Case Report

Current Role of Endoscopic Ultrasonography in Rectal Cancer Evaluation During Multidisciplinary Therapy

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ABSTRACT: We report the case of a patient presenting in the Gastroenterology Department with intermittent rectal bleeding during the past year. A diagnosis of a low rectal adenocarcinoma was based on colonoscopy examination with biopsies, and staging procedures included transrectal endoscopic ultrasonography and magnetic resonance imaging of the abdomen and pelvis (cT2N0M0). Consequently the patient was referred for pre-operative chemoradiotherapy, achieving a complete clinical response as documented by repeated EUS and MRI examinations. Transanal endoscopic microsurgery with pathological assessment of the resected specimen revealed residual adenocarcinoma, highlighting the limitations of current imaging methods, and the constant need of technological improvements.

KEYWORDS: *rectal cancer, staging, endoscopic ultrasonography, magnetic resonance imaging, chemoradiotherapy*

Introduction

Treatment of rectal cancer has seen significant improvements over the last decades and the current concept of management is that of a multidisciplinary care plan involving surgery, chemo- and radiotherapy, as well as the recently added biological therapies with anti-angiogenetic effects (1). Radiotherapy combined with chemotherapy in the neoadjuvant setting has led to improved outcomes related to a better local control of the disease and reduction in both acute and delayed morbidity. Furthermore, patients that show good response to preoperative treatment also have better survival rates (2). Consequently the diagnostic investigations for rectal cancer have evolved as high resolution imaging is essential for accurate evaluation of each patient, enabling an individualized treatment strategy. Current imaging modalities used for preoperative staging of rectal cancer, as well as for re-staging and follow-up include endorectal ultrasonography, magnetic resonance imaging (MRI), computed tomography (CT) and positron emission tomography scan (PET) (3). These should be used as complementary techniques to the best interest of the patient and based on local expertise and availability (4).

Case report

A 39-year-old male patient presented to the Gastroenterology Department complaining of intermittent rectal bleeding for almost a year, without changes in bowel habits, abdominal pain nor any weight loss. His only comorbidity was allergic asthma diagnosed since he was 20 years old, for which he had been taking short-acting bronchodilators. He was a non-smoker and did not acknowledge alcohol consumption. Clinical examination revealed a normal weight patient, in good physical condition, without skin pallor, with blood pressure 120/80 mmHg, pulse rate 68 bpm, and no abdominal pain on palpation. Laboratory investigations showed values between normal ranges, including haemoglobin levels, liver biochemistry, and kidney function tests. Colonoscopy was performed which revealed a rectal tumour located between 3 and 6 cm from the anal verge (Figure 1a). Histopathological examination of the endoscopic biopsies demonstrated a moderately differentiated (G2) invasive adenocarcinoma.

Further diagnostic workup included a transrectal endoscopic ultrasonography (EUS) by using a radial frontal view echoendoscope for local and regional staging, which showed a hypoechoic mass located on the posterior rectal wall with mural invasion limited to the

muscularis propria (T2) (Figure 1b). No lymph nodes were visualized in the tumour vicinity (N0), nor around the iliac vessels. An increased intratumoural vascular signal was detected during Doppler studies, and contrast examination was added to the EUS revealing homogenous arterial tumour enhancement and wash-out in the venous phase (Figure 2a,b).

