Three-dimensional ultrasound in the preoperative staging of rectal cancer. State of the art

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Imaging modalities such as endorectal ultrasoundography (ERUS), pelvic magnetic resonance (MRI) and computed tomography play a fundamental role in evaluating rectal cancer preoperatively, planning surgical procedures, and selecting patients for neoadjuvant therapy. Based on the best available evidence, ERUS is recommended to accurately discriminate between T1 and T2 lesions, for low rectal cancer, defined as 0-5cm from the anal verge, if local excision (with transanal endoscopic microsurgery) is considered. MRI is the best modality to detect mesorectal fascia invasion and to predict circumferential resection margin involvement. Both modalities have similar limitations in distinguishing metastatic from benign lymph node in the mesorectum. Due to higher panoramicity and multiplanar reconstruction, three-dimensional ERUS allows to visualize the spatial relationship of the rectal tumor in the context of the surrounding structures, improving the accuracy of ultrasonographic staging. Technological advances and perspectives of ERUS under investigations are represented by real-time color elastography, Doppler US and contrast-enhanced US.

Keywords: Early cancer, endorectal ultrasound, rectal cancer, staging, three-dimensional ultrasound

INTRODUCTION

The great transformation in the management of rectal cancer has increased the importance of accurate preoperative staging on decision-making1,2. Depth of penetration and nodal status in rectal neoplasms guide therapeutic decisions to perform local excision or transanal endoscopic microsurgical excision, to take the patient directly for radical surgery or to offer neoadjuvant chemoradiotherapy (CRT)1,2. Available technologies for accurately staging rectal cancer are computed tomography (CT), magnetic resonance imaging (MRI) and endorectal ultrasound (ERUS)1. ERUS has many advantages over CT and MRI. First the ERUS probe is placed in close proximity to the area of interest and the resolution and imaging quality are thus greatly enhanced. Second it is an office-based procedure of short duration and is well tolerated by patients. Third it is relatively low cost. The recent advent of three-dimensional (3D) US with post-processing modality (Volume Rendering) has further improved the accuracy of this technique3. Due to higher panoramicity, multiplanar reconstruction allows to visualize the spatial relationship of the rectal tumor in the context of the surrounding structures.

In this review, the technical aspects of 3D-ERUS and its influence on the management and outcome of patients with rectal cancer are described.

3D-ERUS TECHNIQUE

Many types of ultrasound probes have been used to evaluate the rectal wall and the adjacent structures. Images are best achieved with mechanical radial transducers with a 360° field of view with a frequency range of 6-16 MHz and a focal length (depth of penetration) of 2-5cm (type 2052, B-K Medical Analogic, Herlev, Denmark)3. Inside the head of the this probe, two crystals are assembled back to back. The assembly can rotate inside the transducer to give a 360° field of view and can be moved inward and outward for a distance of 60mm in 60 seconds for a 3D automatic acquisition. The full length of acquisition is achieved by touching two buttons at the base of the transducer, without any discomfort for the patient and without any movement of the probe within the tissue. The probe is long enough (270mm) to cover the entire length of the rectum and to reach into the sigmoid colon.
The set of 300 aligned transaxial 2D images is instantaneously reconstructed into a high resolution 3D image for real time manipulation and volume rendering. The 3D volume can also be archived for offline analysis on the ultrasonographic system or on PC with the help of dedicated software. It is possible to select coronal, anterior-posterior or posterior-anterior and sagittal right-left views, together with any oblique image plane. The 3D image can be rotated, tilted and sliced to allow the operator to infinitely vary the different section parameters, visualize the lesion at different angles and measure accurately distance, area, angle, and volume. Volume Render Mode (VRM) is a special feature that can be applied to high-resolution 3D data volume so information inside the cube is reconstructed to some extent. By use of a combination of 4 different postprocessing parameters (opacity, luminance, thickness and filter), the volume-rendered image provides better visualization performance when there are not large differences in the signal levels of pathologic structures compared with surrounding tissues.

