Original Study

Incidence and Outcomes of Patients With Mismatch Repair Deficient Rectal Cancer Operated in 2016: A Nationwide Cohort From The Netherlands

Eline G.M. van Geffen,[1,2] Cornelis R.C. Hogewoning,[3] Sanne-Marije J.A. Hazen,[1,2] Tania C. Sluckin,[1,2] Marilyne M. Lange,[2,4] Petur Snaebjornsson,[5] Regina G.H. Beets-Tan,[6,7] Corrie A.M. Marijnen,[8,9] Cornelis Verhoef,[10] Myriam Chalabi,[11] Pieter J. Tanis,[2,10,12] Miranda Kusters,[1,2] Tjeerd S. Aukema[13], behalf of the Dutch Snapshot Research Group

Abstract

This study explored t mismatch repair deficient (dMMR) in rectal cancer, comparing outcomes with mismatch repair proficient (pMMR) cases in 1645 patients. DMMR tumors (46/1645) achieved pathological complete response more often, despite similar long-term oncological outcomes. While dMMR tumors showed an adequate response to neoadjuvant chemoradiotherapy, promising immunotherapy results stress the importance of MMR-testing.

Introduction: Data regarding the incidence and outcomes of mismatch repair deficient (dMMR) rectal cancer is limited. This study characterizes dMMR rectal cancer patients, comparing response after neoadjuvant radiotherapy and oncological outcomes to mismatch repair proficient (pMMR) rectal cancer patients. **Method:** A retrospective cross-sectional cohort study was conducted in 67 Dutch centers. Data including patient and tumor characteristics, radiological and pathological reports and oncological follow-up outcomes were gathered from documentation in electronic patient files for patients who underwent a curative resection for primary rectal cancer in 2016. MMR-status was verified in pathology reports from immunohistochemistry or PCR microsatellite instability testing. **Results:** MMR-status was determined in 1645 (54.9%) of 3001 stage I-IV rectal cancer patients, of which 46 (2.8%) were dMMR. Median follow up was 50 months (IQR 38-55). MMR-status was determined more often in younger patients. DMMR tumors were more locally advanced (cT4 23.9% vs. 8.8%, $P = .010$), and more distally located (mean distance to anorectal junction 3.6 cm vs.

Group information: All participating collaborative authors appear at the end of the article.

[1]Department of Surgery, Amsterdam UMC location Vrije Universiteit Amsterdam, Amsterdam, The Netherlands
[2]Treatment and Quality of Life and Imaging and Biomarkers, Cancer Center Amsterdam, Amsterdam, The Netherlands
[3]Department of Surgery, St. Antonius Ziekenhuis, Nieuwegein, The Netherlands
[4]Department of Pathology, Amsterdam UMC location Vrije Universiteit Amsterdam, Amsterdam, The Netherlands
[5]Department of Pathology, Netherlands Cancer Institute Amsterdam, The Netherlands
[6]Department of Radiology, Netherlands Cancer Institute, Amsterdam, The Netherlands
[7]GROW School of Oncology and Developmental Biology, University of Maastricht, Maastricht, The Netherlands
[8]Department of Radiation Oncology, Leiden University Medical Center, Leiden, The Netherlands
[9]Department of Radiation Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands
[10]Department of Surgical Oncology and Gastrointestinal Surgery, Erasmus MC Cancer Institute, Rotterdam, The Netherlands
[11]Department of Gastrointestinal Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands
[12]Department of Surgery, Amsterdam UMC location University of Amsterdam, Amsterdam, The Netherlands
[13]Department of Surgery, HagaZiekenhuis, The Hague, The Netherlands

Submitted: Mar 5, 2024; Revised: Nov 3, 2024; Accepted: Dec 7, 2024; Epub: xxx

Address for correspondence: M. Kusters, MD, PhD, Department of Surgery, Amsterdam UMC, Vrije Universiteit, De Boelelaan 1117, 1081 HV Amsterdam, Cancer Center Amsterdam, Po-Box 7057, 1007 MB, Amsterdam, The Netherlands.
E-mail contact: m.kusters@amsterdamumc.nl

https://doi.org/10.1016/j.clcc.2024.12.003

Please cite this article as: Eline G.M. van Geffen et al, Incidence and Outcomes of Patients With Mismatch Repair Deficient Rectal Cancer Operated in 2016: A Nationwide Cohort From The Netherlands, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2024.12.003

5.3 cm, $P = .004$) than pMMR tumors. While radiological response after neoadjuvant (chemo)radiotherapy was similar, pathological complete response was significantly higher in dMMR compared to pMMR tumors (24.0% vs. 10.0%, $P = .039$). Four-year local recurrence, distant metastases, cancer-specific or overall survival rate between patients with dMMR or pMMR tumors were similar. **Conclusion:** In this population-based cohort, 2.8% of rectal cancers in which MMR-status was determined were subtyped as dMMR. Surprisingly, dMMR was associated with higher pathological complete response rate to neoadjuvant (chemo) radiotherapy than pMMR. MMR-status did not impact oncological outcomes.

Clinical Colorectal Cancer, Vol. 000, No.xxx, 1–10
Keywords: Rectal cancer, Deficient MMR, Pathological complete response, Standard-of-care neoadjuvant therapy, Immunotherapy

Introduction

Worldwide, colorectal cancer (CRC) records 1.9 million new cases annually, with a 65% average 5-year survival rate.[1] Prognostic determinants of CRC include patient characteristics, clinicopathological factors, treatment factors, host response factors and genomic factors.[2,3] Mismatch repair (MMR) status, observed in approximately 13% of CRC, has emerged as a standard addition to the list of relevant tumor characteristics. MMR deficiency (dMMR) results from epigenetic silencing, mutations or deletions of the MMR proteins leading to failure in correcting DNA replication errors.[4] dMMR CRC differs from MMR-proficient (pMMR) CRC, with a higher grade and more proximal location.[5] While stage 1 to 2 dMMR CRC shows more favorable prognostic outcomes than pMMR CRC,[6] this benefit diminishes in stage 3 tumors and is arguably reversed in the metastatic setting; the latter in the preimmunotherapy era.[7] Recent studies highlight poor response of dMMR colon cancer to (neo)adjuvant chemotherapy,[8] whereas neoadjuvant immunotherapy yields a remarkably good response.[9,10] Advancing knowledge of tumor-specific characteristics and behavior, emphasize the increasing importance individualized oncological workup and tailored treatment strategies.

In rectal cancer, the focus on achieving organ preservation is growing, emphasizing the importance of radiological response evaluation and assessment of MMR-status. Current Dutch guidelines recommend routine determination of MMR-status for patients below the age of 70, with uniform recommendations for neoadjuvant treatment for dMMR and pMMR rectal cancers.[11] Hypothetically, patients with dMMR rectal cancer, similar to dMMR colon cancer, could respond less to standard-of-care (SoC) neo-adjuvant therapy, which might reduce organ preservation chances. Scarce literature on this topic shows contradictory results.[12-15]

Moreover, immunotherapy has shown promising results in small cohorts of dMMR rectal cancer patients, enabling organ perservation.[16,17] In this evolving treatment landscape, and while awaiting long-term outcomes for dMMR rectal cancer postimmunotherapy, this nationwide retrospective study aimed to evaluate dMMR rectal cancer incidence, possible differences in clinicopathological risk factors and response after SoC neo-adjuvant therapies between dMMR and pMMR tumors and assess the impact of MMR-status on surgical and oncological outcomes.

