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Emerging therapeutic strategies in Lynch syndrome-associated colorectal cancer and the role of MMR testing

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Abstract

Lynch syndrome is the most common hereditary cancer predisposition, accounting for 1-5% of colorectal cancer cases, and is driven by germline mutations in DNA mismatch repair genes. Despite established diagnostic criteria, such as the Amsterdam guidelines, Lynch syndrome remains largely underdiagnosed. To address this gap, universal tumour screening has been introduced for all newly diagnosed cases of colorectal cancer and endometrial cancer, significantly improving early detection. The surgical management of colorectal cancer in patients with Lynch syndrome remains controversial. While extended colectomy reduces the risk of metachronous colorectal cancer, surgical strategies must be carefully individualised based on patient-specific factors. Chemoprevention with aspirin has shown promise in reducing the risk of colorectal cancer, with ongoing trials investigating optimal dosing. Immunotherapy, particularly immune checkpoint inhibitors, has revolutionised the treatment of Microsatellite Instability-High/deficient Mismatch Repair colorectal cancer, offering durable responses and significant survival benefits. In addition, the neoadjuvant use of immune checkpoint inhibitors is paving the way for non-surgical interventions, potentially transforming the management of colorectal cancer in patients with Lynch syndrome. A multidisciplinary approach and continued research are essential to optimise cancer prevention, treatment and quality of life for people with Lynch syndrome.

Keywords

Lynch syndrome, colorectal cancer, DNA mismatch repair, universal tumour screening, immunotherapy

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Introduction

Lynch syndrome (LS) is the most common hereditary cancer predisposition condition, affecting approximately 1 in 279 individuals in the general population.[1] It accounts for 1-5% of all colorectal cancer (CRC) cases and 8-15% of those diagnosed before the age of 50.[2] LS results from an autosomal dominant genetic disorder caused by germline mutations in one of the four DNA mismatch repair (MMR) genes: *MLH1, MSH2, MSH6*, or *PMS2*.[3] These genes play a critical role in correcting base mismatches and insertion/deletion loops that occur during DNA replication and recombination, resulting in defective MMR pathway that drives tumorigenesis. Additionally, deletions or mutations in the *EPCAM* gene can also cause LS by impairing MSH2 transcription.

Patients with LS have an increased lifetime risk of developing multiple malignancies, most notably endometrial cancer (with a lifetime risk of 30-51%) and urinary tract cancers (lifetime risk of 2-20%), with CRC being the most common.[4] The Amsterdam criteria, first introduced in the 1990s and later revised in 1999, provided a basic framework for identifying families likely to have LS.[5,6] In 1996, the National Cancer Institute (NCI) convened an international commission to establish the Bethesda Guidelines, which were designed to identify individuals with LS who should undergo testing for microsatellite instability (MSI), a hallmark of MMR deficiency.[7] Despite these advances, clinical application of these guidelines has proven to be suboptimal, with up to 28% of LS diagnoses potentially missed.[8] CRCs associated with LS often exhibit distinct pathological features, including high microsatellite instability (MSI-H) and loss of MMR protein expression on immunohistochemistry (IHC). To address the underdiagnosis of LS, universal tumour screening (UTS) has been introduced, whereby all newly diagnosed cases of CRC and endometrial cancer cases are routinely tested for MMR deficiency or MSI.[9] The application of UTS is particularly relevant in detecting de novo pathogenic variants (PVs), which are relatively rare in LS (approximately the 1-5% of LS patients), but may play a significant role in cases without a family history of cancer. Traditional reliance on family history alone has likely underestimated the prevalence of de novo PVs, as these variants are more frequently observed in younger patients and in families where prior genetic testing has not been conducted.[10]

