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Treatment of Microsatellite-Unstable Rectal Cancer in Sporadic and Hereditary Settings

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Abstract

Microsatellite instability is rare in rectal cancer and associated with younger age of onset and Lynch syndrome. All rectal cancers should be tested for microsatellite instability prior to treatment decisions. Patients with microsatellite instability are relatively resistant to chemotherapy. However, recent small studies have shown dramatic response with neoadjuvant immunotherapy. Patients with Lynch syndrome have a hereditary predisposition to cancer and thus an elevated risk of metachronous cancer. Therefore, while "watch and wait" is a well-established practice for sporadic rectal cancers that obtain a complete clinical response after chemoradiation, its safety in patients with Lynch syndrome has not yet been defined. The extent of surgery for patients with Lynch syndrome and rectal cancer is controversial and there is significant debate as to the relative advantages of a segmental proctectomy with postoperative endoscopic surveillance versus a therapeutic and prophylactic total proctocolectomy. Surgical decision making for the patient with Lynch syndrome and rectal cancer is complex and demands a multidisciplinary approach, taking into account both patient- and tumor-specific factors. Neoadjuvant immunotherapy show great promise in the treatment of these patients, and further maturation of data from prospective trials will likely change the current treatment paradigm. Patients with Lynch syndrome and rectal cancer who do not undergo total proctocolectomy require yearly surveillance colonoscopies and should consider chemoprophylaxis with aspirin.

Keywords

- rectal cancer
- MSI-H
- microsatellite unstable
- MMR-D
- Lynch syndrome

Microsatellite-unstable cancers are defined as tumors with neoplastic cells that harbor a high number of mutations within short, repeated sequences of deoxyribonucleic acid (DNA) (microsatellites), caused by a deficiency of the DNA mismatch repair (MMR) system. MMR proteins are responsible for repairing errors in DNA transcription, and when cells are deficient in these proteins, DNA replication errors and corresponding mutations accumulate. This results in tumor microsatellite lengths to deviate more significantly from the length of "normal" tissue microsatellites.[1] When microsatellite testing shows mutations (deviation from "normal" length) in 30% or more microsatellites, the term microsatellite instability-high (MSI-H) applies.[2] MMR deficiency is one of three generally accepted distinct pathways through which colorectal cancer arises (the other two being chromosomal instability and CpG island methylator phenotype or CIMP).[3]

There are four MMR proteins that are most often deficient in microsatellite-unstable rectal cancer: MLH1, MSH2, MSH6, and PMS2. Therefore, MSI-H cancers can also be described as being MMR deficient (MMR-D) in contrast to MMR proficient (MMR-P). MSI-H cancers can either be associated with a hereditary syndrome or occur sporadically as a result of epigenetic changes. In hereditary syndromes, referred to as Lynch syndrome (previously named hereditary nonpolyposis colorectal cancer or HNPCC), a germline pathogenic variant (PV) is present at birth in one of the MMR genes. In sporadic cases, mutations are usually related to the

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CIMP pathway. DNA hypermethylation of *MLH1* promoter prevents MLH1 transcription and thus suppresses MMR function of MLH1.[4,5] CIMP is highly associated with *BRAF* mutation, and therefore the presence of *BRAF* mutation (or *MLH1* hypermethylation) can be used to help identify sporadic MSI-H colorectal cancers[6,7] as Lynch patients typically do not have mutated *BRAF*.[8–10] A PV in the *EPCAM* gene can result in *MSH2* inactivation and so clinically *EPCAM*-associated Lynch syndrome has a cancer risk profile equivalent to patients with *MSH2* PV.[11]

Microsatellite stability is typically assessed via polymerase chain reaction (PCR) and MMR protein expression via immunohistochemistry (IHC). IHC is cheaper, faster, and requires less tissue for analysis as compared with PCR and therefore is often used as the first screening modality for pathologic exam.[8] However, if IHC results are negative for a patient with a strong family history of Lynch-associated cancers, additional tumor testing with PCR should be considered as a 5 to 10% false negative rate has been reported with IHC.[8,12]

Similar to IHC, there is a 5 to 15% reported false negative rate with standard PCR testing for MSI.[12] Next-generation sequencing is the final method to determine microsatellite stability which can examine hundreds to thousands of sequences between tumor and control to assess for variation.[13]