Methods

The Snapshot Rectal Cancer 2016 study is a retrospective national cross-sectional cohort study including all 2016 rectal cancer resection in 67/69 Dutch hospitals providing rectal cancer care. Patients selection utilized the Dutch ColoRectal Audit (DCRA), a mandatory registry containing baseline characteristics and short-term (<90 days) surgical outcomes. Patients under watch and wait were excluded due to incomplete registration. Between October 2020 and February 2022, local collaborative teams including surgeons and residents in surgery received a study specific data collection manual and gathered a standard set of additional detailed information on diagnostics, treatment, and oncological outcomes from electronic patient files with a 4-year follow-up period. A more detailed description of this Snapshot design can be found in previous publications.[18]

MMR-Status

Local collaborators validated MMR-status derived from the DCRA database after additional instruction concerning MMR terminology. During data validation, pathology reports from 2016 to 2022, including those from recurrence or metastasis, were checked for immunohistochemical staining (IHC) of MMR proteins or microsatellite instability (MSI). Abnormal IHC (loss of expression of MLH1, MSH2, MSH6, or PMS2) or MSI were both classified as dMMR, while normal IHC and MSS were categorized as pMMR. When neither IHC was conducted nor MSI was tested, the MMR-status was categorized as undetermined. If data validation was impossible, patients were excluded from analyses.

Outcomes and Definitions

This study aimed to compare tumor- and treatment-related characteristics among patients with dMMR, pMMR and undetermined MMR-status, including neoadjuvant therapy, surgical procedure, complications and pathological outcomes. Treatment decisions, following Dutch guidelines, were based on the multidisciplinary team's evaluation, offering CRT (25 × 2Gy or 28 × 1.8Gy with concomitant capacetibine) for locally advanced tumors, short-course RT (5 × 5Gy) or direct surgery for intermediate risk tumors and low risk tumors were offered direct surgery. In general, no adjuvant therapy was offered. For the analysis of surgical complications, pelvic sepsis was defined as anastomotic leakage, presacral

Please cite this article as: Eline G.M. van Geffen et al, Incidence and Outcomes of Patients With Mismatch Repair Deficient Rectal Cancer Operated in 2016: A Nationwide Cohort From The Netherlands, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2024.12.003

abscess or any other abscess related to the tumor or surgery. Missing values were reported in Appendix 1.

Clinical and pathological response after neoadjuvant therapy were analyzed for pMMR and dMMR tumors. Clinical response was categorized based on restaging MRI reports without central review, and classified as clinical complete or partial response, stable disease, or progressive disease. Pathological response after 5 × 5Gy RT with long interval or CRT was categorized into pathological complete response (pCR; absence of microscopic tumor cells in the surgical specimen, including tumor bed and lymph nodes [ypT0N0]) or not.

For analyses of oncological outcomes, patients without synchronous metastases (<3 months of resection) were excluded, and 4-year local recurrence (LR)-rate, metachronous distant metastases (DM)-rate and cancer-specific survival were compared between dMMR and pMMR tumors.

Statistics

Analyses were conducted in SPSS Statistics (Version 28, IBM, Chicago, IL). Baseline characteristics were presented as numbers with percentages for categorical data and mean with standard deviation (SD) or median with interquartile range (IQR) depending on distribution. Groups were compared using X^2 or independent t-tests. Kaplan-Meier survival analysis with the log-rank test assessed oncological outcomes and survival probabilities. With exception from the baseline characteristics, results of the undetermined group are provided as information regarding the bias to test, but p-values were calculated for dMMR versus pMMR only. A *P*-value of <.05 was considered statistically significant.

Ethics

The Medical Ethic Committee of the Amsterdam UMC approved the study protocol in 2020. The Dutch Medical Research Involving Human Subjects Act was deemed not applicable. Local Institutional Review Boards granted approval in each center, and determined whether informed consent was required or patients were given the opportunity to opt-out.

Results

In 3001 patients (Fig. 1), MMR-status had been determined in 1645 (54.8%); 46 (2.8%) were dMMR and 1599 (97.2%) were pMMR. Inter-hospital variation in determining MMR-status ranged from 13.2% to 94.1%. MMR-status was determined in 77.4% of patients aged <70, compared to 24.8% in patients aged ≥70 ($P < .001$). Median follow-up for those with a determined MMR-status was 50 months (IQR 38-56).

Determined Versus Undetermined MMR-Status

Table 1 displays baseline characteristics of the whole cohort and MMR-status determination. There was no significant difference in clinical T (cT) stage between both groups. However, clinical N (cN) stage was significantly lower for undetermined MMR-status (cN0 48.9% vs. 43.5%, $P = .004$). Moreover, slightly higher rates of complete tumor and regional nodal response were found in the undetermined group ([y]pT0 9.8% vs. 5.5%, $P < .001$; [y]pN0 68.5% vs. 64.0%, $P = .011$) compared to the determined group.

dMMR Versus pMMR Tumors

Compared with pMMR, dMMR patients were more often females (50.0% vs. 35.9%, $P = .050$), and presented more frequently with multiple rectal tumors on colonoscopy (11.0% vs. 2.9%, $P = .008$). Primary MRI showed higher cT-stage for dMMR tumors (T4 25.0% vs. 9.3%, $P = .010$), and location closer to the anorectal junction (ARJ) (mean distance 3.6 cm vs. 5.3 cm, $P = .008$). Consequently, an APR was performed more often in dMMR patiënts (34.8% vs. 22.9%, $P < .001$). pT-stage was similar for both groups, but pN-stage was lower for dMMR tumors ([y]pN0 83.7% vs. 63.4%, $P = .019$, Table 1).

Clinical and Pathological Response After Neoadjuvant Therapy

Of those who received 5 × 5Gy RT followed by a long interval or CRT as neoadjuvant therapy, a restaging MRI was performed in 572 (of 658, 87%) pMMR tumors and 20 (of 25, 80%) dMMR tumors. Clinical response was similar, but pathological response was better in the dMMR group (Table 2); in this group 6 of 25 patients achieved a pCR (24.0%), compared to 66 of 657 (10.0%) in the pMMR group ($P = .039$). For patients with a pCR, dMMR tumors were more often cT4 on primary MRI compared to pMMR tumors (66.7% vs. 12.3%, $P = .006$), while neoadjuvant treatment pMMR and dMMR tumors was (pMMR 86.4% CRT and 13.6% 5 × 5Gy RT; dMMR 83.3% CRT and 16.7% 5 × 5Gy RT).

Oncological Outcomes

In patients without synchronous metastasis, the 4-year LR-rate was 4.7% for dMMR, compared to 9.6% for pMMR tumors ($P = .280$, Fig. 2A). After 4 years, DMs were present in 19.3% of dMMR patients, compared to 23.9% of pMMR patients ($P = .762$, Fig. 2B). Also, cancer specific survival (CSS) and overall survival (OS) were similar for patients with dMMR and pMMR tumors (CSS 89.3% vs. 86.5%, $P = .996$; OS 85.5% vs. 82.2%, $P = .990$, respectively, Fig. 2C/D). Due to comparable oncological outcomes and a low number of dMMR tumors, multivariable analyses were not conducted.

Discussion

In this 2016 Dutch, cross-sectional cohort of 3001 patients who underwent surgical resection for rectal cancer, MMR status was determined in 1645 patients and 46 had a dMMR tumor (2.8%). The incidence is similar to previous studies, which report an incidence of approximately 3%.[19,20] The dMMR cohort consisted of significantly more women, advanced cancers, and distally located tumors, with a higher pCR rate after neoadjuvant (C)RT. Despite these differences, oncological outcomes (LR, DM, OS and CSS) were comparable. To our knowledge, this is the first population based cohort of dMMR rectal cancer patients with appropriate follow up.