ERUS is usually performed with the patient positioned in the left lateral decubitus (Sims position). Before inserting the probe into the rectum, a digital rectal examination must be performed to identify size, morphology and location of the tumor, if it is low enough. If there is a stenotic annular lesion, the finger can determine whether it will allow easy passage of the probe. The transducer is covered by a latex balloon (water standoff condom) that is held in place over a transducer collar by two round rubber rings. Before starting the procedure, the balloon is filled with degassed water to remove air bubbles. Inflating the balloon with degassed water during the procedure (at varying volumes, due to different diameters of rectal ampulla) allows acoustic coupling between the transducer and the rectal wall. When using the 2052 probe, it is mandatory to introduce the transducer through a dedicated proctoscope, inserted into the rectum to pass the proximal border of the rectal mass. This also ensures dispersion of the balloon around the tip of ultrasound probe as it extends from the distal tip of the proctoscope. Reusable metal sigmoidoscopes or disposable proctoscope (A.4522, Sapimed, Alessandria, Italy) are available. The use of dedicated proctoscope facilitates the positioning of the probe or easy passage of the probe into strictures as well as observation of its exact localization with respect to the distance from the anal verge. If air, blood or stool gets between the balloon and the rectal wall, it will prevent correct visualization of the rectal wall. To avoid this, a rectal enema is administered two hours before the examination. The rectum can also be gently irrigated prior to passage of the probe. It may, however, be necessary to remove the probe to further irrigate the rectum under direct vision to achieve the complete cleansing of the rectum. The proctoscope and ultrasound probe may then be reintroduced to repeat the ultrasound examination with optimal images. Once the 20cm scored mark on the shaft of the probe is at the proximal end of the proctoscope, the proctoscope is then pulled back on the probe as far as possible, thus exposing the transducer for at least 4 cm beyond the end of the proctoscope. The balloon is then instilled with 30-60cc of water, the volume of fluid usually needed to gain optimal imaging. Higher frequencies provide better resolution of the sphincter muscles and of the rectal wall layers, whereas pararectal tissue and lymph nodes are more accurately assessed using lower frequencies. To achieve the most accurate staging, biopsy should be performed after ERUS or at least three weeks before, otherwise, the accuracy of the exam could be significantly altered by edema or clots that could interfere with the correct evaluation of the case, understaging or overstaging the neoplasm. For a correct examination it is
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of particular importance to keep the probe at the center of the rectal ampulla, with the balloon filled. The entire tumor should be scanned because depth of infiltration could vary at different points of the tumor itself. The perirectal fat is examined for suspicious lymph nodes. The search for lymph nodes should be made in the proximal part of the tumor. 3D spatial reconstruction will aid in the differentiation between nodes and vascular structures.

US ANATOMY OF THE RECTUM

The normal rectum is approximately 15cm in length and has a maximum diameter of 4cm. It is continuous with the sigmoid colon superiorly at the level of the third sacral segment and courses inferiorly along the curve of the sacrum to pass through the pelvic diaphragm and become the anal canal. It is surrounded by fibrofatty tissue that contains blood vessels, nerves, lymphatics and small lymph nodes. The upper third (12-15cm) is covered anteriorly and laterally by the pelvic peritoneum. The middle third (7-11cm) is only covered with peritoneum anteriorly, where it curves anteriorly onto the bladder in the male and onto the uterus in the female. The lower third of the rectum (up to 6cm from the anal verge) is below the peritoneal reflection and is related anteriorly to the bladder base, ureters, seminal vesicles and prostate in male and to the uterus, cervix and vagina in female.

The rectal wall consists of 5 layers surrounded by perirectal fat or serosa. On ultrasound the normal rectal wall is 2-3 mm thick and is composed of a five-layer structure. Good visualization depends on maintaining the probe in the center lumen of the rectum and having adequate distension of a water-filled latex balloon covering the transducer to achieve good acoustic contact with the rectal wall. It is important to eliminate all bubbles within the balloon to avoid artifacts that limit the overall utility of the study. The rectum can be of varying diameters and therefore the volume of water in the balloon may have to be adjusted intermittently. The five layers represent:

1. The first hyperechoic layer: the interface of the balloon with the rectal mucosal surface;
2. The second hyperechoic layer: the mucosa and muscularis mucosae;
3. The third hyperechoic layer: the submucosa;
4. The fourth hyperechoic layer: the muscularis propria (in rare cases seen as 2 layers: inner circular and outer longitudinal layer);
5. The fifth hyperechoic layer: the serosa or the interface with the fibrofatty tissue surrounding the rectum (mesorectum). The mesorectum contains blood vessels, nerves and lymphatics and has an inhomogeneous echo pattern. Very small, round to oval, hypoechoic lymph nodes should be distinguished from blood vessels which also appear as circular hypoechoic structures.

