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Mini Review

New Ultrasonic Techniques for Colorectal Cancer Imaging

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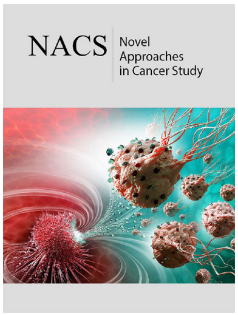

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Abstract

Colorectal cancer (CRC) is the third most common cancer and the second cancer-related cause of mortality in the world, with increasing incidence in some developing countries and in the young population. Colonoscopy is the gold standard tool for CRC screening because it can detect and remove precancerous lesions in the same procedure, and its widespread use in people older than 50 years of age may be the cause of declining CRC incidence in this group. However, some precancerous lesions may be missed by colonoscopy and progress to CRC before the next screening, a fact that demonstrates the need to search for new affordable and sensitive imaging techniques. In this minireview we highlight the main ultrasound methods that have been studied experimentally and clinically with the potential to improve CRC detection, diagnosis and follow-up.

Keywords: Colorectal neoplasms; Diagnostic imaging; Ultrasonography; Ultrasound bio microscopy

Introduction

Colorectal cancer (CRC) is the third most common cancer diagnosed in the world and the second cancer-related cause of mortality in both men and women [1]. Despite of being about three times more incident in transitioned countries, the mortality rates for CRC are higher in transitioning countries, and these two discrepancies reflect that improvements in survival are due to the adoption of best practices in cancer treatment and management [2]. CRC presents a variation of incidence trends in different geographic regions: increasing incidence in some countries (such as China, Russia, Canada, The United Kingdom and Brazil) and decreasing incidence in others (including The United States, France and Japan) [3]. However, the overall declines in CRC incidence in countries such as The United States are masking an increasing incidence in young adults: from the mid- 1980 through 2013, rates of CRC incidence increased by 2.4% per year in adults aged 20-29 years and by 1.0% per year in adults aged 30-39 years [4]. It is estimated that by 2030 the incidence rates for colon and rectal cancer in the US population will increase by 90% and 124%, respectively, for patients 20 to 34 years of age [5]. The declining CRC incidence in groups aged older than 50 years may be a reflect from the widespread screening in this population, which rose from 38% in 2000 to 59% in 2013 [6]. Fecal occult blood tests, flexible sigmoidoscopy and colonoscopy were the most common screening test modalities among older adults in The United States until 2005 [7]. By 2005, colonoscopy had become the most common imaging screening test modality for CRC in older adults [7], with its use among US adults aged 50 years and older reaching 60% in 2015 [8].

CRC Diagnostic

The U.S. Multi-Society Task Force of Colorectal Cancer recommended CRC screening to average-risk persons (persons without a family history of colorectal neoplasia) beginning at age 50 years with colonoscopy being offered first [9]. Currently, the American Cancer Society recommends regular CRC screening for adults aged 45 and older with either a high-sensitivity stool-based test or an imaging exam [10]. Screening aims to reduce CRC incidence and mortality by removal of adenomatous polyps and by detection and treatment of early-stage cancers [11-12]. Usually, CRC arises from adenomas in an "adenoma-carcinoma sequence", a series of histopathological events associated with molecular alterations that can take more than 10 years to complete. In the Western population, the incidence of polyps among people aged 50 or older is 22-54% [13-14]. Moreover, about 30% of diagnosed CRC had evolved from serrated lesions, which can be classified as hyperplastic polyps (not considered precancerous),

sessile serrated polyps and traditional serrated adenomas [9]. In these cases, colonoscopy has the advantage to detect and remove precancerous lesions in the same procedure, reaching an estimated 53% reduction in CRC-induced mortality rates [11].

In terms of imaging modality tools for detection of all precancerous colorectal lesions, colonoscopy is still the gold standard one, being the most commonly performed procedure for CRC screening and surveillance in the United States [11]. Colonoscopy is advantageous in providing a clear visualization of the intestinal mucosal surface and in detecting and preventing CRC through polypectomy. However, since colonoscopy performs a superficial inspection of the mucosa, information from the other colonic layers are missed. Moreover, some patients diagnosed with CRC after a clear recent colonoscopy discloses the fact that a percentage of precancerous lesions could be undetected during the procedure. It is estimated that up to 6% of all CRC cases are caused by undetected polyps that progressed during the period between two colonoscopic procedures [15]. In a multicohort analysis from North American studies, 9167 participants who had adenomas removed during a first colonoscopy were followed until the subsequent colonoscopic procedure. From the 58 interval CRC detected cases, 52% were classified as resultant from probably missed lesions [16], suggesting that nearly half of interval colorectal cancers could be attributed to undetected lesions. In a study evaluating 314,872 colonoscopies performed by 136 gastroenterologists between 1998 and 2010, each 1% increase in the adenoma detection rate was associated with a 5% decrease in the risk of a fatal interval CRC [14], therefore indicating that missed adenomas during colonoscopy increase the CRC incidence and mortality. A recent meta- analysis estimated the general adenoma miss rate of tandem colonoscopies as 21%, when no auxiliary technique was employed in both procedures, and as 29% when the second colonoscopy was performed with an auxiliary technique [17]. These two findings claim that current colonoscopy auxiliary methods can improve the adenoma detection rate and, therefore, there is a need to search for new affordable and sensitive imaging methods to improve CRC diagnosis and follow-up.

