Review Article

Lynch Syndrome in Urologic Malignancies — What Does the Urologist Need to Know?

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Lynch Syndrome (LS) entails a defective DNA mismatch repair system, which is the postreplicative proofreading and editing system, ensuring our genome's integrity. LS predisposes to several cancers, most commonly colorectal and endometrial cancers. LS occurs in approximately 1 in 250−1000 people.

LS is associated with urological malignancies with upper tract urothelial carcinoma the most common, although still clinically underestimated. Other urologic malignancies possibly associated with LS include bladder, prostate, testis, and renal cell carcinoma. Ascertaining their true prevalence in LS is mandatory for their and their relatives' diagnosis and treatment. Awareness regarding identifying patients at risk for LS through assessment of personal and familial oncologic history is critical among urologists. UROLOGY 134: 24−31, 2019. © 2019 Elsevier Inc.

The constellation of associated hereditary cancers which would eventually be recognized as Lynch Syndrome (LS) was initially reported in 1913 by Aldred S. Warthin and, at that time, called "Cancer Family Syndrome."[1] Subsequently, Henry T. Lynch contributed to the concept of genetic cancer syndrome.[2] In 1984, Boland renamed "Cancer Family Syndrome" to LS,[3] which was recognized as one of first hereditary cancer-prone syndromes. The incidence of LS is approximately 1 in 250-1000 individuals,[4] and colorectal and endometrial tumors are the most common cancers among patients with LS accounting for 1%−4% of all colorectal cancer cases.[5] However, gastric, small bowel, hepatobiliary system, urothelial tumors of the upper tract (UTUC) and ovary are also part of the LS constellation.[6] More recently, evidence has suggested a mechanistic link between LS and other cancers including glioblastomas,[7] pancreas,[8] breast,[9] prostate,[10] and adrenocortical tumors.[11] Muir−Torre syndrome, a variant of LS, is characterized by sebaceous and other skin tumors.[12]

LS is a genetically acquired condition of defective DNA mismatch repair (MMR) system. The MMR system functions as a postreplicative proofreading and editing mechanism, maintaining the genome integrity. In LS, MMR mutations can lead to the development of several cancers. More specifically, LS-associated cancers develop because of autosomal dominant heterozygous germline mutations in 1 of the 4 main MMR genes. These include the: (1) mutL homologue 1 (MLH1), (2) mutS homologue 2 (MSH2), (3) or 6 (MSH6), or (4) post-meiotic segregation increased 2 (PMS2). Additionally, LS-associated cancer can occur resulting from mutations in the epithelial cell adhesion molecule (EPCAM) gene, located upstream of the MSH2 gene. EPCAM affects MSH2 expression through epigenetic silencing caused by promoter methylation.[13]

According to the National Comprehensive Cancer Network (NCCN) guidelines, the cumulative cancer risk between the various MMR genes differs. MSH2 and MLH1 gene variant carriers entail a cumulative colorectal cancer risk of 30%-80% up to age 70; and endometrial cancer risk of 14%-60%.[14] Furthermore, the risk of gastric cancer is higher in Japan, reaching 24%,[15] while being lower in western countries (6%-13%).[14] In the 2 other MMR genes, MSH6, and PMS2, the cumulative cancer risk for colorectal cancer and endometrial cancer are 10%-22%,[14] and 16%-71%,[14] respectively. The cumulative cancer risk of UTUC in MSH2 and MLH1 gene mutation carriers is 1%-7%.[14]

While most cancers in the LS spectrum are beyond the scope of urologists' practice, UTUC is the third most common LS-associated tumor (5%) and is considered part of the LS-tumor spectrum.[16] Although UTUC tumors are relatively rare, accounting for approximately 5% of all urothelial malignancies, there is data showing a considerably higher incidence in LS patients.[16] Moreover, there is evidence suggesting that bladder, prostate, kidney, and testicular germ cell tumors may also be related to LS, but the data is still unclear and contradictory.

Conflict of Interests: *None*.

Financial Disclosure: *This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors*.