Endorectal US allows an accurate visualization of all pelvic organs adjacent to the rectum: the bladder, seminal vesicles and prostate in male and the uterus, cervix, vagina and urethra in female. Intestinal loops can also easily identified as elongate structures.

PREOPERATIVE US STAGING OF RECTAL CANCER

Rectal tumours appears as hypoechoic lesions that infiltrate, interrupt and distort different wall layers and are staged according to the level of invasion through the rectal wall. The fibrofatty tissue surrounding the rectum contains blood vessels, nerves and lymphatics and has an inhomogeneous echo pattern. Very small, 2-3mm, round to oval hypoechoic lymph nodes may be seen and must be distinguished from blood vessels, which are also circular hypoechoic areas, but when followed longitudinally, they are seen to extend further than the corresponding diameter and can often be seen to branch and elongate in a longitudinal fashion, confirming that this is a blood vessel and not a node. Metastatic lymph nodes appear as hypoechoic round masses in the mesorectal fat. They tend to be larger, not homogeneous and more round, with well-defined borders.

On ERUS, rectal tumors are staged according to the level of invasion through the rectal wall, corresponding to the stages of the TNM classification. To differentiate between ultrasonographic staging and pathologic staging, ultrasound stages are labeled with the prefix “u”:

Stage uT0: Benign lesion or in situ neoplasm;
Stage uT1: Cancer infiltrating submucosa;
Stage uT2: Cancer infiltrating muscularis propia;
Stage uT3: Cancer infiltrating the rectal wall through serosa or perirectal fat;
Stage uT4: Cancer infiltrating perirectal organs or structures
Stage uN0: No regional metastatic nodes
Stage uN1: Metastatic nodes

ERUS criteria to determine the depth of tumor invasion are as follows:

(a) benign lesion (uT0): hypoechoic mass within the second hypoechoic mucosal layer. The submucosal hypoechoic layer remains intact around the entire breadth of the tumor (Fig.1). Carcinoma in situ (pTis) is included in this group because it cannot be differentiated from benign adenoma by ultrasound imaging alone;

(b) submucosal cancer (uT1): tumor invading the submucosal layer. These lesions are stratified into two subtypes: uT1-slight (slightly irregularity of the submucosa) and uT1-massive (massive irregularity). Small focal disruption of the submucosal layer but with the fourth hypoechoic muscular layer intact are also classified as uT1-massive tumor;

(c) lesions with distinct break of the submucosal layer and invasion of the muscular layer (uT2). Sonographic diagnosis of tumor invasion of the muscularis propria is based on thickening of this layer. The muscularis propria is represented by a thin hypoechoic layer adjacent to the hyperechoic submucosal interface. As the tumor is also hypoechoic, early muscular invasion is difficult to detect. The surrounding hyperechoic layer corresponding to the perirectal fat interface remains intact (Fig.2);

(d) perirectal fat invasion (uT3) is diagnosed sonographically by the presence of irregularity of the outer hyperechoic layer that corresponds to the perirectal fat interface (Fig.3). These findings should be associated with disruption of the hyperechoic layer corresponding to the submucosa and thickening of the hyperechoic layer representing the muscularis propria. Distinction can be done between early T3 (<2mm invasion of the perirectal fat) and advanced T3 (>2mm invasion of the perirectal fat). Contiguous organs are not involved;

(e) uT4 lesions are locally invasive into contiguous organs such as bladder, uterus, cervix, vagina, prostate and seminal vesicles. Sonographically there is a loss of the normal hyperechoic interface between the tumor and the adjacent organ. The inability of ERUS to distinguish between malignant infiltration or peritumoral inflammation results in a somewhat lower staging accuracy with regard to T4 cancers. Frank stenosis also precludes precise endosonographic evaluation and angulation of the probe to the tumor axis also can cause misinterpretation;

