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Review

A collaborative review of the microsatellite instability/deficient mismatch repair phenotype in patients with upper tract urothelial carcinoma

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Objective

To perform a collaborative review of the literature exploring the microsatellite instability/deficient mismatch repair (MSI/dMMR) phenotype in patients with upper tract urothelial carcinoma (UTUC).

Method

A collaborative review of the literature available on Medline was conducted by the Cancer Committee of the French Association of Urology to report studies describing the genetic mechanisms, investigation, prevalence and impact of the MSI/dMMR phenotype in UTUC patients.

Results

The predominant genetic mechanism leading to the MSI/dMMR phenotype in UTUC patients is related to the constitutional mutation of one allele of the MMR genes *MLH1*, *MSH2*, *MSH6* and *PMS2* within Lynch syndrome. Indications for its investigation currently remain limited to patients with a clinical suspicion for sporadic UTUC to refer only those with a positive testing for germline DNA sequencing to screen for this syndrome. With regard to technical aspects, despite the interest of MSIsensor, only PCR and immunohistochemistry are routinely used to somatically investigate the MSI and dMMR phenotypes, respectively. The prevalence of the MSI/dMMR phenotype in UTUC patients ranges from 1.7% to 57%, depending on the study population, investigation method and definition of a positive test. Younger age and a more balanced male to female ratio at initial diagnosis are the main specific clinical characteristics of UTUC patients with an MSI/dMMR phenotype. Despite the conflicting results available in the literature, these patients may have a better prognosis, potentially related to more favourable pathological features. Finally, they may also have lower sensitivity to chemotherapy but greater sensitivity to immunotherapy.

Conclusion

Our collaborative review summarises the available data from published studies exploring the MSI/dMMR phenotype in UTUC patients, the majority of which are limited by a low level of evidence.

Keywords

upper tract urothelial carcinoma, radical nephroureterectomy, microsatellite instability, Lynch syndrome, prognostic factors, chemotherapy, immunotherapy

Introduction

Upper tract urothelial carcinoma (UTUC) is rare and accounts for approximately 5%–10% of all urothelial malignancies [1]. This translates into an estimated annual incidence of 1–2 cases per 100 000 inhabitants, with men being more than twice as likely to develop UTUC than women [2] at a median age of >70 years [3]. Although UTUCs and urothelial carcinomas of the bladder share most of the same risk factors, these disparate tweens can largely differ from a genomic perspective, with a lower frequency of *TP53*, *RB1* and *ERBB2* gene alterations in UTUC, for example [4,5]. In addition, the constitutional mutations of one of the two alleles of the DNA mismatch repair (MMR) system genes *MLH1*, *MSH2*, *MSH6* and/or *PMS2*, which define Lynch syndrome, dramatically increase the risk of developing UTUC as compared to the general population [6,7], with a cumulative UTUC prevalence of 10% in patients diagnosed with this syndrome [8].

From a molecular perspective, inactivation of the two alleles of the MMR genes is required to induce the loss of expression of the corresponding protein (*MLH1*, *MSH2*, *MSH6* or *PMS2*), which results in the deficient MMR (dMMR) phenotype. This can lead to genomic instability, especially in microsatellites, which are short tandem repeat DNA sequences of one to six nucleotides distributed throughout the human genome, mainly near coding regions. When the MMR system is deficient, the length of these microsatellites can largely vary, resulting in the microsatellite instability (MSI) phenotype.

Interestingly, the MSI/dMMR phenotype represents an important prognostic and predictive biomarker routinely used in the management of several malignancies [9]. For example, a recent Phase III trial has shown that patients with MSI/dMMR metastatic colorectal cancer benefit more from immunotherapy using pembrolizumab than chemotherapy as first-line treatment [10]. However, the investigation of the MSI/dMMR phenotype is not part of routine clinical practice for UTUC patients, possibly because data are more scarce and sometimes even conflicting. Thus, our aim was to conduct a collaborative review of the literature describing the genetic mechanisms, investigation, prevalence and impact of the MSI/dMMR phenotype in UTUC patients.

Materials and Methods

This was a collaborative review by the Cancer Committee of the French Association of Urology using the Medline database (<https://pubmed.ncbi.nlm.nih.gov>). The following keywords were used, either individually or in combination: ‘upper tract urothelial carcinoma’; ‘microsatellite instability’; ‘mismatch repair’; ‘Lynch’. Only scientific publications describing the genetic mechanisms, investigation, prevalence,

and impact of the MSI/dMMR phenotype in UTUC patients were included, with no time period or language restriction. Articles were evaluated based on their relevance and methodology by two authors (P.E.G. and G.C.T.). Overall, 60 references published between 1991 and 2023 were included in our collaborative review, on agreement with the senior author (T.S.).