In 2016 the Dutch CRC guideline recommended MMR determination in patients <70 years:[11]; this was adhered to in 77.4% in this cohort. This inevitably introduces a selection bias. Consequently, the determined group had a lower age, lower ASA-classification, more primary anastomoses and more pelvic sepsis. Baseline differences in pT/N-stage with a trend towards more (y)pT0/N0 in

Please cite this article as: Eline G.M. van Geffen et al, Incidence and Outcomes of Patients With Mismatch Repair Deficient Rectal Cancer Operated in 2016: A Nationwide Cohort From The Netherlands, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2024.12.003

Table 1 Baseline, Treatment and Tumor Characteristics of the Cohort.

Variable	Whole Cohort (n = 3001)	Undetermined MMR (n = 1356, 45.2%)	Determined MMR (n = 1645, 54.8%)	*P*-Value	pMMR (n = 1599, 97.2%)	dMMR (n = 46, 2.8%)	*P*-Value
	n (%)	n (%)	n (%)		n (%)	n (%)	
Sex: male	1944 (64.8)	896 (66.1)	1048 (63.7)	.176	1025 (64.1)	23 (50.0)	**.050**[a]
Mean age in y (SD)	67.1 (10.1)	72.6 (8.5)	62.6 (9.0)	**<.001**	62.7 (8.9)	59.6 (11.7)	.081
Mean BMI (SD)	26.6 (4.6)	26.6 (4.1)	26.6 (4.9)	.691	26.6 (4.9)	25.9 (4.8)	.355
ASA-classification I/II	2430 (81.8)	1021 (76.3)	1409 (86.4)	**<.001**	1371 (86.5)	38 (84.4)	.672
III/IV	539 (18.2)	318 (23.7)	221 (13.6)		214 (13.5)	7 (15.6)	
Previous malignancy (excl BCC)	387 (18.2)	213 (19.8)	174 (16.6)	.057	167 (16.5)	7 (20.0)	.583
No. of primary tumors (colonoscopy) 1	2891 (97.2)	1310 (96.6)	1581 (96.1)	.470	1541 (97.1)	40 (89.0)	**.008**
2+	84 (2.8)	33 (2.4)	31 (3.1)		46 (2.9)	6 (11.0)	
Distance to the ARJ in cm on primary MRI (SD)	5.1 (3.6)	5.1 (3.5)	5.1 (3.6)	.642	5.3 (3.6)	3.6 (3.0)	**.004**
Above the sigmoid take off	301 (11.0)	121 (10.0)	180 (11.8)	.121	179 (12.1)	1 (2.3)	.050
Clinical T category (MRF±) T1	125 (4.4)	55 (4.4)	70 (4.5)	.188	67 (4.5)	3 (6.8)	**.010**
T2	816 (29.0)	397 (31.4)	419 (27.1)		410 (27.3)	9 (20.5)	
T3 (MRF-)	980 (34.9)	419 (33.1)	561 (36.3)		551 (36.7)	10 (22.7)	
T3 (MRF+)	586 (20.8)	257 (20.3)	329 (21.3)		318 (21.2)	11 (25.0)	
T4	269 (9.6)	118 (9.3)	151 (9.8)		140 (9.3)	11 (25.0)	
Tx	35 (1.2)	18 (1.4)	17 (1.1)		17 (1.1)	0 (0.0)	
Clinical N category N0	1319 (45.9)	629 (48.9)	690 (43.5)	**.004**	673 (43.7)	17 (37.8)	.666
N1	856 (29.8)	383 (29.8)	473 (29.8)		459 (29.8)	13 (31.1)	
N2	681 (23.7)	267 (20.8)	414 (26.1)		400 (26.0)	13 (31.1)	
Nx	16 (0.6)	7 (0.5)	9 (0.6)		9 (0.6)	0 (0.0)	
Synchronous metastases[b]	208 (6.9)	82 (6.1)	126 (7.7)	.084	125 (7.8)	1 (2.2)	.254
Neoadjuvant therapy none	1214 (43.6)	624 (46.0)	683 (41.5)	.002	668 (41.8)	15 (32.6)	.167
5 × 5 short interval	418 (15.3)	181 (13.3)	279 (17.0)		273 (17.1)	6 (13.0)	
5 × 5 long interval	280 (10.0)	151 (11.1)	148 (9.0)		145 (9.1)	3 (6.5)	
CRT	878 (31.2)	400 (29.5)	535 (32.5)		513 (32.1)	22 (47.8)	
Surgical procedure LAR	1707 (56.9)	692 (51.0)	1015 (61.7)	**<.001**	998 (62.4)	17 (37.0)	**<.001**
APR	693 (23.1)	311 (22.9)	382 (23.2)		366 (22.9)	16 (34.8)	
HP	384 (12.8)	235 (17.3)	149 (9.1)		143 (8.9)	6 (13.0)	
Local excision	200 (6.7)	113 (8.3)	87 (5.3)		84 (5.3)	3 (6.5)	
Proctocolectomy	15 (0.5)	5 (0.4)	10 (0.6)		7 (0.4)	3 (6.5)	
Total exenteration	2 (0.1)	0 (0.0)	2 (0.1)		1 (0.1)	1 (2.2)	
Surgical technique open	496 (17.7)	200 (16.1)	296 (19.0)	**.045**	281 (18.5)	15 (34.9)	**.007**
Minimally invasive	2305 (82.3)	1043 (83.9)	1262 (81.0)		1234 (81.5)	28 (65.1)	
Pelvic sepsis	374 (14.5)	155 (12.5)	247 (16.1)	**.008**	246 (16.3)	2 (5.1)	.060
Deviating ostomy[c]	894 (52.3)	343 (51.1)	540 (53.2)	.389	528 (52.9)	12 (70.6)	.147
Margin status R0	2776 (93.7)	1252 (93.9)	1524 (93.6)	.788	1482 (92.7)	42 (91.3)	.532

(*continued on next page*)

Please cite this article as: Eline G.M. van Geffen et al, Incidence and Outcomes of Patients With Mismatch Repair Deficient Rectal Cancer Operated in 2016: A Nationwide Cohort From The Netherlands, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2024.12.003

Table 1 (*continued*)

Variable	Whole Cohort (n = 3001)	Undetermined MMR (n = 1356, 45.2%)	Determined MMR (n = 1645, 54.8%)	*P*-Value	pMMR (n = 1599, 97.2%)	dMMR (n = 46, 2.8%)	*P*-Value
	n (%)	n (%)	n (%)		n (%)	n (%)	
R1	186 (6.3)	82 (6.1)	104 (6.4)		100 (6.3)	4 (8.7)	
(y)p T category T0	224 (7.5)	133 (9.8)	91 (5.5)	**<.001**	85 (5.3)	6 (13.0)	.183
T1	483 (16.1)	244 (18.0)	239 (14.5)		231 (14.4)	8 (17.4)	
T2	905 (30.2)	409 (30.2)	496 (30.2)		486 (30.4)	10 (21.7)	
T3	1267 (42.2)	525 (38.7)	742 (45.1)		722 (45.2)	20 (43.5)	
T4	119 (4.0)	44 (3.2)	75 (4.6)		73 (4.6)	2 (4.3)	
Tx	3 (0.1)	1 (0.1)	2 (0.1)		2 (0.1)	0 (0.0)	
(y)p N category N0	1848 (66.0)	851 (68.5)	997 (64.0)	**.011**	961 (63.4)	36 (83.7)	.019
N1	653 (23.3)	282 (22.7)	371 (23.8)		365 (24.1)	6 (14.0)	
N2	297 (10.6)	110 (8.8)	187 (12.0)		186 (12.3)	1 (2.3)	
Nx	3 (0.1)	0 (0.0)	3 (0.2)		3 (0.2)	0 (0.0)	
Adjuvant therapy				**<.001**			.904
None	2919 (97.3)	1338 (98.7)	1581 (97.3)		1536 (96.1)	45 (97.8)	
Radiotherapy	13 (0.4)	2 (0.1)	11 (0.7)		11 (0.7)	0 (0.0)	
Chemotherapy	63 (2.1)	15 (1.1)	48 (2.9)		47 (2.9)	1 (2.2)	
Chemotherapy and radiotherapy	6 (0.2)	1 (0.1)	5 (0.3)		5 (0.3)	0 (0.0)	

Table of baseline, surgical and pathological tumor characteristics of the cohort and stratified by MMR-status.
[a] $P = .499$.
[b] <3 months of surgery.
[c] As a percentage of those who underwent a LAR.
Missing values can be found in Appendix 1.
Abbreviations: APR = abdominoperineal resection; ARJ = anorectal junction; ASA = American Society of Anesthesiologists Physical Status; BCC = basal cell carcinoma; BMI = body mass index; CRT = chemoradiotherapy; HP = Hartmann's procedure; LAR = lower anterior resection; MRF = mesorectal fascia.
Bold values indicate a p-value <.05.

