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Case Series

Submucosal Regrowths after Watch and Wait in Rectal Cancer: A Case Series

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Abstract

This article aims to create awareness about the possibility of submucosal regrowth in neoadjuvant-treated rectal cancer patients managed non-operatively as a new alternative to the far more common intraluminal regrowth's. Additionally, it highlights the important role of MRI in the follow up of these patients. Three patients who achieved a complete clinical response (cCR) after neoadjuvant (chemo) radiotherapy developed a rectal cancer regrowth in the submucosal layer without any signs of intraluminal disease. These regrowth's were primarily diagnosed by MRI including diffusion-weighed imaging (DWI) whereas concomitant endoscopy and digital rectal examination did not reveal any regrowth. All three patients were operated and the presence of an adenocarcinoma in the rectal wall was confirmed by pathological analysis. Although uncommon, these cases show that a regrowth can occur in the submucosal layer, while being undetectable in the lumen. Importantly, MRI played a fundamental role in diagnosing these regrowth's at a very early stage.

Keywords: Magnetic Resonance Imaging (MRI); Non-Operative Management; Regrowths; Submucosa; "Watch and Wait"

Introduction

In the past years organ-preserving management of rectal cancer has become increasingly popular. The Watch and Wait (W&W) strategy as an alternative to surgical resection for rectal cancer derives from the preliminary study of Angelita Habr-Gama [1] and its clinical relevance has internationally been supported by multiple studies in the years thereafter [2-6]. The main goal of this approach is to preserve the rectum and subsequently prevent the surgery-related complications that can occur in up to 35% of operated patients. Rectal cancer surgery is associated with mortality as well as with short and long term complications that can permanently affect patients' quality of life [7]. In the Netherlands, patients with stage II (T3cd-4 N0) and III (T any N1-2) rectal cancer are treated with neoadjuvant (chemo) radiotherapy (nCRT), according to either the national guidelines or prospective trials [8]. In particular, patients with stage II rectal cancer are commonly offered Short-Course radiotherapy (SCRT, 5 x 5 Gy) followed by subsequent resection or delayed surgery as it has been shown to reduce the risk

of recurrences and increase long-term survival compared to surgery alone [8-10]. On the other hand, stage III patients with high-risk morphological characteristics (mesorectal fascia involvement, extramural vascular invasion (EMVI) or extramesorectal disease) are treated pre-operatively with long course chemo radiotherapy (LCCRT, 25 x 2 Gy + concomitant twice-daily capecitabine 825 mg/m2) in order to reduce the tumour volume and increase the rate of R0 resections [8]. Based on the evaluation of the response to pre-operative treatments, patients with residual tumour are operated with Total Mesorectal Excision (TME) while those with a clinical complete response (cCR) enter a strict follow up protocol according to the principles of W&W, nowadays still exclusively offered in the context of clinical studies. Surveillance after cCR consists of periodic digital rectal examination (DRE), rectoscopy and magnetic resonance imaging (MRI) [6,11-14]. In more recent years, MRI is increasingly being used together with diffusion-weighed imaging (DWI) [3,15]. Combined, these investigations are aimed at early detection of potential regrowth's. Although most patients achieving a cCR experience a sustained response over time, between 15 to 30% [1,2,11,13,16,17] of patients develop a regrowth, most likely in the first 2 to 3 years of follow up [11,13,16,17]. Traditionally, a regrowth is diagnosed in the rectal lumen although mesorectal and more rarely pelvic regrowth's have also been described in literature [11,13]. In this article, we discuss three patients who were successfully treated with nCRT for rectal cancer. After achieving a cCR, all three patients were managed non-operatively and developed a submucosal regrowth during follow up. Interestingly, no signs of regrowth were visible in the rectal lumen. All three patients are included in the Wait and See Trial (registered as NCT03426397) and one patient is registered in the International Watch and Wait Database (IWWD). The Wait and See Trial is an ongoing Netherlands and Belgium-wide prospective observational study including patients with any stage, pathology-confirmed, primary rectal cancer who have achieved cCR after undergoing neoadjuvant LCRCT or SCRT with delay. All included patients are evaluated for response to nCRT with DRE, endoscopy and MRI 1.5 or 3.0 Tesla including DWI. Follow up lasts 5 years and consists of periodic DRE, carcinoembryonic antigen (CEA) measurements, rectoscopy and MRI. Additionally, for the first 3 years total-body CT scans are performed to exclude distant metastases. The IWWD is an international registry that collects retrospective and prospective data of patients who have not been operated for a rectal cancer of any stage after neoadjuvant treatment, irrespective of the type of treatment and of the reason why surgery has been omitted. Collected data is used to provide better understanding of the risks, benefits and outcomes of W&W approaches, both oncological and functional. The database is coordinated by the Clinical Research Centre of the Leiden University Medical Centre (LUMC) [18].