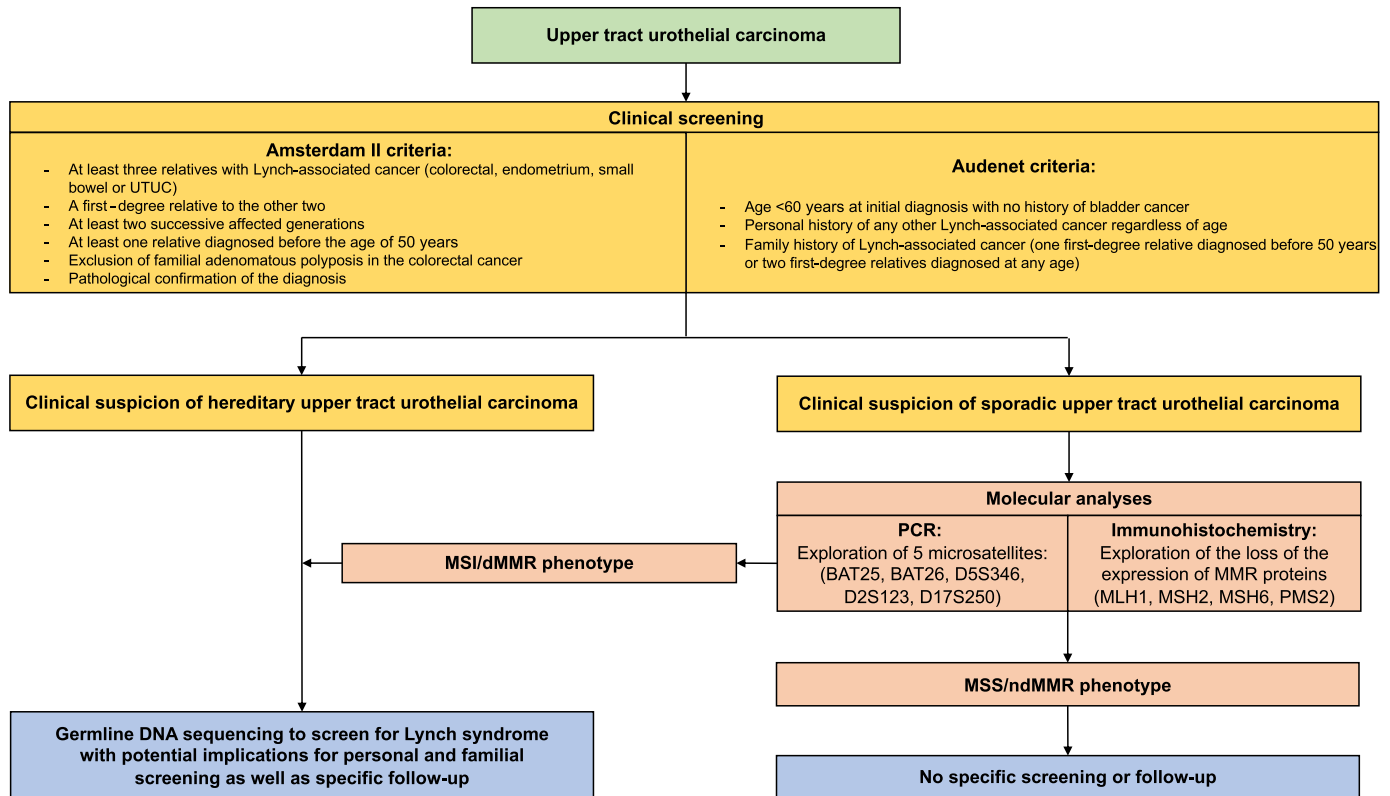
Results

Genetic Mechanisms Leading to the MSI/dMMR Phenotype

The inactivation of the two alleles of the MMR genes *MLH1*, *MSH2*, *MSH6* and/or *PMS2* inducing the MSI/dMMR phenotype in UTUC patients is largely related to mutations or epigenetic events that can occur either constitutionally or somatically. With regard to epigenetic events, it has been demonstrated that hypermethylation of the promoters of the *MLH1*, *MSH2*, *MSH6* and/or *PMS2* genes can lead to transcriptional silencing, with a loss of expression of the corresponding proteins. However, few studies have focused on the molecular analysis of promoter methylation of these genes in UTUC patients. Only one retrospective study involving 163 patients treated with radical nephroureterectomy (RNU) reported that hypermethylation of the *MLH1* gene promoter was present in 12% of them at the somatic level, while no tumour exhibited hypermethylation of the *MSH2* gene promoter [11]. In that study, a strong association between the *MLH1* gene hypermethylation and MSI phenotype was also observed.

The MSI/dMMR phenotype observed in UTUC patients, however, is mostly related to Lynch syndrome, formerly known as hereditary non-polyposis colorectal cancer, which also predisposes to the development of colorectal, endometrial, ovarian, biliary duct, and specific central nervous system tumours. This autosomal dominant genetic disease results from the constitutional mutation of one of the alleles of the MMR genes *MLH1*, *MSH2*, *MSH6* and/or *PMS2*, with inactivation of the second allele occurring in the tumour either through somatic mutations or epigenetic events. Interestingly, constitutional mutations of the *MSH2* gene are most commonly observed in UTUC patients with Lynch syndrome. Indeed, constitutional mutations of the *MSH2*, *MLH1* and *MSH6* genes have been found in 63%–100%, 0%–25%, and 0%–15% of these patients, respectively [7]. In addition, constitutional mutations of the *MSH2* gene were associated with a significantly higher risk of developing UTUC (6.9%) as compared to those of *MSH6* (2.9%) and *MLH1* (2.2%) genes in a retrospective study from 2015, leading to a 75-fold increased risk of developing UTUC as compared to the general population [12]. More specifically, *MSH2*-mutated patients could have a 43- and 62-fold increased risk of developing UTUC in the renal pelvis and ureter, respectively [13].

Fig. 1 Indications for the investigation of the microsatellite instability (MSI)/deficient mismatch repair (dMMR) phenotype in patients with upper tract urothelial carcinoma (UTUC). MMR, mismatch repair; MSS, microsatellite stable; ndMMR, non-deficient mismatch repair.



Investigation of the MSI/dMMR Phenotype

Indications

There is currently no consensus on the indications for the investigation of the MSI/dMMR phenotype in UTUC patients but this could mainly serve as a triage test to refer those with a positive result for germline DNA sequencing to screen for Lynch syndrome [3]. However, the use of the Amsterdam II criteria [14] or those proposed by Audenet et al. [15] – corresponding to a simplification of the Amsterdam II criteria in addition to age < 60 years at initial diagnosis with no history of bladder cancer and/or a personal history of Lynch-associated cancer – and, more anecdotally, the use of the PREMM₅ predictive model [16] can help to directly identify UTUC patients with a clinical suspicion of hereditary disease. Importantly, these patients may represent up to 20% of UTUC cases [15] who could forgo MSI/dMMR testing to directly benefit from germline DNA sequencing, given that even a negative result would not rule out hereditary disease that is suspected based on clinical criteria. Nonetheless, these clinical criteria have shown limited diagnostic performance in identifying hereditary UTUC [17]. Thus, investigation of the MSI/dMMR phenotype would likely be useful for the other 80% of UTUC patients with a clinical suspicion of sporadic

disease [15] to refer only those with a positive result for germline DNA sequencing as well (Fig. 1).

Methods

As opposed to investigation of constitutional mutations of MMR genes based on the analysis of germinal DNA, that of the MSI/dMMR phenotype is performed at the somatic level on tumour DNA. In daily practice, the direct method involving PCR and the indirect method with immunohistochemistry can be used to determine the MSI and dMMR phenotypes from paraffin-embedded tumour tissue at a low cost, respectively.

With regard to PCR, investigation of the MSI phenotype is based on the comparative analysis of amplification products obtained from tumour and normal tissue sample DNAs. The panel of genetic markers recommended by the Bethesda consensus meeting consists of five microsatellites including two mononucleotide markers (BAT25 and BAT26) and three dinucleotide markers (D5S346, D2S123 and D17S250) [18]. Tumours with instability in at least two of the five markers are MSI–High (MSI–H), while those with instability in only one marker are MSI–Low (MSI–L). The microsatellite stable (MSS) phenotype is characterised by the absence of any instability. It is noteworthy that the use of MSIsensor has also

been described to investigate the MSI phenotype based either on tissue [19] or cell-free DNA [20]. However, given that this method relies on paired tumour-normal genome sequencing for comprehensive investigation of human genome, implying higher cost than PCR or immunochemistry, MSIsensor is currently not part of routine diagnostic procedures, although it could shortly be more widely used in daily practice to optimise investigation of the MSI phenotype.

With regard to immunohistochemistry, investigation of the dMMR phenotype is based on the analysis of the primary antibodies anti-MLH1, anti-MSH2, anti-MSH6 and anti-PMS2 binding to the corresponding proteins using tumour tissue sections to assess their expression, mostly based on immunofluorescence [3]. Absence of detection of the antibody–antigen complex in the tumour indicates the loss of expression of the corresponding protein and the dMMR phenotype, while its detection indicates the non-deficient MMR phenotype (ndMMR).

