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Short report

Microsatellite instability in young patients with rectal cancer: molecular findings and treatment response

REACCT Collaborative

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Members of the REACCT Collaborative are co-authors of this study and are listed under the heading Collaborators and in *Appendix S1*.

Introduction

A major research focus of the past few decades in colorectal cancer has been deciphering the underpinning biomolecular processes in order to guide therapeutic decision-making and optimize outcomes. Several forms of genetic instability have been described in colorectal cancer. Chromosomal instability is the hallmark of 85 per cent of cases, whereas microsatellite instability (MSI) is identified in approximately 15 per cent[1].

MSI, a well defined feature of defective DNA mismatch repair (MMR), may be due to sporadic epigenetic silencing of the *MLH1* gene or constitutive mutations in one of the MMR genes (Lynch syndrome)[2]. Immunohistochemistry is used to classify tumours as MMR-deficient or MMR-proficient, whereas PCR is used to identify MSI. Dichotomization of colorectal cancer on the basis of MMR or MSI status is now recommended routinely for all patients, regardless of age at diagnosis or family history.

Apart from representing an important screening tool for Lynch syndrome, MSI status may also provide valuable prognostic and therapeutic information. MSI is associated with improved disease-specific survival[3,4]. Controversy exists regarding whether MSI confers a relative resistance to 5-fluorouracil chemotherapy, and about the impact of MSI status on response to neoadjuvant chemoradiotherapy[5–9].

One of the biggest epidemiological crises facing the world of surgical oncology is the rapidly rising incidence of early-onset rectal cancer, defined as diagnosis before the age of 50 years[10–13]. The reasons for this increase are unclear. Although overlapping key drivers are implicated in both early- and late-onset disease, a number of notable biomolecular differences have been observed[14–17]. Early-onset rectal cancer is more likely to occur in the context of a hereditary cancer syndrome, but the majority of cases are sporadic and microsatellite stable (MSS)[18,19]. As young patients have historically represented a small proportion of cases, the impact of microsatellite status on disease-specific outcomes in this patient group is unknown. Individual institutional data in isolation are insufficient for meaningful analyses. The REACCT Collaborative was established to aggregate large-volume real-world data from specialist centres across the world. The objective of this study was to evaluate the impact of microsatellite status on oncological outcomes in patients aged less than 50 years diagnosed with rectal cancer.

Methods

A complete description of the study methodology is available in *Appendix S2*. In brief, this was a retrospective international multicentre observational cohort study aiming to assess the clinicopathological features, molecular characteristics, and disease-specific outcomes of patients diagnosed with early-age onset rectal cancer over 20 years (2000–2020). Inclusion criteria were adults aged between 18 and 49 years with a histologically confirmed diagnosis of non-metastatic rectal cancer undergoing surgery with curative intent and with known MSI status. Data were provided by members of the REACCT Collaborative. Patients who fulfilled the inclusion criteria of the study were selected from the REACCT Collaborative database. Collected data included baseline patient demographics, clinical stage, surgical and treatment data, histopathological and molecular features, and cancer-specific as well as overall survival information. MSI was determined by PCR or immunohistochemistry (IHC). Loss of MMR proteins *MLH1*, *PMS2*, *MSH2* or *MSH6* on IHC was classified as MSI. A hereditary cancer syndrome was defined by diagnosis of a constitutive pathogenic variant on germline testing.

Results

Baseline demographics

A total of 400 patients aged less than 50 years diagnosed with rectal cancer over a 20-year interval were included in the study. This represents 9.1 per cent of the total with early-onset colorectal cancer in the REACCT Collaborative database. Of these 400 patients, 50 had tumours with defined MSI. The remaining 350 had MSS tumours. Median age was 43 (range 23–49) years and 204 patients (58.3 per cent) were men (*Table 1*). MSI was associated with a first-degree relative with colorectal cancer. Women accounted for 58 per cent of the MSI group. There was no difference in clinical stage between the two groups. The majority of patients given neoadjuvant therapy received long-course chemoradiotherapy.

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Table 1 Comparison of demographics and clinicopathological data

	Overall ($n = 400$)	MSI ($n = 50$)	MSS ($n = 350$)	P†
Age (years)*	43 (23–49)	39 (26–49)	48 (23–49)	0.293‡
Men	204 (51.0)	21 (42)	183 (52.3)	0.137
First-degree relative with colorectal cancer	41 (10.3)	10 (20)	31 (8.9)	0.009
cTNM stage				
I–II	97 (24.3)	9 (18)	88 (25.1)	0.091
III	208 (52.0)	28 (56)	180 (51.4)	0.091
Unknown	95 (23.8)	13 (26)	82 (23.4)	
Neoadjuvant CRT	248 (62.0)	31 (62)	217 (62.0)	1.000
(y)pTNM stage				
I	117 (29.3)	14 (28)	103 (29.4)	1.000
II	126 (31.5)	25 (50)	101 (28.9)	0.005
III	157 (39.2)	11 (22)	146 (41.7)	0.008
Pathology				
Pathological complete response	44 (17.7)	10 (32)	34 (15.7)	0.044
R0 resection	372 (93.0)	47 (94)	325 (92.9)	1.000
Hereditary cancer syndrome	26 (6.5)	15 (30)	11 (3.1)	<0.001
Adjuvant chemotherapy	249 (62.3)	28 (56)	221 (63.1)	0.189