MSI is seen more often in proximal colon cancers, particularly right-sided colon cancer.[1] It is relatively uncommon in rectal cancer,[14] and for all ages, prevalence of MSI in rectal cancer in nonhereditary patients has been estimated as 2.7 to 6.7%.[15,16] In younger patients with rectal cancer, MSI is somewhat more common, although still rare: an international database of rectal cancer diagnosed under age 50 found a 12.5% (50/400) rate of MSI.[17] In general, younger patients with MSI-H tumors are more likely to have Lynch syndrome than older patients with MSI-H tumors. Data from the Colon Cancer Family Registry was analyzed and showed that 39% of young-onset MSI-H colorectal cancers (diagnosed prior to age 50) were associated with Lynch syndrome. Conversely, only 8.6% of patients diagnosed with MSI-H colorectal cancer after age 50 were found to have a germline mutation.[18] Since the vast majority of sporadic MSI-H cancers are right-sided, MSI-H rectal cancer has been shown to be highly associated with Lynch syndrome.[14,17,19,20] Cercek et al report rates of 84% association with Lynch.[19] Additionally, *MSH2* and *MSH6* PVs seem to account for approximately three-quarters of MSI-H rectal cancers.[19,20]

In general, MSI-H colon cancers have a more favorable prognosis as compared with microsatellite stable colon cancers.[1,21] Large clinical data sets have shown that MMR-D colorectal cancers are more likely to present at an earlier stage as compared with MMR-P colorectal cancers.[21] This earlier stage of presentation appears to also hold true for rectal cancer.[17] Other studies have suggested that MMR-D colorectal cancer may be less likely to metastasize as compared with MMR-P colorectal cancer.[22]

Given the relative rarity of MSI-H rectal cancer and the heterogeneity in both patients and treatment regimens, it is unclear whether MMR-D rectal cancer has a more or less favorable prognosis as compared with MMR-P rectal cancer but there is some evidence that MMR-D prognosis may be more favorable.[17,20]

Approach to the Patient

As in any rectal cancer, the clinician must first stage the disease and assure complete evaluation of the entire colon and rectum. Given the association with Lynch syndrome, the clinician must ensure that this endoscopic exam is high quality, with assessment for both synchronous cancer and adenomatous precursor lesions. As in any other rectal cancer, staging should include a contrast-enhanced computed tomography scan of the chest and abdomen, and magnetic resonance imaging (MRI) of the pelvis, and a carcinoembryonic antigen level.

Because MMR status can substantially impact treatment decisions, all rectal cancers should ideally be tested for MMR expression or MSI status on initial biopsy. In cases in which there is not enough tumor material to conduct MMR or MSI testing, the biopsy should be repeated to obtain the necessary tissue to enable accurate diagnosis.[19] There is evidence that MSI status can change over the course of treatment, with radiation causing some MSI-P cancers to become MMR-D.[23,24] As these mutations are acquired they are less likely to impact overall treatment. Therefore, tumor biopsy need not be repeated after neoadjuvant therapy, unless treatment with immunotherapy is contemplated. Of note, one study examined the MMR status of synchronous and metachronous colorectal cancers, and found that one of four patients had primary tumors with discordant MMR status.[25] Interestingly, synchronous rectal cancers with differing microsatellite stability status have been reported in the literature,[26] and therefore tissue should be obtained from any discrete rectal tumor identified. In these situations, the MSI-H mutations are more likely to be acquired. In some instances, tumors initially determined to be MMR-D may actually be MMR-P. In one international trial (CheckMate 142) this occurred in 14/74 patients including 5 patients who had a clinical history of HNPCC.[27] Thus, unexpected responses to therapy should always prompt the clinician to reexamine the foundational clinical data.

As mentioned above, MMR-D rectal cancer seems to have a high likelihood of being related to Lynch syndrome. Sporadic cancers which are MSI-H are usually due to hypermethylation of *MLH-1* (which is also associated with a V600E mutation in *BRAF*). Therefore, if MLH-1 deficiency is found on IHC, it is common practice to reflexively check for hypermethylation and/or *BRAF* mutation. If *MLH-1* is hypermethylated or if *BRAF* is mutated, the patient can be assumed to have acquired MSI.[28] On the other hand, if *MLH-1* is not hypermethylated, or if any one of the other MMR proteins are deficient, it is highly likely that the patient has Lynch syndrome and should be referred to a genetic counselor for confirmatory germline genetic testing. Given that some patients with a hereditary predisposition to cancer may be unaware of a family history of cancer (due to adoption, young

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age of death, small family size) and also that germline mutations can arise de novo,[29] it is essential that genetic testing be obtained in these patients, even without a known family history of cancer. Prior to germline genetic testing, consultation with a genetic counselor is critical to help the patient understand the implications of genetic testing, both for themselves and for their families, and provide support for the patients and family members during the process.