Table 2 Response After Neoadjuvant Therapy

	Undetermined	pMMR	dMMR	*P*-Value dMMR vs. pMMR
Clinical response on restaging MRI[a]	n = 458	n = 572	n = 20	.876
Progressive disease	4 (0.8)	7 (1.2)	0	
Stable disease	22 (4.8)	32 (5.6)	1 (5.0)	
Partial or complete response	432 (94.3)	533 (93.2)	19 (95.0)	
Pathological response	n = 548	n = 657	n = 25	**.039**
No/partial response	447 (81.6)	591 (90.0)	19 (76.0)	
Complete response	101 (18.4)	66 (10.0)	6 (24.0)	

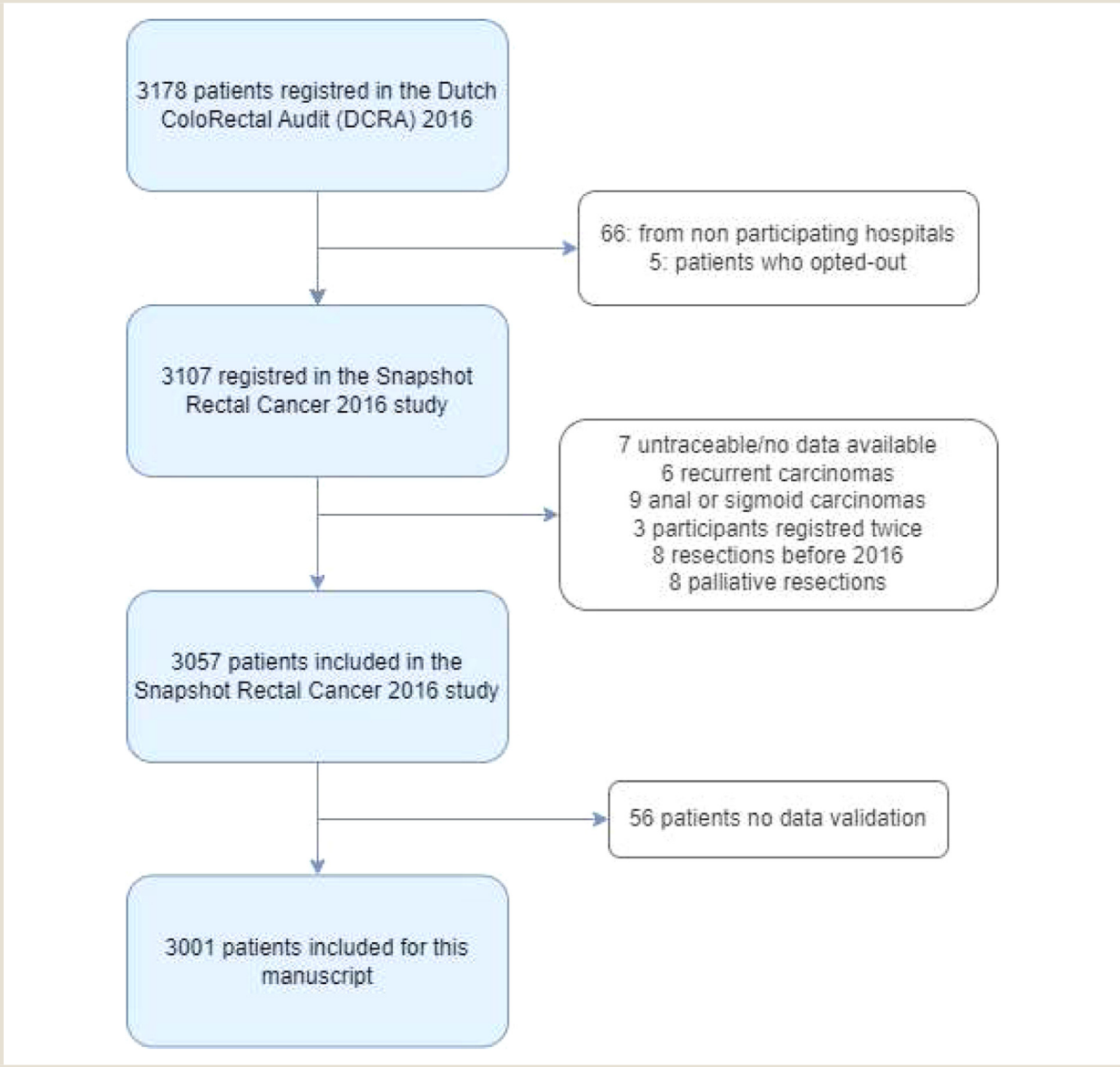
[a]Clinical response on restaging MRI as indicated by the radiologist in the radiological report.
Bold values indicate a p-value <.05.

the undetermined group, might result from IHC/MSS analysis sometimes being performed on the TME-specimen, which is not possible for those who have achieved pCR. Although the 2015 hereditary colorectal cancer guideline recommends analysis to be performed on biopsies,[21] it unknown for our cohort whether MMR-status was determined on biopsies, resection specimens or on metastases.

Baseline differences between dMMR and pMMR rectal cancers are less easily explained. While the dMMR rate in females only slightly surpasses that in males, this finding is novel for rectal cancer patients. Literature suggests a protective role of estrogen in dMMR colorectal cancer occurrence, with an increased risk postmenopause.[22] In this cohort, based on the mean age of 60 years, most women are likely to be postmenopausal, which might contribute to this finding.[23] However, this effect is mainly related to hypermethylated sessile serrated lesions, uncommon in rectal cancer.[24] The retrospective nature of this study limits conclusions to a small association between dMMR rectal cancer and sex, prompting larger studies investigating the role of estrogens and hypermethylated lesions in dMMR rectal cancer to gain insights into possible causal pathways. dMMR, associated with Lynch syndrome, aligns with hereditary cancer marked by tumor multiplicity.[25,26]

Please cite this article as: Eline G.M. van Geffen et al, Incidence and Outcomes of Patients With Mismatch Repair Deficient Rectal Cancer Operated in 2016: A Nationwide Cohort From The Netherlands, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2024.12.003

Figure 1 Flowchart of patient selection.