Values in parentheses are percentages unless indicated otherwise; *values are median (range). MSI, microsatellite instability; MSS, microsatellite stable; CRT, chemoradiotherapy. †χ^2 or Fisher's exact test, except ‡Mann–Whitney *U* test.

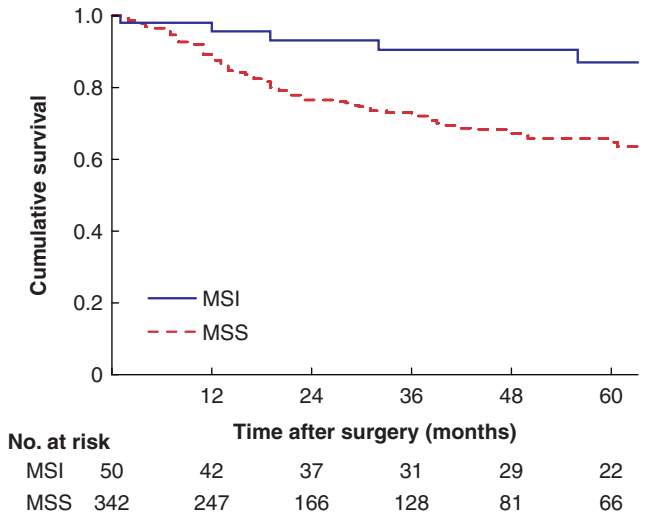

Fig. 1 Kaplan–Meier curve of disease-free survival for patients with stage I–III disease according to microsatellite status

MSI, microsatellite instability; MSS, microsatellite stable.

Pathological features

There were no significant differences in differentiation, or lymphovascular, extramural venous or perineural invasion between the two groups. A pathological complete response (pCR) was more common among the MSI group (32 *versus* 15.7 per cent; $P = 0.044$). Patients with MSI were less likely to have pathological node-positive disease (22 *versus* 41.7 per cent; $P = 0.008$).

Molecular characteristics

MSI tumours were more likely to occur in the context of genetic predisposition. A hereditary cancer syndrome was diagnosed in 15 patients (30 per cent) with MSI tumours compared with 11 (3.1 per cent) with MSS lesions (hazard ratio (HR) 13.21, 95 per cent c.i. 5.63 to 30.97; $P < 0.001$). Only 36 patients (72.0 per cent) in the MSI group and 230 (65.7 per cent) in the MSS group had undergone genetic testing at the time of data collection.

Survival

Survival data were available for 392 patients (98.0 per cent). Overall median follow-up was 35 (range 1–197) months. In the MSI group, median overall survival was 58 (1–197) months, with 1-, 3-, and 5-year overall survival rates of 100, 95, and 89 per cent respectively. Corresponding values in the MSS group were 32 (1–158) months, and 96, 90, and 84 per cent. Median disease-free survival was 57 (1–197) months in the MSI group and 23 (1–158) months in the MSS group. In patients with MSI, the disease-free survival rate at 1, 3, and 5 years was 98, 90, and 87 per cent respectively, compared with 89, 72, and 66 per cent among those with MSS tumours (*Fig. 1*). On subanalysis based on pathological stage, survival was better in the MSI group for stage I, II, and III disease, but the differences were not statistically significant.

Disease recurrence

No patient in the MSI group developed locoregional disease recurrence compared with 24 patients (6.9 per cent) in the MSS group ($P = 0.159$). Five patients (10 per cent) with MSI developed metastatic disease compared with 72 (20.6 per cent) in the MSS group ($P = 0.084$).

Factors predictive of disease-specific outcomes

On univariable analysis, in the MSI group, no variable was significantly associated with disease recurrence. In the MSS group, lymphovascular, extramural, and perineural invasion, non-pCR, and node positivity were significantly associated with worse disease-free survival in univariable analysis. In multivariable analysis, only lymphovascular invasion (HR 2.83, 95 per cent c.i. 1.09 to 7.31; $P = 0.032$) and adjuvant chemotherapy (HR 4.89, 1.29 to 18.63; $P = 0.020$) were significantly associated with disease recurrence.