Case Specifics

Three patients have been treated in the Leiden University Medical Centre (LUMC) in Leiden, the Netherlands, between March 2019 and December 2020. The LUMC is a tertiary referral centre for organ preservation strategies in rectal cancer patients.

Case 1

Firstly, we present a 43-year-old woman who was diagnosed with a cT3N1M0 rectal adenocarcinoma. The patient had a history of Irritable Bowel Syndrome and rectal bleedings that were neglected for years and were eventually investigated with a colonoscopy. Among the three removed polyps, only a rectal semi-circular lesion of 4 cm at a distance of 8.5 cm from the anorectal junction was malignant. The histological analysis reported a well differentiated, mismatch repair proficient (MMRp) adenocarcinoma. At the time of diagnosis the tumour reached the perirectal fat, one mesorectal node had malignant features, no distant metastases were detected in the thorax and abdomen and CEA was <1 mcg/l. The patient received SCRT (5 x 5 Gy) followed by re-assessment after 7 weeks after the end of radiotherapy, according to the schedule presented in the Stockholm III trial [10]. At the time of restaging, both the MRI and the endoscopy showed a non-suspicious scar at the former location of the tumour, CEA was 0.8 mcg/l, while DRE was difficult to perform given the location of the original tumour. For that reason, it has been decided together with the patient to proceed with a non-operative management according to the W&W principles. Six months after the end of radiotherapy, both the rectoscopy and the MRI confirmed a cCR. At nine months follow up, the MRI described a small hyperintense rectum wall thickening with diffusion restriction, while the rectoscopy reported a sustained cCR. This finding was confirmed by the MRI performed three months later (Figure 1a and b), at which time the rectoscopy confirmed the presence of an intraluminal regrowth (Figure 1c and d). After discussing the case within the multidisciplinary panel and with the patient, it was agreed to perform a laparoscopic Low Anterior Resection (LAR). Surgery was well tolerated and no major complications arose. However, symptoms as pain, fatigue and alteration of the defecation patterns in terms of consistence, frequency and urgency persisted for months. The pathology report on the surgical specimen confirmed the presence of a well differentiated ypT2N0 rectal adenocarcinoma, without (lymph) vascular invasion (Figure 1e). The most relevant interventions and investigations are summarised in chronological order in Figure 2.