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Submitted: April 23, 2019, accepted (with revisions): July 5, 2019

https://doi.org/10.1016/j.urology.2019.07.004
0090-4295

In this review, we will attempt to summarize what is currently known and on the incidence, diagnosis, screening, and recommended treatment of LS-associated urologic malignancies. We aim to increase awareness among urologists regarding this common hereditary cancer syndrome.

MATERIALS AND METHODS

We searched PubMed for available literature on LS combined with each specific urologic malignancy including UTUC, bladder urothelial carcinoma, prostate cancer (PC), testicular germ cell tumors, and renal cell carcinoma. We obtained all relevant studies focusing on incidence, diagnosis, pathology, treatment, and follow-up of these LS-associated malignancies. Search terms included "Lynch syndrome," combined with "Upper tract urothelial carcinoma," "Urothelial bladder cancer," "transitional cell carcinoma," "prostate adenocarcinoma," "Testicular germ cell tumor," and 'Renal cell carcinoma." References from review articles and guidelines were also assessed to develop a narrative review. Standard electronic search methods were used (PubMed database). No limits were set on publication date. All searches were performed using standard search techniques with the exclusion of non-English language, nonhuman studies, editorials/letters, and case reports.

DIAGNOSIS

LS-associated cancers ensue following an MMR gene mutation. This results in a somatic loss of function of the remaining wild-type allele of the affected MMR gene, causing an accumulation of downstream genetic mutations. These cancers commonly manifest microsatellite instability (MSI). Microsatellites are short recursive DNA nucleotide sequences (1-5 long) dispersed throughout the genome. These sequences are constant along a germ-line with a yet unclear function. They can be used as markers in the search for genetic instability. MSI testing is performed using the polymerase chain reaction (PCR). MSI is defined as changes in the length of recursive microsatellite regions, causing single base point mutations, which result due to defective MMR activity.[6] In comparison to sporadic colorectal cancer, with an MSI prevalence of 15%, LS-associated colorectal cancer, manifests MSI in more than 90% of cases.[17] Immunohistochemistry (IHC) can be used to complement MSI testing, by evaluating the expression of the MLH1, MSH2, MSH6, and PMS2 proteins in tumor tissues.[17]

Although sensitive, MSI is not specific for LS-associated cancers, as 15% of sporadic colorectal cancers also demonstrate MSI,[17] as previously mentioned. Sporadic cancers with MSI are commonly characterized by epigenetic silencing of MMR through promoter hypermethylation, especially of MLH1[18] and by BRAF gene mutations.[19] Consequently, BRAF mutation and MLH1 methylation tests can be used to distinguish LS-associated from sporadic colorectal cancers.[19] Furthermore, MSI in sporadic cancers has also been shown to result from biallelic somatic mutations and loss of heterozygosity.[20] These emphasize the need for confirmatory germline mutation testing to distinguish LS from sporadic cancers harboring MMR defects.

Initially, the Amsterdam criteria (Table 1a and 1b) or Bethesda guidelines (Table 1c) were used to identify candidates for LS genetic testing. The Amsterdam I criteria (Table 1a) was established to determine whether family members should be classified as potential LS carriers,[21] and the revised Amsterdam II criteria (Table 1b) were created to incorporate associated extracolonic cancers. The Amsterdam II criteria entail a specificity of 98%, but due to the low sensitivity of 22%,[18] the revised Bethesda guidelines were formulated, entailing an increased sensitivity of 82%, but at the cost of a lower specificity of 77%.[17] These criteria have been shown to miss as many as 27% of individuals with LS.[22] Another important limitation of these criteria is their increased focus on colorectal and endometrial cancer, with little relevance to other known LS-associated cancers. Therefore, universal screening for LS using MSI and IHC for the MMR proteins has been implemented in a steadily growing number of institutions. To date, this has largely been adapted only in colorectal and endometrial cancer cases[23] and has just recently begun in UTUC.[24] Notwithstanding their improved effectiveness, MSI and IHC testing may still miss between 13% and 23% of LS patients, and entail especially low sensitivity for detecting MSH6 and PMS2 mutation carriers.[22]