Prevalence of the MSI/dMMR Phenotype

Currently, only retrospective reports with heterogeneous study populations, investigation methods and definitions for positive testing have evaluated the prevalence of the MSI/dMMR phenotype in UTUC patients, showing highly variable results, ranging from 1.7% [21] to 57% [22]. Table 1 summarises the results of studies reporting the prevalence of the MSI/dMMR phenotype in UTUC.

MSI Phenotype Determined Using PCR or MSIsensor:

In 11 studies using PCR, the prevalence of the MSI phenotype ranged from 1.7% to 46% [21,23–32]. In particular, a French study reported that only 7% of the included 58 UTUC patients harboured an MSI phenotype [29], whereas Schneider et al. observed a prevalence of the MSI phenotype of 28.2% in a larger population of 128 UTUC patients, including 22.7% with MSI-H and 5.5% with MSI-L [32]. These differences could partly be explained by the varying definition of the MSI phenotype, encompassing MSI-L patients [26,28] or not [21,23–25,27,29–32], and the number of markers analysed to determine it. For example, Catto et al. [25] showed that the prevalence of the MSI phenotype increased from 16.9% to 26.8% when the number of analysed microsatellites increased from 5 to 10. Using MSIsensor, the prevalence of the MSI phenotype was 6.2% in a cohort of 194 UTUC patients [5].

dMMR Phenotype Determined Using Immunohistochemistry:

In 18 studies using immunohistochemistry, the prevalence of the dMMR phenotype ranged from 2.4% to 57%, with an

even larger variation than that observed for the MSI phenotype [21,22,25,27,28,30–42]. Although the vast majority of these studies reported a prevalence ranging from 2.4% to 26.3% [21,27,28,30–42], two studies found a higher prevalence [22,25]. Interestingly, the study with the highest prevalence of 57% included 44 UTUC patients with only pelvic/colorectal disease [22], while the two most recent multicentre studies reported a prevalence of 3% and 4.6% in 156 and 66 UTUC patients, respectively [21,42]. Except for Garcia-Tello et al. [34] and Wang et al. [38], all studies analysing the four MMR proteins have shown a higher prevalence of the loss of expression of MSH2 and/or MSH6 as compared to MLH1 and PSM2 [21,28,30–32,35–37,39–41].

Comparison of MSI and dMMR Phenotypes

Although most studies using PCR and immunohistochemistry concomitantly found a higher prevalence of the dMMR phenotype [21,25,27,30], Ito et al. reported a similar prevalence of MSI and dMMR phenotypes [31]. In addition, two studies reported a higher prevalence of the MSI phenotype [28,32]. This suggests that the MSI phenotype could result from the loss of expression of other MMR genes or another mechanism. In addition, Calandrella et al. and Ju et al. both reported that a minority of dMMR patients had a concomitant MSI phenotype [37,40], highlighting the limited concordance between these two phenotypes. This is also supported by the lack of correlation between the somatic downregulation of MMR proteins and MSI phenotype in UTUC patients without Lynch syndrome [43].

Prognostic Impact of the MSI/dMMR Phenotype

The patient, tumour and molecular characteristics of UTUC patients with an MSI/dMMR phenotype could differ from those with an MSS/ndMMR phenotype and potentially impact survival. Table 2 summarises the main patient and tumour characteristics of UTUC patients with an MSI/dMMR phenotype, while Table 3 summarises the survival data of UTUC patients with an MSI/dMMR phenotype.

Clinical Characteristics

Younger age at initial diagnosis, a more balanced gender distribution and lower exposure to environmental carcinogens are the three most obvious clinical characteristics of patients with hereditary-like [15] or Lynch-associated UTUC [44,45]. Similarly, of the 12 studies reporting median age at initial diagnosis of UTUC patients with an MSI/dMMR phenotype [25,26,28–31,35–37,39–41], 10 and five studies found that this was <70 years [25,28–31,35,37,39–41] and <65 years, respectively [28,29,31,35,40]. Although two studies did not find any significant differences in median age between UTUC

Table 1 Prevalence of the microsatellite instability/deficient mismatch repair phenotype in patients with upper tract urothelial carcinoma.

| Studies | N | Investigation method | MSI phenotype | | dMMR phenotype | | |
|---------------------------------|-----|----------------------|---------------|--------------------------------|----------------|--|--|
| | | | N (%) | MSI-H/MSI-L/MSI-L + MSS, n (%) | N (%) | Loss of protein expression, n (%) | Combined loss of protein expression, n (%) |
| Blaszyk et al. 2002 [23] | 67 | PCR | 21 (31.3) | 21 (31.3)/NR/46 (68.7) | NA | NA | NA |
| Hartmann et al. 2003 [24] | 132 | PCR | 35 (26.5) | 35 (26.5)/NR/97 (73.5) | NA | NA | NA |
| Catto et al. 2003 [25] | 71 | PCR | 9 (12.7) | 9 (13)/10 (14)/62 (87) | NA | NA | NA |
| | 69 | IHC | NA | NA | 27 (39.1) | MLH1: 27 (39.1) MSH2: 20 (29.0) | NR |
| Amira et al. 2003 [26] | 24 | PCR | 11 (46) | 6 (25/ 5 (21))/18 (75) | NA | NA | NA |
| Roupret et al. 2005 [27] | 80 | PCR | 14 (17.5) | 14 (17.5)/NR/66 (82.5) | NA | NA | NA |
| | 194 | IHC | NA | NA | 21 (26) | MSH2: 21 (26) | NR |
| Ericson et al. 2005 [28] | 194 | PCR | 14 (7.2) | 9 (4.6)/5 (2.6)/185 (95.4) | NA | NA | NA |
| | 200 | IHC | NA | NA | 11 (5.5) | MLH1: 2 (1) MSH2: 7 (3.5) MSH6: 8 (4) PMS2: 2 (1) | MLH1 + PMS2: 2 (1) MSH2 + MSH6: 6 (3) MSH6 alone: 2 (0.9) MSH2 alone: 1 (0.5) |
| Mongiati-Artus et al. 2006 [29] | 58 | PCR | 4 (7) | 4 (7)/NR/54 (93) | NA | NA | NA |
| Bai et al. 2013 [33] | 132 | IHC | NA | NA | 4 (3) | MLH1: 0 (0) MSH2: 4 (3) | NR |
| Ehsani et al. 2014 [22] | 44 | IHC | NA | NA | 25 (57) | MLH1: 8 (18) MSH2: 25 (57) | NR |
| Garcia-Tello et al. 2014 [34] | 80 | IHC | NA | NA | 21 (26.3) | MLH1: 11 (13.6) MSH2: 0 (0) MSH6: 0 (0) PMS2: 21 (26.3) | NR |
| | 215 | IHC | NA | NA | 14 (7) | MLH1: 0 (0) MSH2: 12 (5.6) MSH6: 14 (7) PMS2: 0 (0) | MSH2 + MSH6: 12 (5.6) |
| Metcalfe et al. 2017 [30] | 87 | PCR | 5 (5.7) | 5 (5.7)/2 (2.3)/82 (94.3) | NA | NA | NA |
| | 115 | IHC | NA | NA | 13 (11.3) | MLH1: 0 (0) MSH2: 6 (5.2) MSH6: 13 (11.3) PMS2: 0 (0) | MSH2 and MSH6: 6 (5.2) |
| Urakami et al. 2018 [36] | 143 | IHC | NA | NA | 7 (5) | MLH1: 0 (0) MSH2: 7 (5) MSH6: 5 (3.5) PMS2: 0 (0) | MSH2 + MSH6: 5 (3.5) |
| Ju et al. 2018 [37] | 10* | PCR | 4 (40) | 4 (40)/NR/113 (96.6) | NA | NA | NA |
| | 117 | IHC | NA | NA | 10 (9) | MLH1: 1 (0.9) MSH2: 1 (0.9) MSH6: 9 (7.7) PMS2: 1 (0.9) | MLH1 + PMS2: 1 (0.9) MSH2 + MSH6: 1 (0.9) MSH6 alone: 8 (6.8) |
| Audenet et al. 2019 [5] | 194 | MSI Sensor | 12 (6.2) | 12 (6.2)/NR/NR | NA | NA | NA |
| Wang et al. 2019 [38] | 108 | IHC | NA | NA | 9 (8.3) | MLH1: 6 (5.6) MSH2: 1 (0.9) MSH6: 1 (0.9) PMS2: 7 (6.5) | NR |
| Ito et al. 2019 [31] | 164 | PCR | 4 (2.4) | 4 (2.4)/3 (1.8)/160 (97.6) | NA | NA | NA |
| | | IHC | NA | NA | 4 (2.4) | MLH1: 0 (0) MSH2: 3 (1.8) MSH6: 4 (2.4) PMS2: 0 (0) | MSH2 + MSH6: 3 (1.8) MSH6 alone: 1 (0.6) |