Role of Ultrasound Imaging in CRC Diagnosis

Ultrasound (US) is an imaging technique that carries the advantages of being affordable, widely available, able to provide real time images and of not using ionizing radiation. Conventional transabdominal ultrasound can be used to detect colonic diseases and CRC, although it is not the first choice screening method, because it has limited access to the entire colon, caused by tissues and organs interposed between the colon and the probe that block the transmission of the US beam. To overcome this limitation, an endoluminal US transducer can be used in the detection and staging of colorectal lesions. When used to assess *muscularis propria* invasion for rectal cancer staging, the endoluminal ultrasonography has a specificity higher than that of magnetic resonance (86% and 69%, respectively) [18]. Endoluminal US can also be combined with colonoscopy, forming the endoscopic US (EUS) imaging technique. For rectal tumors, EUS and magnetic resonance imaging have been considered the standard staging modalities for several years [19-20] and for early T1 cancers with an option for local excision, EUS is the first choice because of its superior near-field resolution [21].

Using a standard US transducer with a frequency bandwidth of 3.5-17MHz, it is possible to distinguish all concentric layers of the rectal wall: the first echogenic layer is the Epithelium/mucosae, followed by a hypoechoic layer of muscularis mucosae, an echogenic ring of submucosa, an hypoechoic layer of *muscularis propria* and finally the hyperechogenic ring of adventicia/serosa [22]. In order to improve ultrasonic imaging resolution and accurately detect CRC depth, higher US frequencies must be used and that was the case of using 20MHz frequency endoluminal US to determine, accurately, if gastrointestinal tumors were restricted to the mucosa and submucosa layers [23-25]. Ultrasonic techniques using even higher frequencies (40-50MHz), named ultrasound biomicroscopy (UBM), are able to perform imaging of living tissues with near microscopic resolution. UBM using miniaturized endoluminal transducers, named endoluminal UBM (eUBM) and performed simultaneously with colonoscopy has been evaluated in the detection and follow-up of colorectal lesions in murine models of CRC [26-27]. eUBM presented a sensitivity superior to colonoscopy in the detection of colorectal lesions (0.93 and 0.83, respectively) [26] and was able to correctly detect all colonic tumors and lymphoid infiltrates during follow-up [27], suggesting that high frequency endoluminal US could be used combined to colonoscopy, improving polyp detection rates.

US can be associated to ultrasound contrast agents (UCA), usually microbubbles (1-7μm) injected in a peripheral vein, which appear in the target tissue, increasing echogenicity and improving imaging delineation. The combined use of EUS with UCA introduces an image modality named CEUS (contrast-enhanced ultrasound) with improved imaging contrast that allows the visualization of perfusion, enabling real-time assessment and quantification of the colonic microvasculature. UCA flow inside the microvasculature can be measured as time-intensity curves (TIC), based on the time for wash-in and wash-out, allowing to determine the time to peak enhancement and the amount of enhancement [28]. In a clinical evaluation with 51 patients, transabdominal CEUS was able to differentiate between inflammatory bowel diseases and CRC, since colon cancer tissue showed later enhancement and slower wash-out with less speed to reach peak intensity [29]. The ability of a contrast-enhanced endoscopic ultrasound (CE- EUS) to assess vascular perfusion patterns in CRC tissue was also clinically evaluated in 42 patients. In this case, parameters generated from the TIC analysis could predict tumoral N staging and microvascular density, confirmed by CD31 immunostaining, suggesting that CE-EUS represents a feasible imaging technique for real-time angiogenesis measurement that may help in the choice of first-line therapy and the establishment of prognosis [30]. An emerging area of ultrasound imaging is the conjugation of UCAs to antibodies directed to target specific proteins involved in tumorigenesis and inflammation, enabling real-time protein expression measurements. To evaluate CRC vascularization, several studies have associated transabdominal US with Vascular Endothelial Growth Factor

receptor 2 (VEGFR2)-targeted UCAs in murine models, achieving accurate assessments of tumor angiogenesis [31-34].

Photoacoustic (PA) imaging combines laser and ultrasound: transmitted nanosecond pulses of laser light (near infrared or visible) into tissue to yields rapid thermoelastic expansion that emits broadband ultrasound pulses. These pulses are received by an ultrasound transducer to construct a PA image, with contrast determined by optical absorption of tissue components such as hemoglobin, melanin, water or lipids. Because the hemoglobin in blood is a strong optical absorber, PA is suitable for imaging the vasculature and oxygenation, so the magnitude of ultrasonic emission reveals physiological patterns of biological tissues [35]. Recently, a photoacoustic microscopy with acoustic resolution (AR-PAM) was able to detect the typical disorganized tissue structure and distorted vascular distribution of human CRC fresh tissue, in an *ex vivo* analysis, suggesting that PA imaging may assist in CRC diagnosis and therapy monitoring in the future [36].

Conclusion

Current CRC screening techniques based mainly on colonoscopy has halved the mortality of CRC, which nevertheless figures as the second most deadly cancer. Ultrasonic waves have been used in the development of new auxiliary imaging techniques aiming to improve the detection and diagnosis of CRC. In this context, photoacoustic and endoluminal high frequency ultrasound that can be associated to colonoscopy and ultrasound contrast agents, have become promising new tools to accurately detect, diagnose and stage CRC, as well as to monitor tumor vascularization.

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Conflict of Interest Statement

None declared.

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