Finally, Lynch patients often present younger than other colorectal cancer patients and may desire future childbearing. Because radiation, chemotherapy, and surgery have fertility implications for patients of both genders, the clinician must specifically inquire about the patient's desires for biologic parenthood prior to commencing treatment, so that the patient can be referred to fertility preservation experts if appropriate. For patients fearful of passing Lynch syndrome on to their progeny, preimplantation genetic testing is a newer option for patients undergoing in vitro fertilization.[30]

Neoadjuvant Therapy

Treatment of rectal cancer should always include multidisciplinary evaluation in a standardized "tumor board" format.[31] The standard of care for stage II and III rectal cancer below the anterior peritoneal reflection is neoadjuvant therapy to minimize the risks of local recurrence.[32,33] Recently, many rectal cancer centers have embraced a total neoadjuvant therapy (TNT) approach which gives all of the intended chemotherapy in the neoadjuvant setting.[34] Neoadjuvant chemotherapy is often better tolerated than adjuvant chemotherapy after proctectomy and this approach has been shown to result in a greater percentage of patients receiving all of the recommended chemotherapy. Additionally, a substantial proportion of patients may obtain a complete clinical response after this therapy and be eligible for a "watch and wait (WW)" protocol and avoid surgery unless evidence of tumor regrowth is identified.[35,36] However, MSI-H colon cancer is relatively resistant to chemotherapy. This is likely due to the fact that many traditional chemotherapeutic agents require an intact DNA repair system to be effective.[2,37,38] Not surprisingly, MMR-D rectal cancer appears to share this resistance to chemotherapy.[19]

Given that MSI-H tumors tend to be relatively resistant to chemotherapy, induction chemotherapy and consolidation chemotherapy may have limited value in these patients and therefore the use of TNT in these patients is controversial. If chemotherapy is elected, the patients must be followed carefully as the tumors may progress on chemotherapy.[19] In MSI-H rectal cancer, radiation has the larger role in neoadjuvant therapy and chemotherapy is mostly utilized as a radiosensitizer. Thus, the standard approach for locally advanced MSI-H rectal cancer would be long-course chemoradiation with reassessment of response. If no downstaging is required (nonthreatened margins, adequate distal margin to allow for restorative surgery after resection), short-course radiation may be an acceptable alternative. Of course, if metastatic disease is found, immunotherapy should also be considered.[39–41]

Several studies have suggested that MMR unstable tumors have less downstaging with neoadjuvant chemoradiation as compared with MMR-P patients[42] and are less likely to obtain a complete pathologic response.[43] Conversely, other studies have suggested strong chemoradiosensitivity for microsatellite-unstable rectal cancer[19] with some authors reporting improved downstaging as compared with microsatellite stable rectal cancer.[17,20] Variability in outcomes is likely related to the relative rarity of MSI-H rectal cancer and the significant heterogeneity in clinical characteristics of patients and treatment regimens chosen.

Immunotherapy is a well-established option for metastatic MSI-H cancers, including rectal cancer.[39] Emerging evidence from small series with short-term follow-up demonstrates that immunotherapy has a role in neoadjuvant therapy for MSI-H rectal cancer,[44] and may allow organ preservation without radiation or surgery.[45] A seminal trial out of Memorial Sloan Kettering used upfront immunotherapy to treat locally advanced MSH-H rectal cancer in 12 patients and found that all patients were able to obtain a complete clinical response (as determined by endoscopy, positron emission tomography, digital rectal exam, and MRI) without the addition of chemotherapy or radiation with at least 6 months of follow-up.[45] Currently, these options are not available outside of investigational studies, but show great promise to change the treatment paradigm for MMR-D rectal cancer in the near future. The patient and clinician should exercise caution as the long-term benefit, duration of response, and organ preservation rates have not yet been established. Since patients with Lynch syndrome have a germline predisposition to cancer, nonoperative management with immunotherapy likely entails an increased risk for metachronous colorectal neoplasia. Therefore, in the absence of larger series with mature follow-up data, this treatment approach remains controversial and should be reserved for patients enrolled in clinical trials with intense long-term surveillance.

