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ENDOSCOPIC INNOVATIONS IN DIAGNOSIS AND MANAGEMENT OF COLORECTAL CANCER

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Summary

Colonoscopy is the gold standard in diagnosis of colorectal cancer that in most instances arises from precursor lesion, adenomatous polyp. However, white ligh forward viewing colonoscopy is not a pefect method, up to a quarter of adenomas are being missed during standard procedures. Therefore, new techniques and technologies are being developed in order to increase adenoma detection rate, either through better resolution and magnification of the image (high-definition, high-magnification endoscopes) or by augmenting the overview of colonic mucosa (Full Spectrum Endoscopy colonoscope, Third-Eye Retroscope). Besides adenoma detection, new technologies allow better tissue characterisation and in vivo discrimination between non-neoplastic and neoplastic lesions (conventional chromoendoscopy, virtual chromoendoscopy, confocal laser endomicroscopy, endocytoscopy). In additon to diagnostic procedures, therapeutic techniques are also evolving. Formerly, all of the flat or depressed colorectal lesions, encountered during colonoscopy, were reffered to surgery. Today, endoscopic mucosal resection is becoming a routine method for the treatment of early gastrointestinal mucosal lesions of less than 2 cm in diameter. For larger lesions, endoscopic submucosal dissection, a state-of-the-art technique, is indicated, but currently carried out only in tertiary centres.

Endoscopic innovations are leading into new era of colorectal cancer diagnosis and management, hopefully resulting in decrease of incidence, morbidity and mortality.

Keywords: colorectal cancer; diagnosis; diasease management; colonoscopy; innovations.

INTRODUCTION

Colorectal cancer (CRC) is second most common cancer among Croatian men and women and second leading cause of death from cancer [1,2]. It is also among five most common cancers worldwide and although it is more common in richer

countries, incidence of the disease is rising in some developing countries [2,3]. As opposed to other common cancers such as lung, breast and prostate, where the focus is early detection, CRC can be prevented since the majority of CRCs arise from precursor lesions, adenomatous polyps [4]. Indeed, studies have confirmed that removal of adenomatous polyps leads to reduction of cancer and subsequent reduction of mortality [5]. Given the above, CRC screening is widely recommended with colonoscopy being the gold standard for CRC diagnosis [6]. However, standard white light forward viewing colonoscopy is not a perfect method, reported adenoma miss rates are up to 27% [7-12]. Therefore, new endoscopic techniques and technologies are being developed in order to reduce adenoma miss rates and the incidence of interval cancer. It is recommended for every colorectal lesion encountered on colonoscopy to be removed and examined by a pathologist, a costly strategy that increases the risk of polypectomy complications [6,13]. Regarding the latter, new technologies are emerging designed to enable in vivo tissue characterization (''optical biopsies'') and ''leave in situ'' approach for hyperplastic polyps or ''resect and discard'' approach for diminutive adenomatous polyps [14]. Information obtained by ''optical biopsies'' also impact therapeutic strategy selection since tissue biopsies are not recommended prior to endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). EMR and ESD are endoscopic techniques for removal of flat pre-cancerous and cancerous lesions, that can, in carfeully selected patients, replace surgery [15,16]. In this review we will perlustrate advances in endoscopy regarding colon cancer diagnosis and management. Even though some commercially accessible for more than a decade, many technologies are not widely available due to their price and the need for expertise in interventional gastroenterology.

ENDOSCOPIC INNOVATIONS IN COLON CANCER SCREENING

Colonoscopy is the gold standard in CRC screening however, for moderate risk population, it has its limitations. Patients percieve bowel preparation, crucial for adequate examination, upleasant, the procedure carries the small risk of bowel perforation and in case of sedation, cardiopulmonary complications. Accordingly, many adult patients opt for other, less invasive procedures including stool based tests (guiac-based fecal occult blood test, fecal immunochemical test, stool DNA test) and full or partial structural exams (flexible sigmoidoscopy, double-contrast barium enema, computed tomographic colonography) [6,13].

Currently, a new endoscopic procedure, colon capsule endoscopy (CCE), that may be useful for improving compliance with CRC screening, is being evaluated.