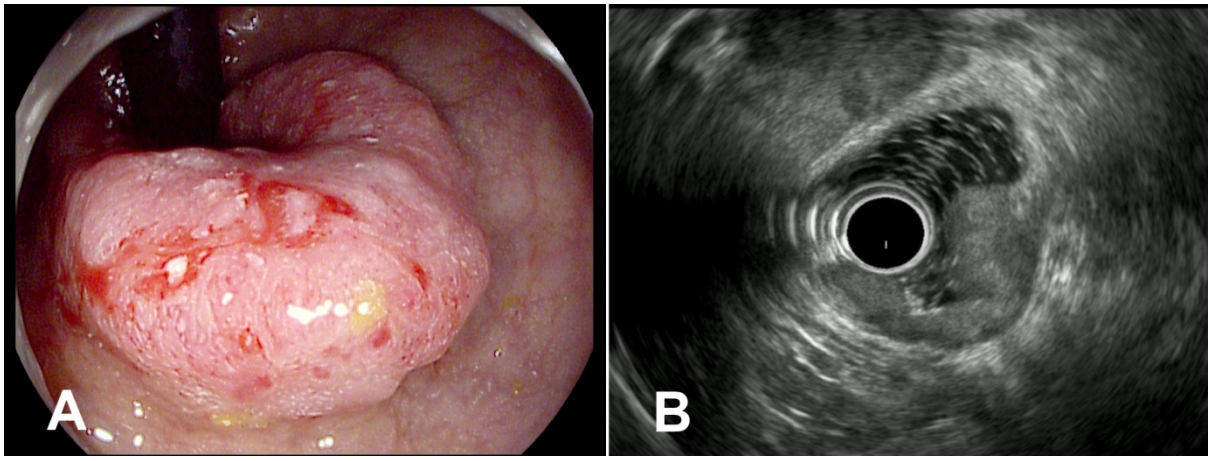

Fig.1.Pretherapeutic imaging of the rectal tumour including (A) high definition colonoscopy (image in retroversion) and (B) transrectal EUS which showed a hypoechoic mass on the posterior rectal wall with invasion limited to the muscularis propria (T2) and no visible perirectal lymph nodes (N0)

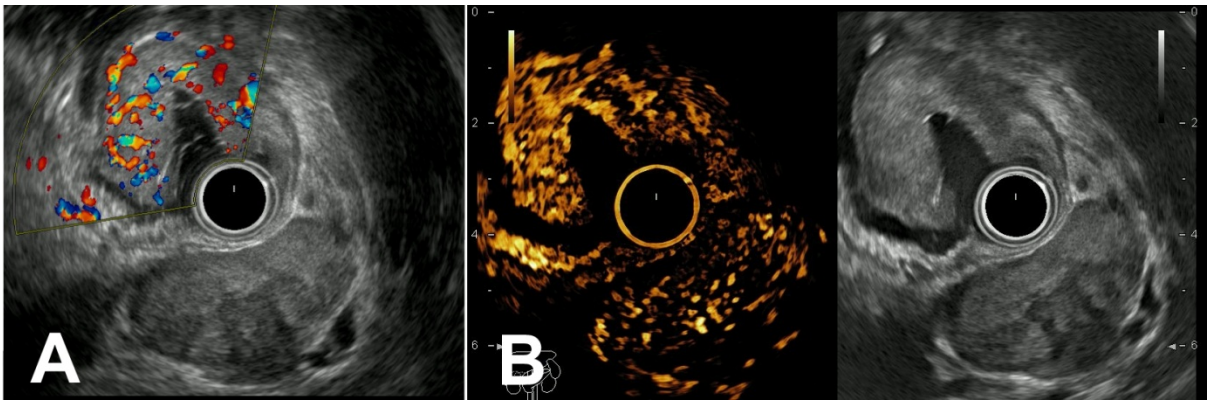

Fig.2. (A) Doppler examination during EUS revealed increased intratumoural vascular signal; (B) Contrast enhanced EUS image showing homogenous tumour enhancement during the arterial phase (contrast image on the left and conventional B mode examination on the right).

Magnetic resonance imaging (MRI) of the abdomen and pelvis was also performed which showed a fatty liver with only a 4 mm cystic lesion in the fifth segment and thickening of the posterior rectal wall mucosa, without any suspicious lymph nodes or peritoneal fluid. Carcinoembryonic antigen levels were between normal ranges.

After consultation with an oncologist the patient was referred for chemoradiotherapy (CRT) with intent to avoid extensive surgery. External radiotherapy was applied in a total dose of 50.4 Gy, 1.8 Gy/fraction by using the volumetric modulated arc therapy (VMAT) technique. Concomitant radiosensitizing chemotherapy with oral capecitabine was administered.

Four weeks after completing CRT we performed EUS for restaging purposes which showed only slight thickening of the mucosa on the posterior rectal wall, just above the anal canal but with all ultrasonographic layers preserved. The anal sphincter appeared normal and also there were no visible perirectal lymph nodes. On endoscopic examination a scar was visible above the dentate line with no residual macroscopic tumour tissue (Figure 3a,b). Multiple biopsies were taken which showed chronic inflammation, some atypia which were classified as reactive, and dilated cystic glands. At MRI examination slight thickening of the posterior rectal wall was also noted post-CRT, but with no suspicious enhancement.