Assessment of Response to Neoadjuvant Treatment and "Watch and Wait"

After neoadjuvant treatment the patient should be assessed for response with digital rectal exam, flexible proctoscopy, and MRI. Special attention should be given to residual tumors that are invading adjacent structures or threatening the circumferential resection margins as this will guide the extent of surgery. Attaining a R0 resection with total mesorectal excision is essential. If the tumor has a complete response to neoadjuvant therapy, organ preservation with a "WW" approach should be discussed with the patient.[35] Due to the rarity of MSI-H rectal cancer and the fact that WW is a relatively new treatment paradigm, the patient must be counseled that there is little long-term data regarding the risk of tumor regrowth and the survival for this approach with MSI-H tumors, but represents a reasonable treatment approach in a motivated patient. In patients with MSI-H tumors due to Lynch syndrome, in addition to the concern for tumor regrowth with WW, one must also consider the

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increased risk for metachronous cancer.[46] As discussed above, there is currently no long-term data available regarding outcomes of nonoperative management in rectal cancer patients with Lynch syndrome, and this approach requires an established multidisciplinary team with expertise in the nonoperative management of rectal cancer and Lynch syndrome surveillance.

Surgical Considerations for Patients with Lynch Syndrome

Since the risk of metachronous colorectal cancer is significantly elevated in the patient with Lynch syndrome, the standard of care for the Lynch patient involves prophylactic extended resections for colon cancer (which would typically be a total abdominal colectomy with ileorectal anastomosis). Risk-reducing extended resection is more controversial in the Lynch patient with rectal cancer, due to the need for a total proctocolectomy (TPC) with end-ileostomy or ileal pouch anal anastomosis (IPAA), which is a more complicated surgery with a higher risk for perioperative complications and more significant functional implications.[47] In locally advanced rectal cancer requiring neoadjuvant chemoradiation, the functional outcomes are further compromised due to pelvic irradiation. Therefore, if a J-pouch is contemplated, there is some rationale to avoid radiation in rectal cancer at relatively lower risk for local recurrence, such as those that are in the proximal rectum, where the circumferential radial margin is not threatened, and when the surgeon can assure a high-quality total mesorectal excision. Conversely, radiation after J-pouch construction typically results in poor pouch function, and so if radiation is ultimately required, the pouch outcomes will be much better with preoperative radiation as opposed to adjuvant radiation therapy.[48]

The rationale for TPC in Lynch patients with rectal cancer is based on studies demonstrating that the risk of metachronous cancer in the remaining colon in patients treated with proctectomy alone is high. Win et al queried the Colon Cancer Family Registry and were able to extrapolate a cumulative risk of metachronous colon cancer of 19% at 10 years and 69% at 30 years.[49] Importantly, these patients were undergoing colonoscopic surveillance, suggesting that prophylactic surgery might be the only effective risk-reducing approach for a young Lynch patient. In another study using Cleveland Clinic's Jagelman Registry data to examine the risk of metachronous colon cancer after proctectomy in patients meeting the Amsterdam criteria, Kalady et al reported that 51.5% of patients developed a high-risk adenoma or cancer after proctectomy.[50] Together, these studies provide rationale for considering prophylactic proctocolectomy in patient with Lynch syndrome and rectal cancer.

It is clear that proctocolectomy prevents cancer development, but some argue that this comes at the expense of additional morbidity without impacting overall survival. A study from MD Anderson examined their Colorectal Surgery and Gastrointestinal Genetic Counseling Database and identified 62 patients over 20 years with MSI-H rectal cancers. Seventy-four percent of patients had an identified germline PV and 98% of patients met the revised Bethesda criteria. They found no difference in 5-year overall survival between patients undergoing segmental or extended resections for rectal cancer although there was a 17% rate of metachronous colon cancer at a median of 7.8 years in the patients who underwent segmental resection.[20]

A recent publication from the prospective Lynch syndrome database evaluated the incidence of metachronous colorectal cancer and colorectal cancer-related deaths occurring in Lynch syndrome patients stratified by MMR PV undergoing colonoscopic surveillance following a previous cancer diagnosis.[46] The cumulative incidences for subsequent colorectal cancer were 46, 48, and 23% for pathogenic *MLH1*, *MSH2*, and *MSH6* carriers, respectively. The mean time from last colonoscopy to cancer diagnosis was 31.8 months (median 27 months) with a 94% five-year and 91% ten-year survival,[46] demonstrating that even under endoscopic surveillance the risk for metachronous colorectal cancer remains significant, but is different for *MLH1* and *MSH2* versus *MSH6* PV carriers, and is associated with good survival.

