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Surgical decision-making following neoadjuvant immunotherapy for dMMR rectal cancer; case reports and review of the literature

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Introduction

Treatment options in locally advanced rectal cancer are rapidly evolving and standards of care have considerably changed during the last few decades [1]. Neoadjuvant short-course or long-course radiotherapy, with or without concomitant chemotherapy, combined with total mesorectal excision-based surgery has increased complete response (CR) rates, decreased local recurrence rates and increased survival rates [2]. In the Nordic health care setting, the RAPIDO concept based on short-course (5 Gy x 5) radiotherapy followed by four cycles of Capecitabine and Oxaliplatin has been implemented as standard of care for locally advanced rectal cancer [3].

Deficient mismatch-repair (dMMR) characterizes 15–20% of right-sided colon cancers and about 3% of rectal cancers, where it signifies an underlying germline alteration compatible with Lynch syndrome in 90% of the cases [4]. In rectal cancer, dMMR represents a negative predictor of pathologic CR (pCR) after standard treatment with chemoradiation. Further, the addition of radiotherapy and chemotherapy may not provide survival benefit in these patients and disease progression has been demonstrated in a subset of locally advanced dMMR rectal cancers during neoadjuvant FOLFOX treatment [5–7].

dMMR tumors have a high mutational burden with multiple missense, indel and frameshift mutations, which result in a high number of neoantigens and an immunogenic phenotype with a high number of tumor-infiltrating lymphocytes. In colorectal cancer dMMR therefore represents an actionable predictive biomarker for immunotherapy with checkpoint inhibitors. The Checkmate 142 study evaluated combination therapy with the anti-CTLA4 antibody ipilimumab and the anti-PD1 antibody nivolumab in patients with advanced dMMR tumors. The study demonstrated 69% objective responses and 13% CR and established a role for immunotherapy in dMMR colorectal cancer where other therapies had failed [8,9]. The KEYNOTE-177 trial introduced immunotherapy in the first-line setting in treatment-naïve patients with dMMR metastatic colorectal cancer. The results

led to a shift in first-line treatment principles for metastatic dMMR colorectal cancer with 16.5 months progression-free survival for patients treated with pembrolizumab (200 mg every 3 weeks) compared to 8.2 months for chemotherapy and CR in 13.1% of patients treated with pembrolizumab compared to 3.9% with chemotherapy [10].

Further trials moved immunotherapy into the neoadjuvant setting. The NICHE trials investigated the effect from treatment with one dose of ipilimumab (1 mg/kg) and two doses of nivolumab (3 mg/kg) followed by surgery with 6 weeks in non-metastatic colon cancers. The results were impressive with major pathological responses in 97%, pCR in 69% and no disease recurrences in the dMMR colon cancer cohort [11–13]. Perhaps the most remarkable results come from limited-sized, investigator-initiated trial with 6 months of neoadjuvant dostarlimab in patients with stage II–III dMMR rectal cancer [14]. This trial aimed to administer standard chemoradiotherapy and surgery unless patients received CR after neoadjuvant immunotherapy with the primary endpoints sustained complete response 12 months after neoadjuvant immunotherapy or pCR. After minimum 6 months follow-up of the first 12 patients treated all patients showed clinical CR with no patient yet undergoing chemoradiotherapy or surgery [14].

At present, neoadjuvant immunotherapy is suggestive as a new standard approach in dMMR locally advanced rectal cancer. Data are, however, restricted to case reports and a limited-sized, single-institution trial with additional studies ongoing (Table 1) [14–20]. These developments imply new and highly promising treatment alternatives for patients with Lynch syndrome, though long-term follow-up will be needed to define the exact role of immunotherapy in the future treatment algorithm for dMMR rectal cancer [21]. We here report the outcome of neoadjuvant immunotherapy with pembrolizumab in two patients with locally advanced rectal cancer to add to the growing data on efficacy of immunotherapy in operable rectal cancer.

Table 1. Summary of patients with dMMR rectal cancer reported with neoadjuvant immunotherapy.