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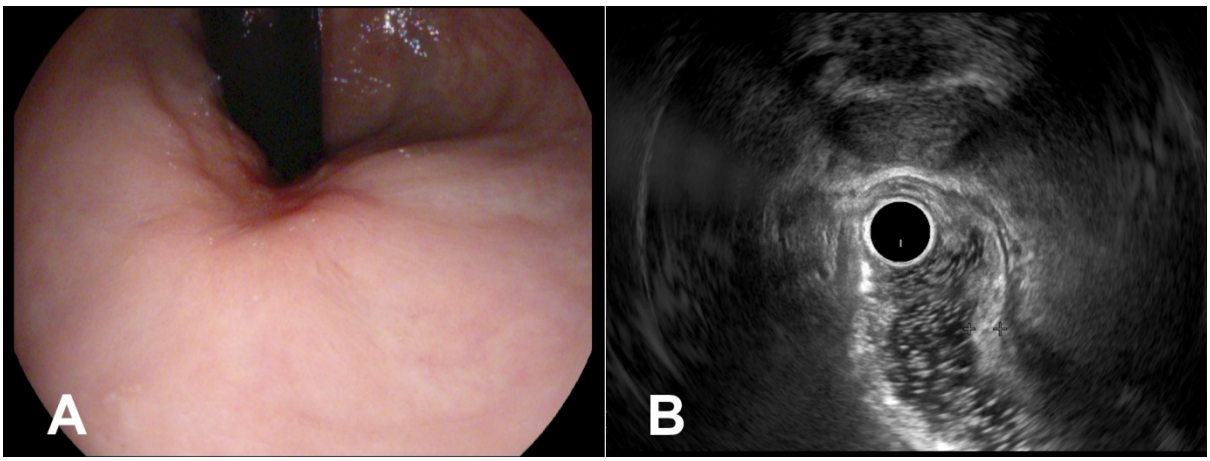

Fig.3. (A) Endoscopic examination after CRT with visible scar above the dentate line and no residual macroscopic tumour tissue; (B) EUS showing slight thickening of the mucosa on the posterior rectal wall (between cross markers)

After consultation with the oncologist and surgeon, transanal endoscopic microsurgery was performed 10 weeks after completing CRT, with excision of a fragment of the rectal wall and mesorectum. Histopathological examination of the surgical sample revealed areas of well differentiated adenocarcinoma infiltrating the muscular layer and the perirectal fatty tissue. There were no signs of perineural, lymphatic or vascular invasion and the resection margins were tumour free. Consequently the case was classified as ypT3NxMx, and further extensive surgery was recommended.

Discussion

Colorectal cancer is an important health burden worldwide, as the third most common cancer in men and the second in women (5). Rectal cancer incidence represents about 35% of the total colorectal cancer incidence, i.e. 15-25/100 000/year (6). During the last few decades treatment of rectal cancer has evolved as a consequence of advances in imaging techniques and therapeutic strategies, and current management is based on a more individualized approach which is best decided by a multidisciplinary team including at least a surgeon, an oncologist, radiotherapist and a radiologist. The introduction of total mesorectal excision (TME) among surgical techniques, and the use of neoadjuvant CRT for improved local control of the disease, have led to significantly better outcomes for the patients (7). With advanced radiation methods integrated into current practice complete clinical response can be obtained preoperatively, and with less acute and late toxicity (2). Accurate staging is therefore mandatory both for the initial diagnosis as well as for re-staging after CRT and for patient follow-up. Available methods include CT scans mainly for assessment of distant metastases, MRI, transrectal EUS and positron-emission tomography (PET-CT) (6).

