LebensBlicke
Stiftung Früherkennung Darmkrebs

Interview with Prof. Guido Costamagna

Extraxts of his curriculum vitae:

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• Director, Digestive Endoscopy Unit, Policlinico A. Gemelli, Università Cattolica S. Cuore, Rome, Italy.

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His main areas of interest amongst many others:

- Endoscopy and Gastroenterology Clinical Trials
- Research and development in Digestive Endoscopy

Questions: Professor Dr. J. F. Riemann (**JFR**), Executive Chairman of LebensBlicke, Foundation for the Prevention of Colorectal Cancer (www.lebensblicke.de):

JFR: Dear Guido, you are a well know specialist in endoscopy and also very much engaged in the evaluation of colon capsule endoscopy. Colon cancer is one of the most common cancers in Europe. With g-FOBT and colonoscopy there are two well investigated procedures for detection and even prevention of this cancer at hand, which in many countries are even paid by insurance companies. What is the rationale to introduce colon capsule endoscopy (CCE) in this context?

GC: Colon capsule endoscopy (CCE) is not intended to replace colonoscopy, but it should be considered a complementary test to colonoscopy in selected patients. Colonoscopy is the “gold” standard for colon evaluation and it will remain the reference endoscopic procedure for the next years. However, there are challenges associated with colonoscopy being perceived as an invasive procedure, usually associated by patients’ fear of discomfort and inconvenience as well as psychological inhibition. For these reasons, colorectal cancer screening uptake is still low, especially when compared with the high rate of attendance of other cancer screening programs (breast, cervical and prostate). In order to overcome the limitations related to the invasiveness of colonoscopy, a non-invasive test may be proposed in patients who deserve colonoscopy for CRC prevention and refuse colonoscopy. Among non-invasive tests, however, imaging tests might be preferred over non-imaging tests (i.e. fecal tests), because of the ability to detect pre-neoplastic and non-neoplastic conditions that may be regarded as clinically useful (e.g. vascular malformations). For these reasons, in my opinion colonoscopy is the

procedure of choice for CRC prevention, however, when a non-invasive imaging test is required, CCE should be considered as one of the preferable options, which was also the opinion by almost 30 worldwide GI experts who did the voting during the ESGE guideline meeting for CCE.

JFR: Can you tell us a little more in detail how the non invasive CCE works? Is the preparation similar to that for colonoscopy?

GC: Now the second generation of colon capsule system is available. The new system includes new developments of colon capsule (Colon Capsule 2 – CCE-2), data recorder and software for video processing and viewing. The new CCE-2 is 11.6 x 31.5 mm in size. It has 2 imagers with a much wider angle of view that has been increased to 172° degrees for each imager, allowing nearly 360^0 degrees coverage of the colon. Furthermore, in order to enhance colon visualization and to save battery energy, the capsule is equipped with an adaptive frame rate.

This represents a major progress over the previous version. CCE-2 captures 35 images per second when in motion and 4 images per second when it is virtually stationary. This advanced system for the control of capsule image rate is the result of a bidirectional communication between CCE-2 and the new data recorder that, besides storing the images transmitted from the capsule, also controls the capsule image rate in real time, analysing the capsule images. To further save battery energy, as well as to allow automatic identification of the small bowel, CCE-2, instead of going into a “sleep” mode, continues to work at a low rate of only 14 images per minute until small bowel images are automatically detected, then it switches into the adaptive frame rate. At this point, the data recorder buzzes and vibrates and displays instructions on its liquid crystal diode (LCD) screen to alert the patient to continue the preparation protocol, assisting and guiding the physician and the patient through the procedure. The software (Rapid 8 software) for advanced video processing and viewing has also been implemented. Regarding the regimen of preparation, a bowel preparation is specifically designed for colon capsule endoscopy.

Compared to colonoscopy, the cleansing procedure is the same. Similarly to colonoscopy, a clean colon is necessary to accurately explore the colonic mucosa, CCE being unable to suck or wash the mucosa. However, differently from conventional endoscopy, an additional bowel preparation after swallowing of the capsule is required to promote capsule propulsion, since the colon has only few spontaneous longitudinal contractions per day. For this reason, one or two boosters of sodium phosphate (NaP) have been added to the usual preparation of polyethylene glycol solution (PEG) adopted for colonoscopy (4L of split-dose).