Age/sex	Lynch syndrome	Tumor Stage	Mesorectal fascia involved	Treatment	Treatment cycles	Radiologic response	Definitive surgery	Pathologic response	Clinical response	Reference
27/male	yes	T4bN2 ^a	Yes	Nivolumab (3 mg/kg)	6	CR	yes	ypT0N0	CR	Zhang et al. 2017
62/female	yes	T4bN2 ^a	No	#Nivolumab (3 mg/kg)	6	CR	no	–	CR	Zhang et al. 2017
27/female	yes	T3N2 ^a	Yes	Ipilimumab (1 mg/kg) and nivolumab (3 mg/kg)	2	CR	yes	ypT0N0	CR	Mans et al. 2020
81/male	NA	T3cN1/T1-2N0	Yes	followed by nivolumab Pembrolizumab (200 mg)	11	CR	no	–	CR	Demisse et al. 2020
55/male	yes	T3cN1	Yes	*Ipilimumab (1 mg/kg) and nivolumab (3 mg/kg)	3	CR	no	–	CR	Demisse et al. 2020
				followed by maintenance with nivolumab	7					
38/female	yes	T3N2M0	Yes	FOLFOX combined with pembrolizumab (200 mg)	7	CR	yes	ypT0N0	CR	Demisse et al. 2020
33/male	yes	T3N2 ^a	Yes	Ipilimumab (1 mg/kg) and nivolumab (3 mg/kg)	2	CR	yes	ypT0N0	CR	Trojan et al. 2021
38/female	yes	T4N+	NA	Dostarlimab (500 mg every 3 weeks)	9	CR	no	–	CR	Cercek et al. 2022
30/female	yes	T3N+	NA	Dostarlimab (500 mg every 3 weeks)	9	CR	no	–	CR	Cercek et al. 2022
61/female	no	T1/T2N+	NA	Dostarlimab (500 mg every 3 weeks)	9	CR	no	–	CR	Cercek et al. 2022
28/female	no	T4N+	NA	Dostarlimab (500 mg every 3 weeks)	9	CR	no	–	CR	Cercek et al. 2022
53/female	yes	T1/T2N+	NA	Dostarlimab (500 mg every 3 weeks)	9	CR	no	–	CR	Cercek et al. 2022
77/female	yes	T1/T2N+	NA	Dostarlimab (500 mg every 3 weeks)	9	CR	no	–	CR	Cercek et al. 2022
77/female	no	T1/T2N+	NA	Dostarlimab (500 mg every 3 weeks)	9	CR	no	–	CR	Cercek et al. 2022
55/female	yes	T3N+	NA	Dostarlimab (500 mg every 3 weeks)	9	CR	no	–	CR	Cercek et al. 2022
68/male	no	T3N+	NA	Dostarlimab (500 mg every 3 weeks)	9	CR	no	–	CR	Cercek et al. 2022
78/female	no	T3N0	NA	Dostarlimab (500 mg every 3 weeks)	9	CR	no	–	CR	Cercek et al. 2022
55/female	yes	T3N+	NA	Dostarlimab (500 mg every 3 weeks)	9	CR	no	–	CR	Cercek et al. 2022
27/male	no	T3N+	NA	Dostarlimab (500 mg every 3 weeks)	9	CR	no	–	CR	Cercek et al. 2022
68/male	yes	T2N0	No	Pembrolizumab (200 mg every 3 weeks)	10	CR	yes	ypT0N0	CR	Present study
60/female	no	T3bN2 ^a	Yes	Pembrolizumab (200 mg every 3 weeks)	11	CR	yes	ypT0N0	CR	Present study

^aLateral lymph node involvement observed.^b Patient treated with neoadjuvant chemoradiotherapy without response prior to immunotherapy.

Patients

Two patients with advanced dMMR rectal cancer have in our institution during 2022–2023 chosen up-front neoadjuvant treatment with immunotherapy. Both patients have performed written informed consent for research reporting and the study has been ethically approved by the Lund University Ethics Committee.

Case 1

A 68-year-old man, WHO performance status 0, with a family history of cancer restricted to a father with colorectal cancer at age 90 presented with change in bowel habits and macroscopic blood in stool. Endoscopy verified a polypoid, broad-based, bleeding 3-cm rectal tumor 11 cm from the anal verge and additionally diagnosed two adenomas, one 1.5-cm

adenoma 12 cm from the anal verge and a smaller colon adenoma that was locally extracted. CEA was <2. Histopathology showed high-grade dysplasia in the rectal tumor and low-grade dysplasia in both adenomas, which were classified as tubulovillous adenomas. The rectal tumor showed an heterogeneous lymphocytic infiltrates with an intermediate (10–40%) level of tumor-infiltrating lymphocytes (TIL).