Table 1. (a) - Amsterdam I criteria; (b) Amsterdam II criteria; (c) Revised bethesda diagnostic criteria

(a) Amsterdam I Criteria[24] (1991)
Three or more family members, one of whom is a first-degree relative of the other 2, with a confirmed diagnosis of colorectal cancer
Two successive affected generations
One or more colon cancers diagnosed before age 50 y
*Patient with familial adenomatous polyposis need to be excluded
(b) Amsterdam II Criteria[18] (1999)
Three or more family members (one of whom is a first-degree relative of the other 2) with hereditary nonpolyposis colorectal cancer related cancers
Two successive affected generations
One or more colon cancers diagnosed before age 50 y
*Patient with familial adenomatous polyposis need to be excluded
(c) Revised Bethesda Diagnostic criteria[17] (2003)
Colorectal cancer diagnosed at an age younger than 50 y
Presence of synchronous or metachronous colorectal cancer, or another LS- associated tumor (tumor of the colorectum, endometrium, stomach, ovary, pancreas, ureter, renal pelvis, biliary tract, brain, small bowel, sebaceous glands, and keratoacanthomas)
Colorectal cancer with MSI-high pathologic-associated features (Crohn-like lymphocytic reaction, mucinous/signet cell differentiation, or medullary growth pattern) diagnosed in an individual younger than 60 y old
Patient with diagnosed in at least 1 first-degree relative younger than 50 y old
Patient with colorectal cancer and colorectal cancer or LS-associated tumor at any age in 2 first-degree or second-degree relatives

* Remark

SCREENING AND SURVEILLANCE

Existing standardized population-based colorectal cancer screening protocols have failed to provide early detection or prevention for most LS colorectal cancer patients, as most of these occur at younger ages.[23] This has promoted initiatives to explore universal LS screening at a population level. In 2009, it was recommended that all colorectal cancers were screened for LS using either IHC or MSI testing.[25] A positive screening test is followed by genetic consultation and DNA testing for MMR mutations for LS confirmation. The NCCN guidelines recommend genetic testing for LS in patients younger than 50 with colorectal and endometrial cancer, who meet the Amsterdam II criteria, or the revised Bethesda guidelines, and for patients with a known LS family history.[14] The European Association of Urology (EAU) guidelines recommend that UTUC patients undergo germline DNA sequencing testing for LS if they are younger than 60, have a personal history of LS, or have 1 first degree relative younger than 50 with LS-associated cancer, or 2 first degree relatives with LS-associated cancer at any age.[26] Early diagnosis of LS enables the potential ability to reduce cancer risk through intensive screening, follow-up programs, and prophylactic surgery.

The implementation of universal screening of LS is still controversial for several reasons. First, is the unclarity regarding which testing platform should be used. IHC is the most commonly used method, achieving high-quality, low-cost, and easily interpretable results.[27] In contrast, the PCR based analysis used to identify EPCAM gene mutations or MLH1 promoter hypermethylation, is more difficult to incorporate in a screening setting. This is due to the lack of PCR capabilities in many laboratories, cost issues, and inadequate pathologist training required for interpreting the results.[28] Second, universal molecular testing of colorectal cancers can miss up to 28% of LS patients, even when using the most liberal clinical criteria supported by the revised Bethesda guidelines.[29] Third, is reaching a consensus on which patients need to be screened. The College of American Pathologists recommends following NCCN guidelines for colorectal cancer, although this recommendation has not been adopted by most pathology organizations.[28] For endometrial cancer patients, the consensus is that patients younger than 50 should be screened. However, the implementation of current methods would result in more than one-fourth of patients being missed.[29] Therefore, the Association of Molecular Pathology has recommended comprehensive testing, using both IHC and PCR platforms, on all new cases of colorectal cancer.[28] MSI and IHC testing synergistically result in roughly 94% concordance rate in both colorectal and endometrial cancer.[30] Third, issues of cost, reimbursement, and benefit in screening have not been studied sufficiently.