(f) the sonographic features of lymph nodes generally can be distinguished into four groups: 1) if lymph nodes are not visible by ultrasound, the probability of lymph node metastasis is low; 2) hypoechoic lymph nodes are often benign and result from non-specific inflammatory changes; 3) hypoechoic lymph nodes larger than 5mm are highly suggestive for lymph node metastasis; 4) lymph nodes larger than 5mm with mixed echogenic patterns cannot be classified accurately but should be considered metastatic. The criteria used to identify metastatic lymph nodes in most of the studies are echogenicity, border demarcation and node diameter. Inflamed, enlarged lymph nodes appear hypoechoic, with well defined borders. Most of the sound energy is reflected because the lymphatic tissue has not changed. In contrast, metastatic lymph nodes that have been completely replaced by the tumour do not provide the normal tissue architecture and appear hypoechoic with an echogenicity similar to the primary tumour. Malignant lymph nodes tend to be round in shape rather than oval, have discrete borders and are most commonly found adjacent to the primary tumour or in the mesorectum proximal to the tumour (Fig.4).
Imaging modalities are central to the investigation and management of rectal cancer. Patients with early cancer are candidate to local treatments or radical resections, while patients with advanced tumours need preoperative CRT. Patients exhibiting a good response to neoadjuvant treatments can be directed towards less extensive surgery or minimally invasive alternatives. In order to best achieve all these objectives, imaging should be performed according to state-of-the-art principles. There is, therefore, a need for recommendations regarding the different imaging modalities in the staging of rectal cancer. In 2012 the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) published the guidelines for standardised imaging for staging and restaging of rectal cancer. The guidelines were constructed through consensus amongst 14 abdominal imaging experts and consensus was reached by in 88% of 236 items discussed. There was a 100% agreement that ERUS remains the imaging method of first choice to differentiate between T1 and T2 tumours if local resection is being considered. Regarding the differentiation between T2 and T3 tumours, 67% of agreement was reached that either ERUS or MRI can be used. Positron emission tomography (PET) or PET/CT was not an option for 92% of the experts. For restaging after a long course of CRT, it was agreed that MRI should be performed routinely. A clear consensus was reached that the following items should be included in the imaging report of primary staging: 1) the distance from the anal verge or anorectal junction to the lower pole of the tumour; 2) the tumour length; 3) the T-stage and any tumour deposit within the mesorectum; 4) the smallest distance (mm) between the tumour and the mesorectal fascia; 5) the circumferential location of the tumour within the wall; 5) the N-stage. Regarding nodal assessment, experts all recommended that size in the range of 5-8mm should remain the prime criterion for malignancy. However, no single diameter threshold is sufficiently accurate to differentiate benign from malignant nodes.

Similar recommendations were published by the Cancer Care Ontario Preoperative Assessment for Rectal Cancer Guideline Development Group (GDG), the National Institute for Health and Clinical Excellence (NICE), the New Zealand Guidelines Group (NZGG), the Scottish Intercollegiate Guidelines Network (SIGN), the Program in Evidence-Based Care (PEBC), the American College of Radiology, and the Italian Society of Colorectal Surgery. Based on the best available evidence, ERUS has been recommended to accurately discriminate between T1 and T2 lesions, for low rectal cancer, defined as 0-5cm from the anal verge, if local excision (with transanal excision of transanal endoscopic microsurgery) is being considered. Submucosa and muscularis propria of the rectal wall cannot be consistently differentiated on MRI. ERUS should not be used to predict circumferential resection margin (CRM) involvement. MRI has the best diagnostic accuracy (94%) to detect mesorectal fascia invasion. The importance of CRM status was presented by the Magnetic Resonance Imaging and Rectal Cancer European Equivalence (MERCURY) study as predictor of recurrence and need for neoadjuvant therapy. The results showed that CRM-involved tumours identified by MRI had lower 5-year disease-free and recurrence-free survival. In addition, CRM involvement was associated with metastatic disease. Recent studies, however, have reported that ERUS is able to identify CRM of low rectal tumours confined to the anterior wall, with very good results.

