Introduction

Tumor DNA mismatch repair (MMR) deficiency testing has become an indispensable test in metastatic colorectal cancer (mCRC) due to the high efficacy of immunotherapy in patients with deficient MMR (dMMR) status. Heterogeneous MMR status may associate with refractoriness to immunotherapy. We aimed to study the concordance in MMR status between primary and paired metastasis in mCRC.

Methods

Our study included 84 mCRC patients with both primary and matched metastatic sites. Immunohistochemistry was used to determine the MMR patterns of primary lesions and metastases. A pooled analysis including 913 cases was used to determine the frequency and organ-specific heterogeneity of MMR status. The relationship between MMR phenotype heterogeneity and clinical outcomes was investigated.

Result

Fig. 1 MMR IHC for Case 1 in 400x. Primary tumor with intact MLH1 (A), MSH2(B), MSH6(C) and PMS2(D). Metastatic tissue from the liver with intact MLH1(E), MSH2(F), MSH6(G) and absent PMS2(H). MMR IHC for Case 16 in 400x. Primary tumor with intact MSH2(J) and MSH6(K), absent MLH1 (I) and PMS2(L). Metastatic tissue from the peritoneum with intact MLH1(M), MSH2(N), MSH6(O) and absent PMS2(P).

Fig. 2 (A) MMR status between primary tumors and metastatic tumors. (B) Correlation between metastatic site and discrepancy regarding MMR status. (C) MMR status between primary tumors and metastatic tumors in pool analysis. (D) Organ-specificity of MMR status between primary and matched metastatic tumors in patients with dMMR_PT. (E) Organ-specificity of MMR status between primary and matched metastatic tumors in patients with pMMR_PT. (I: pMMR_PT/dMMR_MT; II: dMMR_PT/pMMR_MT; III: dMMR_PT/dMMR_MT)

Fig. 3 (A) Incidence of MMR state heterogeneity between primary tumors and metastatic tumors in different organs. (B) The incidence of MMR state heterogeneity between metastatic tumors and primary tumors with dMMR (dMMR_PT or pMMR (pMMR_PT) in different organs. (C) Proportion of mismatch repair protein with heterogeneous expression. (D) Proportion of patients with different types of mismatch repair protein heterogeneity.

Fig. 4 (A) Comparison of overall survival in patients with dMMR_PT versus pMMR_PT. (B) Comparison of overall survival in patients with pMMR_PT with pMMR_MT versus dMMR_MT. (C) Comparison of overall survival in patients with or without MMR protein heteroexpression between primary and metastatic tumors. (Cohort Y, patients with MMR protein heteroexpression between primary and metastatic tumors; Cohort N, patients without MMR protein heteroexpression between primary and metastatic tumors).

Summary

- 10 (11.9%) of the patients had MMR status heterogeneity between primary and metastatic tumours. Prevalence of heterogeneous MMR patterns is significantly higher in patients with dMMR_PT than patients with pMMR_PT and which was also verified in the pooled analysis (P<0.001). MMR status discordance between primary and metastatic tumours was more common in patients with peritoneal metastases (10.67%).
- For dMMR_PT, the discrepancy regarding MMR status was observed in patients with liver, lung, ovary, peritoneum, and distant lymph node metastasis. For pMMR_PT, the discrepancy was more likely to be limited to liver (26/440) or peritoneal (7/112) metastasis (P=0.02). The patients with isolated heterogeneous expression of MSH6 and PMS2, as well as paired heterogeneous expression of MSH2/MSH6 and MLH1/PMS2, were relatively higher. Patients with MMR status heterogeneity or not had comparable OS (P=0.452).

Conclusion

- Heterogeneous MMR patterns exist in a subset of mCRC patients, especially in patients with dMMR primary tumors.
- Testing the metastatic site might be valuable in cases of peritoneal metastasis as the discordance of MMR status potentially could affect immune surveillance and immunotherapy.