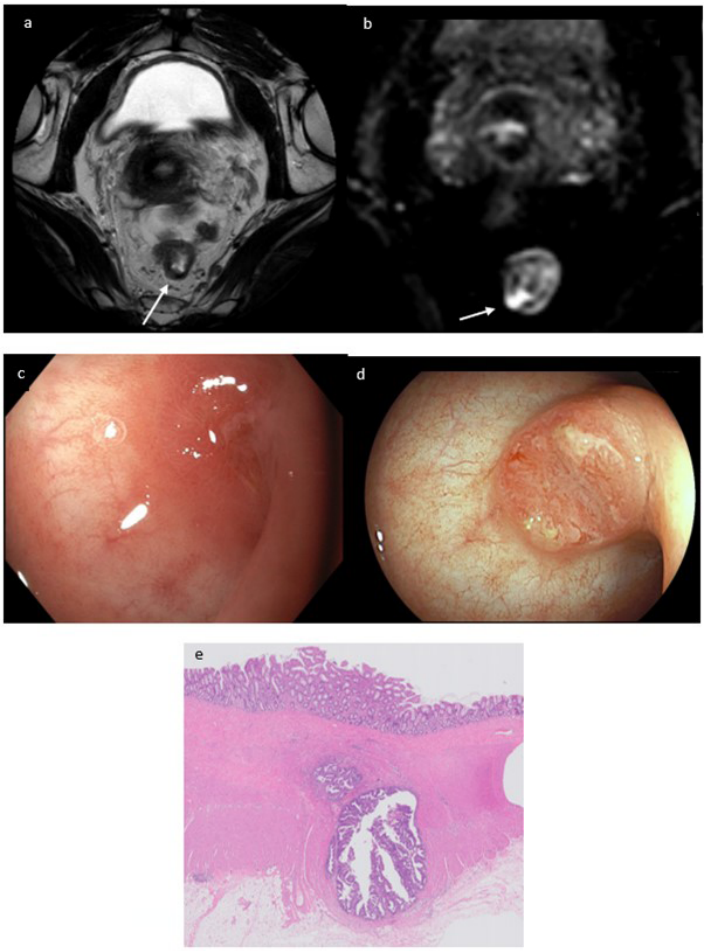

Figure 1: Patient 1. (a) T2 transversal Multicoil MRI image and (b) DWI MRI image from the MRI investigation that identified the submucosal regrowth (white arrows). Endoscopic images taken during (c) the last rectoscopy that confirmed a cCR and (d) the rectoscopy performed at the time of radiological detection of a submucosal regrowth. (e) H&E stained slide showing a slightly irregular, but non-dysplastic mucosal surface and fibrosis of the submucosal stroma, extending in the muscular wall. The low-grade intestinal adenocarcinoma is situated in the muscular wall reaching up to, but not infiltrating the perimuscular fat tissue. The tumour is sharply demarcated and not surrounded with abundant desmoplastic stroma or lymphocytic infiltrate. There is no associated (lympho) vascular invasion or perineural invasion. cCR = clinical Complete Response; DWI = Diffusion Weighed Imaging; H&E = Haematoxylin and eosin.

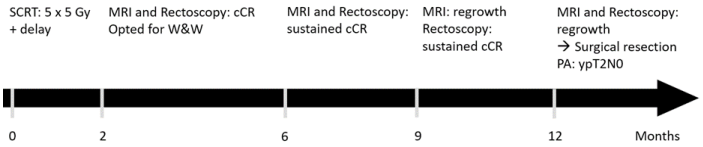

Figure 2: Patient 1. Timeline of the most relevant interventions and investigations. SCRT = Short Course Radiotherapy; cCR = clinical Complete Response; W&W = Watch and Wait