Table 1 (continued)

| Studies | N | Investigation method | MSI phenotype | | dMMR phenotype | | |
|------------------------------|-----|----------------------|---------------|--------------------------------|----------------|--|---|
| | | | N (%) | MSI-H/MSI-L/MSI-L + MSS, n (%) | N (%) | Loss of protein expression, n (%) | Combined loss of protein expression, n (%) |
| Schneider et al. 2020 [32] | 128 | PCR | 29 (22.7) | 29 (22.7)/7 (5.5)/99 (77.3) | NA | NA | NA |
| | | IHC | NA | NA | 24 (18.8) | MLH1: 4 (3.1) MSH2: 17 (13.3) MSH6: 14 (10.9) PMS2: 4 (3.1) | MLH1 + PMS2: 3 (2.3) MSH2 + MSH6: 12 (9.4) |
| Gayhart et al. 2020 [39] | 74 | IHC | NA | NA | 9 (12.2) | MLH1: 1 (1.4) MSH2: 3 (4.1) MSH6: 6 (8.1) PMS2: 3 (4.1) | MSH2 and MSH6: 3 (4.1) MLH1 and PMS2: 1 (1.4) |
| Calandrella et al. 2022 [40] | 7* | PCR | 3 (42.9) | 1 (14.3)/2 (28.6)/6 (85.7) | NA | NA | NA |
| | 27 | IHC | NA | NA | 5 (18.5) | MLH1: 2 (7.4) MSH2: 5 (18.5) MSH6: 5 (18.5) PMS2: 3 (11.1) | MSH2 + MSH6: 2 (7.4) MSH2 + MSH6 + PMS2: 1 (3.7) MSH2 + MSH6 + PMS2 + MLH1: 2 (7.4) |
| Shang et al. 2022 [41] | 175 | IHC | NA | NA | 19 (10.9) | MLH1: 3 (1.7) MSH2: 12 (6.9) MSH6: 8 (4.6) PMS2: 5 (2.9) | MSH2 + MSH6: 6 (3.4) MLH1 + PMS2: 3 (1.7) |
| Kullmann et al. 2023 [21] | 243 | PCR [†] | 4 (1.7) | 4 (1.7)/NR/230 (94.7) | NA | NA | NA |
| | 156 | IHC | NA | NA | 5 (3.2) | MLH1: 0 (0) MSH2: 2 (1.3) MSH6: 4 (2.6) PMS2: 1 (0.7) | MSH2 and MSH6: 2 (1.3) |
| Fontugne et al. 2023 [42] | 64 | IHC | NA | NA | 3 (4.7) | MSH2: 2 (3.1) MSH6: 3 (4.7) PMS2: 0 (0) | MSH2 and MSH6: 2 (3.1) |

IHC, immunohistochemistry; MSI, microsatellite instability; MSI-H, microsatellite instability-high; dMMR, deficient mismatch repair; NA, not applicable; NR, not reported. *Upper tract urothelial carcinoma patients with a dMMR phenotype. [†]Nine invalid cases (3.6).

patients with an MSI/dMMR and those with an MSS/ndMMR phenotype [23,27], Ito et al. [31] reported a lower median age in those with a concomitant dMMR and MSI-H phenotype. In addition, nine of the 16 studies [21,25–33,35–39,41] reporting the male to female ratio at initial diagnosis in these patients, showed that this was <2 [25,26,28–30,32,35,36,38], although six reports providing comparative statistics did not show any significant difference from MSS/ndMMR patients [23,25,27,30,31,41]. However, no difference was found in tobacco exposure between MSI/dMMR and MSS/ndMMR patients [23,30,37,41]. As expected, one study reported that patients with an MSI phenotype had more non-urological cancers than those with an MSS phenotype [23].

Tumour Characteristics

Patients with UTUC and an MSI phenotype are more likely to harbour bilateral and papillary disease [24,33,39]. In addition, a higher prevalence of ureteric disease has been reported in UTUC patients with Lynch syndrome [46], but

the available evidence evaluating tumour location in those with an MSI/dMMR phenotype is conflicting. In 17 studies reporting tumour location in these patients [21,22,25–29,31–33,35–41], the prevalence of pelvicalyceal, ureteric and multifocal disease was 0%–76.2%, 0%–100%, and 0%–31%, respectively. Although there was no significant difference between UTUC patients with an MSI/dMMR and those with an MSS/ndMMR phenotype in seven studies providing comparative statistics [21,23,24,27,30,31,41], the report by Catto et al. [25] showed that those with an MSI-H vs an MSI-L/MSS phenotype were more likely to develop ureteric vs pelvicalyceal disease ($P = 0.019$).