Similarly, Quezada-Diaz et al queried the Memorial Sloan Kettering Hereditary Colorectal Cancer Family Registry to determine the risks of metachronous colorectal cancer by PV after segmental colectomy. In their retrospective study all patients were undergoing surveillance colonoscopy although the precise interval was not specified. They found that at 10 years, 12% of all Lynch patients would develop metachronous colorectal cancer, but no patients with *MSH6* or *PMS2* PVs would do so. They concluded that segmental colectomy with close colonoscopic surveillance is a reasonable option for carefully selected *MSH6* and *PMS2* patients. Notably, two patients with *PMS2* did develop a metachronous colorectal cancer at 20 and 37 years after resection and one patient with *MSH6* developed a metachronous colorectal cancer 46 years after resection. Therefore, it is important to remember that the risk of metachronous cancer in *MSH6* and *PMS2* is lowered but not eliminated with colonoscopic surveillance.[51]

Adding to the complexity of surgical decision making in rectal cancer is that the majority of the data supporting segmental resection in Lynch syndrome was taken from studies looking at all colorectal cancer and is not specific to rectal cancer. Because Lynch syndrome cancers are most commonly right-sided, a patient whose index surgery is a proctectomy with their right colon intact may have a higher incidence of metachronous cancer than a patient who underwent a right or an extended right colectomy for an index right colon cancer.

Ultimately, the decision whether to undergo segmental proctectomy or TPC (with either restorative IPAA or permanent end-ileostomy) must clearly be an individualized one and discussed carefully with the patient to allow for a well-informed decision. Factors favoring a TPC ± IPAA include: young age, early-stage rectal cancer with a low risk for recurrence (not necessitating radiation), synchronous high-risk lesions, high-risk PV (*MLH1* and *MSH2*), good sphincter function, patient's fear of cancer, or anticipated poor compliance with life-long close endoscopic surveillance. On the other hand, older patient age, significant medical comorbidities, advanced-stage rectal cancer (with higher potential for recurrence than developing a metachronous colon cancer), poor sphincter function, need for pelvic radiation, low-

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risk PV (*MSH6* and *PMS2*), and anticipated good compliance with high-quality colonoscopic surveillance are factors that tip the scale toward a proctectomy without prophylactic total colectomy.

Finally, the colorectal surgeon must consider that patients with Lynch syndrome also have an elevated rate of endometrial cancer. Given that proctectomy will involve a pelvic dissection, the uterus should be assessed by a gynecologist prior to surgery and risk-reducing surgery with prophylactic hysterectomy with or without bilateral salpingo-oophorectomy should be considered.[52] Endometrial cancer risk up to age 70 has been reported as 35.2% (*MLH1*), 46.5% (*MSH2*), 41.1% (*MSH6*), and 12.8% (*PMS2*).[7] Therefore, in Lynch patients who are postmenopausal or who have completed child-bearing, a risk-reducing hysterectomy with or without bilateral salpingo-oophorectomy is generally performed at the time of proctectomy after a discussion of risks and benefits.[47]

Surveillance

Systematic surveillance for MSI-H patients should proceed similarly to standard surveillance for rectal cancer, according to the National Comprehensive Cancer Network guidelines. Colonic surveillance for metachronous neoplasia in the patient with sporadic MSI-H rectal cancer would follow routine guidelines with colonoscopies at 1 and 3 years after cancer diagnosis, then lifelong colonoscopies at a 5-year interval (with increased frequency if high-risk adenomas are found). Patients with Lynch syndrome who do not undergo a TPC should undergo Lynch-specific colonic surveillance, with lifelong frequent high-quality colonoscopy at 1-year intervals. Finally, chemoprophylaxis with aspirin should be discussed with these patients. The CAPP2 trial (Concerted Action Polyposis Prevention) is a multi-institutional, international, double-blinded randomized controlled trial comparing 600 mg daily aspirin prophylaxis to placebo in 861 patients with Lynch syndrome. Long-term follow-up (10–20 years) analysis has shown a decrease in the incidence of colorectal cancer from 13% (for those taking placebo) to 9% (for those taking aspirin) for patients who were compliant for a 2-year course of treatment without significant differences in adverse events or compliance between the two groups.[53,54]

Conclusion

In summary, many aspects of the care of the microsatellite-unstable patient with rectal cancer proceed according to the well-established practice of care for any rectal cancer patient, with the significant consideration of a limited benefit chemotherapy and a potential very promising role for immunotherapy. For the Lynch patient, surgeons must additionally consider risk-reducing surgery such as prophylactic colectomy and hysterectomy (with or without oophorectomy), careful attention to postoperative surveillance, and the fact that long-term outcomes of organ preservation have not been studied in the Lynch patient.

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Conflict of Interest
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