The main role of NaP booster is to accelerate CCE transit through both the small and large bowel within the limited operating-time of the CCE battery (i.e. 10 hours). Differently from initial studies in which high doses of NaP were used, low doses of NaP are now included in the regimen of preparation for CCE-2, in order to reduce the risk of adverse events. In detail, one booster of 30mL with 1 L of water is required when the capsule had entered the small bowel, and one of 15-25 mL with 0.5L water 3 hours later if the capsule had not been egested by that time which is the case in about 50% of patients.

JFR: Meanwhile quite a few data are available concerning the efficacy of this technique. What are the most important results?

GC: To date, two studies evaluated the CCE-2 in comparison to colonoscopy that was considered the gold standard: an Israeli multicenter trial and a European multicenter trial. Both trials have used a similar methodology: colonoscopy was independently performed within 8-10 hours after capsule ingestion and colon capsule endoscopy was prospectively compared with colonoscopy for the detection of colorectal polyps and masses in a cohort of patients scheduled for colonoscopy and having known or suspected colonic disease. Overall more than 200 patients were enrolled. Patients were considered having a significant finding when polyps ≥ 6mm and ≥ 10 mm or masses were detected. Per-patient CCE-2 sensitivity for polyps ≥ 6 mm ranged between 84-89% and ≥ 10 mm was 88% in both trials. Specificity for polyps ≥ 6mm ranged between 64-76% and 89-94% for polyps ≥ 10 mm.

The relatively low specificity for ≥ 6-mm polyps observed in these series was explained by a substantial rate of false-positive polyps because of size mismatch. In these series no missed cancers were reported: overall 4 cancers were detected by CCE-2 and were confirmed at colonoscopy. During the last DDW, the results from a large US multicenter trial were presented. In this study, the second generation CCE system was compared in a sixteen-center study with colonoscopy in a cohort of patients classified as average risk for colorectal cancer screening. Differently from the Israeli and European trials, the recorded capsule video was reviewed by central readers and blinded colonoscopy was performed 4-6 weeks post CCE procedure. The colonoscopist unblinded the capsule report at the end of the procedure and repeated the procedure when the capsule reported “false positive” lesion ≥ 6 mm. A total of 884 subjects were enrolled. The capsule sensitivity for detecting subjects with adenomas ≥ 6 mm and ≥ 10 mm was 88% and 92%, and the specificity was 82% and 95%, respectively.

Then we have the interesting chapter of incomplete colonoscopy. In such cases several radiologic methods have traditionally been used, but more recently, capsule endoscopy was also shown to be accurate. A French study published by Pioche in Endoscopy in 2012 and more recently papers published by Alarcon in Clin Gastroenterol & Hepatol (2013) and Triantafyllou in GIE (2013), homogeneously demonstrated that CCE is a feasible and safe tool for colon mucosa visualization in patients with incomplete colonoscopy being able to complete the colon visualization in the majority of the patients. However no comparative trials between CCE and radiology are available, to date. For this reason, in my Unit in Rome, we designed a study with the aim to compare CCE and CTC in a prospective cohort of patients with incomplete colonoscopy.

100 patients were enrolled. CCE and CTC were both able to achieve complete colonic evaluation in 98% of cases. In a per-patient analysis for polyps ≥6 mm, the CCE diagnostic yield was 2-folds higher than CTC (CCE detected 24 patients with at least 1 polyp ≥6 mm and CTC 12 patients); and this difference was statistically significant (p=0.02). Also when considering larger polyps (≥10 mm), CCE diagnostic yield was higher (5% for CCE and 3% for CTC), but the difference was not statistically significant (p=0.549). Both the tests show a high positive predictive value for polyps ≥6 mm and ≥10 mm being 96% and 86%, and 83% and 100% for CCE and CTC, respectively. The results of this trial confirmed that both colon capsule endoscopy and CT colonography were of comparable efficacy in completing colon evaluation after incomplete colonoscopy; however, the overall diagnostic yield of CCE was superior to CT colonography.

JFR: Is there any decision making so far at this point how to proceed with diminutive polyps?