The goal of UTS is to better identify patients with LS and to ensure appropriate genetic counselling and management for families at risk. The workflow of the UTS has been well documented in the consensus recommendations of the Italian Association for Familial and Inherited Gastrointestinal Tumours (AIFEG).[11] According to UTS, all cases of CRC and endometrial cancer should undergo IHC analysis for the MMR proteins: MLH1, MSH2, MSH6 and PMS2. A negative staining result for MSH2, MSH6, or PMS2 on IHC warrants genetic counselling as it suggests a possible germline mutation in one of these MMR genes. However, in cases where MLH1 shows loss of expression, further testing is required due to the possibility of somatic *MLH 1* promoter hypermethylation, a common non-hereditary cause of *MLH1* inactivation. In addition, the presence of a *BRAF* V600E mutation in CRC rules out LS-related MLH deficiency.[12,13] Therefore, in cases where MLH1 is negative on IHC, BRAF V600E mutation testing and/or *MLH1* promoter methylation analysis should be performed before genetic counselling for LS is considered. Identification of *BRAF* V600E or MLH1 promoter hypermethylation would indicate that the MLH1 loss is likely to be sporadic and not due to LS. Interestingly, recent evidence has shown that *BRAF* V600E immunohistochemistry may serve as a reliable alternative to molecular testing for this mutation.[14] Efforts to improve the performance of UTS include emerging protocols that integrate mainstreaming of LS diagnosis through oncologist-driven counselling. A promising example of this is the ItaLynch study, an ongoing multicentre Italian project evaluating the feasibility of mainstreaming as a diagnostic algorithm for LS.[15]

Characteristics of LS-associated CRC

LS is associated with a significantly increased lifetime risk of CRC compared to the general population. The Prospective Lynch Syndrome Database (PLSD), launched by the European Hereditary Tumour Group (EHTG) in 2012, represents the most comprehensive resource for studying cancer risk in LS patients, collecting data from specialised LS centres worldwide.[16] Another valuable resource is the International Mismatch Repair Consortium (IMRC), a retrospective database that includes patients who have not undergone the standardised surveillance applied to PLSD patients. In 2022, a comparison of data from PLSD and IMRC reported the cumulative incidence of CRC by the age of 75 years: for *MLH1*, the male/female CRC incidence was 40-51.9%/27-41.3%; for *MSH2*, 34-49.6%/23-38.7%; for *MSH6*, 13.4-16%/8.1-16.8%; and for *PMS2*, 7.1-10.7%/5.6-7.9%.[17] The average age at diagnosis of CRC varies considerably depending on the specific gene mutation: approximately 44 years for *MLH1* and *MSH2* carriers, 42 to 69 years for *MSH6*, and 61 to 62 years for *PMS2* mutation carriers.[18]

Studies have shown that regular endoscopic surveillance, including colonoscopy at least every three years, significantly reduces the risk of CRC in LS patients.[19] The latest European guidelines suggest that MLH1 and MSH2 mutation carriers should start colonoscopy at 25 years of age and repeat endoscopy every two to three years. Patients with MSH6 and PMS2 mutations can start surveillance later, at 35 years of age, with repeat colonoscopy every two to three years or every five years for PMS2 mutation

carriers.[20] Standard high quality white-light endoscopy is not inferior to pancolonic chromoendoscopy for LS surveillance and adenoma detection rate when performed by dedicated endoscopists.[21,22]