Although the implementation of universal colorectal and other LS-associated cancers screening is feasible, it is demanding and raises many unanswered questions regarding clinical and economic impact. From a practical perspective, screening of patients with only "red flags" could be more easily achievable, especially in resource-limited settings.[31]

Similarly, surveillance protocols of LS patients are still considered uncharted territory. The effectiveness of surveillance in LS patients has only been demonstrated in colorectal cancer patients, reducing mortality by 65%, utilizing a 3-year endoscopic surveillance protocol.[32] For known LS patients and for those who are at risk, the current recommended surveillance guidelines for the most prevalent LS-associated cancers are shown in supplemental Table 1.

LYNCH SYNDROME-ASSOCIATED UROLOGIC MALIGNANCIES

There are specific gene mutations in LS which are more associated with urologic malignancies. MSH2 mutations have been shown to increase the risks of several types of extra-colonic tumors,[33] most notably, UTUC. MSH2 mutations are found in 77% of ureteral tumors and 74% of renal pelvic tumors, resulting in 82% of families with MSH2 mutations developing urinary tract cancers.[34] Other urologic malignancies have been described as part of the LS spectrum. These include bladder, prostate, testis, and renal cell carcinoma (RCC).[1,10,34,35] Table 2 summarizes the most important features of urologic malignancies in LS.

UTUC

UTUC entails the highest risk for association with LS, as first reported by Vasen in 1990.[36] Subsequent studies investigating families meeting the Amsterdam or Bethesda criteria have demonstrated an increased risk of 4-17 times and 8-22 times for renal pelvis and ureteral urothelial carcinoma, respectively.[21] LS-associated UTUC has a reported lifetime individual risk of between 2.9% and 28%.[37] This vast reported range in incidence is likely due to the variability in screening and inadequate evaluation of patients at risk. The germline mutation rate in LS-associated UTUC is 63%-100%,[33,38,39] 0%-25%,[33,38,39] and 0%-15%[33,38,39] for MSH2, MLH1, and MSH6 mutations, respectively. MSH2 mutation carriers have a 75-300 times higher risk of UTUC, compared with the general population.[33] Using IHC, loss of MMR protein in LS-associated UTUC has been shown in 0%-14%,[39] 0%-100%,[39] 0%-17%,[39] and 0%-83%[39] for MLH1/PMS2 loss, MSH2 only loss, MSH6 loss, and MSH2/6 loss, respectively. Additionally, MSI has been shown in 32%-71% of cases.[24,39]

Some morphologic characteristics have been suggested to be more prevalent in MMR-deficient UTUC tumors. However, to date, no reproducible morphologic feature has been recognized to be sensitive or specific enough to suggest LS with certainty.[40] In a recently published study, the authors performed next generation targeted sequencing of UTUC from 17 patients with known germline

Table 2. Important clinical features of Lynch syndrome in urologic malignancies

	Incidence in Lynch Syndrome Patients	Age	Gender Association	Commonly Associated Mutation	Remarks
Upper tract	2.9%-28%	Early 60s (10-15 y earlier than the general population)	Higher incidence in females	MSH2	1. Ureteral tumors are more common (51%) 2. More prone to bilateral tumors 3. Better response to adjuvant chemotherapy
Bladder	1%-20%	Late 50s (10-15 y earlier than the general population)	Higher incidence in females	MSH2	
Prostate	Up to 30%	Same incidence as the general population		MSH2, MSH6	
Testicular	Unclear if increased			MLH1, MSH2	
Renal cell carcinoma	Unclear if increased			MSH2, MSH6	

mutations in an LS-associated gene, attempting to characterize the genomic landscape of these tumors and compare the results with those from a cohort of patients with a presumed sporadic UTUC.[41] Many of the driver genes identified in the LS and sporadic UTUC cohorts were similar (FGFR3, KDM6A, PIC3CA, and TP53), but some differences in the genomic profiles were observed. The median number of mutations per tumor was significantly higher in LS-associated UTUC than sporadic UTUC (58 vs 6, $P < .001$). There was an excess rate of frameshift mutations (8%), and copy-number alterations were relatively uncommon. Mutation of some specific genes were found to be almost exclusive to LS-associated UTUC (CIC, NOTCH1, NOTCH3, and RB1).[41] An additional important finding was the identification of an R248C hotspot mutation in FGFR3 that may serve as a potential biomarker for LS in patients with UTUC.[41]