The available evidence evaluating the impact of the MSI/dMMR phenotype on tumour grade and stage in UTUC patients is also highly conflicting. In 17 studies reporting tumour grade in these patients [21–29,31,33,35–40], the prevalence of high-grade disease was 0%–100%. Although seven studies did not find any significant differences in tumour grade between UTUC patients with an MSI/dMMR and those with an MSS/ndMMR phenotype

[25–27,30,31,37,41], the report by Garcia-Tello et al. involving 80 individuals treated with RNU showed that the loss of expression of the MLH1 protein was associated with a higher proportion of low-grade disease ($P = 0.02$) [34]. Nonetheless, the MSI phenotype was significantly associated with the presence of high-grade disease ($P = 0.03$) in the study by Blaszyk et al. [23], which included 67 individuals treated with RNU.

With regard to tumour stage, the prevalence of \geq pT2 disease in UTUC patients with an MSI/dMMR phenotype was 0%–100% in 16 studies reporting this information [21–29,31,32,36–39,41]. Although there was no significant difference between UTUC patients with an MSI/dMMR and those with an MSS/ndMMR phenotype in six studies providing comparative statistics [26,27,30,31,37,41], the report by Garcia-Tello et al. [34] showed that the loss of expression of the PMS2 protein was associated with a lower disease stage ($P = 0.05$). In addition, Catto et al. [25] observed a higher proportion of \leq pT1 disease in UTUC patients with an MSI-H vs those with an MSI-L/MSS phenotype ($P = 0.01$).

Molecular Characteristics

Most molecular studies have focused on UTUC patients with Lynch syndrome, showing that they have a higher mutational burden than those with sporadic UTUC [45]. In addition, the luminal/Uro A molecular subgroup and *FGFR* gene mutations are highly enriched in these patients [47]. Although the vast majority of UTUC patients with an MSI/dMMR phenotype have Lynch syndrome, Audenet et al. [5] have confirmed that the MSI-H phenotype could also be associated with a higher mutational burden in UTUC patients, regardless of this syndrome. Interestingly, Wang et al. also observed an inverse correlation between the expression of GATA3 and MMR proteins in these patients, which could indicate an adverse prognosis of the dMMR phenotype, given that GATA3 is associated with tumour necrosis, high-grade features and extensive lymphovascular invasion leading to faster metastatic spread [38]. Similarly, Calandrella et al. [40] found an inverse correlation between the expression of nectin 4 and MSH2 or MSH6 proteins in a preliminary study including 27 UTUC patients. Finally, a larger report evaluating various tumour types including 46 genitourinary tract malignancies showed that the loss of expression of MLH1 and MSH2 proteins was associated with an increased expression of programmed death ligand 1 (PD-L1) [48].

Survival

Although the MSI/dMMR phenotype is generally considered a favourable prognostic factor in colorectal and endometrial cancers [49,50], the data available in the literature are conflicting for UTUC patients. Indeed, in a retrospective

study by Rouprêt et al. [27] evaluating 80 RNU specimens, the MSI-H phenotype observed in 17% of included patients was associated with significantly prolonged overall survival as compared to the MSI-L or MSS phenotypes (37 vs. 21 months, respectively). The same report also suggested that the 26% of included UTUC patients with a loss of expression of MSH2 protein had significantly prolonged overall survival as compared to those with a ndMMR phenotype (34 vs. 22 months, respectively) [27]. Similarly, Garcia-Tello et al. found a higher rate of 10-year cancer-specific survival for patients with a dMMR vs ndMMR phenotype (85% vs 65.9%, respectively) [34].

However, Schneider et al. [32] did not find any significant difference in overall and recurrence-free survival between UTUC patients with an MSI-H vs MSI-L/MSS phenotype or those with a dMMR vs ndMMR phenotype. Blaszyk et al. [23] also reported similar cancer-specific survival between UTUC patients with an MSI-H phenotype and those with an MSI-L/MSS phenotype. Similarly, Wang et al. and Shang et al. did not observe any association between the dMMR phenotype and recurrence-free [38,41] or cancer-specific survival [41]. Furthermore, Ju et al. and Ito et al. did not find any impact of the concomitant dMMR and MSI-H phenotype on overall survival [31,37]. Finally, a large cohort study reported similar recurrence-free, cancer-specific and overall survival between patients with clinical suspicion for hereditary-like or sporadic UTUC without molecular or genetic confirmation [15].

Impact of the MSI/dMMR Phenotype on Treatment Efficacy

Surgical Treatments

Although no report has specifically evaluated the impact of the MSI/dMMR phenotype on the efficacy of surgical treatments for UTUC patients, a recent meta-analysis of 43 studies conducted between 1996 and 2020 showed that the 5-year cancer-specific survival of those with Lynch syndrome was 91% after RNU [51]. Furthermore, two observational studies described long-term oncological outcomes of surgical treatments in Lynch syndrome patients. On the one hand, Aarnio et al. [52] analysed the outcomes of 12 patients with a constitutional mutation of the *MLH1* or *MSH2* genes treated with either RNU ($n = 11$) or segmental ureterectomy ($n = 1$). After a median follow-up of 5.6 years, the authors observed two recurrences requiring chemotherapy and one death due to widespread metastatic progression. The 5-year cancer-specific and overall survival were 91% and 81%, respectively [52]. On the other hand, Hubosky et al. [53] favoured the use of conservative management with endoscopic laser ablation of UTUC followed by surveillance in 13 patients with a constitutional mutation of the *MSH2* gene, including 73%

Table 2 Clinical and tumor characteristics of upper tract urothelial carcinoma patients with a microsatellite instability/deficient mismatch repair phenotype.