However, despite surveillance, 23-39% of patients with LS who have previously undergone surgery for CRC will develop metachronous CRC (mCRC) during their lifetime.[23] This evidence clearly has implications for the decision-making process, when a CRC is found in patients with LS and surgery needs to be planned. Kalady et al.[18] retrospectively analysed 296 patients meeting the Amsterdam criteria and found that segmental colectomy was associated with a significantly higher risk of developing mCRC compared with total colectomy/ileorectal anastomosis. Specifically, 25% of patients in the segmental colectomy group developed a second CRC, compared to 11% in the total colectomy group.[18] In a systematic review by Anele et al., [24] which included 871 patients with LS, segmental colectomy was associated with a 22.8% rate of mCRC, compared with 6% in the total colectomy group. Further evidence from the StOET database classified mCRC risk according to germline mutation, identified *MLH1*, *MSH2*, and *EPCAM* carriers as having a higher risk, whereas *MSH6* and *PMS2* carriers had a lower risk. In this cohort, mCRC occurred in 12% of patients with high-risk variants who underwent extensive colectomy, compared with 32% of those who underwent segmental colectomy. For low-risk variants, no patients developed mCRC after extensive colectomy, compared with 16% of those who underwent partial colectomy.[23] Quezada-Diaz et al.[25] supported these findings by reporting no mCRC in a series of 33 PMS2 and MSH6 patients after a median follow-up of 4.46 years. Interestingly, Roh et al.[26] found no significant difference in mCRC rates between LS patients who underwent segmental versus total colectomy when regular colonoscopy surveillance was performed. This suggests that, although many studies indicate a higher risk of mCRC following segmental resection, genetic variants, adenoma history, and other factors also play a critical role. In a large cohort study, Signoroni et al.[27] found that pathogenic variants in *MLH1* and *MSH2* were independent risk factors for mCRC, as was a personal history of colorectal adenomas. Conversely, female gender and total colectomy were protective factors.[28] A key question in the management of patients with LS is whether strategies aimed at reducing mCRC rates also improve overall survival (OS). Data from the PLSD show that the crude OS after CRC as a subsequent cancer in LS patients is as high as 91%, with no significant differences based on the type of pathogenic variant.[29] Similarly, studies comparing OS and CRC-specific survival in patients with LS who underwent segmental or extended resection found no significant difference.[30] In a larger cohort of 527 Dutch patients with LS, the presence of mCRC was also not associated with an increased risk of death.[23] It is important to note that much of the survival data on LS patients was collected before the advent of immunotherapy, which has dramatically improved outcomes in LS-related CRC. Finally, Sinisalo et al.[20] found that the cumulative risk of mCRC after standard resection was 20% at 10 years and 47% at 25 years after, compared with 4% and 9% after extended surgery. The relatively long interval to subsequent CRC suggests that segmental colectomy remains a viable option for certain patients, particularly the elderly who may not tolerate the changes in bowel habits associated with extended surgery. Based on this evolving landscape, the optimal surgical management of LS patients must consider both clinical and molecular data. Decisions should be made in a multidisciplinary setting, taking into account the patient's age, comorbidities, specific gene mutation, history of adenomas, and presence of synchronous tumours. Taken together, these studies provide evidence that although the risk of mCRC is higher than after segmental colectomy than extended resection, it is highly variable and the therapeutic approach needs to be carefully individualised.

Surgical management and quality of life

Historically, surgery has played an important role in the management of hereditary CRC risk, either as a preventive measure or as a treatment for an existing tumour. In LS populations, the risk of CRC is not high enough to recommend prophylactic colectomy in the absence of CRC until regular bowel surveillance is performed. In this setting, surgery may be prophylactic or therapeutic:

1. *Prophylactic total colectomy*: This procedure is performed in LS patients diagnosed with CRC to not only remove the malignancy but also to extend the resection to the entire colon (sparing the rectum or sigmoid colon), thereby reducing the risk of mCRC.
2. *Therapeutic partial colectomy*: The standard oncological segmental colectomy is performed to treat the tumour by removing only the diseased portion of the colon. Although effective in treating the current malignancy, this approach does not reduce the risk of subsequent mCRC because it spares unaffected bowel segments.

The 2021 European guidelines published by the European Hereditary Tumour Group (EHTG) and the European Society of Colorectal Surgeons (ESCP) emphasise that subtotal colectomy is the preferred surgical option for *MLH1* and *MSH2* mutation carriers who are at higher risk of developing mCRC.[31] However, the guidelines highlight that extended colectomy has not been definitively shown to improve overall survival (OS) in patients with LS. Therefore, surgical decisions should be made in a multidisciplinary context, taking into account patient-specific

considerations such as age, gender, personal priorities, and the expected functional and quality of life outcomes after resection.

In 2020, a retrospective analysis by Urso et al.[32] examined surgical outcomes and quality of life in 165 patients with LS who underwent total colectomy with ileorectal anastomosis versus segmental colectomy. Their results showed no significant difference in morbidity or mortality between the two surgical approaches. However, patients in the total colectomy group had worse bowel function than those who underwent segmental resection, although this did not translate into a notable difference in overall quality of life.[32] Similarly, You et al.[33] reported comparable rates of major complications and overall quality of life between patients who underwent subtotal colectomy and those who underwent segmental colectomy. Another notable study by Haanstra et al.[34] of 104 patients with LS (51 who underwent segmental resection and 53 who underwent total colectomy), found that despite worse bowel function and reduced social activity in the total colectomy group, global health status was similar in both groups. These findings suggest that although functional outcomes may differ, the psychosocial and quality of life outcomes remain largely equivalent, allowing for a patient-centred surgical decision that takes into account both functional preservation and cancer prevention.