Case 2

The second patient is a man aged 50 years without comorbidities. Because of rectal bleedings and an alteration of defecation patterns, a MRI was performed that led to the diagnosis of a cT3N1M0 rectal cancer without high risk characteristics at 6 cm distance from the anal verge. At the time of diagnosis, the colonoscopy showed multiple polyps in the colon and confirmed the presence of a rectal adenocarcinoma and CEA was 3.2 mcg/l. Given the characteristics and the stadium of the tumour, this patient received SCRT with delay. Eleven weeks after the completion of SCRT, the rectoscopy reported a cCR while on MRI images a non-specific residual thickening of the rectal wall was described. Therefore, the multidisciplinary panel suggested to prolong the waiting period and the MRI performed at 15 weeks after the end of SCRT also confirmed the cCR. Thirteen months after the completion of SCRT, the MRI report described a small rectal wall thickening that grew into the mesorectal fat tissue with hyperintense T2 signal and diffusion restriction (Figure 3a and b), compatible with a regrowth that was not visible at the concomitant rectoscopy. Based on the results of the MRI, an echo-endoscopy-guided biopsy was performed within three weeks (Figure 3c and d) and pathological examination of the biopsy confirmed presence of malignant cells. The CEA at the same time point was 2.4 mcg/l, which did not differ from the previous measurement. Agreement was found among the multidisciplinary panel and the patient for laparoscopic LAR, which caused no major complications. The pathological report described a ypT3N0 rectal adenocarcinoma. However, no alteration of the rectal mucosa was visible at macroscopical evaluation of the surgical specimen. The most relevant interventions and investigations are summarised in chronological order in Figure 4.

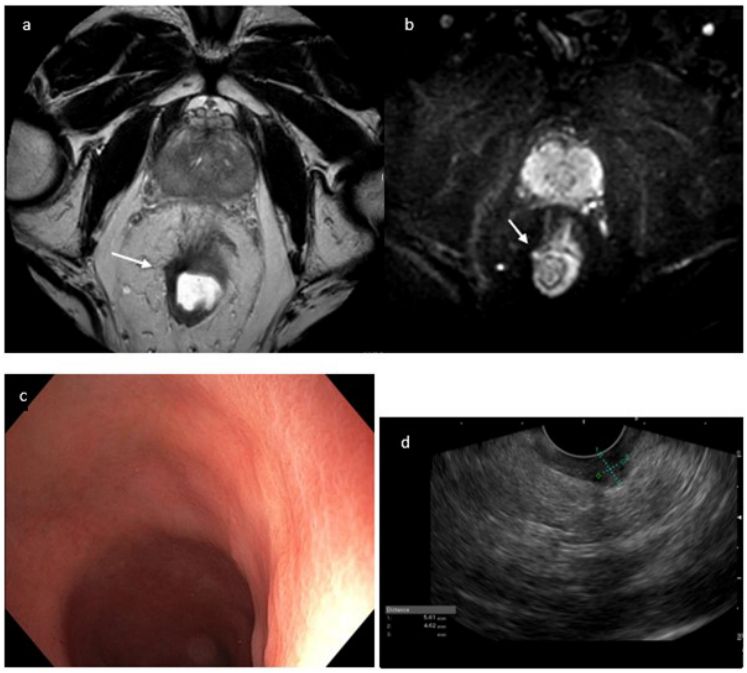

Figure 3: Patient 2. (a) T2 transversal Multicoil MRI image and (b) DWI MRI image from the MRI investigation that identified the submucosal regrowth (white arrows). echo-endoscopic images taken during (c) the last rectoscopy that confirmed appearance of cCR and (d) the echo-endoscopy performed at the time of detection of a submucosal regrowth on MRI. The echo-endoscopy shows a 5,5 x 4,5 mm hypoechogenic alteration in the submucosa that reaches to the muscular layer (green dotted lines). cCR = clinical Complete Response; DWI = Diffusion Weighed Imaging

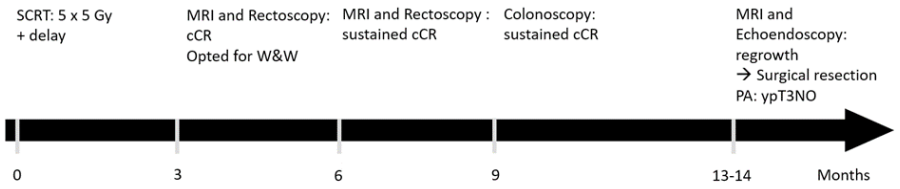

Figure 4: Patient 2. Timeline of the most relevant interventions and investigations. SCRT = Short Course Radiotherapy; cCR = clinical Complete Response; W&W = Watch and Wait