Universal point of care testing using the Amsterdam II and IHC criteria in consecutive UTUC patients identified 13.9% of patients harboring potential LS and 5.2% were confirmed to harbor disease.[24] These data suggest that LS-associated UTUC is largely underestimated, with lacking awareness about this syndrome among urologists, most likely contributing to this. Although UTUC will likely not be the primary LS-associated lesion identified, it could be the presenting malignancy in a small subset of patients, and therefore must be recognized earlier, rather than later.

When compared to sporadic UTUC tumors, LS-associated UTUC is more common among women, diagnosed at younger ages (62 vs 70 years), and exhibiting a higher proportion of ureteral tumors (51% vs 28%).[42] Additionally, patients are more prone to develop bilateral tumors and may exhibit a better response to adjuvant chemotherapy following radical nephroureterectomy (RNU).[43] A promising unvalidated risk assessment tool, developed specifically for patients with UTUC includes gender, age, and personal and family history of LS-associated cancer.[44] The EAU supports the usage of this tool to select patients who are suitable for further LS investigation. These include patients younger than 60 with a personal history of LS-associated cancer, or with a first-degree relative younger than 50 with LS-associated cancer, or with 2 first-degree relatives at any age, with LS-associated cancers.[26]

In 2015 a panel of UTUC experts had recommended surveillance in patients with known LS, who have not yet developed UTUC.[45] These recommendations entailed (1) yearly urinary analysis with a threshold of 3 red blood cells per high power field for further investigations. (2) CT scans performed for follow-up of colorectal cancer is to also include a urographic phase. (3) Cystoscopy should only be performed if retrograde pyelography is done as well. Due to low sensitivity of 29%, urine cytology alone was not recommended. In LS patients with a family history of UTUC, especially those with MSH2 mutations, annual urine dipstick test, and cytology should be performed, in addition to yearly renal ultrasound or CT urography.

Once LS-associated UTUC has been diagnosed, the available surgical options include nephron-sparing surgery (NSS), and the standard RNU with bladder cuff removal. Tumor risk stratification guidelines should guide what treatment is chosen.[26] Low-risk UTUC could be treated by NSS, yielding similar oncologic results as RNU, with lower adverse effects. Since LS-associated UTUC tumors occur at a younger age, with a higher risk of bilateral disease, conservative management has obvious advantages. This has been suggested in 1 study, using minimally invasive surgery with ureteroscopic laser ablation, preserving renal parenchyma.[46] However, this management strategy must be carefully considered due to significant recurrence rates of high-risk disease and need for frequent endoscopic surveillance. These are required to enable early diagnosis of recurrent UTUC and newly emerging bladder tumors. Although bladder tumors are not generally considered part of the LS spectrum, they can develop following NSS or RNU with an incidence of 26%-45%.[46] Currently, there are no data regarding whether there is any difference in intravesical recurrences between sporadic and LS-associated UTUC. However, compared to sporadic UTUC, there is evidence demonstrating an overall- and cancer specific-survival benefit for administering adjuvant cisplatin-based chemotherapy following RNU in patients with LS-associated locally advanced or high-risk UTUC.[43]

Patients with LS-associated UTUC require a strict follow-up protocol to enable early diagnosis of recurrences and diagnosis of other more prevalent LS-associated malignancies. In general, as these cancers occur approximately 10-15 years earlier than in non-LS patients, surveying for all LS-associated malignancies should be initiated at a considerably earlier age. Raised awareness about the increased risk of other LS-associated cancers is mandated with early referral to appropriate specialists and pertinent management.