Even though similar to small bowel device, the capsule is bigger (11x32 mm vs. 11x26 mm) with video capture components on both ends of the capsule. After initial activation, the colon capsule captures images for 5 minutes, then transits into sleep mode for 2 hours. Once reactivated, approximately at the level of terminal ileum, the capsule records images for about 10 hours. Data are recorded via an antenna - lead array similar to that used in other capsule endoscopy procedures. Images are then transferred from a recording device to a workstation for formal review and report generation.

CCE has been shown to be a safe procedure when used in average-risk individuals with a very low rate of technical failures (3%) and a high capsule excretion rate of about 90% [17,18].

As in all other forms of screening, any positive findings require conventional colonoscopy for tissue sampling or polypectomy.

Quality of screening colonoscopy is measured by adenoma detection rate and cecal intubation rate. Factors impacting procedure quality, besides bowel preparation and colonoscopist's proficiency, include patient's compliance conditioned by abdominal discomfort and pain, the presence of subtle, flat or depressed lesions that are difficult to detect with standard endoscopic equipment and lesion location in ''blind spots'' of colonic mucosa [13].

When it comes to improving patient comfort and increasing cecal intubation rate, water infusion techniques and cap-assisted colonoscopy have shown promising results.

For appropriate mucosa visualization, colon folds need to be separated. Standard air insufflation colonoscopy provides good visualization but also distends and elongates the colon, increasing the likelihood of patient discomfort. Water infusion techniques (''water immersion'' and ''water exchange'') use water adjunct to air. Water helps open colon folds with less comparative distention, which significantly reduces pain during colonoscopy, decreases the need for sedation drugs and increases the completion rate in patients with prior difficult colonoscopies [19-22].

Cap-assisted colonoscopy uses transparent caps attached to the distal tip of the colonoscope thus helping in depressing colonic folds in order to improve visualization of their proximal aspects. It was initially suggested that the technique might be of benefit for polyp detection, however, studies did not confirm this hypothesis. They did however report reduced cecal intubation times and improved cecal intubation rates. The same accounted for procedures in patients in whom cecal intubation initially failed with standard colonoscopy [22,23].

Standard forward viewing colonoscopes visualise the colon from the flexible tip of the instrument, with an angle of view up to 170° and as mentioned above a high adenoma miss rate is partially due to their inability to detect lesions hidden in the ''blind spots'', such as the internal lining of flexures and proximal aspects of folds. In order to surpass this obstacle and get a better overview of colonic mucosa, Full Spectrum Endoscopy (FUSE) colonoscope and Third-Eye Retroscope have been designed.

FUSE colonoscope allows a high resolution 330 degrees "full spectrum" viewing of the colonic lumen while maintaining technical features and capabilities of a standard 140 and 170 degrees colonoscope.

The FUSE system consists of a main control unit and a video colonoscope with three cameras on the left-side, front and rightside of the flexible tip. Video images are displayed on three contiguous monitors corresponding with each individual camera [24-26].

Third-Eye Retroscope is a probe based device that is retroflexed 180 degrees after being advanced through the working channel of the colonoscope. It provides a 135 degrees retrograde view of the colon on the same monitor as a forward viewing colonoscope. However there are some limitations inherent to the device that confine its use in every day practice. First, thorough suctioning of colonic debris must be done during insertion of the colonoscope due to a 50% reduced suctioning capacity when the retroscope is in position. A second disadvantage is that the Third-Eye Retroscope needs to be removed from the working channel in case an accessory device is required, such as a biopsy forces or a polypectomy snare, which is bothersome and increases the procedural time [22,27].

For both FUSE colonoscopy and Third-Eye Retroscope colonoscopy preliminary studies have reported significant reductions in the proportion of missed adenomas in comparison with standard 170 degrees view straight-forward colonoscopy, even though reductions were more modest with Third-Eye Retroscope than those described for FUSE colonoscopy [22,24-27].