Case 3

The third patient is a woman aged 59 years with a history of hypertension and hip prostheses. During the colonoscopy performed in the context of national CRC screening a voluminous polyp with a diameter of 40 mm was detected at 10 cm from the anal verge. The polyp was resected with a endoscopic submucosal dissection (ESD). The pathology report described a well differentiated, MMR-proficient adenocarcinoma which developed within a tubulo-villous adenoma. The tumour invaded the deep resection margins, which hampered the definition of a precise T stage and defined the intervention as non-radical. Subsequent radiological investigations detected possible tumour invasion into the perirectal fat and two suspicious mesorectal nodes (cT2-3N1). Therefore neoadjuvant treatment was advocated and the patient received LCCRT (25 x 2 Gy + concomitant twice-daily capecitabine 825 mg/m2). CEA level was 3.0 mcg/l and 2.2 mcg/l before and after nCRT, respectively. At reassessment six weeks after the last radiotherapy administration, both the MRI and the endoscopy described a cCR. Based on the good response to nCRT, a non-operative management was chosen and the patient was included in the Wait and See Trial. The MRI performed at 18 months follow-up described for the first time a regrowth-suspicious wall thickening (Figure 5a and b), while the endoscopy performed at the same time point did not show any tumour growth (Figure 5c). The echo-endoscopy performed thereafter confirmed the presence of a submucosal lymph node (Figure 5d) and pathological examination of the biopsy taken in the same session confirmed the presence of malignant cells. CEA

level was 2.4 mcg/l. The multidisciplinary panel and the patient agreed on laparoscopic LAR with permanent colostomy. The post-operative course was characterised by perioperative ureteral injury that was treated laparotomically within one week. The pathology report of the surgical specimen described a ypT2N1b low grade rectal adenocarcinoma. In particular the report described a 2.0 cm-large tumour in the rectal wall with lymph vascular and extramural vascular invasion, two metastatic lymph nodes and one tumour deposit in the perirectal fat tissue (Figure 5e and f). Despite the multiple high risk features for nodal and distant metastases, none have been detected at this point. The most relevant interventions and investigations are summarised in chronological order in Figure 6.