Rectal cancer

Rectal cancer accounts for only 2.7-6.7% of all MSI-H CRC cases.[35,36] However, a significant proportion of MSI-H rectal cancers are associated with LS, particularly in cases of early-onset rectal cancer.[37,38] Despite this, rectal cancer remains relatively rare in patients with germline mismatch repair (MMR) deficiency.[39]

There are currently no substantial data on the more invasive surgical option of extending colorectal surgery to include proctocolectomy for primary or metachronous rectal cancer. However, European guidelines recommend standard resection (such as anterior resection or abdominoperineal resection) for the first occurrence of primary rectal cancer. Proctocolectomy may be considered for *MLH1, MSH2*, and *MSH6* carriers who develop rectal cancer after a previous CRC.[31] For *PMS2* carriers, the current evidence is insufficient to make clear recommendations.[40] Meanwhile, NCCN and American guidelines do not provide specific recommendations on surgical strategies for primary or metachronous rectal cancer in LS patients.[40,41] Recent advances in immunotherapy offer new options for the treatment of MSI-H rectal cancer. A landmark study by Cercek et al.[37] showed that all 12 patients with MSI-H rectal cancer achieved complete and sustained responses after treatment with dostarlimab, a PD-1 checkpoint inhibitor. Following these findings, any treatment strategy for rectal cancer in patients with LS must consider immune checkpoint inhibitors (ICIs) as the primary therapy option, with surgery reserved for cases of incomplete response or disease recurrence.[37]

Chemoprevention

Chemoprevention involves the use of chemical agents to reduce cancer risk and has emerged as a promising strategy for reducing CRC incidence and mortality in patients with LS. The Colorectal Adenoma/Carcinoma Prevention Program 2 (CAPP2) trial investigated the efficacy of aspirin in this context. In this trial, 861 patients with LS were randomised to receive either 600 mg of aspirin daily or a placebo. After a median follow-up of 10 years, the incidence of CRC was significantly lower in the aspirin group (9%) compared with the placebo group (13%), with a hazard ratio (HR) of 0.65 (95% CI 0.43-0.97; $p = 0.035$).[42,43] Notably, no significant adverse events were reported with aspirin use. Supporting these findings, Ait Ouakrim et al.[44] conducted a study of 1858 LS patients in the Colon Cancer Family Registry. Their research showed that aspirin use was associated with a reduced risk of CRC (from 1 month to 4.9 years: HR = 0.49, 95% CI = 0.27 to 0.90, P = .02; for ⩾5 years: HR = 0.25, 95% CI = 0.10 to 0.62, P = .003), as did ibuprofen use (from 1 month to 4.9 years: HR = 0.38, 95% CI = 0.18 to 0.79, P = .009; for ⩾5 years: HR = 0.26, 95% CI = 0.10 to 0.69, P = .007), compared with less than one month of use.[44] Current guidelines support these findings. The NCCN guidelines suggest that aspirin may be used to reduce the future risk of CRC in patients with LS, emphasising that the optimal dose and duration of therapy should be individualised.[41] Similarly, the American College of Gastroenterology recommends that aspirin be considered for chemoprevention, but advises that its administration be weighed against the potential risks, benefits, and adverse effects.[45,46] Ongoing research continues to refine our understanding of the role of aspirin in chemoprevention. The randomised, double-blind CAPP3 trial is currently evaluating the effect of low, moderate and high doses of daily aspirin on the incidence of LS-associated CRC (NCT02497820). This trial aims to provide more detailed information on the optimal dosing strategies to maximise the chemopreventive benefits of aspirin in this high-risk population.[47]

