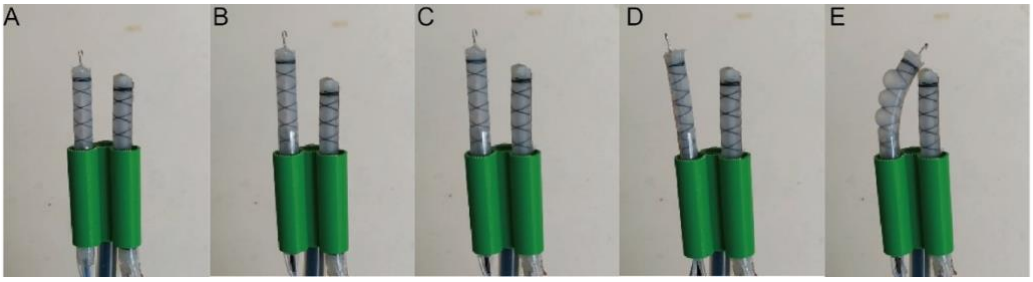


FIGURE 44 - SLIDING BENDING OF THE ARMS

The RED+ platform includes the miniaturized robotic hood, two controllers linked through a LAN cable to a high-level control unit NUC which collects and process data in C ++ language and send the output data to the unit for low-level data management (Micro Controller Unit - MCU), namely *Arduino UNO,* which controls the actuators and air supply. The system architecture is described and presented in Figure 26.

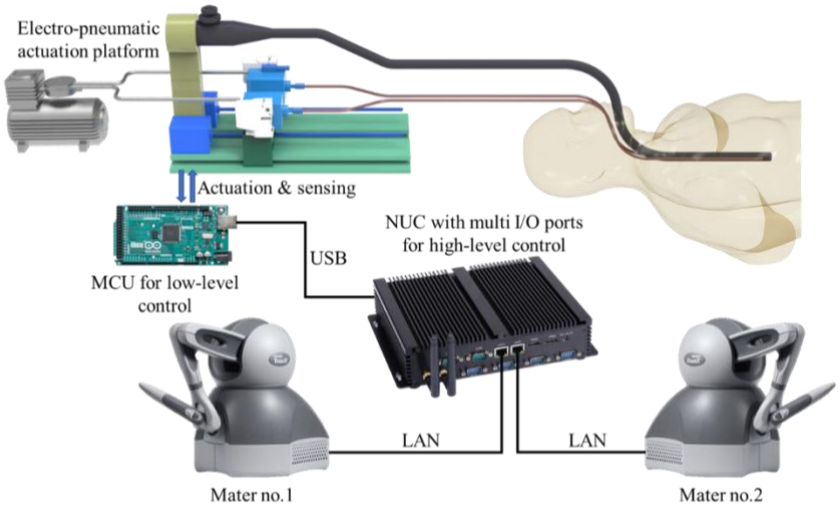


FIGURE 26 - ILLUSTRATION OF THE NEW RED PLATFORM COMMUNICATION UNITS

The bench test demonstrated that the soft arm could develop a lifting force of 1.4 N, compared to range of 0.59 N and 1.21 N needed for the correct dissection, and a pulling force of 1 N, compared to the range of 0.18 N and 1.09 N needed for the correct dissection[38]. The arm can reach a banding angle of 90° at a pressure of 1.5 bar and it is widely far from the rupture pressure, estimated at 3.5 bar. We were also able to reduce the dimension of the hood to 30mm in length and 23mm the diameter, compared to the 50mm length and 26mm dimeter of the previous version.

A commercial endoscope can drive the capsule through the bowel and supplies the visual asset.

Once the capsule, the control units, the actuators, and air supplies were assembled we were able to perform a training session, which involved about 3 hours and afterwards we were able to perform bench tests, model tests and ex vivo tests.
During the bench test we set the velocity of the movement of the arms, the extent of the banding angle of the single arm, and the stop point of the rotation, forward and backward movements. During these tests it was necessary to implement the capsule with some visual markers on both arms, indicating the maximum and minor extension of the forward and backward linear movements, we set the "blind angle" of the rotational movements in a more comfort position (lateral for the knife). It was also tested the controller configurations to achieve the best user-friendly setting.
Once the controller interface was established, we started bench, on model and ex vivo tests aimed to check the ability of RED+ to reach a specific target on a flat plane and in a more realistic operative theatre.
The targets used were some modelling clays shaped to be a cylinder of 10mm x 5mm and a flat shape 5mm x 20mm positioned at 5cm from the tip of the capsule. The tests were successful, RED+, coupled with a standard colonoscope, was able to reach the targets and manipulate them, applying the right forces and the coordination of the movements of both arms was successful.
In conclusion, the treatment of colorectal cancer is a crucial aspect of public health systems. Screening programs have led to the detection of a growing number of early-stage neoplastic lesions. The Trans anal Endoscopic Microsurgery technique shows promise in treating rectal lesions, technical constraints hinder the effectiveness of Endoscopic Mucosal Resection and Endoscopic Submucosal Dissection techniques for lesions throughout the GI tract. The RED+ Robotic Platform aims to overcome these limitations by extending the precision of microsurgical dissection to the entire colon using standard operating endoscopes, thereby eliminating the need for expensive specialized tools.
Tests conducted thus far have allowed us to build the first operative prototype of the RED+, which include the miniaturized robotic hood, the controller interface, NUC and MCU setting and the actuators and air supply. These tests have also confirmed that once assembled, the device maintains the necessary visual and operational field characteristics for accurate dissection.

We are aware that future development is necessary we have identified these crucial aspects to be implemented:

- Enhance the view of the of the tips of the instruments, playing on the configuration of the capsule itself, with a prototype which can rapidly switch from the *mickey mouse* configuration to the *reverse mickey mouse* configuration

- Achieve an operative configuration with a distance between the tips of the instruments and the tip of the endoscope approximately of 45mm

- Reduce the length of the stiff component of the capsule, considering we always must respect a 1:1 proportion between stiff and soft components length

- Provide a reset button near the operator to reset the capsule to the neutral configuration

- implement the controller of the arms with a position mapping system

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