| Studies | N | Investigation method | MSI/dMMR phenotype, n (%) | Median age (years) | Male to female ratio |
|---------------------------------|-----|----------------------|---|-------------------------|---------------------------|
| Blaszzyk et al. 2002 [23] | 67 | PCR | MSI-H: 21 (31.3) MSI-L/MSS: 46 (68.7) P | NR NR >0.05 | NR NR >0.05 |
| Hatmann et al. 2003 [24] | 132 | PCR | MSI-H: 35 (26.5) MSI-L/MSS: 97 (73.5) | NR NR | NR NR |
| Catto et al. 2003 [25] | 71 | PCR | P MSI-H: 9 (12.7) MSI-L/MSS: 62 (87.3) P | NR 67* 68* NR | NR 0.4 NR 0.3 |
| Amira et al. 2003 [26] | 24 | PCR | MSI: 11 (46) MSS: 13 (54) P | 73 68 NR | 1.75 5.5 NR |
| Roupret et al. 2005 [27] | 80 | PCR | MSI-H: 14 (17.5) MSI-L/MSS: 66 (82.5) P | NR NR NR >0.05 | 2.5 2.9 NR >0.05 |
| Ericson et al. 2005 [28] | 200 | IHC | dMMR: 21 (26) ndMMR: 59 (74) P | NR NR >0.05 | 2.5 2.9 >0.05 |
| | | IHC | dMMR: 11 (5.5) ndMMR: 189 (94.5) P | 60 NR NR | 0.36 NR NR |
| Mongiati-Artus et al. 2006 [29] | 58 | PCR | MSI-H: 4 (7) MSI-L/MSS: 54 (93) P | 41.5 68 NR | 1 2.9 NR |
| Bai et al. 2013 [33] | 132 | IHC | dMMR: 4 (3) ndMMR: 128 (97) P | NR NR NR | 3 NR NR |
| Ehsani et al. 2014 [22] | 44 | IHC | dMMR : 25 (57) | NR | NR |
| Garcia-Tello et al. 2014 [34] | 80 | IHC | dMMR: 21 (26.3) ndMMR: 59 (78.7) P | NR NR NR | NR NR NR |
| Harper et al. 2017 [35] | 215 | IHC | dMMR: 14 (7) ndMMR: 201 (93) P | 64* NR NR | 1.8 NR NR |
| Metcalfe et al. 2017 [30] | 115 | IHC | dMMR: 13 (11.3) ndMMR: 102 (88.7) P | 68 NR NR | 0.6 1.3 0.2 |
| Urakami et al. 2018 [36] | 143 | IHC | dMMR: 7 (5) ndMMR: 136 (95) P | 71 NR NR | 0.4 NR NR |
| Ju et al. 2018 [37] | 117 | IHC and PCR | dMMR and MSI-H: 4 (3.4) Non dMMR and MSI-H: 113 (96.6) P | 69 67 NR | 3 1.9 NR |
| Wang et al. 2019 [38] | 108 | IHC | dMMR: 9 (8.3) ndMMR: 99 (91.7) P | NR NR NR | 0.8 1.4 NR |
| Ito et al. 2019 [31] | 164 | IHC and PCR | dMMR and MSI-H: 4 (2.4) ndMMR and (MSI-L or MSS): 160 (97.6) P | 59 72 0.02 | 4 3 0.6 |
| Schneider et al. 2020 [32] | 128 | PCR | MSI-H: 29 (22.6) MSI-L/MSS: 99 (77.4) P | NR NR NR | 1.1 NR NR |
| | | IHC | dMMR: 24 (18.8) ndMMR: 104 (81.2) n | NR NR NR | NR NR NR |
| Gayhart et al. 2020 [39] | 74 | IHC | dMMR: 9 (12.2) ndMMR: 65 (87.8) P | 67 NR NR | 3.5 NR NR |
| Calandrella et al. 2022 [40] | 7** | PCR | MSI-H/MSI-L: 3 (43) MSS: 4 (57) P | 57 NR NR | NR NR NR |
| | | IHC | dMMR: 5 (18.5) ndMMR: 22 (81.5) P | 65 NR NR | NR NR NR |
| Shang et al. 2022 [41] | 175 | IHC | dMMR: 19 (10.9) ndMMR: 156 (89.1) P | 67 NR 0.03 | 2.2 1.3 0.6 |
| Kullmann et al. 2023 [21] | 243 | PCR | MSI-H: 4 (1.7) MSI-L/MSS: 239 (98.3) P | NR NR NR | 3 NR NR |

IHC, Immunohistochemistry; MSI, microsatellite instability; MSS, microsatellite stability; dMMR, deficient mismatch repair; ndMMR, non-deficient mismatch repair; NR, not reported; PCR, Polymerase Chain Reaction. Note: Bold values indicate significance of $P < 0.05$. *Mean age. †Tumor location was not reported for two patients. ‡The loss of expression of MLH1 protein was associated with a lower grade ($P = 0.02$). §The loss of expression of PMS2 protein was associated with a lower stage ($P = 0.05$). ¶Stage \geq pT1. **UTUC patients with a dMMR phenotype.