Immunotherapy

Globally, approximately 15% of stage II-III CRC and around 5% of stage IV CRC exhibit a defect in the mismatch repair genes (dMMR/MSI-H), with roughly 30% of these cases being associated with LS.[48–51] The dMMR/MSI-H phenotype is a predictive biomarker for the efficacy of immune checkpoint inhibitors (ICIs), and immunotherapy has radically changed the management and the prognosis of patients with dMMR/MSI-H metastatic CRC

in the recent years.[52] These patients experienced worse outcomes when treated with chemotherapy compared to their pMMR/MSS counterparts.[53] Initial results of the role of ICIs in dMMR/MSI-H CRC have been reported in the metastatic setting, where they have shown unprecedented high and durable response rates and impressive survival improvements in later lines. Table 1 shows the key clinical trials of immunotherapy in dMMR/MSI-H CRC. The CheckMate-142 study, a multicohort, non-randomised, open-label phase II trial, evaluated nivolumab (an anti-PD1 monoclonal antibody), either alone or in combination with ipilimumab (an anti-CTLA-4 monoclonal antibody), in previously treated patients with dMMR/MSI-H metastatic CRC.[53,54] In a cohort of patients who had progressed after at least one prior line of standard chemotherapy, nivolumab monotherapy achieved an overall response rate (ORR) of 31.1% (95% CI 20.8 - 42.9) and a disease control rate (DCR) of 69% (95% CI 57 - 79). At five years of follow-up, progression-free survival (PFS) and overall survival (OS) rates were 36% and 49%, respectively. The combination of nivolumab and ipilimumab showed even more impressive results, with an ORR of 55% (95% CI 45.2 - 63.8) and a DCR lasting for more than 12 weeks of 80% (95% CI 71.5 - 86.6), along with five-year PFS and OS rates of 54% and 71%, respectively, at 48 months.[55] Lenz et al.[56] reported the results from the first-line cohort of CheckMate-142 treated with nivolumab and ipilimumab, with an ORR and a DCR rates of 69% (95% CI 53 - 82) and 84% (95% CI 70.5 - 93.5), respectively. At 64 months of follow-up, median PFS and OS were not reached, with 60-month PFS and OS rates of 55% and 67%, respectively.[56] Across all cohorts, approximately one-third of reported patients had a clinical history of LS and no differences were observed compared to sporadic dMMR/MSI-H metastatic CRC. These results underscore the potential of immunotherapy to offer durable responses and long-term survival benefits for patients with dMMR/MSI-H CRC, including those with a clinical history of LS, with no significant differences in outcomes between LS-associated and sporadic dMMR/MSI-H metastatic CRC cases.

To answer the question of which is the better first-line treatment in this population, KEYNOTE-177 trial, a randomised phase III trial in treatment-naïve patients with dMMR/MSI-H metastatic CRC, compared pembrolizumab (another anti-PD1 monoclonal antibody) with standard first-line chemotherapy. Pembrolizumab showed superior efficacy with a median PFS (mPFS) of 16.5 months compared to 8.2 months for chemotherapy (hazard ratio (HR) 0.60; 95% CI 0.45 - 0.80, p=0.0002). At final analysis, after a median follow-up of 44.5 months, median OS (mOS) was not reached in the pembrolizumab arm compared to 36.7 months in the chemotherapy arm (HR 0.74, 95% CI 0.53 - 1.03, p=0.036).[57] Although no statistically significant difference in OS was observed, likely due to high crossover rates (60% of patients in the chemotherapy arm crossed over to ICIs at progression), pembrolizumab became the standard of care for first-line treatment in this population. In addition, ICIs were safer and easier to use than chemotherapy. In KEYNOTE-177, grade 3-4 treatment-emergent adverse events (AEs) occurred in 22% of patients in the pembrolizumab arm compared to 66% in the chemotherapy arm. The ongoing CheckMate-8HW trial continues to evaluate the comparative efficacy of nivolumab plus ipilimumab versus standard chemotherapy in the first-line setting for patients with dMMR/MSI-H metastatic CRC. Initial results indicate that the ICI combination (nivolumab plus ipilimumab) significantly prolongs PFS compared to standard chemotherapy (mPFS not reached vs. 5.3 months, HR 0.21, 95% CI 0.14 - 0.32, $p<0.0001$), and the benefit was observed in all pre-specified patient subgroups.[58] The study will provide additional information on the efficacy and safety of nivolumab plus ipilimumab compared to nivolumab alone. The toxicity profile of ICIs is generally well tolerated, with patient-reported outcomes from multiple trials showing clinically meaningful improvements in quality of life and symptom control during treatment, both in monotherapy and combination regimens.[59,60] As reported above, the "revolution" of ICIs has occurred in metastatic disease, first in later lines and then in the first line setting, where it is now standard of care following the Food & Drugs Administration and European Medical Agency approval of pembrolizumab, while the combination of nivolumab and ipilimumab is approved only in refractory disease.[61]