Reflex testing for MMR showed loss of MSH6 with retained expression of MSH2, MLH1 and PMS2 in the rectal tumor and in the colonic adenoma, whereas the rectal adenoma showed normal, retained expression for all four MMR proteins. Microsatellite instability (MSI) analysis based on a multiplex PCR-based method showed a MSI-high phenotype in the rectal tumor. MRI staged the rectal tumor as T2N1 with a 7-mm lateral lymph node, no signs of extramural venous invasion (EMVI-) and no threatened mesorectal fascia

(MRF-) (Figure 1). CT scan, MRI liver and PET-CT showed two suspected liver metastases (which were during follow-up found to represent hemangiomas). The patient underwent direct genetic analysis, which confirmed Lynch syndrome with a MSH6 c2779dup alteration (p.Ile927Asnfs*8), class 5 alteration.

The multidisciplinary treatment conference recommended neoadjuvant radiotherapy and chemotherapy according to the RAPIDO concept. Based on the patient's preference and a discussion in the local oncology team, the patient was offered neoadjuvant treatment with pembrolizumab (200 mg every 3 weeks). Endoscopy, PET-CT scans and MRI were planned at 3 and at 6 months. The patient reported local symptom relief after two treatment cycles and did not experience any side-effects from treatment. At 3 months, endoscopy showed a 3-cm tumor with similar macroscopic appearance as at diagnosis. PET-CT scan showed remaining metabolic activity and MRI classified the tumor as T2N0 with tumor regression grade (TRG) 2. The patient received 10 cycles of treatment without any immunotherapy-related complications. After 6 months, endoscopy verified a polyp at 12 cm and showed a 2-cm mucosal irregularity, but no clear

tumor tissue, at the primary tumor site. PET-CT showed retained metabolic activity, which may in retrospect represent the nearby pMMR polyp. MRI classified the tumor as T1/T2N0, TRG2 (Figure 1). Surgery was recommended based on suspected remaining tumor and lack of data on the management in the specific setting. The patient underwent an uncomplicated low anterior resection with loop-ileostomy. Microscopic investigation of the specimen showed a complete clinical response with lack of viable tumor, ypT0N0 with no metastases in 39 lymph nodes. Five months postoperatively the patient underwent an uncomplicated stoma closing and remains disease-free.

Case 2

A 60-year-old woman, WHO performance status 0, without any family history of cancer presented with change in bowel habits and macroscopic blood in the stool. Endoscopy verified a 4-cm lobulated and polypoid rectal tumor in the dorsal rectal wall, 6 cm from the anal verge. Microscopy verified an adenocarcinoma with high immune infiltration (TIL 40-90%). Reflex testing for MMR revealed loss

