A CROSS-SECTIONAL ANALYSIS FROM A REAL-WORLD COHORT OF MICROSATELLITE INSTABILITY COLORECTAL CANCER (MSI-CRC) PATIENTS WITH METASTATIC DISEASE FROM THE SPANISH RETUD REGISTRY

REGISTRY RETUD

TTD GRUPO DE TRATAMIENTO DE LOS TUMORES DIGESTIVOS

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BACKGROUND

- High microsatellite instability (MSI-H) is a well described subset of colorectal cancer (CRC) tumors, found in approximately 4-5% of metastatic patients[1,2]. The introduction of immune checkpoint inhibitors (ICI) has led to an improvement in survival outcomes and quality of life of MSI-H metastatic CRC patients[3-5].
- Currently, ICI's are the treatment of choice for treatment-naïve MSI-H patients[6], and ongoing clinical trials are attempting to combine immunotherapy with chemotherapy, targeted therapy, or other immunotherapy drugs[7-9].
- This work provides real world data regarding the management and clinical outcomes of a cohort of MSI-H metastatic CRC patients treated under clinical practice conditions in Spain.

METHODS

- The RETUD Registry (NCT06711211) is a national, multicenter registry conducted in Spain which includes patients diagnosed with gastrointestinal tumors and is promoted by the Spanish Group for the Treatment of Digestive Tumors (Grupo Español de Tratamiento de Tumores Digestivos, TTD).
- In this cross-sectional analysis we evaluated a real-world cohort of MSI-H metastatic colorectal cancer patients diagnosed from 1st January 2017 to 29th April 2024.
- Herein we present a descriptive analysis of patients baseline characteristics, molecular profile, systemic treatments, treatment response and survival outcomes. Tumoral response was evaluated according to RECIST 1.1 criteria. First line progression-free survival (PFS) and Overall survival (OS) analyzed by Kaplan-Meier method, presented along with 95% confidence intervals (CI), and stratified according to treatment (chemotherapy vs. immunotherapy).

RESULTS

Patient disposition and characteristics

- At database cut-off, data from 679 patients with MSI-H CRC were retrieved from the RETUD Colorectal Cancer database. Of them, 214 (31.5%) were classified as patients with metastatic disease (at diagnosis or upon recurrence of disease). Patient sociodemographic and clinical characteristics at diagnosis are described in **Table 1**.

Molecular characteristics

- Molecular tests were performed according to the institutions local standards and clinical practice procedures. All patients included in this analysis presented MSI-H, and additionally, other molecular findings were detected in those patients with available tests.
- Next Generation Sequencing (NGS) analyses were performed in 53 (24.8%) patients.
- Molecular findings other than MSI-H are depicted in **Table 2**.

Treatments and surgical interventions

- One hundred sixty-three (n= 163, 76.2%) patients underwent surgery related to disease under study, mostly resection of primary tumor (n= 158, 96.9%) but also surgery for metastatic disease (n=42, 25.8%).
- Locoregional treatment (including radiation) was administered to 22 (10.3%) patients. The most frequent procedures were radiotherapy (50%), followed by SBRT/IMRT (27.3%), radiofrequency (13.6%) and cryoablation (4.6%).
- A total of 191 (89.3%) patients received systemic therapy. **Figure 1** shows treatment intention **(A)** and exposure **(B)**. First line systemic treatment was administered to 187 (97.1%) patients: 92 (49.2%) pembrolizumab, 83 (44.4%) chemotherapy (CT), 4 (2.1%) other ICIs, 8 (4.3%) not reported.

Table 1. Patient baseline characteristics

Patient characteristics	N=214
Age at diagnosis (years), median (min, max)	69.6 (26-96)
Female sex, n (%)	115 (53.7)
Caucasian race/ethnicity, n (%)	209 (97.7)
Lynch syndrome [a], n (%)	17 (10.7)
Cancer family history [b], n (%)	124 (62.9)
Cancer personal history, n (%)	52 (24.4)
Tumor stage at primary diagnosis, n (%)	
I	4 (1.9)
II	26 (12.1)
III	66 (30.8)
IV	118 (55.1)
Location of tumor at primary diagnosis [c], n (%)	
Right colon	160 (74.8)
Left colon	37 (17.3)
Rectum	19 (8.9)
ECOG performance status at metastasis [d], n (%)	
0	66 (32.5)
1	108 (53.2)
2	25 (12.3)
3	4 (2.0)
Location of metastatic sites [e], n (%)	
Liver	84 (39.3)
Lymph distant nodes	71 (33.2)
Peritoneal	76 (35.5)
Lung	41 (19.2)
CEA (ng/mL) [f], median (IQR)	6.9 (2.5-26.0)
CA199 (IU/mL) [g], median (IQR)	20.4 (8.8-108.5)