GC: Most colon polyps discovered at screening are diminutive, with negligible risk of harboring advanced features (high grade dysplasia, villous component or malignancy). Moreover, 40% of diminutive colon polyps are hyperplastic rather than adenomatous. Diminutive lesions identified by a non-invasive test may also be missed by the post-test colonoscopy, because of the imperfect sensitivity of the latter for diminutive lesions. For this reason, diminutive polyps do not represent a primary target for non-invasive imaging tests. By extrapolating data from CT colonography studies that modelled the impact of colonoscopy or continued surveillance for diminutive polyps discovered at CT colonography, it can be concluded that referral for removal of diminutive lesions found at CCE might carry an unjustified burden of costs and complications relative to minimal gain in clinical efficacy. Moreover, studies on the second generation of CCE only provide accuracy data for >6 mm lesions, its specificity for diminutive lesions being largely unknown.

The only exception for post-CCE referral for diminutive polyps is the simultaneous presence of at least 3 of these lesions. Polyp multiplicity has appeared as a strong predictive factor of subsequent advanced neoplasia development in post-polypectomy follow-up studies.

JFR: What evidence level is necessary in order to be recommended as an important tool for colon cancer detection and its precursor lesions? Are the current data sufficient (German S3 guidelines for Colorectal Cancer do not recommend the procedure due to missing RCT`s)?

GC: To date, there is data available with average risk patients (FDA registration file) showing good accuracy, however, we do not have trials that evaluated the potential role of the capsule in colorectal cancer screening programs. This means that we do not know if the capsule might have a role in CRC screening programs and, if yes, which could be its role. Only few and preliminary data are available on the possible adherence to CCE in a screening setting. We only have a cost-effectiveness analysis published by Hassan in Endoscopy that compared the CCE with colonoscopy in a screening setting. Although CCE was not a cost-effective alternative when assuming an equal adherence, it became an efficient option when assuming that adherence to CCE was higher compared to colonoscopy for CRC screening, a feature which has to be evaluated to support the assumption that CCE may play a role in CRC screening.

JFR: To get evidence-based data more large clinical trials are necessary. Would a prospective randomized controlled trial i(immunological)-FOBT versus CCE makes sense? Would you recommend other trials?

GC: Two big trials are planned in Europe. Both will enroll patients attending in organized screening programs. It is an Italian multicenter trial (CCANDY trial- Colon Capsule Advanced Neoplasia Diagnostic Yield) aimed to assess the accuracy (sensitivity and specificity) and the positive and negative predictive value (PPV and NPV) of CCE, compared to conventional colonoscopy, in detecting CRC and advanced adenomas, among subjects with a positive FIT, attending in an organized population screening program.

We started with the enrollment of patients a couple of weeks ago and at the end 400 patients will be enrolled. In the Netherlands, in Rotterdam, Prof. Kuipers designed the so-

called ORCA (Population C**OIon** cance**R** screening by **Ca**psule endoscopy) trial aimed to determine the uptake and diagnostic yield of primary population screening for CRC by means of CCE. They will enroll asymptomatic volunteers aged 50 – 75 years by means an active invitation process until 1000 participants have been included. Soon, an Irish prospective comparison study will be published in Endoscopy. CCE was compared to colonoscopy in patients attending within the second round of FIT bowel screening. The Authors aimed to assess the sensitivity, specificity, and negative and positive predictive value of CCE compared to colonoscopy in an FIT positive colorectal cancer screening cohort. CCE was demonstrated to be a safe and effective means of detecting cancer and polyps in a positive FIT screening cohort, suggesting that CCE would be a useful 'filter test' in this situation, reducing the number of colonoscopies performed by 71%. I think that the results of this trial and the forthcoming results of the Italian and Dutch trials will clarify the potential role of colon capsule in the screening programs.

JFR: Are there anyhow established indications for CCE now? Could CCE be seen as a possible filter for those who do not need colonoscopy?

GC: The ESGE guidelines recommend the use of CCE in average risk subjects, while patients at high risk for CRC, because of alarm symptoms or signs, a family or a personal history of CRC should be referred to colonoscopy. However, in patients not compliant or unable to undergo colonoscopy, the use of CCE could be discussed with the patient. CCE is a feasible and safe tool for colon mucosa visualization in patients with a previous incomplete colonoscopy. To date, there is insufficient data to support the use of CCE in the diagnostic work-up or in the surveillance of patients with suspected or known inflammatory bowel disease. Based on preliminary data, CCE may be useful to monitor inflammation in ulcerative colitis, which may help to guide therapy

JFR: What are the limitations, what kind of complications are possible and how often do they occur? In brief: how safe is CCE?