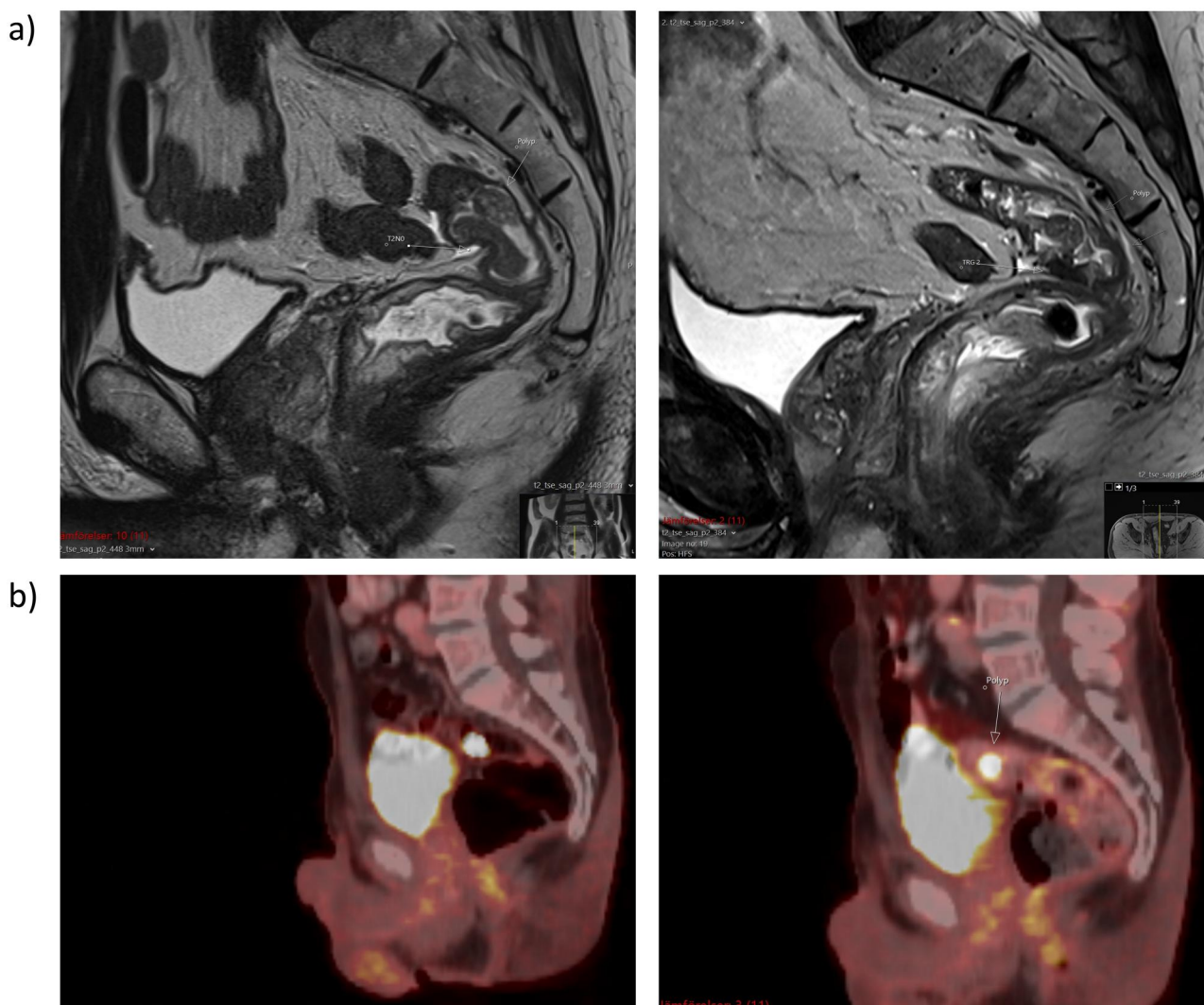


Figure 1. Case 1. a) MRI pre-treatment (left) and post-treatment (right). b) PET-CT scans after 3 months of treatment (left) and post-treatment (right). The polyp located near the malignant tumor remains unaffected by treatment.

of MSH2 and MSH6 expression with retained expression of MLH1 and PMS2. Direct testing for Lynch syndrome did, however, not reveal any disease-predisposing genetic alteration. MRI showed a locally advanced rectal cancer that was radiologically staged as a T3bN2, EMVI+, MRF+ with a presacral and a lateral lymph node, respectively (Figure 2).

The multidisciplinary treatment conference recommended neoadjuvant radiotherapy and chemotherapy according to the RAPIDO concept. Based on the patient's preference and a discussion in the local oncology team, the patient was offered neoadjuvant treatment with pembrolizumab (200 mg every 3 weeks). PET-CT scans were planned at 3 and at 6 months. During treatment the patient experienced gradual symptom relief. At 3 months MRI and PET-CT showed a mixed response with response of the primary tumor and the lateral lymph node, but progression of the presacral lymph node (Figure 2). Radiologic tumor stage was T3bN1b, MRF-, EMVI-, TRG2-3. Since further progression could jeopardize curative intent, the MDT recommended complementary short-course radiotherapy, 5 Gy x 5, which the patients received after 8 cycles of Pembrolizumab. Following radiotherapy an additional 3 cycles of pembrolizumab were administered to a total of 11 cycles. Follow-up PET-CT and MRI classified the tumor as T2N1b, MRF-, EMVI- (Figure 2). Endoscopy after complete neoadjuvant therapy revealed a 1.5-cm mucosal irregularity in the dorsal rectal wall. Surgery was recommended based on suspected remaining tumor and lack of data on the management in the specific setting. The patient underwent low anterior resection with loop-ileostomy. The specimen showed no remaining tumor and was classified as ypT0N0 with no metastases in 16 lymph nodes. Postoperatively, the patient developed a post-operative

anastomotic leakage, which was surgically drained. A CT scan after 6 months showed no recurrence. The patient is well and stoma closing is planned.