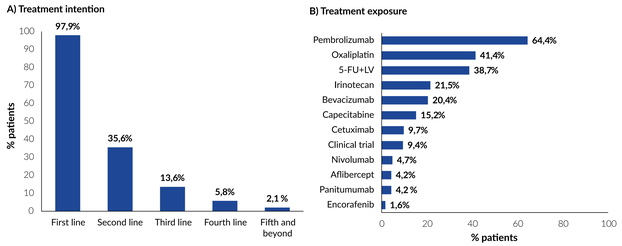
a. Missing data for 55 patients; b. Missing data for 17 patients; c. Patients with more than 1 primary tumor; the percentage may be over 100%. Missing data for 4 patients; d. Missing data for 11 patients; e. Patients with more than one metastatic site, the percentage may be over 100%; f. Missing data for 35 patients; g. Missing data for 86 patients.

Table 2. Targetable molecular findings

Targetable molecular findings	Value
KRAS mutation, n (%)	43 (20.1)
NRAS mutation, n (%)	6 (2.8)
BRAF mutation, n (%)	105 (49.1)
MLH1 promoter hypermethylation, n (%)	31 (14.5)
HER2 amplification, n (%)	1 (0.5)
NTRK fusion, n (%)	6 (2.8)
ALK fusion, n (%)	1 (0.5)

N=214 ptients. Missing data for: 37 patients (*KRAS* mutation), 42 patients (*NRAS* mutation), 16 patients (*BRAF* mutation), 78 patients (*MLH1* promoter hypermethylation), 163 patients (*HER2* amplification), 189 patients (*NTRK* fusion), 195 patients (*ALK* fusion)

Figure 1. Treatment intention (A) and treatment exposure (B)

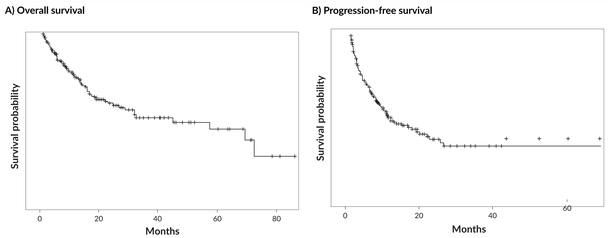


N=187 patients receiving systemic treatment (missing data for 4 patients).

Treatment response and survival outcomes

- At data extraction, 95 (44.4%) patients have died and 3 (1.4%) were declared lost to follow-up. The main cause of death was disease progression (70.5%), followed by not related intercurrent illness/ events (11.6%), disease-related complications (10.5%), and toxicity (1.1%).
- The overall response rate (ORR) was 54.2% for patients who received immunotherapy and 37.3% for patients receiving chemotherapy.
- At a median follow-up period of 17.4 months, the median OS and PFS were 32.6 and 11.1 months respectively for the entire population **(Figure 2)**
- According to the Kaplan-Meier curves, MSI-H CRC patients treated with chemotherapy in first line showed shorter OS and PFS in contrast to immunotherapy-treated patients, although no comparative analyses were performed **(Figure 3)**.

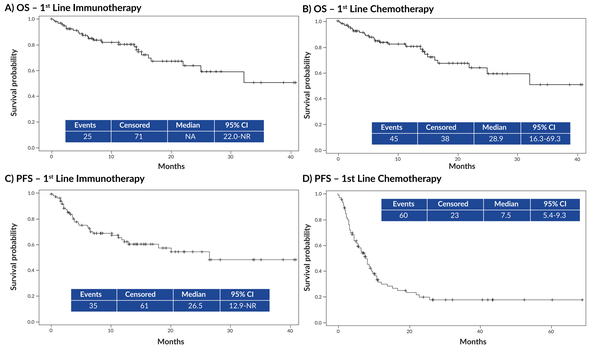
Figure 2. Overall survival and Progression-free survival in the overall metastatic subset of patients



Events	Censored	Median	95% CI
73	114	32.6	22.0-72.4

Events	Censored	Median	95% CI
97	90	11.1	8.2-17.9

Figure 3. First line Overall survival and Progression-free survival. Immunotherapy and chemotherapy



CONCLUSIONS

- This work provides valuable real-world data from a cohort of MSI-H metastatic CRC patients treated under clinical practice conditions in Spain, describing the treatment patterns and survival outcomes.
- Our data shows the clinical benefit obtained in OS and PFS from the administration of immunotherapy to MSI-H CRC patients in first line, in contrast to other conventional therapies such as chemotherapy.
- These findings are consistent with the literature, although it should be considered that the data obtained from this work is purely descriptive and no comparison analyses were conducted.

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