To date, there are no established predictive factors and the benefit of ICIs is observed regardless of gender, ECOG performance status, age, primary tumour location, mutational status (some concerns about RAS mutations), PD-1/PD-L1 expression or LS. In early stage-CRC, MSI status serves both as a prognostic marker, predicting lower recurrence rates in stage II and low-risk stage III disease (T1-3, N1), and as a predictive marker of resistance to adjuvant chemotherapy.[62] For stage II patients with intermediate risk of recurrence (i.e. with one minor risk factor among high nuclear grade, vascular invasion, lymphatic invasion, perineural invasion, tumour presentation with obstruction, preoperative CEA >5 ng/ml) adjuvant chemotherapy with fluoropyrimidine is usually recommended.[63]

However, in the presence of dMMR, fluoropyrimidine alone has shown no survival benefit and may even be detrimental, making these patients candidates for close follow-up rather than adjuvant chemotherapy.[64,65] For dMMR/MSI-H CRC (defined by T4 tumours or perforation, fewer than 12 lymph nodes removed, or the presence of at least two minor risk factors), there is evidence to support the use of adjuvant fluoropyrimidine chemotherapy with oxaliplatin, and patients are still offered adjuvant doublet treatment.[66,67] However, the most promising

Table 1. Key clinical trials of ICIs in dMMR/MSI-H CRC.

Early-stage disease

Study Name	Phase	Intervention	Setting	Number of patients	Primary Endpoint	Response	DFS	OS	Adverse Events	Median follow-up
NICHE (70,71)	Proof of concept	Nivolumab + Ipilimumab	Neoadjuvant, dMMR/ MSI-H and pMMR/MSS stage I-III CRC	32 (dMMR) 30 (pMMR)	Safety, feasibility	PR: 100% in dMMR; 30% in pMMR pCR 69% in dMMR	100% in dMMR	Not yet available	G3 AEs 12%, G4 0%	25 mo
NICHE-2 (72)	II	Nivolumab + Ipilimumab	Neoadjuvant, dMMR/ MSI-H stage III colon cancer	112	Safety, 3y DFS	PR 98%; pCR 68%	100%	Not yet available	G3-4 AEs 4%	26 mo
Cercek et al. (75)	II	Dostarlimab	Neoadjuvant, dMMR/ MSI-H stage II/III rectal cancer	47	Response rate, sustained cCR	cCR 100% (41 evaluable)	100% sustains cCR (20 evaluable)	Not yet available	G3-4 AEs 0%	28.9 mo
UNICORN (NCT ID: NCT05845450)	II	Botensilimab ± Balstilimab	Neoadjuvant, dMMR/ MSI-H and pMMR/MSS rT3-4 N0-2 CRC	14 (dMMR) 14 (pMMR)	mPR rate	Not yet availale	Not yet availale	Not yet available	Not yet availale	Not yet availale