IMAGING INNOVATIONS FOR DETECTION AND DIFFERENTIATION OF COLORECTAL NEOPLASIA

The aim of colonoscopy is to detect adenomatous, pre-cancerous polyps, remove them and thus reduce CRC related morbidity and mortality. However, not all polpys are adenomatous but reliable differentiation between adenomatus and hyperplastic lesions is not possible solely according to the macroscopic lesion characteristics on white light illumination (accuracy 59-84%). Therefore, it has been recommended for all encountered lesions to be resected and submitted to pathology. New technologi-

es enable better visualization (high-definition and high-magnification endoscopes) and enhanced characterization of lesions (conventional and virtual chromoendoscopy, confocal laser endomicroscopy, endocytoscopy). Besides macroscopic features such as size and surface characteristics, microvascular pattern and pitt patern are being evaluated. With introduction of new parameters, endoscopists can more reliably differentiate between neoplastic and non-neoplastic lesions, apply more economical ''leave in situ'' or ''resect and discard'' approach for small hyperplastic polyps and diminutive adenomas respectively, but also estimate the risk of submucosal invasion, crucial for guiding therapeutic decision on whether endoscopic or surgical operation will be carried out.

The video capabilities of color images of standard definition endoscopes are based on traditional television broadcast formats. Advances in technology have resulted in increased number of pixels and increased resolution. Current high-resolution or high-definition endoscopes produce images with resolutions that range from 850,000 pixels to more than 1 million pixels, allowing them to discriminate objects that are only 10 to 71 microns in diameter.

At baseline, standard-resolution and high-resolution endoscopes magnify the endoscopic images 30 to 35 times. High-magnification endoscopes are defined by the capacity to perform optical zoom using movable lens in the tip of the endoscope thus magnifying images up to 150 times [22,28].

Conventional chromoendoscopy (dye assisted colonoscopy) involves topical application of stains or pigments to highlight surface contours.

The procedure is carried out using standard endoscopic equipment in addition of a special spray catheter essential to deliver a fine mist of dye to the mucosa. In diagnosing colonic neoplasia methylene blue, crystal violet and, most commonly, indigo carmine, are used.

Indigo carmine is a contrast stain that pools into crevices between epithelial cells, highlighting small or flat lesions and defining irregularities in mucosal architecture, particularly when used with high-magnification or high-definition endoscopy.

Pancolonic chromoendoscopy, recommended for neoplasia surveillance in patients with long-standing colitis [14], significantly increases the rate of detection of small neoplastic and flat lesions, but this technique requires an excessive volume of dye and a significantly prolonged procedure. Therefore, in average-risk patients, colonoscopists use “selective” chromoendoscopy for further examination of surface structure and mucosal crypt (pit) pattern of any subtle mucosal irregularity detected during standard colonoscopy [29].

Virtual chromoendoscopy refers to the use of image enhancement technologies built into the colonoscope system to alter the white-light image and enhance visu-

alization of mucosal surface architecture and capillary pattern. All commercially available systems work differently, but have a key aim of reducing the amount of red light in the image and of narrowing the bandwidth of blue and green light.

Narrow band imaging (NBI) separates white light into red, green, and blue using a special optical filter. Red light is eliminated and the contribution of blue and green wavelengths increased. Since mucosal hemoglobin selectively absorbs blue light, and the mucosa surrounding blood vessels reflects it, the contrast of the image is increased and the mucosal micro-vessel architecture can be estimated in fine detail. In the colon and rectum, microvessels form a ring, and each ring surrounds its respective gland. A deformed microvessel suggests a deformed neoplastic gland. Neoplastic changes result in a change in the form, density, and size of microvessels, and colorectal lesions can therefore be diagnosed [31,32].

FUJINON Intelligent Color Enhancement (FICE) is a computed spectral estimation technology that enhances the visibility of mucosal and vascular details by narrowing the bandwidth of light. FICE enables the endoscopist to choose between different wavelengths for optimal examination of the colon mucosa [14,22].

I-SCAN utilizes the same spectral estimation technology as FICE technology, and applies a digital color filter to images to emphasize lesions [14,22].

Even though the effect of pancolonic virtual chromoendoscopy on adenoma and polyp detection seems limited studies have reported high accuracy of both conventional and virtual chromoendoscopy (NBI, FICE and i-SCAN) [14, 30-32] in differentiation between adenomatous and hyperplastic polyps, therefore, **European Society of Gastrointestinal Endoscopy** suggests that they can be used, under strictly controlled conditions, for real-time optical diagnosis of diminutive (≤5mm) colorectal polyps to replace histopathological diagnosis [14].

