Introduction: DNA deficient mismatch repair (dMMR) genes are associated with microsatellite instability and good prognosis in early stage colorectal cancer (CRC). However dMMR is rare in metastatic CRC (mCRC) and little is known about its influence on treatment response rate (RR). Our primary objective was to compare the RR of mCRC patients according to dMMR status.

Methods: Case-control study that compared the RR by RECIST 1.1 in mCRC patients treated with chemotherapy according to dMMR status. All digital images were retrieved for RR evaluation by a single radiologist blinded to dMMR results. dMMR was defined as loss of immunohistochemistry expression of at least one of the MMR genes (MLH1, MSH2, MSH6 e PMS2). Cases were dMMR and controls were proficient MMR (pMMR) patients, in a 1:2 fashion. Based on clinical and molecular features, dMMR patients were classified as probable Lynch or sporadic.

Results: From January 2009 to January 2013, 762 out of 1270 patients were eligible and screened for dMMR: N = 27 (3.5%) had dMMR and N = 735 (96.5%) had pMMR mCRC. Given the rarity, 14 dMMR cases outside the inclusion period were included (total 41 dMMR cases) and 84 controls (pMMR). By intention-to-treat analysis, dMMR patients had lower RR to first-line oxaliplatin-based chemotherapy, compared with pMMR (RR = 9.7% vs 28.6%; OR: 0.27, 95% CI: 0.07-0.91, p = 0.032). Patients with probable Lynch-related mCRC presented higher RR than subjects with probable sporadic dMMR (16% vs 0). dMMR was associated with BRAF mutations and was prognostic in intention-to-treat analysis, particularly in sporadic subgroup (29.8 vs 5.9 months, p = 0.025).

Conclusion: This study suggests that the dMMR phenotype is predictive of resistance to oxaliplatin-based chemotherapy. Apparently, such resistance is more pronounced in the sporadic dMMR phenotype, suggesting biological heterogeneity within the dMMR mCRC subgroup.