Mismatch Repair Deficient, Stage II/III Rectal Cancer: Real-World Patient, Tumour, and Treatment Characteristics in the Netherlands

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Background

- A subset of stage II/III rectal tumours (2–5%) are dMMR; the rest are classified as pMMR[1,2]
- Recently, a prospective phase II trial for dMMR stage II/III RC showed that six months of neoadjuvant treatment with dostarlimab, a PD-1 inhibitor, induced a 100% clinical complete response rate and allowed for organ preservation[3]
- Reported evidence on clinical differences between dMMR vs pMMR stage II/III RC is limited

Aim

- To describe and compare patient and tumour characteristics and treatment patterns for patients with dMMR vs pMMR stage II/III RC

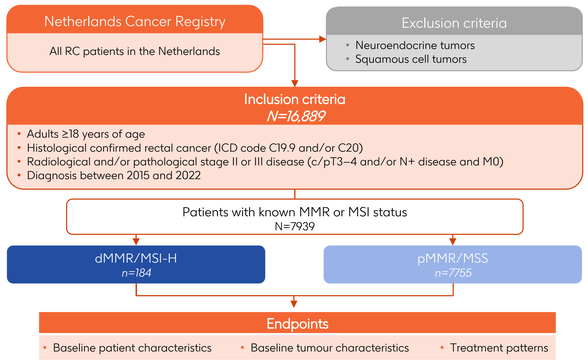
Methods

- This was an observational, retrospective real-world cohort study utilizing data collected in the NCR (**Figure 1**)
  - Adult patients who were diagnosed with stage II/III RC between 2015 and 2022 with known MMR status were included
  - The index date was the date of the diagnosis

Statistical analysis

- Differences in baseline characteristics were evaluated using:
  - For categorical variables: the chi-square test or Fisher's exact test as appropriate
  - For continuous variables: two-sample unpaired T-tests
- A two-sided P-value of <0.05 was considered statistically significant

Figure 1: **Study design**



Results

Baseline patient characteristics

- Of the 7939 patients included, 2.3% (n=184) had dMMR tumours and 97.7% (n=7755) had pMMR tumours (**Table 1**)
- Patients with dMMR tumours were younger (mean age 57.0 vs 61.5 years, *P*<0.001)

Baseline tumour characteristics

- Patients with dMMR tumours were of more advanced cT stage, cN stage, differentiation, and BRAF mutation (**Table 2**)
- Patients with dMMR tumours were more likely to have mucinous or signet ring cell adenocarcinoma than those with pMMR tumours (**Table 2**)

Treatment patterns

- Neoadjuvant treatment followed by resection was most common in both cohorts
- Treatment type differed between cohorts: chemoradiation plus systemic therapy was more commonly reported, whereas radiotherapy alone was less commonly reported, for dMMR patients
- More patients in the dMMR cohort received only neoadjuvant treatment compared with pMMR, while in the pMMR cohort, more patients received upfront resection (**Table 3**)

Table 1: **Baseline patient characteristics by MMR status**

Patient characteristic	dMMR n = 184	pMMR n = 7755	*P*-value*
Age, mean (SD)	57.0 (13.0)	61.5 (10.1)	<0.001
Sex, n (%)			0.11
Female	80 (43.5)	2901 (37.4)	
Male	104 (56.5)	4854 (62.6)	
Year of diagnosis, n (%)†			0.56
2015	12 (6.5)	395 (5.1)	
2016	28 (15.2)	995 (12.8)	
2017	31 (16.8)	1208 (15.6)	
2018	22 (12.0)	1243 (16.0)	
2019	21 (11.4)	1126 (14.5)	
2020	22 (12.0)	895 (11.5)	
2021	30 (16.3)	1060 (13.7)	
2022	18 (9.8)	833 (10.7)	
WHO performance status, n (%)			0.67
0	87 (67.4)	3834 (68.3)	
1	39 (30.2)	1496 (26.7)	
2	3 (2.3)	228 (4.1)	
3	0	47 (0.8)	
4	0	7 (0.1)	
Missing	55	2143	
ASA score, n (%)			0.55
I	33 (20.1)	1339 (18.7)	
II	105 (64.0)	4609 (64.4)	
III	24 (14.6)	1147 (16.0)	
IV	2 (1.2)	58 (0.8)	
Missing	20	602	