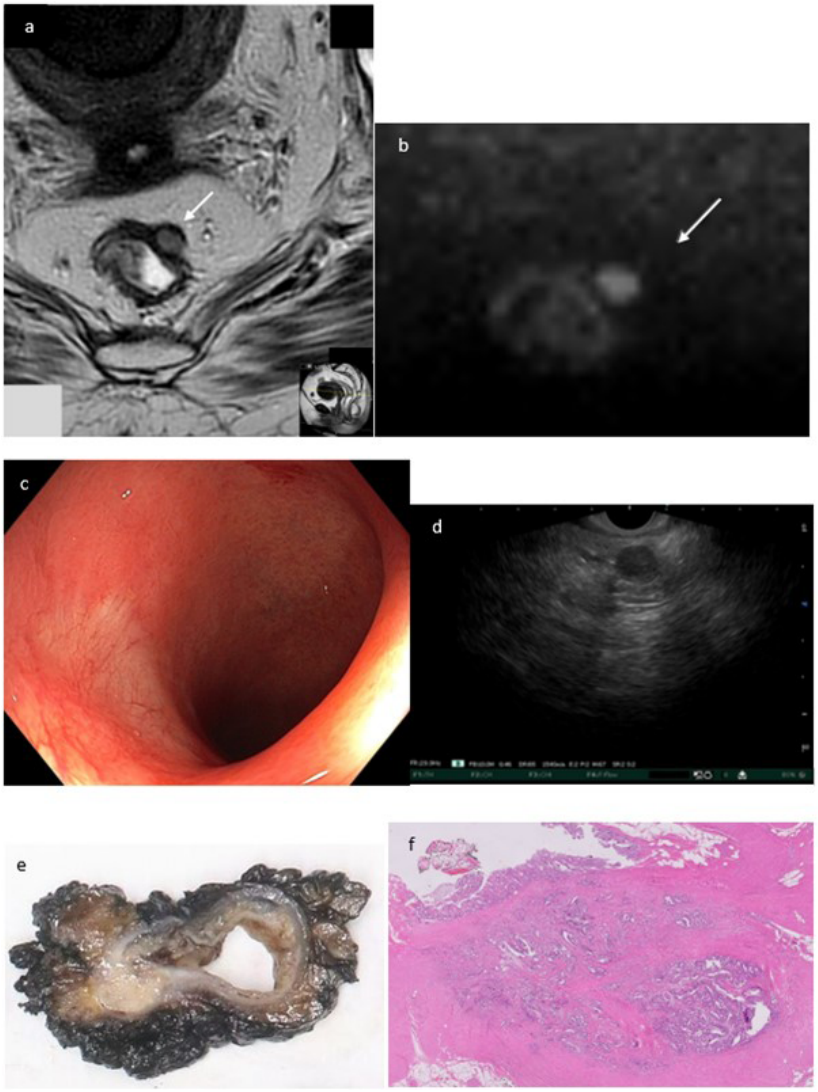

Figure 5: Patient 3. (a) T2 transversal Multicoil MRI image and (b) DWI MRI image from the MRI investigation that confirmed the development of a submucosal regrowth. (Echo) endoscopic images taken during (c) the last rectoscopy that confirmed appearance of cCR and (d) the echo-endoscopy performed at the time of detection of a submucosal regrowth on MRI. The echo-endoscopy shows a 12mm submucosal lymph node. (e) Photography of a section of the surgical specimen that macroscopically shows a neoplastic lesion without direct contact with the mucosal layer. (f) H&E stained slide with regular intestinal mucosa. The clearly demarcated intestinal adenocarcinoma is situated in the submucosa and extends to the muscular layer. cCR = clinical Complete Response; DWI = Diffusion Weighed Imaging; H&E = Haematoxylin and eosin.

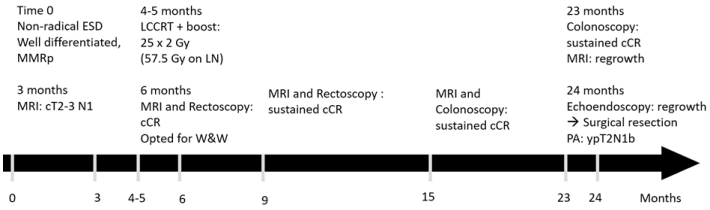

Figure 6: Patient 3. Timeline of the most relevant interventions and investigations. ESD = Endoscopic Submucosal Dissection; MMRp = Mismatch Repair proficient; LCCRT = Long Course Chemo-Radiotherapy; LN = Lymph Nodes; cCR = clinical Complete Response; W&W = Watch and Wait