Metastatic disease

Study Name	Phase	Intervention	Setting	Number of patients	Primary Endpoint	Response	PFS	OS	Adverse Events	Median follow-up
CheckMate-142 (53)	II	Nivolumab	Refractory (progressed to at least 1 prior line of treatment) dMMR/MSI-H mCRC	74	ORR	ORR 31% DCR 69%	50%	73%	G3-4 AEs 20.3%	12 mo
CheckMate-142 (79)	II	Nivolumab ± Ipilimumab	Refractory (progressed to at least 1 prior line of treatment) dMMR/MSI-H mCRC	119	ORR	ORR 65% DCR 81%	mPFS NR	mOS NR	G3-4 AEs 32%	50.9 mo
CheckMate-142 (56)	II	Nivolumab + Ipilimumab	Treatment-naïve (1st line) dMMR/MSI-H mCRC	45	ORR	ORR 71%	mPFS NR; 55% (60 mo)	mOS NR; 67% (60 mo)	G3-4 AEs 20%	64 mo
KEYNOTE-177 (57)	III	Pembrolizumab (cohort A), CT (cohort B)	Treatment-naïve (1st line) dMMR/MSI-H mCRC	307	PFS OS	ORR 45 vs 33%	mPFS 16.5 vs 8.2 mo	mOS NR vs 36.7 mo	G⩾3 AEs 22 vs 66%	44.5 mo
CheckMate-8HW (58)	III	Nivolumab (arm A), Nivolumab + Ipilimumab (arm B), CT (arm C; only in 1st line)	Part 1: all lines dMMR/ MSI-H mCRC Part 2: treatment-naïve (1st line) dMMR/MSI-H mCRC	303 (1st line)	PFS arm B vs arm C (1st line); PFS arm B vs arm A all lines (not yet available)	Not yet available	mPFS NR (arm B) vs 5.8 mo (arm C); pending results of arm A and B in all lines	Not yet available	G3-4 AEs 12 vs 10% (arm B vs C)	24.3 mo

PR: Pathologic Response, pCR: Pathologic Complete Response, cCR: Clinical Complete Response, mPR: Major pathological response, ORR: Overall Response Rate, DCR: Disease Control Rate, PFS: Progression Free Survival, OS: Overall Survival, AE: Adverse Events, mo: months; NR: not reached; CT: chemotherapy.

developments are in the neoadjuvant setting, where ICIs have the potential to further revolutionise treatment paradigms. Neoadjuvant chemotherapy for CRC has potential advantages over postoperative treatment, such as shrinking tumours before surgery (reducing the risk of incomplete resection), reducing tumour cell shedding during surgery and eradicating micrometastases, thereby improving the chances of cure.[68] The FOxTROT trial was designed to evaluate the effects of six weeks of neoadjuvant chemotherapy with fluoropyrimidine and oxaliplatin in patients with locally advanced operable CRC (cT3/T4 and/or N+). The trial demonstrated significant benefits, including significant histopathological downstaging, fewer incomplete resections, and a reduction in residual or recurrent disease within two years compared with adjuvant chemotherapy alone (16.9% vs. 21.5%, rate ratio (RR) 0.72, 95% CI, 0.54 - 0.98; p=0.037).[69] However, the study showed that dMMR/MSI-H tumours showed less moderate/greater regression after neoadjuvant chemotherapy than pMMR/MSS (7% vs. 23%, p<0. 001), and no reduction in 2-year disease recurrence could be demonstrated in the neoadjuvant arm comparing patients with dMMR/MSI-H tumours (RR 0.86, IC 95% 0.42 - 1.76, p=0.68) and patients with pMMR tumours (RR 0.69, IC 95% 0.50 - 0.97, p=0.043). Because of the excellent results of ICIs in advanced disease, attempts have been made to extend their use into the neoadjuvant setting.

The exploratory NICHE study was one of the first to explore this approach, evaluating a single dose of ipilimumab and two doses of nivolumab in patients with resectable dMMR/MSI-H CRC. In pMMR/MSS patients, the same regimen was combined with celecoxib, followed by surgery within six weeks.[70] In the dMMR/MSI-H cohort, the results were remarkable, with a 100% pathological response rate among the 32 patients enrolled, 69% of whom achieved a pathological complete response (pCR).[71] The subsequent NICHE-2 study is validating the same combination in a larger cohort of dMMR/MSI-H patients. The study enrolled 112 patients with dMMR/MSI-H colon cancer, 77% of whom had high-risk stage III disease based on radiological staging. Pathological responses were observed in 99% of patients and pCR in 67%, while grade G3-4 adverse events occurred in 3% of patients. After a median follow-up of 13 months, no recurrence was observed after surgery.[72] The above studies excluded extraperitoneal rectal cancer, the management of which remains complex and requires multimodal treatment, including neoadjuvant chemotherapy and radiation.[73] Recently, treatment algorithms have shifted towards a total neoadjuvant therapy, which has been shown to significantly improve pCR rates compared to standard chemoradiation. This shift allows for the possibility of watchful waiting and organ preservation in in those who are clinically complete responders.[74] However, dMMR/MSI-H LARC may not have the same benefit of neoadjuvant induction chemotherapy observed in pMMR/MSS tumours. Recently, a landmark study by Cercek et al. investigated six months of dostarlimab, an anti-PD1 monoclonal antibody, in a single-arm trial in patients with dMMR/MSI-H stage II and III rectal cancer.[75] Those who achieved a clinical complete response (cCR) were managed with a watch-and-wait approach, while standard chemoradiation and surgery were reserved for non-responders. Early results were exceptional, with 100% of patients achieving cCR and none requiring surgery. In addition, no G3-4 AEs were documented. After a median follow-up from first treatment of 28.9 months, all 20 patients with sustained cCR remained disease-free.[76] These impressive results have set dostarlimab as a new standard for neoadjuvant treatment in dMMR/MSI-H LARC.[77]