*Value corresponds to the whole category and tests for differences between the dMMR and pMMR cohorts
†Patient numbers lower in 2020 and 2022 due to the COVID pandemic and earlier cut-off date for inclusion of patients, respectively

Table 2: **Baseline tumour characteristics by MMR status**

Tumour characteristic, n (%)	dMMR n = 184	pMMR n = 7755	*P*-value*
TNM cT-stage			0.006
T1	1 (0.5)	56 (0.7)	
T2	17 (9.2)	639 (8.2)	
T3	117 (63.6)	5763 (74.3)	
T4A	11 (6.0)	410 (5.3)	
T4B	31 (16.8)	725 (9.3)	
Tx	7 (3.8)	162 (2.1)	
TNM cN-stage			0.006
N0	46 (25.0)	2362 (30.5)	
N1	60 (32.6)	3045 (39.3)	
N2	76 (41.3)	2293 (29.6)	
Nx	2 (1.1)	55 (0.7)	
Differentiation grade			<0.001
Good	5 (3.0)	105 (1.5)	
Moderate	129 (78.2)	6660 (92.4)	
Poor	31 (18.8)	440 (6.1)	
Anaplastic	0	3 (0.0)	
Missing	19	547	
Histology			<0.001
NFI	1 (0.5)	6 (0.1)	
Adeno	158 (85.9)	7341 (94.7)	
Mucinous	18 (9.8)	358 (4.6)	
Signet ring cell	4 (2.2)	48 (0.6)	
Medullar	2 (1.1)	0	
BRAF status			<0.001
Wildtype	22 (81.5)	372 (92.8)	
Mutant	5 (18.5)	29 (7.2)	
Missing	157	7354	
RAS status			0.220
Wildtype	9 (60.0)	220 (51.4)	
Mutant	6 (40.0)	208 (48.6)	
Missing	169	7327	

*Value corresponds to the whole category and tests for differences between the dMMR and pMMR cohorts

Table 3: **Treatment patterns according to MMR status**

Treatment pattern, n (%)	dMMR n = 184	pMMR n = 7755	*P*-value*
Treatment			0.033
Neoadjuvant treatment only	36 (19.6)	1080 (13.9)	
Neoadjuvant treatment and resection	114 (62.0)	4726 (60.9)	
No neoadjuvant treatment (upfront resection)	34 (18.5)	1843 (23.8)	
No treatment received	0	106 (1.4)	
Neoadjuvant treatment type			<0.001
Chemoradiation + systemic therapy	104 (56.5)	3493 (45.0)	
Radiotherapy only	34 (18.5)	2033 (26.2)	
Radiotherapy + systemic therapy	8 (4.3)	240 (3.1)	
Chemotherapy only	2 (1.1)	26 (0.3)	
Targeted therapy	2 (1.1)	14 (0.2)	
No neoadjuvant treatment	34 (18.5)	1949 (25.1)	
Resection of primary tumour	148 (80.4)	6569 (84.7)	0.14
Adjuvant treatment	10 (5.4)	437 (5.6)	1

*Value corresponds to the whole category and tests for differences between the dMMR and pMMR cohorts

Conclusions

- The proportion of patients with dMMR RC was comparable to reported literature[1, 2]
- Approximately half of patients with RC included in the NCR between 2015 and 2022 were not tested for MSI or MMR status, which may limit the interpretation of these data
- Patient, tumour, and treatment characteristics differ significantly between patients with dMMR and pMMR tumours
- Future analyses will involve matched patients with dMMR and pMMR tumours to examine differences in treatment efficacy, clinical outcomes, and patient-reported outcomes between matched dMMR and pMMR RC patients in order to aid interpretation of ongoing clinical trials with immunotherapy for dMMR stage II/III RC

Abbreviations

ASA, American Society of Anesthesiologists classification; BRAF, B-RAF proto-oncogene serine/threonine kinase; c, clinical assessment data; dMMR, mismatch repair deficient; ICD, International Classification of Diseases; M, metastases; MMR, mismatch repair; MRI, magnetic resonance imaging; MSI-H, microsatellite instability-high; MSS, microsatellite stable; N, node; NCR, Netherlands Cancer Registry; NFI, no further information; p, pathological data; PD-1, programmed cell death protein 1; pMMR, mismatch repair proficient; RAS, rat sarcoma; RC, rectal cancer; SD, standard deviation; T, tumour; TNM, tumour, node, metastasis; WHO, World Health Organization

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