Discussion

Increased understanding of the biomolecular processes that underpin tumour development has enabled the molecular stratification of patients with colorectal cancer. The most commonly used molecular classification system in clinical practice

dichotomizes colorectal cancer into tumours with MSI and those that are MSS. Unsurprisingly, tumours that arise from different oncogenic pathways differ clinically. In this study of 400 patients with early-onset rectal cancer, tumours in 12.5 per cent demonstrated MSI. MSI was associated with reduced a likelihood of nodal positivity, an increased rate of pCR, and improved disease-specific survival. MSI tumours were also more likely (but not exclusively) to occur in the context of a hereditary cancer syndrome.

Epidemiological and registry-based studies[10,20,21] have demonstrated an alarming increase in early-onset colorectal cancer worldwide over the past four decades. This increase has been predominantly driven by a rise in the rate of distal tumours[11]. Historically, men have accounted for a greater proportion of patients with rectal cancer than women. A recent nationwide Swedish registry-based study[22], however, reported a male-to-female incidence rate ratio of 1.07 in adults aged 18–49 years, compared to 1.71 among those aged over 49 years. MSI has been shown to have a female preponderance, in particular among patients with proximal colonic tumours[23]. In the present study, although there were more men overall, women accounted for the majority of patients (58 per cent) in the MSI group. This is in contrast to the findings of a large North American nationwide study[24] of all-age rectal cancer in which the majority of patients in both MSI and MSS groups were men (60.8 and 61 per cent respectively). The impact of female sex on the risk of early-age rectal cancer or presence of MSI remains to be defined.

An emerging focus of modern management of rectal cancer is the role of the molecular profile in therapeutic decision-making. Neoadjuvant chemoradiotherapy is the standard of care for locally advanced disease, but the pathological response varies considerably. Achieving a pCR is a positive prognostic indicator, associated with outstanding locoregional control[25,26]. A noteworthy result from these data is the enhanced pCR rate in young patients with MSI rectal cancer. This opens the possibility of organ preservation in this specific group. It is known that disease-free survival with a pCR is excellent, so it may be possible to consider avoiding operation in some of these patients[27]. It should be remembered that these are otherwise healthy individuals in whom socioeconomic, psychosocial and quality-of-life factors are arguably more important. Thus, it will be important to build on the knowledge base being acquired from discrete-choice experimental data in patients with a pCR resulting from chemoradiotherapy for oesophageal cancer. In those studies, it was found that patients were prepared to give up life-years to avoid the potentially disabling symptoms due to the anatomical, physiological, and social impact of major surgical excision[28]. In particular, the negative impact on genitourinary function that may arise as a result of major pelvic surgery and the established risk of poor lower gastrointestinal function (low anterior resection syndrome) may be avoided with an organ-preserving approach[29,30]. The socioeconomic advantages to eliminating major surgery in this youthful population group is intuitively better. However, there are negative consequences to neoadjuvant chemoradiotherapy which include (but are not limited to) diminished fertility, pelvic fractures, and neuropathy[31–33]. Clearly, research to acquire discrete-choice experimental information from patients in this distinct patient group is needed to inform patient–doctor decision-making.

Despite receiving more treatment, young patients with rectal cancer have disease-specific survival similar to that of their older counterparts[18]. Oncological outcomes according to MSI status, however, are limited. In the present study, patients with MSI had better disease-specific survival. Statistical differences were purposely not assessed because these data represent real-world data which can be relatively crude. Where that is the case, the use of statistics could be misleading. Nonetheless, the absolute difference of 21 per cent in 5-year disease-free survival (MSI *versus* MSS: 87 *versus* 66 per cent) is certainly clinically significant. As expected, overall survival did not differ between groups.

MSI status is an important screening tool for genetic cancer predisposition, such as Lynch syndrome. Constitutive pathogenic mutations in the MMR genes lead to defective MMR, of which MSI is a well defined feature[2]. In the present study, 6.5 per cent of patients overall were diagnosed with a genetic predisposition. These data, in keeping with other series, suggest that rectal cancer in young adults is infrequently due to a hereditary cancer syndrome (albeit more frequently than in their older counterparts)[18]. For MSI tumours, however, almost one in three patients had a genetic predisposition (MSI *versus* MSS: 30 *versus* 3.1 per cent), highlighting the importance of reflective genetic testing in this group. Despite young age at disease onset being a hallmark of genetic predisposition, the majority of cases of early-onset colorectal cancer are sporadic with MSS tumours[16,34]. As the full spectrum of genes implicated is unknown, however, it is possible that a proportion of patients with sporadic disease actually harbour mutations not yet identified[19,35]. Advances in next-generation sequencing with multigene panel testing will unveil this spectrum.