Lastly, the follow-up protocol of LS patients who undergo RNU is similar to non-LS patients, and should include cystoscopy and cytology at 3 months and then annually, combined with a CT urography every 6 months and then annually.[26] Although CT urography is the supported imaging modality by the EAU guidelines, MRI is valid alternative as well, if CT is contraindicated, and when minimizing lifelong imaging-associated radiation exposure is appropriate.[26]

Bladder cancer

Conventionally, urothelial bladder tumors have not been considered to be part of the "classic" LS tumor spectrum, with an MSI rate of 3%-5%,[47] although one older study found it to be as high as 28%.[48] While LS patients are at an increased risk of UTUC, data regarding bladder urothelial carcinoma association has been lacking. Nonetheless, some published data have suggested an increased risk of bladder urothelial cancer, especially when the *MSH2* gene is mutated.[34] These data demonstrated that LS patients have an increased incidence of bladder urothelial cancer (1-20%), more prevalent in younger patients (59.6 vs. over 70), with a higher female to male ratio than in sporadic cases.[34] The MSH2, MLH1, and MSH6 germline mutation rate in LS-associated bladder cancer is 69-79%,[33,38,39] 10-29%,[33,38,39] and 0%-19%,[33,38,39] respectively. The loss of MMR by IHC in LS patients occurs in 0%-12%,[33,39] 0%-10%,[33,39] and 53-71%[33,39] of MLH1/PMS2, MSH6 only, and MSH2/6 loss, respectively. The proposed association of bladder urothelial cancer to LS could be due to intraluminal seeding from the initial UTUC tumor. Supporting this explanation is the fact that MSH2 mutation was present in both UTUC and urothelial bladder tumor in a study analyzing patients with synchronous tumors.[34] There is increasing evidence showing that relatives of LS patients with MSH2 mutations are at increased risk not only for UTUC but for urothelial bladder cancer as well, albeit with lower penetrance than seen in UTUC. Some suggest that screening for urothelial bladder carcinoma should be considered in patients with known MSH2 mutations, and their first-degree relatives.[34] In contrast, other studies have shown contradicting results with no increased risk observed for bladder urothelial carcinoma in any of the germline MMR mutations.[49]

Prostate cancer

LS patients with PC demonstrate MSI in approximately 20%-65% of cases, primarily harboring MSH2 and MSH6 mutations.[50] The cumulative lifetime risk of PC among MMR mutation carriers has been proposed to be as high as 30%, compared with 18% in sporadic tumors.[51] The germline mutation rate in LS-associated PC has been shown to be 50%-79%,[11,52] 0%-32%,[11,52] 5%-22%,[11,52] and 0%-11%[11,52] for MSH2, MLH1, MSH6, and PMS2, respectively. IHC as shown loss of MLH1 or PMS2, MSH2/6, and MSH6 only in 6%-13%,[11] 50%-63%,[11] and 6%[11] of cases, respectively. A meta-analysis analyzing 23 studies of PC in LS patients demonstrated that men with LS have a higher risk of PC if they had a history of colorectal cancer, or if they had mutation-carrying relatives.[53] The meta-analysis also demonstrated that 74% of PCs in mutation carriers were MMR protein deficient, especially those with MSH2 mutations.[53] Other studies examining the association of LS to PC, have shown an increase of almost 5-fold in the rate of PC diagnosis among men with LS, over a 10-year period.[39] A recent case series of more than 1300 PC cases, demonstrated a 3.1% rate of high-MSI, of whom 21.9% carried a germ-line mutation in a LS-associated gene,[10] with the most common being MSH2.[52] Interestingly, the presumed LS-associated PC does not seem to occur at an earlier age or being more advanced at diagnosis.[53] PC is a malignancy of the elderly, very uncommon before the age of 50. At this relatively young age, other LS-associated cancers usually manifest, and LS patients more commonly die of colorectal cancer, preventing PC, from ever developing. This could potentially mask the incidence of LS-associated PC and would explain its general low incidence.