Three-dimensional ERUS offers a significant advantage over conventional 2D-ERUS for the accurate evaluation of rectal cancer. In a preliminary study, Kim et al. (20) showed that the accuracy of 3D-ERUS was 90.9% for pT2 whereas that of 2D-ERUS was 84.8%. Lymph node metastases were accurately predicted by 3D-ERUS in 84.8% of patients, whereas 2D-ERUS predicted the disorder in 66.7%. Although the findings did not show 3D-ERUS to have a statistically significant advantage over 2D-ERUS, stereoscopic visualization provided easier and more complete understanding of lymph nodes. We conducted a prospective study to compare accuracy of 3D-ERUS with high frequency US probe to conventional 2D-ERUS in the preoperative staging of early invasive rectal cancer. Eighty-nine consecutive patients with rectal villous lesions were examined using both imaging modalities. Overall accuracy of the 2D-ERUS-based evaluation of vil-lo-us lesions was lower than that of 3D-ERUS-based evaluation (77.1%, vs. 85.7%). In the evaluation of SM-s lesions the accuracy of 3D-ERUS was significantly superior to 2D-ERUS-based

**FIGURE 4.** THREE-DIMENSIONAL ENDORECTAL ULTRASOUND. METASTATIC LYMPH-NODE (N) VISUALIZED IN THE SAGITTAL PLANE (SEE CRITERIA IN THE TEXT)
evaluation \( (p=0.029) \). These findings showed 3D-ERUS to have a significant advantage over 2D-ERUS for the accurate evaluation of superficial submucosal cancer invasion. Stereoscopic visualization provided easier and more complete understanding of depth of submucosal invasion 6.

Technological advances and perspectives of ERUS are represented by real-time colour elastography, Doppler US and contrast-enhanced US 19. Elastography is a qualitative method that indicates tissue stiffness on colour maps and would help for the differentiation between adenoma and adenocarcinomas 21. Normal rectal wall displays medium stiffness, similar to that of the perirectal fat tissue. Doppler US allows the assessment of the flow rate, flow characteristics, flow direction and flow type. The perirectal vessels and the intramural vessels of the submucosal plexus have a linear aspect without any penetration of the rectal wall. A great number of perirectal tortuous vessels, which penetrate the rectal wall, are considered to be pathological. It would be very useful in post-operative follow-up, enabling the differentiation between residual tumour/tumour recurrence and postoperative scarring. Colour and pulsed Doppler US help differentiate between benign and malignant lymph nodes. Contrast-enhanced US is based on the intravenous administration of contrast agent. This may reveal an inconsistent intake of the contrast medium into tumour area and disease-free area. Aggressive malignant tumours have a high degree of angiogenesis, with marked inhomogeneous imaging in 90% of cases. Large tumours can be characterized by low uptake or lack of uptake due to the presence of intramural necrosis.

In conclusion, 3D-ERUS measures the volume, the exact size of the tumour, identifying its spatial position and the relationships with adjacent tissues. It the best modality for early rectal cancer staging and for the differentiation between malignant tumours and adenomas.

**SUMMARY**

Dijagnostičke procedure kao što su endorektalna ultrasonografija (ERUS), magnetna rezonanca karlice (MRI) i kompjuterizovana tomografija imaju odlučujuću ulogu u preoperativnoj evaluaciji karcinoma rekturna, planiranju hirurške procedura i selekciji pacijenata za preoperativnu terapiju. Prema dosadašnjim podacima, ERUS se preporučuje kao metoda za precizno razlikovanje T1 od T2 lezija, kod niskih karcinoma rekturna, lokalizovanih 0-5 cm od analnog otvora, ukoliko se lokalna ekscizija (transanalna ekscizija ili transanalna endoskopska mikrohirurgiija) razmata kao mogućnost lečenja. MRI je najbolja metoda za detekciju mezorektalne fascije i proceniti njena infiltracija tumorom. Obe metode imaju nedostatke u smislu razlikovanja od metastatskih limfnih žležda u mezorektumu. Zahvaljujući svojim tehničkim mogućnostima, 3D-ultrasonografija je u mogućnosti da nam vizualizuje prostorni odnos tumora rekturna sa okolnim strukturama, što unapređuje tačnost ultrasonografskog stigna-a. Tehnološki napredak i perspektive ERUS predstavljeni su „real-time colour” elastografijom, Doppler ultrasonografijom u kontrastnom ultrasonografijom.

Ključne reči: rani karcinom, endorektalni ultrazvuk, karcinom rekturna, 3d-ultrazvuk

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