Autofluorescence imaging (AFI) endoscopy is based on real-time detection of natural tissue fluorescence emitted by endogenous molecules, after excited by a certain wavelength. Differences in fluorescence emission between neoplastic and non-neoplastic tissues are captured during endoscopy and visualized as magenta or green color, respectively. The device is activated by a push-button on the handle of the endoscope. Recently, AFI has been connected to a high-resolution endoscope and to the NBI system, giving rise to a combined modality called endoscopic trimodal imaging. However, as opposed to above mentioned technologies, studies on benefit of AFI reported conflicting results [14,22,33,34].

Confocal laser endomicroscopy (CLE) and endocytoscopy are emerging endoscopic technologies that permit high-resolution assessment of gastrointestinal mucosal histology.

Confocal laser endomicroscopy provides microscopic images during ongoing endoscopy that trained endoscopists are able to evaluate on-site. The technology is based upon the principle of illuminating a tissue of interest with a low-power laser and then detecting fluorescent light reflected from the tissue. Intravenous injection of fluorescin is used to highlight the vasculature, lamina propria, and intracellular spaces of tissue being examined, in addition of topical acriflavine for nuclei staining [35-37].

Similar to CLE, endocytoscopy aims to enable real-time microscopic imaging of the mucosa in vivo. The main difference between CLE and endocytoscopy is that endocytoscopy is based solely on high-level magnification using optical lenses and only the very superficial layer of the mucosa can be imaged. In addition, the lens must come into direct contact with the tissue being examined. As with confocal endomicroscopy, acquisition of quality images requires application of a contrast agent. Typically, topical application of methylene blue or a combination of methylene blue with crystal violet is used [35].

For both CLE and endocystoscopy, probe-based systems are commercially available. The indications are still being defined. In general, these procedures are used to target biopsies of abnormal tissue and decrease biopsies of normal tissue [35].

ENDOSCOPIC INNOVATIONS IN EXCISION PROCEDURES FOR COLORECTAL LESIONS

Endoscopic treatment is recommended for benign lesions and early colorectal tumors with no evidence of enlarged lymph nodes or lymph node metastasis.

There are various established polypectomy techniques for endoscopic removal of polypoid colorectal lesions carried out in most of the gastroenterology centers. When it comes to flat or depressed colorectal lesions and laterally spreading tumors (LSTs), before the introduction of endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), the latter currently performed only in tertiary centers, patients have been reffered to surgery with outcomes such as hemicolectomy or stoma formation, that greatly impacted the quality of life.

Careful characterization of lesions is mandatory in order to avoid incomplete treatment or unnecessary surgery. While lesions confined to superficial mucosa and up to 20 mm in diameter can be successfully treated with EMR, larger ones with higher possibility of submucosal invasion require ESD with en bloc resection for an accurate pathological evaluation. In cases of submucosal invasion of less than 1000 microns where the risk of lymph node metastasis is less than 1%, ESD is considered therapeutical. On the other hand, for deeper invasion, the risk is substantially increased, therefore, in such cases ensuing surgery is warranted [15].

Predictors of submucosal invasion, besides size [38], evaluated using convential or virtual chromoendoscopy with high definition-high magnification colonoscope, include invasive type pit pattern, distorted capillary architecture and nodular mixed or pseudo-depressed LST surface morphology [15,39].

EMR, even though technically more difficult than standard polypectomy, is considered its variation and has become a routine method for the treatment of early gastrointestinal mucosal lesions. Typically, after marking the margins with electrocautery, a solution is injected into the submucosa to lift the lesion for easier removal and to provide a cushion to help protect the deeper layers of the bowel wall from mechanical or electrocautery damage followed by lesion resection using a mucosectomy device (grasping forceps, electrocautery snare, ligation device). The improved version of EMR, EMR with pre-cutting, is applied when the tumor location is not convenient for the traditional EMR operation [15,16,40].

EMR en block resection is feasible for lesions up to 20 mm but for larger ones, EMR can only be conducted in piecemeal fashion. Since piecemeal resection carries a high risk of local reccurence (0-55%) and prevents pathologist from reliably determining the status of the resection margins, intensive post-EMR colonoscopic surveillance is required (follow up at 2 to 6 months) [16].