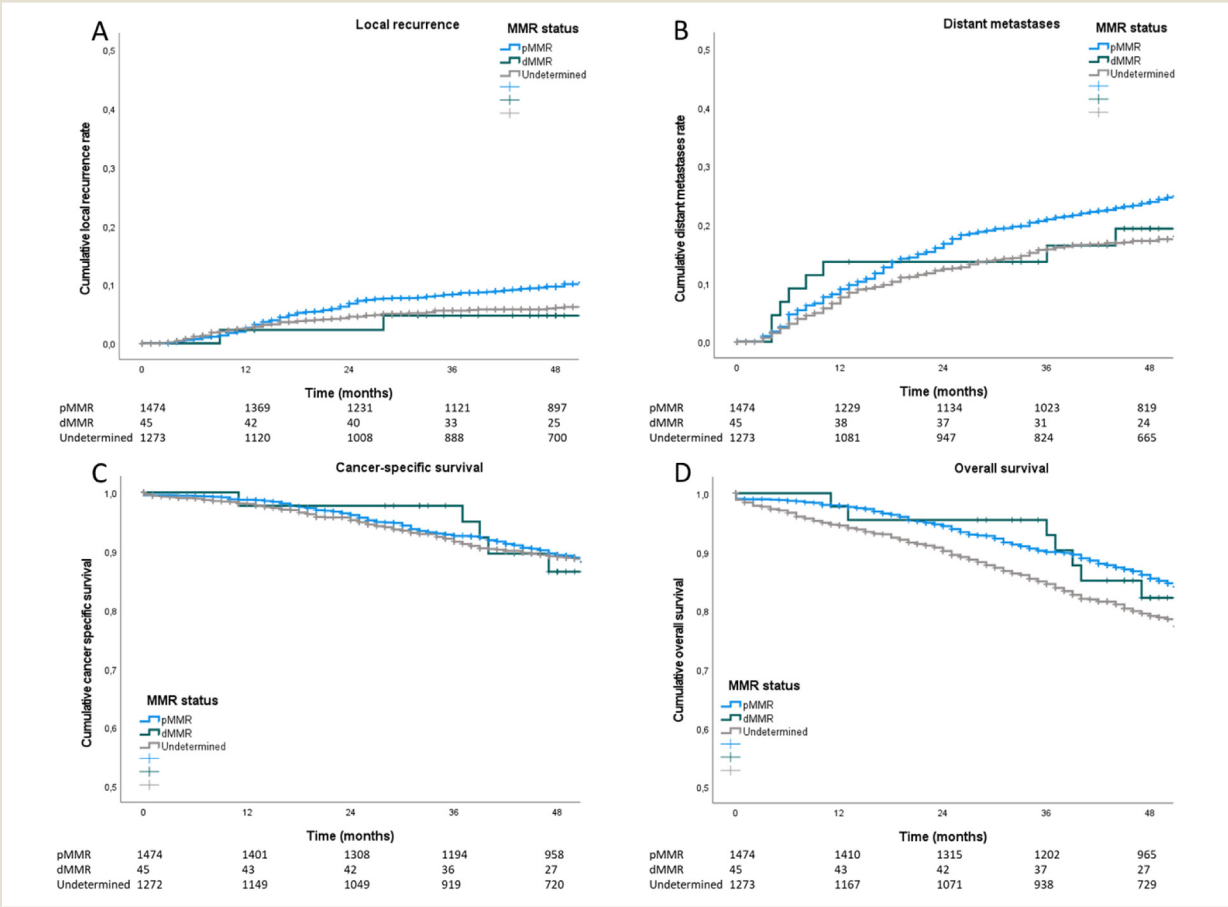


This study reinforces findings with more tumors on colonoscopy in the dMMR group. Interestingly, dMMR tumors tend to be located closer to the ARJ on MRI compared to pMMR tumors, unlike dMMR colon cancer, which are more often located in the proximal part of the colon.[27,28] While the type of surgical procedure was not standardized across participating centers, a higher APR need for dMMR tumors supports this finding. These location-related differences of dMMR rectal cancers have not been previously described.

While lacking central MRI review, using data based on radiology reports, this study found a similar radiological response after neoadjuvant (C)RT on restaging MRI, while a pCR was observed more often in dMMR tumors. Existing literature is inconclusive, while a study based on a nationwide American database showed a reduction in pCR in locally advanced dMMR rectal cancer (5.9% vs. 8.9% for pMMR) after treatment with CRT,[12] and Swets et al. reported a trend towards a more favorable response in the pMMR group,[13] a study by Charara et al. showed increased response rates in dMMR tumors,[14] and a meta-analysis by O'Connel found no differences between both subtypes.[15] A possible explanation for the higher pCR rate observed in the dMMR group might be the interaction between neoadjuvant radiotherapy and the tumor's impaired DNA repair mechanisms. The deficient DNA repair in dMMR tumors, combined with their higher tumor mutational burden and increased neoantigen load, results in a more immunogenic tumor microenvironment.[29] Along with the tumor's reduced capacity to repair radiotherapy-induced DNA damage, the increased immune

Please cite this article as: Eline G.M. van Geffen et al, Incidence and Outcomes of Patients With Mismatch Repair Deficient Rectal Cancer Operated in 2016: A Nationwide Cohort From The Netherlands, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2024.12.003

Figure 2 (A-D) Oncological outcomes for dMMR and pMMR rectal cancer. (A) Local recurrence (LR) rate of pMMR and dMMR tumors (4-y LR 9.6% vs. 4.7%, $P = .280$), undetermined 6.0%. (B) Distant metastasis (DM) rate of pMMR and dMMR tumors (4-y DM 23.9% vs. 19.3%, $P = .454$), undetermined 17.2%. (C) Cumulative cancer-specific survival of pMMR and dMMR tumors (4-y cancer-related survival 89.3% vs. 86.5%, $P = .996$), undetermined 89.0%, (D) Overall survival rate of pMMR and dMMR tumors (4-y OS 85.5% vs. 82·2%, $P = .990$), undetermined 79.1%.



activity leads to more effective tumor cell destruction and increased apoptosis in response to radiotherapy.[30]

However, potential selection bias might have also contributed to the higher pCR rate in the dMMR group, as those with clinical (near) complete response treated in a watch-and-wait protocol were not registered in the DCRA and thus not included. While the numbers of dMMR tumors in the watch-and-wait protocol are unknown, this treatment strategy was not yet common practice in the Netherlands in 2016. A misbalance in neoadjuvant treatment because of higher local staging in the dMMR group may have also affected these results. Moreover, pre-operative RT induces loss of MSH-6 expression in 20% of colorectal tumors,[31] which might have had a small effect on outcomes. In spite of these limitations, dMMR rectal tumors respond at least similarly to the standard neoadjuvant treatment regimens as their pMMR counterparts, and are associated with a slight, nonsignificant, decrease in LR-rate (4.7% vs. 9.6%). Further analyses correcting for more advanced staging, type and timing of neoadjuvant therapy might contribute to further understanding, but cannot be obtained from the current study due to the low number of dMMR tumors.

This study could, at least partly, validate the hypothesis that dMMR and pMMR rectal cancers are 2 different entities as they have different baseline characteristics. Despite this, oncological outcomes for dMMR and pMMR rectal cancers were similar, aligning with Swets et al.[13] meta-analysis. Despite the limitation of the low number of dMMR patients, increasing the sample size is not expected to result in clinically relevant differences in oncological outcomes. To our knowledge, this study represents the largest database assessing incidence alongside long-term oncological outcomes in rectal cancer patients. However, future studies could focus on analyzing trends over time in patients with dMMR.

Although this study is the first population-based cohort to describe MMR-status in 3001 rectal cancer patients, only 46 dMMR rectal cancer cases were identified. Caution is needed interpreting the abovementioned results due to this low number of dMMR tumors. Furthermore, analyses lack correction for

Please cite this article as: Eline G.M. van Geffen et al, Incidence and Outcomes of Patients With Mismatch Repair Deficient Rectal Cancer Operated in 2016: A Nationwide Cohort From The Netherlands, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2024.12.003

confounders, such as advanced cT/N-stage. Recurrence patterns could not be investigated due to low numbers of dMMR tumors, as well as limited information about location of recurrent distant disease. Moreover, this cohort does not fully represent rectal cancer in the Netherlands which might have led to a selection bias, as surgical resection is performed in approximately 70% of all patients,[32] while others are treated with endoscopic resection, watch and wait, or palliative care. This study is also limited regarding detailed information on MMR-status, including specimen type (biopsies or surgical resection specimen), staining method (IHC or MSS testing) or the cause of MMR deficiency.

