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Frequency of microsatellite instability (MSI) in upper tract urothelial carcinoma: comparison of the Bethesda panel and the Idylla MSI assay in a consecutively collected, multi-institutional cohort

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ABSTRACT

Aims Upper tract urothelial carcinoma (UTUC) is a rare malignancy with a poor prognosis which occurs sporadically or in few cases results from a genetic disorder called Lynch syndrome. Recently, examination of microsatellite instability (MSI) has gained importance as a biomarker: MSI tumours are associated with a better response to immunomodulative therapies. Limited data are known about the prevalence of MSI in UTUC. New detection methods using the fully automated Idylla MSI Assay facilitate analysis of increased patient numbers.

Methods We investigated the frequency of MSI in a multi-institutional cohort of 243 consecutively collected UTUC samples using standard methodology (Bethesda panel), along with immunohistochemistry of mismatch repair (MMR) proteins. The same tumour cohort was retested using the Idylla MSI Assay by Biocartis.

Results Using standard methodology, 230/243 tumours were detected as microsatellite stable (MSS), 4/243 tumours as MSI and 9/243 samples as invalid. In comparison, the Idylla MSI Assay identified four additional tumours as MSS, equalling 234/243 tumours; 4/243 were classified as MSI and only 5/243 cases as invalid. At the immunohistochemical level, MSI results were supported in all available cases with a loss in MMR proteins. The overall concordance between the standard and the Idylla MSI Assay was 98.35%. Time to result differed between 3 hours for Idylla MSI Assay and 2 days with the standard methodology.

Conclusion Our data indicate a low incidence rate of MSI tumours in patients with UTUC. Furthermore, our findings highlight that Idylla MSI Assay can be applied as an alternative method of MSI analysis for UTUC.

INTRODUCTION

Upper tract urothelial carcinoma (UTUC), including tumours in pyelocaliceal cavities and ureter, is a rare cancer with incidence rates close to 2/100 000 inhabitants per year in Western countries.[1] Overall, UTUC accounts for only 5%–10% of all urothelial tumours, is more often found in people of advanced age, and three times more often in men than in women.[2 3] In contrast to bladder cancer, UTUCs present as an invasive disease at diagnosis in 60% of cases and have a poor prognosis with a 5-year survival of less than 50%.[2] UTUC can be sporadic and is significantly associated with exposure to tobacco and aromatics.[2 4] On the other hand, an autosomal-dominant inherited tumour syndrome called the Lynch syndrome caused by germline mutations in genes of DNA mismatch repair (MMR), increases the risk for developing different tumour types, especially colorectal cancer and endometrial cancer. UTUC related to the Lynch syndrome is relatively rare, with an estimated risk of 6%–15%.[5 6]

The sporadic as well as the hereditary forms of UTUC are associated with microsatellite instability (MSI). A deficient DNA MMR system caused by germline or sporadic mutations of MMR genes lead to a nucleotide length variation of DNA repeat regions called microsatellites.[7] Although previous reports on small patient cohorts indicate that the frequency of MSI in UTUCs is approximately 20%, a uniform description has not been defined to date.[8] It is important to note that the MSI status represents an important prognostic and predictive tumour marker.[9] In many tumour types, MSI is associated with a better outcome and improved response to adjuvant chemotherapy and immunotherapy regimes compared with tumours with stable microsatellite DNA regions.[10–14]

Currently, detection of MSI is mostly performed using the National Cancer Institute (NCI) consensus marker panel accompanied by immunohistochemistry analysis, which results in a time-to-diagnosis period of approximately two working days.[15] With rising diagnostic numbers due to therapeutic options, procedures in terms of testing duration and the specific detection method need to be improved. The Biocartis Idylla MSI Assay is a fully automated, real-time PCR-based molecular test which implements a new set of seven markers for detection