This study has some understandable limitations, including the retrospective nature of data entered (risks incompleteness or heterogeneity) from a study spanning two decades (treatments evolve), but real-world information drives hypotheses. Total neoadjuvant therapy represents an attractive strategy owing to favourable compliance and superior pCR rates[36,37]. Immunotherapy (checkpoint inhibitors perhaps) may be be integrated into neoadjuvant therapy, for which reports of remarkable responses are exciting[38]. Global research collaboration represents the ideal way to coordinate these approaches.

Disclosure. The authors declare no conflict of interest.

Collaborators

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Supplementary material

Supplementary material is available at *BJS* online.

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European Colorectal Congress

28 November – 1 December 2022, St.Gallen, Switzerland

Monday, 28 November 2022

09.50
Opening and welcome
Jochen Lange, St.Gallen, CH

10.00
It is leaking! Approaches to salvaging an anastomosis
Willem Bemelman, Amsterdam, NL

10.30
Predictive and diagnostic markers of anastomotic leak
Andre D'Hoore, Leuven, BE

11.00
SATELLITE SYMPOSIUM
ETHICON

11.45
Of microbes and men – the unspoken story of anastomotic leakage
James Kinross, London, UK

12.15
LUNCH

13.45
Operative techniques to reduce anastomotic recurrence in Crohn's disease
Laura Hancock, Manchester, UK

14.15
Innovative approaches in the treatment of complex Crohn Diseases perianal fistula
Christianne Buskens, Amsterdam, NL

14.45
To divert or not to divert in Crohn surgery – technical aspects and patient factors
Pär Myrelid, Linköping, SE

15.15
COFFEE BREAK

15.45
Appendiceal neoplasia – when to opt for a minimal approach, when and how to go for a maximal treatment
Tom Cecil, Basingstoke, Hampshire, UK

16.15
SATELLITE SYMPOSIUM
Medtronic
Further,Together

17.00
Outcomes of modern induction therapies and Wait and Watch strategies, Hope or Hype
Antonino Spinelli, Milano, IT

17.30
EAES Presidential Lecture - Use of ICG in colorectal surgery: beyond bowel perfusion
Salvador Morales-Conde, Sevilla, ES

18.00
Get-Together with your colleagues
Industrial Exhibition

Tuesday, 29 November 2022

9.00
CONSULTANT'S CORNER
Michel Adamina, Winterthur, CH

10.30
COFFEE BREAK

11.00
SATELLITE SYMPOSIUM
INTUITIVE

11.45
Trends in colorectal oncology and clinical insights for the near future
Rob Glynne-Jones, London, UK

12.15
LUNCH

13.45
VIDEO SESSION

14.15
SATELLITE SYMPOSIUM
BD

15.00
COFFEE BREAK

15.30
The unsolved issue of TME: open, robotic, transanal, or laparoscopic – shining light on evidence and practice
Des Winter, Dublin, IE
Jim Khan, London, UK
Brendan Moran, Basingstoke, UK

16.30
SATELLITE SYMPOSIUM
Takeda

17.15
Lars Pahlman lecture
Søren Laurberg, Aarhus, DK

Thursday, 1 December 2022
Masterclass in Colorectal Surgery
Proctology Day

Wednesday, 30 November 2022

9.00
Advanced risk stratification in colorectal cancer – choosing wisely surgery and adjuvant therapy
Philip Quirke, Leeds, UK

09.30
Predictors for Postoperative Complications and Mortality
Ronan O'Connell, Dublin, IE

10.00
Segmental colectomy versus extended colectomy for complex cancer
Quentin Denost, Bordeaux, FR

10.30
COFFEE BREAK

11.00
Incidental cancer in polyp - completion surgery or endoscopy treatment alone?
Laura Beyer-Berjot, Marseille, FR

11.30
SATELLITE SYMPOSIUM
EVOLUZIONE DISPOSITIVI MEDICI

12.00
Less is more – pushing the boundaries of full-thickness rectal resection
Xavier Serra-Aracil, Barcelona, ES

12.30
LUNCH

14.00
Management of intestinal neuroendocrine neoplasia
Frédéric Ris, Geneva, CH

14.30
Poster Presentation & Best Poster Award
Michel Adamina, Winterthur, CH

15.00
SATELLITE SYMPOSIUM
OLYMPUS

15.45
COFFEE BREAK

16.15
Reoperative pelvic floor surgery – dealing with perineal hernia, reoperations, and complex reconstructions
Guillaume Meurette, Nantes, FR

16.45
Salvage strategies for rectal neoplasia
Roel Hompes, Amsterdam, NL

17.15
Beyond TME – technique and results of pelvic exenteration and sacrectomy
Paris Tekkis, London, UK

19.30
FESTIVE EVENING

Information & Registration **www.colorectalsurgery.eu**