Discussion

While regrowth's are most commonly detected intraluminal through endoscopy and DRE, these three cases show that MRI together with DWI and a dedicated radiologist play an important role in finding regrowth. The location of these "Regrowth's" represents the most innovative aspect of the presented cases, as submucosal regrowth's are rare and to our knowledge they have not been previously described in scientific literature. In fact, the rational for W&W strategy implies that the tumour shrinks towards the mucosa in response to nCRT [19,20]. This theory is supported by numerous studies reporting intraluminal regrowth's [2,5,11,13,17,21,22] and explains the major importance of DRE and endoscopy during surveillance. To our knowledge, very few studies report alternative locations within the bowel wall and no description of their clinical implications is given. In a report from Renehan et al, one submucosal regrowth has been mentioned among 44 patients who were treated non-operatively, but no description has been given of the lesion and of how it was detected and managed [5]. Moreover, two ex-vivo studies report residual cancer cells (RCCs) after nCRT in the deeper layers of the rectal wall while they are missing in the mucosa. In particular, in 73 of 237 surgical samples from patients in both cohorts, RCCs are present in the submucosa while no cancer cells were found in the mucosa and, in 116 patient with ypT2-T4, RCCs were absent in both the mucosa and the submucosa. No correlations with the clinical situation of these patients were disclosed [19,23]. The most likely explanation for the development of regrowth's is the survival of small clusters of RCCs that cannot be identified by the most common surveillance investigations. After the discontinuation of nCRT, these cells are no longer subject to cytotoxic treatments and some restart their uncontrolled duplication. This theory is supported by the commonality of location and histopathological features between the original tumours and the regrowth's in the three presented patients. Additionally, the mechanism of fragmentation offers a possible theoretical explanation to this theory. In this scenario, small clusters of few cancer cells scatter throughout the original tumour bed in response to CRT. These fragments surrounded by abundant fibrotic tissue can be detected in all the layers that had originally been invaded by the tumour. Fragmentation is a common alternative response to the better known and more desirable shrinking of the cancer towards the lumen and can be demonstrated in 40 to 80% of locally advanced rectal cancers [16]. An alternative explanation would be the development of new tumours within the submucosa. However, this collides with the similarities found between the initial tumours and the regrowth's.

Submucosal regrowth's have so far been described in oesophageal cancer, both for squamous cells carcinoma and for adenocarcinoma. In a cohort of 71 non-complete responders to nCRT, 11 (15%) had RCCs in deeper layers of the oesophageal wall while they were absent in the mucosa. Three of these patients had RCCs exclusively in the submucosa [24]. In order to exclude submucosal "Regrowth's" double biopsies in the same locations in the former tumour bed are recommended. The so called bite-on-bite biopsies account for specimens of both the mucosal and the submucosal layers even in the absence of suspect superficial lesions [25]. The findings presented in this article suggest that the follow up for complete responders after nCRT should take into account the possibility of regrowth's in uncommon locations. In fact, despite the oncological safety of W&W with a 5-year overall survival of 85% [17], the 15 to 30% [1,2,11,13,16,17,21] rate of regrowth's is still a concerning aspect and effort should be made towards early detection. As it is widely accepted that early diagnosis could lead to more favourable oncological outcomes, it is important to have a multidisciplinary team of dedicated medical specialists being responsible for the follow up of these patients. These findings underline the important role of MRI and the experience of a dedicated radiologist in the evaluation of response after nCRT, the determination of cCR and the follow up of rectal cancer patients. Such small submucosal regrowth's could be detected by an expert radiologist on MRI T2-images with the aid of DWI. However, they were not detectable by DRE and rectoscopy, which at the time of radiological diagnosis concluded there was a sustained cCR. Due to the increasing experience of radiologists and technical improvements of MRI and DWI after nCRT, a regrowth could effectively be diagnosed at an early stage. Lastly, these findings could suggest to perform an echo endoscopy in case of a radiological suspicion of submucosal regrowth in order to anticipate a possible intervention if the regrowth is confirmed. However, the real costs and benefits of these recommendations should be studied in bigger cohorts. Constant evaluation of the results of the W&W program is mandatory. The role of all modalities in the follow up schedule (physical examination, endoscopy and MRI) should be under constant evaluation. Furthermore, the implementation of new techniques will be investigated and will hopefully further improve the results of organ preserving treatments in rectal cancer patients. In conclusion, all specialists involved in treating patients

with rectal cancer managed according to W&W principles should be aware of the possibility of developing a submucosal regrowth during follow up. In order to improve the quality of the care for the increasing number of patients treated according to the W&W strategy, the institution of dedicated referral centres and multidisciplinary teams is advocated.

Conflict of interest: The authors have no conflicts of interests to declare that are relevant to the content of this article.

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Ethical Approval: The three patients whose data was used within this publication have given written consent to the anonymous use of their clinical information, radiological and pathological images.

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