ESD is indicated for larger lesions in which en block resection using EMR is difficult. It is usually limited to lesions up to 5 cm in diameter but Japanese refferal centers have reported performing ESD on even larger ones. Further indications for colorectal ESD include mucosal tumors with fibrosis, scattered tumors caused by chronic inflammation and residual early tumor lesions after endoscopic operation.

The procedure involves visualization of the edges using virtual chromoendoscopy, marking the edges with argon knife, applying multipoint injections of pre-prepared solution into submucosal tissue. The edge of the lesion is then cut and the lesion stripped using special ESD knives (various knives are commercially available e.g. IT knife, Hook knife, Flex knife, B-knife, Flush-knife, Scissor-type knife, toung-type knife) [41]. The improved technique of ESD, ESD-S, uses a snare insted of the ESD knife to strip the lesion [15,16,40,41].

Complications of both EMR and ESD include bleeding, perforation and local reccurence. Various studies have reported the rates of EMR and ESD complications (perforation rate: EMR: 0-1.3%, ESD 0-8%; postoperative bleeding: ESD EMR 3.6-8.1%, ESD 0.4-11.5%; local tumor reccurence: EMR 0.8-18.1%, ESD 0.4-2%) as well as resection rates (en-block resection: EMR 42.4%, ESD 74-89%) [42-51]. However, the data are hard to compare since indications and the intrinsic aggressiveness of two technques on bowel wall differ. The risk of complications, as well as procedure time (ESD 108±71 min, EMR 29±25) [45], increase with tumor size and unfavorable loca-

tion (procedures are more feasible in rectum compared to colon) [51], but also, over the years, complication rates reported are decreasing.

Overall, EMR is superior to ESD in treatment of benign colorectal lesions since it has low risk of complications, shorter operation time and the characteristics of the operation are relatively simple. However, in case of suspected early carcinoma it is very important to mandate complete resection. ESD has higher resection rate and lower reccurence compared with EMR and provides a better quality of life for patients compared to surgery.

CONCLUSION

New endoscopic techniques and technologies, compared to standard endoscopic equipment, have increased adenoma detection rate and enabled better in vivo characterization of lesions. Also, many experts believe that state-of-the-art techniques in treatment of early colorectal cancer will replace surgery and thus improve patient's quality of life. Endoscopic innovations are leading into new era of colorectal cancer sreening and management, hopefully resulting in reduction of CRC incidence, morbidity and mortality.

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Sažetak

Endoskopske inovacije u dijagnostici i liječenju kolorektalnog karcinoma

Kolonoskopija je zlatni standard u dijagnostici kolorektalnog karcinoma koji u većini slučajeva nastaje iz prekursorske lezije, adenoma. Međutim, standardna kolonoskopija nije savršena metoda; prema rezultatima tandem studija čak četvrtina adenoma ostaje neotkrivena. Stoga se razvijaju nove tehnike i tehnologije koje omogućuju bolju detekciju adenoma uvećanjem i boljom rezolucijom slike (''high-definition'', ''high-magnification'' endoskopi) te boljim pregledom sluznice debelog crijeva (''Full Spectrum Endoscopy'' kolonoskop, ''Third-Eye Retroscope''). Nove tehnologije također omogućuju i napredniju karakterizaciju kolorektalnih promjena i in vivo razlikovanje ne-neoplastičnih i neoplastičnih lezija (konvencionalna kromoendoskopija, virtualna kromoendoskopija, konfokalna laserska endomikroskopija, endocitoskopija). Osim dijagnostičkih, napreduju i terapijske endoskopske metode. Do sada su sve ne-polipoidne kolorektalne promjene liječene kirurški, a danas je endoskopska mukozna resekcija postala rutinska metoda za lezije do 2 cm u promjeru. U slučaju većih promjena inidicirana je endoskopska submukozna disekcija, state-of-the-art tehnika koja se trenutno izvodi samo u tercijarnim centrima.

Inovacije u endoskopiji vode u novu eru dijagnostike i liječenja kolorektalnog karcinoma te nagoviještaju bolju prevenciju i smanjenje incidencije ove česte maligne bolesti.

Ključne riječi: kolorektalni karcinom; dijagnostika; liječenje kolorektalnog karcinoma; kolonoskopija; inovacije.

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