Discussion

Current treatment standards for locally advanced rectal cancer are based on radiotherapy and chemotherapy. dMMR, however, represents a distinct classifier for neoadjuvant treatment that may suggest use of immunotherapy rather than radiotherapy and chemotherapy and could potentially allow non-operative management. At present, clinicians face the dilemma in recommending best treatment option for patients with dMMR non-metastatic, locally advanced rectal cancer. Current options include immunotherapy based on promising data with 100% CR in small case series with limited follow-up or, alternatively, recommending chemoradiotherapy, which represents current standard of care, though the dMMR subgroups seem less responsive and risks disease progression in up to one-third of the patients [5,6,14,20–23].

Data from trials of immunotherapy in dMMR colorectal cancer suggests more robust responses in the neoadjuvant setting compared to the metastatic setting. This observation could potentially be linked to a greater efficiency from immunotherapy in tumors that have not been subject to the potential selection for cells with a resistant phenotype by oncologic treatment. In the study by Cercek et al. therapeutic responses were reported to be rapid with symptom relief after 9 weeks in 81% of the patients [14]. The two patients reported herein experienced symptom relief during treatment. Endoscopy after 6 months of treatment showed remaining mucosal irregularities, but no overt tumor. MRI and

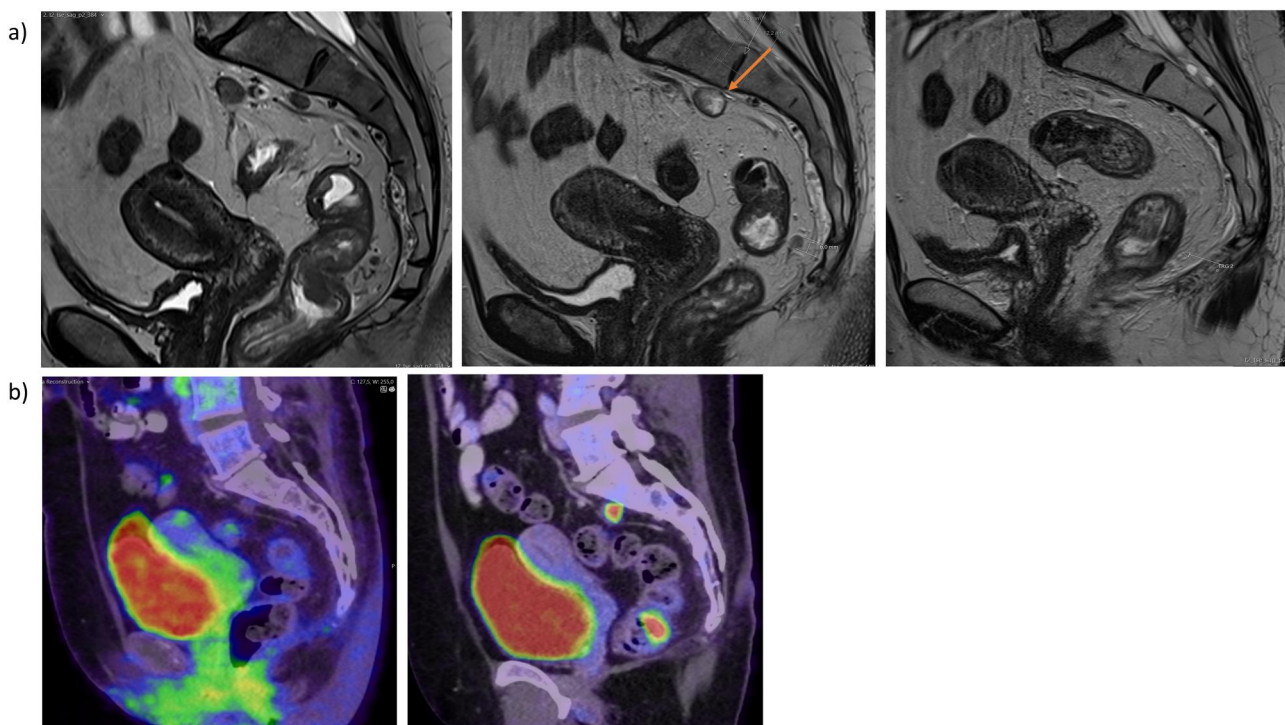


Figure 2. Case 2. a) MRI pre-treatment (left), after three months of treatment (middle) and post radiotherapy and immunotherapy. Suspected progression of the presacral lymph node is marked with an arrow. b) PET-CT scans after 3 months of treatment (left) and after 6 months post-treatment (right).