GC: Concerning the limitations, one of the most relevant is the fact that the colon capsule is only diagnostic. The other problem is that we cannot control the movements of colon

capsule: this means that we cannot control the transit of the capsule in the colon and make it homogeneous, but also we cannot ensure that the capsule will complete the colonic exploration. In my opinion these are limitations that will be overcome in the next few years with some technological developments. Contraindications for CCE are similar to those of small-bowel capsule endoscopy. The use of sodium phosphate (NaP) as a booster should be avoided in patients at increased risk of NaP toxicity. The risk of capsule retention with CCE is very low. CCE has consistently been shown to be a safe procedure: no major complication has been reported in about 3000 procedures. Therefore, we can say that CCE is a safe procedure.

JFR: Are there data about the acceptance of the procedure available?

GC: The group of Prof. Rösch published an interesting trial in BMC Gastroenterol in 2012. It is a prospective study performed to evaluate whether adding capsule colonoscopy to the endoscopic screening options increases uptake. Invitation letters were sent to 2150 persons above the age of 55 insured with a German medical insurance company in an area in Germany (Rinteln, Lower Saxony) with a baseline spontaneous annual screening colonoscopy uptake of 1 %. Both capsule or conventional colonoscopy were offered. Interested persons were given information about the two screening options by local gastroenterologists and examinations were then performed according to screenees' final choice. Interestingly, the option of capsule endoscopy led to a fourfold increase of screening uptake (4.2 % vs. 1 %, $p < 0.001$). Despite similar age distribution in both sex groups, uptake in men was significantly higher (5.6 % vs. 2.8 %, $p = 002$). The present study suggests that offering the option of capsule colonoscopy increases uptake of endoscopic colorectal cancer screening.

On the other hand, the new system offers the advantage of performing the colon capsule endoscopy out-of the clinic. No colorectal imaging test may be performed on an out-of-clinic basis.

This represents a major drawback compared with fecal tests. Because colon capsule endoscopy (CCE) automatically detects small bowel mucosa, it has the potential to become the first colorectal imaging test to be performed out-of-clinic. Sam Adler from Jerusalem last year published in Surgic Endosc a study aimed to evaluate the feasibility and efficiency of CCE when offered as an out-of-clinic procedure. He demonstrated that as an out-of-clinic procedure, CCE is

feasible and easily performed. This was a feasibility study and it did not demonstrate that an out-of the clinic colon capsule endoscopy increases the acceptability. However, it might be argued that a home-based procedure may be associated with better acceptability and potentially with increased adherence to Colorectal cancer screening.

JFR: Where do you see the place of CCE in the near future having in mind that this technique will not be paid by insurance companies and it is very expensive?

GC: I think that the place of CCE comes out from the evidence in the literature. The main evidence relates to incomplete colonoscopy and CCE seems to be a good test in this group of patients, being able to complete the vast majority of the previous incomplete colonoscopy and showing a higher diagnostic yield when compared to CTC. This is also good for the Endoscopist who fails to complete a colonoscopy. In fact these patients can be managed internally in the Endoscopy Unit, without the need of referring them to Radiologists

JFR: Your personal opinion: will CCE become a major player as a noninvasive and presumably safe technique in the broad range of low threshold offers for colon cancer detection? And what further requirements are absolutely necessary for it?

GC: In my opinion CCE will play a role in the future. One of the most intriguing aspect is its potential role as a filter to select patients who need colonoscopy. In this vision, the filter test if effective would select patients with neoplasia only for invasive standard colonoscopy and reduce the number of negative colonoscopies and therefore the burden on endoscopy services, staff and patients. Before this, our priority is to simplify the regimen of preparation in terms of amount of liquids and type of agents used; and to increase the evidence supporting this new endoscopic technology. On the other hand, in order to spread the use of this technology, costs are still an issue. The reduction of costs is out of our business and should be one of the priorities of the producer company.

JFR: Dear Guido, thank you very much for this exciting and interesting interview.