Transrectal ultrasound has been widely used for staging rectal tumours as it represents a fast, well tolerated and accurate method of investigation. It can be performed either with a rigid probe or with a flexible echoendoscope. The advantage of using flexible probes lies in the possibility of imaging more proximal tumours and also assessing lymph nodes along the iliac vessels, offering additional prognostic information (4). Furthermore, the newly developed forward-viewing radial echoendoscope can safely reach lesions located along the entire length of the colon (8). With its ability to depict all layers of the rectal wall EUS can evaluate the depth of tumour invasion (T stage) with high accuracy, ranging in recent studies between 80 and 95% (3), but best performances have been observed for early rectal cancer. For lymph node evaluation EUS is less accurate, with reported rates of 64 to 83% (9). Recent developments in EUS technology have the potential to enhance diagnosis, such as 3-dimensional reconstructions which seem to improve accuracy rates for both T and N staging as compared to conventional EUS (10), or the modules for elastography and contrast enhancement which can offer additional information on the elastic properties, and tumour vascularization, respectively (4). Contrast enhanced EUS enables characterization of lesions based on the vascular enhancement and quantification of perfusion, and although experience in colorectal cancer is currently

limited (11,12) it might prove to be a valuable functional imaging tool by offering prognostic information and predicting tumour response to CRT, based on further research. In the presented case the rectal tumour was well vascularized, as shown by Doppler studies and by using contrast examination during EUS, a feature that might explain the clinical response to CRT, as the radiosensitizing agent can be better delivered to a well vascularized tumour. Follow-up studies on the prognostic role of contrast-enhanced EUS, with the possibility of quantitative assessment of the vascular changes before, and during therapy should be encouraged.

Rectal staging by MRI can be performed with a phased-array surface coil or an endorectal coil, with the latter showing slight better accuracy rates for T staging in some studies (71%-91% as compared to 65%-86% for the surface coil) (9,13). While the use of endorectal coils is hampered by some technical limitations, recent data have shown that 3.0-T MRI with surface coils can improve both tumour and nodal staging accuracy (14,15). Moreover, MRI is particularly useful for the examination of more advanced tumours (T3 and T4), and can also accurately assess the circumferential resection margin (CRM) involvement, an important factor for surgery planning, making up for some of the limitations of EUS.

While preoperative CRT has been widely adopted for rectal cancer, as a means of down-staging the tumour, and improving prognosis, restaging after neoadjuvant treatment is still rather challenging with current imaging modalities, as radiation-induced change are difficult to differentiate from the actual residual tumour. EUS is prone to overstaging the tumour and is not among recommended procedures (6), although it has a better performance in identifying persistent lymph nodes after CRT. The use of MRI for restaging is also suboptimal with poor accuracies for predicting both ypT and ypN, but the recent technology developments, such as diffusion weighted MRI, the use of lymph-nodes specific contrast or perfusion MRI, could possibly improve results (3).

We presented a case of a rectal adenocarcinoma diagnosed in a 39 year-old patient, with complete clinical response to neoadjuvant CRT, as shown by current imaging studies, but with residual tumour on the resected fragment demonstrated by histopathology, as the golden standard. In spite of the increased resolution and additional techniques EUS is not able to detect small deposits of tumour tissue, and we must acknowledge the current limitations of imaging methods while trying to find better alternatives.

A 'watch and wait' protocol has been proposed for patients with complete clinical response after neoadjuvant CRT, in order to spare them from major surgical interventions and morbidity related to such procedures. This approach requires extremely close follow-up with digital rectal examination, rigid proctoscopy, and also new studies (possibly MRI, contrast-enhanced ultrasound, PET-CT), with radical surgery to be performed at any sign of recurrence. However such strategies are currently not evidence based and should not be encouraged outside of a clinical trial (16). Caution is warranted also because complete clinical response does not necessarily imply a complete pathological response, with only 25% to 30% rate of concordance reported between the two concepts (17,18), and in our case, although the imaging studies results were favourable, showing complete clinical remission, histopathological examination of the resected specimen demonstrated residual microscopic adenocarcinoma, highlighting the limitations of re-staging after CRT. The risks and benefits of an active observation approach should be defined by large prospective follow-up studies, based on consistent inclusion criteria.

In the future, changing the paradigm from radical surgical strategies to more conservative approaches will only be possible with advances in imaging procedures and increasing confidence in their ability to accurately re-stage tumours after neoadjuvant therapy, while the solution to these unmet needs will probably arise from the complementary use of both morphological and functional imaging studies, that can deliver the most reliable information.

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