New developments for dMMR tumors involve immunotherapy with good clinical response, with a high rate of clinical complete response and organ preservation.[16,17] Following SoC neoadjuvant therapy, an increasing number of patients is being managed through a watch-and-wait strategy. In cases of cCR after neoadjuvant chemoradiotherapy, pathologic complete response (pCR) rates are substantial (77%), and outcomes related to recurrence and survival are favorable.[33-35] However, immunotherapy appears to be even more effective, particularly in dMMR subtypes. In the NICHE-study, 95% of the dMMR colon cancer achieved (near-) complete response after only 5 weeks of treatment, including 67% pCR.[36] A study with 12 locally advanced rectal cancer patients treated solely with immunotherapy (dostarlimab), reported complete clinical response in all 12 patients, sparing them from surgical resection with no recurrences after 12 months of follow-up.[17] Consequently, the U.S. Food and Drug Administration (FDA) granted Fast Track designation for the treatment of dMMR locally advanced rectal cancer, which has allowed GlaxoSmithKline (GSK) to initiate a global, open-label, phase II clinical trial (AZUR-1) to validate these findings in a multicenter cohort before implementation in international guidelines.[37]

The tumor response after current neoadjuvant regimens of the 2.8% rectal cancer patients with a dMMR tumor will become less imperative if neoadjuvant immunotherapy becomes standard of care for these patients. Given the promising data with neoadjuvant anti-PD-1 therapy, it is crucial to determine MMR-status in all rectal cancer patients for potential enrollment in immunotherapy trials. The shorter duration of treatment compared to (C)RT, possibly in combination with surgical strategies, may be an alternative approach for dMMR rectal tumors.

Conclusion

In this study, dMMR rectal cancer was associated with a higher cT-stage and more distal location. Adequate response after neoadjuvant therapy in dMMR tumors, and a greater likelihood of achieving pCR compared to pMMR tumors. Future results with anti-PD1 therapy for rectal cancer emphasize the importance of MMR-testing in all rectal cancer patients.

Clinical Practice Points

- MMR deficiency (dMMR) results from genetic alterations, and leads to distinct characteristics in colorectal cancer (CRC), such as poor response to neoadjuvant chemotherapy. Moreover, early-stage dMMR CRC is associated with favorable prognostic outcomes, while advanced stage is associated with poor prognosis. In rectal cancer, the focus lays on achieving organ preservation, and the role of MMR-status assessment for this purpose is unknown. There is limited literature on dMMR rectal cancer and there are contradictory results regarding response to neoadjuvant (chemo)radiotherapy and oncological outcomes. Immunotherapy has shown promising results in small dMMR rectal cancer cohorts, potentially aiding organ preservation. In this evolving landscape, dMMR rectal cancer incidence, response to neoadjuvant therapies, and oncological outcomes were assessed.
- In this national cohort study, patients with a determined MMR-status, the incidence of dMMR rectal cancer was 2.8%. dMMR tumors were more locally advanced and more distally located compared to pMMR tumors. Although the radiological response following neoadjuvant (chemo) radiotherapy was comparable, there was a significantly higher pathological complete response (pCR) for dMMR tumors compared to pMMR tumors (24.0% vs. 10.0%, $P = .039$). The 4-year outcomes, including local recurrence, distant metastases, cancer-specific survival, and overall survival rates, showed no significant differences between patients with dMMR and pMMR tumors.
- The incidence of dMMR rectal cancer is low, but these tumors exhibit a higher pCR compared to pMMR tumors after current standard of care neoadjuvant chemoradiation therapy. This will become less imperative if neoadjuvant immunotherapy becomes an alternative approach for these patients, giving promising data with neoadjuvant anti-PD-1 therapy.

Data Sharing Statement

Data will be made available upon reasonable request.

Disclosure

P. Snaebjornsson has done unrelated consultancy for MSD and Bayer and received payment from MEDtalks for educational presentation. M. Chalabi has received institutional grants from MSD and Roche-Genentech, support for attending meetings and/or travel from Bristol Myers Squibb and is a ASCO guidelines committee member for locally advanced rectal cancer.

CRediT authorship contribution statement

Eline G.M. van Geffen: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Cornelis R.C. Hogewoning:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Sanne-Marije J.A. Hazen:** Writing – review & editing, Validation, Data curation. **Tania C. Sluckin:** Writing – review & editing, Validation, Conceptualization. **Marilyne M. Lange:** Writing – review & editing. **Petur Snaebjornsson:** Writing – review & editing. **Regina G.H. Beets-Tan:** Writing – review & editing. **Corrie A.M. Marijnen:** Writing – review & editing. **Cornelis Verhoef:** Writing – review & editing. **Myriam Chalabi:** Writing – review & editing. **Pieter J. Tanis:** Writing – review & editing, Supervision, Funding acquisition. **Miranda Kusters:** Writing – review & editing, Supervision,

Please cite this article as: Eline G.M. van Geffen et al, Incidence and Outcomes of Patients With Mismatch Repair Deficient Rectal Cancer Operated in 2016: A Nationwide Cohort From The Netherlands, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2024.12.003

Resources, Project administration, Methodology, Funding acquisition, Conceptualization. **Tjeerd S. Aukema:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Acknowledgments