Many efforts are underway to redefine the neoadjuvant setting in CRC and to establish the role of ICIs, such as the UNICORN trial (NCT05845450), an academic window-of-opportunity umbrella platform trial of short-course preoperative targeted treatments in patients with highly molecularly selected and resectable CRC. In this trial, two cohorts of dMMR/MSI-H cancers have recently completed planned accrual, one with a single dose of botensilimab and the other with a single dose of botensilimab plus two doses of balstilimab followed by surgery. In ICIs trials for dMMR/MSI-H CRC, approximately one third of patients have LS. Overman et al.[53,54] reported that 36% and 29% of patients in the nivolumab and nivolumab plus ipilimumab cohorts of the CheckMate-142 trial had LS, while Lenz et al.[56] observed an 18% LS prevalence in the first-line nivolumab plus ipilimumab cohort. In the NICHE trial, around 33% of patients had LS, and Chalabi et al. found that 57% of patients in their study carried pathogenic germline alterations in mismatch repair (MMR) genes.[70] dMMR/MSI-H rectal cancers are rarer than their colon counterparts, and the majority of these are associated with LS.[1] Published data from clinical trials have not shown significant differences in ICI outcomes between LS-associated and sporadic dMMR/MSI-H tumours, although some evidence suggests improved survival outcomes in LS patients.[78] ICIs offer not only a strong benefit in terms of survival outcomes, but also, in a non-negligible percentage of dMMR/MSI-H metastatic CRC, the chance of cure by achieving a durable and sustained response or, on the other hand, reconsidering surgery with radical intent. However, given the excellent results in the neoadjuvant setting, immunotherapy has the potential to further radically change current clinical and surgical practice. This could lead to the avoidance of demolitive surgeries allowing strategies of non-operative management and organ sparing approaches. These aspects are critical in patients with LS who may experience multiple tumours and associated surgeries or oncological treatments during their lifetime.

Conclusion

Universal tumour screening for CRC has improved the identification of patients with LS, allowing for more timely interventions. Lynch syndrome (LS) presents unique challenges in the management of colorectal cancer (CRC) due to the high risk of both primary and metachronous tumours. The optimal approach to surgical management of patients with LS remains the subject of ongoing debate, balancing the need to reduce cancer risk with the preservation of quality of life. Current evidence suggests that the choice between segmental and extended colectomy should be individualised, taking into account factors such as the specific MMR gene mutation, patient age, comorbidities and personal preferences. Chemoprevention with aspirin has shown promise in reducing the risk of CRC in patients with LS, although optimal dosing strategies are still being investigated. The ongoing CAPP3 trial is expected to provide valuable insights in this area. ICIs therapy is highly effective in the treatment of LS-related CRC, and the indications for immunotherapy are moving from the curative to the neoadjuvant setting, increasing CRC-specific survival and opening up the possibility of non-surgical treatment not only for rectal cancer, but hopefully also for CRC in the near future. As our understanding of LS continues to evolve, multidisciplinary management and shared decision making remain critical. Future research should focus on refining risk stratification models, optimising surveillance protocols and developing targeted therapies for LS-associated CRC. Ultimately, the goal is to provide personalised care that maximises cancer prevention and early detection while minimising the impact on patients' quality of life.

Authors' contributions

SN and EP: conception and design of the study, protocol development, searching for studies, acquisition, analysis and interpretation of data, drafting the article; FB and EDLU: revision of the article. All authors reviewed the manuscript.

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