| Tobacco smoking, n (%) | Tumor location: pelvicalyceal/ureteral/multifocal n (%) | Tumor architecture, n (%) | High tumor grade, n (%) | ≥pT2, n (%) | pN+, n (%) |
|------------------------|---|---|-------------------------|-------------------------|------------|
| NR | NR/NR/NR | NR | 20 (95) | 6 (29) | NR |
| NR | NR/NR/NR | NR | 33 (72) | 8 (17) | NR |
| >0.05 | >0.05 | NR | 0.03 | NR | NR |
| NR | NR/NR/NR | Endophytic: 23 (66) Papillary: 11 (30.3) Sessile: 3 (8.7) | 33 (94) | 12 (34) | NR |
| NR | NR/NR/NR | Endophytic:17 (17.5) Papillary: NA Sessile: NA | NR | NR | NR |
| NR | >0.05 | < 0.0001 | NR | NR | NR |
| NR | 2 (22.2)/7 (77.8)/0 (0) | Endophytic: 8 (88.9) | 8 (88.9) | 1 (11.1) | NR |
| NR | NR/NR/NR | NR | NR | NR | NR |
| NR | 0.019 | 0.02 | 0.2 | 0.013 | NR |
| NR | 7 (63.6)/3 (27.2)/1 (9.1) | NR | 10 (91) | 5 (45) | NR |
| NR | 12 (92.3)/1 (7.7)/0 (0) | NR | 12 (92) | 4 (31) | NR |
| NR | NR | NR | >0.05 | >0.05 | NR |
| NR | 11 (78.6)/3 (21.4)/0 (0) | NR | 14 (100) | 14 (100) | 0 (0) |
| NR | 41 (62.1)/25 (37.9)/0 (0) | NR | 66 (100) | 66 (100) | 14 (21.2) |
| NR | >0.05 | NR | >0.05 | >0.05 | NR |
| NR | 16 (76.2)/5 (23.8)/0 (0) | NR | 21 (100) | 21 (100) | 3 (14.3) |
| NR | 36 (61)/23 (39)/0 (0) | NR | 59 (100) | 59 (100) | 11 (18.7) |
| NR | >0.05 | NR | >0.05 | >0.05 | NR |
| NR | 8 (72.7)/3 (27.3)/0 (0) | NR | 11 (100) | 3 (27.3) | NR |
| NR | NR/NR/NR | NR | NR | NR | NR |
| NR | NR | NR | NR | NR | NR |
| NR | 1 (25)/2 (50)/1 (25) | NR | 3 (75) | 2 (50) | NR |
| NR | 28 (51.9)/16 (29.6)/8 (14.8) [†] | NR | 46 (85) | 22 (40.7) | NR |
| NR | NR | NR | NR | NR | NR |
| NR | 3 (75)/1 (25)/0 (0) | Papillary: 4 (100) | 4 (100) | NR | NR |
| NR | 98 (76.6)/30 (23.4)/0 (0) | Papillary: 128 (100) | NR | NR | NR |
| NR | NR | NR | NR | NR | NR |
| NR | 25 (100)/0 (0)/0 (0) | Endophytic: 17 (39) | 21 (84) | NR | NR |
| NR | NR/NR/NR | NR | NR | NR | NR |
| NR | NR/NR/NR | NR | NR | NR | NR |
| NR | NR | NR | 0.02[‡] | 0.05[§] | NR |
| NR | 4 (28.6)/8 (57.1)/2 (14.3) | Endophytic: 11 (79) | 14 (100) | 7 (50) | NR |
| NR | 97 (48.3)/76 (37.8)/28 (13.9) | NR | NR | NR | NR |
| NR | NR | NR | NR | NR | NR |
| 9 (69) | NR/NR/NR | NR | NR | NR | NR |
| 58 (58) | NR/NR/NR | NR | NR | NR | NR |
| 0.5 | >0.05 | NR | >0.05 | >0.05 | NR |
| 3 (43) | 1 (14.3)/5 (71.4)/1 (14.3) | NR | 0 (0) | 0 (0) | NR |
| NR | NR/NR/NR | NR | NR | NR | NR |
| NR | NR | NR | NR | NR | NR |
| 3 (75) | 2 (50)/1 (25)/1 (25) | NR | 3 (75) | 3 (75) | NR |
| 92 (81) | 53 (47)/41 (36)/19 (17) | NR | 74 (66) | 65 (58) | NR |
| 1 | NR | NR | >0.05 | >0.05 | NR |
| NR | 6 (66.7)/3 (33.3)/0 (0) | NR | 8 (88.9) | 4 (44.4) | NR |
| NR | 46 (46.5)/52 (52.5)/1 (1) | NR | 86 (86.9) | 61 (61.6) | NR |
| NR | NR | NR | NR | NR | NR |
| NR | 0 (0)/4 (100)/0 (0) | NR | 4 (100) | 4 (100) | NR |
| NR | 85 (53.1)/75 (46.9)/0 (0) | NR | 115 (71.9) | 95 (59.3) | NR |
| NR | 0.052 | NR | 0.6 | 0.15 | NR |
| NR | 17 (58.7)/3 (10.3)/9 (31) | Endophytic: 9 (31) | NR | 22 (75.9) | NR |
| NR | 70 (70.7)/16 (16.2)/13 (13.1) | Endophytic: 2 (2) | NR | 82 (82.8) | NR |
| NR | NR | NR | NR | NR | NR |
| NR | 15 (62.5)/3 (12.5)/6 (25) | NR | NR | 18 (75) [¶] | NR |
| NR | 72 (69.2)/16 (15.4)/16 (15.4) | NR | NR | 86 (82) [¶] | NR |
| NR | NR | NR | NR | NR | NR |
| NR | 3 (33.3)/4 (44.4)/2 (22.2) | Papillary: 9 (100) | 7 (77.8) | 6 (66.7) | NR |
| NR | 37 (56.9)/26 (40)/2 (3.1) | NR | NR | NR | NR |
| NR | NR | NR | NR | NR | NR |
| NR | 0 (0)/3 (100)/0 (0) | NR | NR | NR | NR |
| NR | NR/NR/NR | NR | NR | NR | NR |
| NR | NR | NR | NR | NR | NR |
| NR | 4 (80)/1 (20)/0 (0) | NR | NR | NR | NR |
| NR | 12 (54.5)/10 (45.5)/0 (0) | NR | NR | NR | NR |
| NR | NR | NR | NR | NR | NR |
| 8 (52) | 10 (52.6)/8 (42.1)/1 (5.3) | NR | 19 (100) | 10 (53) | 0 (0) |
| 52 (33) | 79 (50.6)/64 (41)/13 (8.3) | NR | 144 (92) | 101 (65) | 13 (8) |
| 0.5 | 0.8 | NR | 0.2 | 0.3 | 0.4 |
| NR | 2 (50)/2 (50)/0 (0) | NR | 4 (100) | 3 (75) | NR |
| NR | NR/NR/NR | NR | NR | NR | NR |
| NR | >0.05 | NR | NR | NR | NR |

Table 3 Survival of upper tract urothelial carcinoma patients with a microsatellite instability/deficient mismatch repair phenotype.

| Studies | N | Investigation method | MSI/dMMR phenotype, n (%) | Survival | P |
|-------------------------------|-----|----------------------|---|---|-------|
| Blaszyk et al. 2002 [23] | 67 | PCR | MSI-H: 21 (31.3) MSI-L/MSS: 46 (68.7) | Similar CSS in MSI-H and MSI-L/MSS patients | 0.9 |
| Rouprêt et al. 2005 [27] | 80 | PCR | MSI-H: 14 (17.5) MSI-L/MSS: 66 (82.5) | Mean time to OS: 37 ± 22 months Mean time to OS: 21 ± 15 months | 0.003 |
| Garcia-Tello et al. 2014 [34] | 80 | IHC | dMMR: 21 (26) ndMMR: 59 (74) | Mean time to OS: 34 ± 22 months Mean time to OS: 22 ± 16 months | 0.02 |
| | | IHC | dMMR: 21 (26.3) ndMMR: 59 (73.7) | 10-year CSS: 85% 10-year CSS: 65.9% | 0.027 |
| Ju et al. 2018 [37] | 117 | IHC and PCR | dMMR and MSI-H: 4 (3.4) Non-dMMR and MSI-H: 113 (96.6) | OS after mean follow-up of 3 years: 33% OS after mean follow-up of 2 years: 48% | >0.05 |
| Wang et al. 2019 [38] | 108 | IHC | dMMR: 9 (8.3) ndMMR: 99 (91.7) | No association between dMMR phenotype and RFS in univariate Cox regression analysis: HR = 0.7 [0.2–2.9] | 0.6 |
| | | IHC | dMMR: 9 (8.3) ndMMR: 99 (91.7) | No association between dMMR phenotype and CSS in univariate Cox regression analysis: HR = 0.7 [0.2–3.1] | 0.7 |
| Ito et al. 2019 [31] | 164 | IHC and PCR | dMMR and MSI-H: 4 (2.4) ndMMR and (MSI-L or MSS): 160 (97.6) | Median time to OS: 70.4 (14.7–97.5) Median time to OS: 85.5 (0.7–142.5) | 0.4 |
| Schneider et al. 2020 [32] | 128 | PCR | 29 MSI-H: 29 (22.6) | Mean time to OS in the overall cohort = 46.7 (1–236) months without any difference between MSI-H and MSI-L/MSS patients | >0.05 |
| | | PCR | MSI-L/MSS: 99 (77.4) | Mean time to RFS in the overall cohort = 32 (2–153) months without any difference between MSI-H and MSS-L/MSS patients | >0.05 |
| | | IHC | dMMR: 24 (18.8) ndMMR = 104 (81.2) | Similar OS between dMMR and ndMMR phenotype and OS in univariate Cox regression analysis: HR = 0.86 [0.45–1.63] | >0.05 |
| Shang et al. 2022 [41] | 175 | IHC | dMMR: 19 (10.9) ndMMR: 156 (89.1) | No association between dMMR phenotype and RFS in univariate Cox regression analysis: HR = 1.4 [0.76–2.7] No association between dMMR phenotype and RFS in univariate Cox regression analysis: HR = 1.5 [0.5–4.2] | 0.4 |