Collaborators: Arend G. J. Aalbers, Susanna M. van Aalten, Femke J. Amelung, Marjolein Ankersmit, Imogeen E. Antonisse, Jesse F. Ashruf, Henk Avenarius, Renu R. Bahadoer, Frans C. H. Bakers, Ilsalien S. Bakker, Fleur Bangert, Renée M. Barendse, Heleen M.D. Beekhuis, Geerard L. Beets, Willem A. Bemelman, Maaike Berbée, Shira H. de Bie, Robert H. C. Bisschops, Robin D. Blok, Liselotte W. van Bockel, Anniek H. Boer, Frank C. den Boer, Evert-Jan G. Boerma, Leonora S. F. Boogerd, Jaap Borstlap, Wernard A. A. Borstlap, Johanna E. Bouwman, Sicco J. Braak, Manon N. G. J. A. Braat, Jennifer Bradshaw, Amarins T. A. Brandsma, Vivian van Breest Smallenburg, Wim T. van den Broek, Sjirk W. van der Burg, Jacobus W. A. Burger, Thijs A. Burghgraef, David W. G. ten Cate, Heleen M. Ceha, Jeltsje S. Cnossen, Robert R. J. Coebergh van den Braak, Esther C. J. Consten, Maaike Corver, Rogier M. P. H. Crolla, Sam Curutchet, Alette W. Daniëls-Gooszen, Paul H. P. Davids, Emmelie N. Dekker, Jan Willem T. Dekker, Ahmet Demirkiran, Tyche Derksen, Arjen L. Diederik, Anne M. Dinaux, Kemal Dogan, Ilse M. van Dop, Kitty E. Droogh-de Greve, Hanneke M. H. Duijsens, Michalda S. Dunker, Johan Duyck, Eino B. van Duyn, Laurentine S. E. van Egdom, Bram Eijlers, Youssef El-Massoudi, Saskia van Elderen, Anouk M. L. H. Emmen, Marc Engelbrecht, Anne C. van Erp, Jeroen A. van Essen, Hans F. J. Fabry, Thomas Fassaert, Eline A. Feitsma, Shirin S. Feshtali, Bas Frietman, Edgar J. B. Furnée, Anne M. van Geel, Elisabeth D. Geijsen, Ritch Geitenbeek, Anna A. W. van Geloven, Anke H. C. Gielen, Michael F. Gerhards, Hugo Gielkens, Renza A. H. van Gils, Lucas Goense, Marc J. P. M. Govaert, Wilhelmina M. U. van Grevenstein, E. Joline de Groof, Irene de Groot, Robbert J. de Haas, Nadia A. G. Hakkenbrak, Mariska D. den Hartogh, Vera Heesink, Joost T. Heikens, Ellen M. Hendriksen, Iris Hochstenbach, Sjoerd van den Hoek, Erik J. R. J. van der Hoeven, Christiaan Hoff, Anna Hogewoning, Stefan Hoogendoorn, Francois van Hoorn, Karin Horsthuis, René L. van der Hul, Rieke van Hulst, Alexander J.C. Ijtsma, Farshad Imani, Bas Inberg, Martijn P. W. Intven, Pedro Janssen, Chris E. J. de Jong, Jacoline Jonkers, Daniela Jou-Valencia, Bas Keizers, Stijn H. J. Ketelaers, Eva Knöps, Sebastiaan van Koeverden, Sylvia Kok, Stephanie E. M. Kolderman, Fleur I. de Korte, Robert T. J. Kortekaas, Julie C. Korving, Ingrid M. Koster, Jasenko Krdzalic, Pepijn Krielen, Leonard F. Kroese, Eveline J. T. Krul, Derk H. H. Lahuis, Bas Lamme, An A. G. van Landeghem, Jeroen W. A. Leijtens, Charlotte A. Leseman, Mathilde M. Leseman-Hoogenboom, Manou S. de Lijster, Martijn S. Marsman, Milou. H. Martens, Ilse Masselink, Wout van der Meij, Joost R. Meijering, Philip Meijnen, Jarno Melenhorst, Anna H. M. Mennen, David M. Mens Dietrich J. L. de Mey, Julia Moelker-Galuzina, Linda Morsink, Erik J. Mulder, Karin Muller, Gijsbert D. Musters, Joost Nederend, Peter A. Neijenhuis, Lindsey C. F. de Nes, M. Nielen, Jan B.J. van den Nieuwboer, Jonanne F. Nieuwenhuis, Joost Nonner, Bo J. Noordman, Stefi Nordkamp, Pim B. Olthof, Stefan E. van Oostendorp Steven J. Oosterling, Daan Ootes, Vera Oppedijk, Pieter Ott, Ida Paulusma, Koen C. M. J. Peeters, Ilona T. A. Pereboom, Jan Peringa, Zoë Pironet, Floor Piqeur, Joost D. J. Plate, Fatih Polat, Ingrid G. M. Poodt, Lisanne A. E. Posma, Jeroen F. Prette, Bareld B. Pultrum, Seyed M. Qaderi, Fadi Rassam, Jan M. van Rees, Rutger-Jan Renger, Anouk J. M. Rombouts, Lodewijk J. Roosen, Ellen A. Roskott-ten Brinke, Joost Rothbarth, Dennis B. Rouw, Tom Rozema, Heidi Rütten, Harm J. T. Rutten, Marit E. van der Sande, Boudewijn E. Schaafsma, Renske A. Schasfoort, Merel M. Scheurkogel, Arjan P. Schouten van der Velden, Wilhelmina H. Schreurs, Puck M. E. Schuivens, Colin Sietses, Petra C. G. Simons, Marjan J. Slob, Gerrit D. Slooter, Martsje van der Sluis, Bo P. Smalbroek, Anke B. Smits, Ernst J. Spillenaar-Bilgen, Patty H. Spruit, Tanja C. Stam, Jaap Stoker, Omaima el Tahir, Aaldert K. Talsma, Sofieke J. D. Temmink, G. Y. Mireille The, Jeroen A. W. Tielbeek, Aukje A. J. M. van Tilborg, Fiek van Tilborg, Dorothée van Trier, Jurriaan B. Tuynman, Maxime J. M. van der Valk, Inge J. S. Vanhooymissen, G. Boudewijn C. Vasbinder, Cornelis J. Veeken, Laura A. Velema, Anthony W. H. van de Ven, Emiel G. G. Verdaasdonk, Wouter M. Verduin, Tim Verhagen, Paul M. Verheijen, Maarten Vermaas, An-Sofie E. Verrijssen, Anna V. D. Verschuur, Harmke Verwoerd-van Schaik, Roy F. A. Vliegen, Sophie Voets, F. Jeroen Vogelaar, Clementine L. A. Vogelij, Johanna Vos-Westerman, Marianne de Vries, Joy C. Vroemen, Bas S. T. van Vugt, Johannes A. Wegdam, Bob J. van Wely, Marinke Westerterp, Paul P. van Westerveld, Henderik L. van Westreenen, Kevin P. Wevers, Allard G. Wijma, Johannes H. W. de Wilt, Bart W. K. de Wit, Fennie Wit, Karlijn Woensdregt, Victor van Woerden, Floor S. W. van der Wolf, Sander van der Wolk, Johannes M. Wybenga, Edwin S. van der Zaag, Bobby Zamaray, Herman J. A. Zandvoort, Dennis van der Zee, Annette P. Zeilstra, Kang J. Zheng, David D. E. Zimmerman & Marcel Zorgdrager. All authors, the thirteen main authors, and all collaborative authors, contributed substantially in the acquisition of data. All authors read the manuscript critically and granted approval for publication. This Snapshot study was supported by the Dutch Cancer Society (KWF), reference 12768.

References

1. Global Cancer Observatory, https://gco.iarc.fr/, World Health Organisation (WHO), The International Agency for Research on Cancer (IARC), visited on 31-03-2023.
2. Punt CJ, Koopman M, Vermeulen L. From tumour heterogeneity to advances in precision treatment of colorectal cancer. *Nat Rev Clin Oncol*. 2017;14(4):235–246.
3. Marks K, West N, Morris E, Quirke P. Clinicopathological, genomic and immunological factors in colorectal cancer prognosis. *J Br Surg*. 2018;105(2):e99–e109.
4. Amonkar M, Lorenzi M, Zhang J, Mehta S, Liaw K-L. *Structured literature review (SLR) and meta-analyses of the prevalence of microsatellite instability high (MSI-H) and deficient mismatch repair (dMMR) in Gastric, colorectal, and esophageal cancers*; 2019 *JCO*;37:e15074.
5. Phipps AI, Lindor NM, Jenkins MA, et al. Colon and rectal cancer survival by tumor location and microsatellite instability: the colon cancer family registry. *Dis Colon Rectum*. 2013;56(8):937.
6. Popat S, Hubner R, Houlston R. Systematic review of microsatellite instability and colorectal cancer prognosis. *J Clin Oncol*. 2005;23(3):609–618.
7. Battaglin F, Naseem M, Lenz H-J, Salem ME. Microsatellite instability in colorectal cancer: overview of its clinical significance and novel perspectives. *Clin Adv Hematol Oncol*. 2018;16(11):735.
8. Sargent DJ, Marsoni S, Monges G, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. *J Clin Oncol*. 2010;28(20):3219.
9. Chalabi M, Fanchi LF, Dijkstra KK, et al. Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers. *Nat Med*. 2020;26(4):566–576.
10. Zhang X, Wu T, Cai X, et al. Neoadjuvant immunotherapy for MSI-H/dMMR locally advanced colorectal cancer: new strategies and unveiled opportunities. *Front Immunol*. 2022;13:795972.