PET-CT scans showed partial regression, but in case 2 also suspected progression of a presacral lymph node. Though the patients were staged as node positive, cT2N1 and cT3bN1b respectively, after 6 months of treatment both proved to be pT0 upon resection. Hence, these cases suggest a limited benefit from re-staging because of poor accuracy. In the study by Cercek et al. endoscopic CR was after 3 months observed in 5/12 patients and radiologic CR in 2/12 patients [14]. A risk of overstaging of lymph nodes has indeed been reported in dMMR colon cancers [24]. In patients with dMMR colorectal cancers treated with immunotherapy, discrepancies between the results of imaging and endoscopy as compared to pathologic remissions have been reported to be prevalent [25]. Increased immune-cell infiltration, oedema or necrosis may potentially underly these observations, which calls for establishment of multimodal response criteria to safely select patients for non-operative management and watch-and-wait programs.

TME surgery is associated with significant morbidity and functional consequences with low anterior resection syndrome (LARS) reported in 30–80% of patients [26, 27]. This has prompted investigations into non-operative management, the so-called watch-and-wait strategy in the 20–25% of patients that obtain radiologic CR after neoadjuvant therapy [2,28–30]. The first data suggests better physical and global health status and fewer problems with defecation and sexual and urinary tract function, but up to one-third of the patients still experience major low anterior resection syndrome symptoms [31, 2]. Several ongoing trials evaluate the possibility of non-operative management and this concept will likely be particularly relevant for dMMR rectal cancers following immunotherapy [33,34].

The therapeutic developments for dMMR rectal cancer implies that locally advanced rectal cancer should undergo reflex MMR testing to make informed decisions on treatment strategy, though the clinical management of patients with non-metastatic, locally advanced dMMR rectal cancer who have undergone immunotherapy is yet undefined. A non-operative, surveillance-based management could be considered similarly to the watch-and wait strategy after neoadjuvant chemoradiotherapy provided that ongoing studies will with longer follow-up document that CRs are durable and sustained. An alternative approach could be local treatment, such as endoscopic mucosal dissection, that could provide diagnostic information on treatment response and be used for therapeutics [35]. Since most patients with dMMR rectal cancer will have Lynch syndrome and are likely to be young at diagnosis, quality of life and fertility aspects are crucial to consider. The possibility to evade surgery may therefore have significant implications, especially during child-bearing ages. Careful discussion with patients undergoing neoadjuvant immunotherapy is recommended for informed decision on definitive surgery *versus* an organ-sparing approach.

Multiple questions remain to be answered related to the use of neoadjuvant immunotherapy in dMMR rectal cancer, e.g., refined predictive markers, data on optimal timing and strategy for immunotherapy and results from long-term

follow-up. The value of combined radiotherapy and immunotherapy should be evaluated as suggested in the VOLTAGE trial with pCR in 3 or 5 patients with advanced dMMR rectal cancer after treatment with radiotherapy followed by nivolumab [36]. It would also be of interest to evaluate whether there is a difference in immune competence between sporadic dMMR cancers linked to MLH1 hypermethylation and germline dMMR cancers linked to Lynch syndrome. Immunotherapy response mechanisms need to be defined and could be related to, e.g., T-cell infiltration and major histocompatibility complex activity and extrinsic factors such as the gut microbiome could have immune modulatory effects [37].

In summary, the cases presented support immunotherapy as a highly effective neoadjuvant treatment in rectal cancer. The new treatment opportunities in dMMR rectal cancer further enhance multimodal treatment and will likely improve disease control, increase non-surgical management, translate into improved survival and contribute to better quality of life. Multiple studies are ongoing, but treatment designs are heterogenous as regards inclusion criteria, drug combinations, treatment duration and endpoints [38]. Results from ongoing trials such as AVANA (NCT03854799) and TARZAN (NCT04017455) and long-term follow-up from the Cercek study and the NICHE studies as well as development and validation of response criteria will provide important evidence on the road to redefine treatment standards. For the growing number of patients with rectal cancer who undergo non-operative management, quality-controlled surveillance strategies will be crucial to help define risk factors for local regrowth and optime long-term outcomes.

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Data availability statement

Further details are available from the authors upon reasonable request.

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