To date, no level 1 evidence exists showing an increased incidence of PC in LS. However, due to a possibility of such an increased risk, some experts support a trial of prostate-specific antigen testing in MSH2 carriers at an early age between 40 and 50.[49] All studies examining the possible association between LS and PC have only analyzed Caucasian men and data regarding incidence in non-Caucasian men is lacking.

Testicular cancer

The association of LS with testicular cancer is currently unclear. Studies supporting such an association have analyzed refractory rather than primary testicular tumors.[54] A third of refractory tumors and 0%-6% of unselected germ cell tumors were found to have MSI with reduced expression of MLH1 and MSH2,[55] with an increased risk of clinical relapse and death following chemotherapy.[35] Using IHC, loss of MLH1, PMS2, MSH2, and MSH6 has been shown to occur in 0%-4%,[55] 50%-52%,[55] 2%,[55] and 2%[55] of cases, respectively, in unselected germ cell tumors, compared to 0%-36%,[55] 15%-70%,[55] 9%-15%,[55] and 9%-15%,[55] respectively, in refractory germ cell tumors. In contrast, other studies have shown no association with primary testicular tumors demonstrating normal MLH1 and MSH2 expression.[55] This association needs to be further explored before any conclusions can be formulated.

Renal cell carcinoma

RCC is a rare neoplasm in the LS spectrum. However, increased RCC risk has been observed in a large series of LS patients compared to the general population.[38] Moreover, frequent lymphocytic infiltrates, and loss of MMR protein expression have been reported, advocating a possible association between RCC and LS. As in testicular cancer, further research is required to definitively ascertain if a link exists between this malignancy and LS.

THE USE OF IMMUNOTHERAPY IN LYNCH SYNDROME

Immune checkpoints are critical regulators of the immune system, which are required for self-tolerance. Their vital role is to prevent the immune system from attacking cells indiscriminately. The immune checkpoints programmed death 1 (PD-1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA4) pathways are negative feedback systems repressing T-cell cytotoxic immune responses. Immune checkpoint inhibition with antibodies against CTLA4, PD-1 or its associated ligands, has led to phenomenal clinical responses in patients with various types of cancer.[56]

Cancers with high-MSI (as in LS), manifest high mutation rates resulting in the production of mutant immunogenic proteins, associated with a lymphocytic infiltrate.[57] The immunogenicity might be caused by the generation of a large number of neo-antigens, resulting from MMR deficiency (more than 20 times higher than in tumors without MMR deficiency), triggering a significant immune response.[58]

These cancers also overexpress immune-checkpoint proteins (PD-1 and CTLA-4).[58] Clinical trials have shown promising results with immune-checkpoint inhibitors in the treatment of advanced high-MSI colorectal cancer,[59] and recent evidence have also shown a durable effect in PC patients with high-MSI.[10] This could be translated to similar results in all extracolonic, including urologic LS-associated tumors.

CONCLUSION

Urologic malignancies exhibit at least some evidence of a potential association with LS. Determining which urologic malignancies are associated with LS could tremendously impact the diagnosis and treatment of these patients and the recognition of other LS-associated cancers. Importantly, this impacts not only the patients but their relatives as well, who might also be LS-mutation carriers. UTUC is the third-most frequent cancer in LS and is undoubtedly underestimated in clinical practice, with a significant proportion of LS-UTUC tumors wrongfully diagnosed as sporadic tumors.[44] However, aside from UTUC, robust, reproducible data regarding the association of LS to other urologic malignancies is currently lacking.

Notwithstanding current knowledge gaps, urologists must increase their awareness and identify at-risk patients through assessment of personal and familial oncologic history. Enquiring about the history of hereditary colorectal cancer and additional LS-associated cancers should be a standard part of obtaining past medical history. Once LS is established, early detection, referral for appropriate testing, and screening for other LS-associated cancers are critical.

Acknowledgments. We sincerely thank the following individuals for their assistance with this project: Annette Erlich and Cynthia Kuk.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2019.07.004.

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