Please cite this article as: Eline G.M. van Geffen et al, Incidence and Outcomes of Patients With Mismatch Repair Deficient Rectal Cancer Operated in 2016: A Nationwide Cohort From The Netherlands, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2024.12.003

11. NVVH. Colorectaal carcinoom (CRC) [Guideline]. Richtlijnendatabase.Nl2022 [Accessed May 4, 2023]. Available from: https://richtlijnendatabase.nl/richtlijn/colorectaal_carcinoom_crc/startpagina_-_crc.html.
12. Hasan S, Renz P, Wegner RE, et al. Microsatellite instability (MSI) as an independent predictor of pathologic complete response (PCR) in locally advanced rectal cancer: a National Cancer Database (NCDB) analysis. *Ann Surg*. 2020;271(4):716.
13. Swets M, Graham Martinez C, van Vliet S, et al. Microsatellite instability in rectal cancer: what does it mean? A study of two randomized trials and a systematic review of the literature. *Histopathology*. 2022;81(3):352–362.
14. Charara M, Edmonston TB, Burkholder S, et al. Microsatellite status and cell cycle associated markers in rectal cancer patients undergoing a combined regimen of 5-FU and CPT-11 chemotherapy and radiotherapy. *Anticancer Res*. 2004;24(5B):3161–3168.
15. O'Connell E, Reynolds I, McNamara D, Prehn J, Burke J. Microsatellite instability and response to neoadjuvant chemoradiotherapy in rectal cancer: a systematic review and meta-analysis. *Surg Oncol*. 2020;34:57–62.
16. Zhang J, Cai J, Deng Y, Wang H. Complete response in patients with locally advanced rectal cancer after neoadjuvant treatment with nivolumab. *Oncoimmunology*. 2019;8(12):e1663108.
17. Cercek A, Lumish M, Sinopoli J, et al. PD-1 blockade in mismatch repair–deficient, locally advanced rectal cancer. *New Eng J Med*. 2022;386(25):2363–2376.
18. Group DSR, Borstlap W, Deijen C, et al. Benchmarking recent national practice in rectal cancer treatment with landmark randomized controlled trials. *Colorect Disease*. 2017;19(6):O219–OO31.
19. Zhang P, Wang A, Bian C, Zhang J, Jiang C, Zhou H. Evaluation of mismatch-repair and microsatellite-instability status in a Chinese colorectal cancer cohort. *Asian J Surg*. 2024;47(2):959–967.
20. Hause RJ, Pritchard CC, Shendure J, Salipante SJ. Classification and characterization of microsatellite instability across 18 cancer types. *Nat Med*. 2016;22(11):1342–1350.
21. Nederland Ik. Erfelijke darmkanker, landelijke richtlijn, Versie: 2.0. In: Oncoline, editor. richtlijnendatabase.nl2015 . Accessed January 5, 2023.
22. Kim S-E, Paik HY, Yoon H, Lee JE, Kim N, Sung M-K. Sex-and gender-specific disparities in colorectal cancer risk. *World J Gastroenterol*. 2015;21(17):5167.
23. Slattery ML, Potter JD, Curtin K, et al. Estrogens reduce and withdrawal of estrogens increase risk of microsatellite instability-positive colon cancer. *Cancer Res*. 2001;61(1):126–130.
24. De Palma FDE, D'argenio V, Pol J, Kroemer G, Maiuri MC, Salvatore F. The molecular hallmarks of the serrated pathway in colorectal cancer. *Cancers*. 2019;11(7):1017.
25. Pedroni M, Tamassia MG, Percesepe A, et al. Microsatellite instability in multiple colorectal tumors. *Int J Cancer*. 1999;81(1):1–5.
26. Hampel H, Frankel WL, Martin E, et al. Screening for the lynch syndrome (hereditary nonpolyposis colorectal cancer). *New Eng J Med*. 2005;352(18):1851–1860.
27. Stoffel EM, Erichsen R, Frøslev T, et al. Clinical and molecular characteristics of post-colonoscopy colorectal cancer: a population-based study. *Gastroenterology*. 2016;151(5) 870-8. e3.
28. Boland CR, Goel A. Microsatellite instability in colorectal cancer. *Gastroenterology*. 2010;138(6) 2073-87. e3.
29. Shin J-S, Tut TG, Yang T, Lee CS. Radiotherapy response in microsatellite instability related rectal cancer. *Korean J Pathol*. 2013;47(1):1.
30. Zhang Y, Rohde LH, Emami K, et al. Suppressed expression of non-DSB repair genes inhibits gamma-radiation-induced cytogenetic repair and cell cycle arrest. *DNA Repair*. 2008;7(11):1835–1845.
31. Bao F, Panarelli NC, Rennert H, Sherr DL, Yantiss RK. Neoadjuvant therapy induces loss of MSH6 expression in colorectal carcinoma. *Am J Surg Pathol*. 2010;34(12):1798–1804.
32. Giesen L, Olthof P, Elferink M, et al. Changes in rectal cancer treatment after the introduction of a national screening program; increasing use of less invasive strategies within a national cohort. *Eur J Surg Oncol*. 2022;48(5):1117–1122.
33. Du R, Chang Y, Zhang J, et al. Whether the watch-and-wait strategy has application value for rectal cancer with clinical complete response after neoadjuvant chemoradiotherapy: a network meta-analysis. *Asian J Surg*. 2024;47(2):853–863.
34. Han Z, Li M, Chen J, et al. Surgery may not benefit patients with locally advanced rectal cancer who achieved clinical complete response following neoadjuvant chemoradiotherapy. *Asian J Surg*. 2022;45(1):97–104.
35. Sert F, Ozturk M, Yalman D, Ozkok S. Does neoadjuvant rectal score predict treatment outcomes better than the all grading systems used in neoadjuvantly treated rectal cancer? *Asian J Surg*. 2023;46(10):4378–4384.
36. Chalabi M, Verschoor Y, Van den Berg J, et al. LBA7 Neoadjuvant immune checkpoint inhibition in locally advanced MMR-deficient colon cancer: the NICHE-2 study. *Annal Oncol*. 2022;33:S1389.
37. Cercek A, Bachet J-B, Capdevila J, et al. Phase II, single-arm, open-label study of dostarlimab monotherapy in previously untreated patients with stage II/III dMMR/MSI-H locally advanced rectal cancer. *JCO*. 2023;41:TPS3639.

Please cite this article as: Eline G.M. van Geffen et al, Incidence and Outcomes of Patients With Mismatch Repair Deficient Rectal Cancer Operated in 2016: A Nationwide Cohort From The Netherlands, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2024.12.003

Appendix 1. Missing Values

Supplementary Table 1

Missing values of baseline characteristics	pMMR (n = 1599)	dMMR (n = 46)	Undetermined (n = 1356)
Variable	n	n	n
Mean BMI (SD)	9	1	53
ASA-classification	14	1	17
Previous malignancy (excl BCC)	586	11	280
No. of primary tumors (colonoscopy)	12	1	13
Distance to the ARJ in cm on primary MRI (SD)	123	3	142
Location related to the sigmoid take off	122	3	143
Clinical T-stage (MRF±)	96	2	92
Clinical N-stage	2	1	70
Clinical M-stage	0	0	1
Surgical technique	84	3	113
Pelvic sepsis	94	7	117
Margin status	17	0	22
(y)p N-stage	84	3	113

Abbreviations: ARJ = anorectal junction; ASA = American Society of Anesthesiologists Physical Status; BCC = basal cell carcinoma; BMI = body mass index; dMMR = deficient mismatch-repair; MRF = mesorectal fascia; MRI = magnetic resonance imaging ; pMMR = proficient mismatch-repair; SD = standard deviation.

Please cite this article as: Eline G.M. van Geffen et al, Incidence and Outcomes of Patients With Mismatch Repair Deficient Rectal Cancer Operated in 2016: A Nationwide Cohort From The Netherlands, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2024.12.003