CSS, cancer-specific survival; dMMR, deficient mismatch repair; IHC, immunohistochemistry; MSI, microsatellite instability; MSI-H, microsatellite instability-high; MSI-L, microsatellite instability-low; MSS, microsatellite stability; ndMMR, non-deficient mismatch repair; OS, overall survival; RFS, recurrence-free survival.

with low-grade disease. After a median follow-up of 5 years, three patients had local recurrence, seven patients had bladder recurrence, and only one patient had metastatic spread [53]. Thus, laser ablation could be considered a safe option to preserve renal function in Lynch syndrome patients with a more pronounced genetic risk of contralateral recurrence. However, the use of conservative management in these patients is only supported by highly limited efficacy data that may not apply to the overall MSI/dMMR population.

Systemic Treatments

First, the MSI/dMMR phenotype may confer a decreased sensitivity to chemotherapy for UTUC patients. Although no data are currently available for metastatic disease, a

retrospective study analysed a subgroup of 41 UTUC patients treated with adjuvant chemotherapy after RNU, suggesting reduced progression-free survival in those with the MSI-H vs the MSI-L/MSS phenotype [32]. However, this finding contrasts with results from a French multicentre study including 112 UTUC patients treated with adjuvant chemotherapy after RNU, suggesting greater 5-year progression-free, cancer-specific and overall survival in those with clinical suspicion of hereditary-like vs sporadic disease with no molecular or genetic confirmation [54].

Second, the MSI/dMMR phenotype may confer increased sensitivity to immunotherapy for UTUC patients. Although no data are currently available in the peri-operative setting, some case reports of UTUC patients with metastatic disease have been reported in the literature [55,56]. For example,

Castro et al. [55] observed a complete response to immunotherapy in a 45-year-old patient who experienced metastatic recurrence 3 months after RNU followed by adjuvant chemotherapy for UTUC with a loss of expression of MSH2 and MSH6 proteins related to the mutations of the corresponding genes [55]. In addition, in the cohort study by Shang et al. [41] including 175 UTUC patients, 15 patients experienced disease recurrence, including two with a dMMR phenotype who responded to immunotherapy using programmed death 1 (PD-1) blockade. Furthermore, it is noteworthy that the MSI phenotype has been shown to predict response to PD-1 inhibitors in a population of patients with various solid cancers but UTUC patients were not considered in this report [57].

Finally, the molecular characterisation of UTUC in patients with an MSI/dMMR phenotype could provide some insights into the potential interest of using several targeted therapies. For example, the greater prevalence of FGFR mutations or the increased expression of nectin 4 may enhance the sensitivity of these tumours to erdafitinib [47] or anti-nectin 4 conjugated antibodies [40], respectively.

Discussion

Our collaborative review of the literature summarises the available data from published studies reporting on the genetic mechanisms, investigation, prevalence, and impact of the MSI/dMMR phenotype in UTUC patients. Although the use of PCR and immunohistochemistry methods is well established in daily practice to investigate this phenotype, we observed an absolute variation of over 50% in its prevalence between the studies reporting the lowest [21] and highest rates [22]. This could be explained by the heterogeneity in study populations with different geographical origins or clinical characteristics, but also by the heterogeneity in investigation methods using varying genetic marker panels [25] or antibodies [32] with different definitions for positive testing. Furthermore, the lack of concordance between the prevalence of the MSI and dMMR phenotypes suggests that genetic mechanisms other than mutations of MMR genes or hypermethylation of MMR gene promoters could be at play, although Lynch syndrome remains the predominant cause. In addition, this could encourage concomitant investigation of both the MSI and dMMR phenotypes in daily practice to more accurately identify UTUC patients at risk of hereditary disease.

With regard to the prognostic impact of the MSI/dMMR phenotype, we also observed variable results among the included studies. This could be related to the small study populations of these reports, given the low incidence of UTUC in the general population, which is even more pronounced for UTUC patients with an MSI/dMMR phenotype. However, these patients may generally have a

better prognosis, potentially related to more favourable pathological features, which could favour the use of conservative management, given the more pronounced genetic risk of contralateral recurrence, especially in the context of Lynch syndrome.

With regard to the therapeutic impact of the MSI/dMMR phenotype, limited data suggest that it could confer a reduced sensitivity to adjuvant chemotherapy in RNU patients [32]. From a molecular perspective, it is noteworthy that chemotherapy requires the expression of MMR proteins to induce apoptosis in cancer cells [58], with direct consequences for the management of colorectal cancer patients, for example. Indeed, those with Stage II MSI disease are no longer eligible for adjuvant chemotherapy after extirpative surgery, given their better prognosis and poor response to response to 5-FU alone or 5-FU combined with platinum [59]. Furthermore, the MSI/dMMR phenotype could be associated with a higher mutational burden [5], leading to an increased number of neoantigens and tumour immunogenicity, with case reports suggesting a greater sensitivity of these UTUC patients to immunotherapy. Interestingly, pembrolizumab (anti-PD-1 antibody) has become the first-line treatment for those with metastatic MSI-H colorectal cancer [10], while several studies evaluating neoadjuvant immunotherapy for the treatment of localised MSI-H disease have shown promising results [60]. Nonetheless, no sizeable clinical study evaluating the impact of the MSI/dMMR phenotype on the efficacy of chemotherapy and/or immunotherapy are currently available for UTUC patients.

Given the lack of robust data on the prognostic and therapeutic impact of the MSI/dMMR phenotype, indications for its investigation remain limited to the 80% of patients with a clinical suspicion for sporadic UTUC to refer them for germline DNA sequencing in case of positive test results only, given that the other 20% with a clinical suspicion of hereditary disease are directly suitable for genetic analyses. Further higher quality studies are needed before recommending the routine investigation of the MSI/dMMR phenotype in preoperative biopsies and/or RNU specimens in all UTUC patients, especially to tailor the use of neoadjuvant or adjuvant systemic treatments.

To conclude, our collaborative review of the literature reports significant variability in the prevalence of the MSI/dMMR phenotype in UTUC patients, potentially related to different study populations, investigation methods and definitions for positive testing. Its detection should prompt referral for germline DNA sequencing to screen for Lynch syndrome, with important implications for the patient and their relatives in terms of cancer screening. However, other genetic mechanisms can lead to the MSI/dMMR phenotype in UTUC patients, which could be anyhow associated with a better

prognosis – potentially related to more favourable pathological features – as well as a lower sensitivity to chemotherapy and a greater sensitivity to immunotherapy. Nonetheless, these findings are limited by the low level of evidence.

Disclosure of Interests

The authors declare no conflicts of interest.

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