Identifying Lynch Syndrome in Patients With Endometrial Carcinoma: Shortcomings of Morphologic and Clinical Schemas

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Abstract: It has been suggested that reflex testing for Lynch syndrome (LS) using mismatch repair immunohistochemistry and/or microsatellite instability analysis in newly diagnosed colorectal carcinoma (CRC) patients is an emerging standard of care in the United States. The risk of gynecologic malignancy in women with LS approaches and even exceeds that of CRC. Furthermore, gynecologic malignancies are often the sentinel cancers in these patients. There is significant variation in practice, but some groups have similarly recommended deployment of reflex testing strategies in patients presenting with endometrial cancer (EC). The College of American Pathologists has stated that pathologists should recognize the histologic and clinical features that should prompt at least a recommendation for mismatch repair testing. Morphologic and clinical schemas in EC to identify microsatellite unstable/LS tumors are less refined than the colon-centric schemas (Amsterdam, Bethesda, and MsPath). Studies of LS EC are few and interpretation is limited by recruitment strategies and the myriad of definitions and study designs used. Although serous cell type is used to triage ovarian cancer patients for BRCA screening, cell type correlation in LS is less certain but seems to involve a spectrum of cell types. We review the morphologic and clinical features/schemas in LS EC and highlight limitations of restrictive aged-based screening strategies, uncertainty in current clinical schemas and equivocal results of morphologic studies of LS EC. With uncertainty of histologic and clinical schemas, and following developments in CRC, reflex testing of all/vast majority of newly diagnosed EC for LS should be considered.

Key Words: lynch, endometrial cancer, clinical schemas, morphologic schemas, reflex testing

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Mismatch repair deficiency (dMMR) status is increasingly utilized as a prognostic, predictive, and possible germline predisposition/Lynch syndrome (LS) biomarker in colorectal carcinoma (CRC).[1] There is growing recognition of extraintestinal tumors, particularly gynecologic malignancies, in LS. Women with LS have a 40% to 60% and a 10% to 12% lifetime risk of endometrial cancer (EC) and ovarian cancer (OC), respectively, and in 60% of these women, a gynecologic malignancy will be the sentinel malignancy.[2,3] Identification of LS at this juncture will allow implementation of effective colon cancer screening and prevention strategies and identification of at risk and not at risk family members with appropriate cancer screening.

THE ROLE OF PATHOLOGY IN IDENTIFYING PATIENTS WITH LYNCH SYNDROME: MORPHOLOGY VERSUS REFLEX TESTING

Optimal algorithms for the detection of dMMR/LS in patients presenting with relevant tumors are uncertain and practice varies. Typically, family/personal medical history and tumor morphology or topographic location serve as the tocsin followed by mismatch repair immunohistochemistry (MMR-IHC) and/or and microsatellite instability (MSI) analysis with subsequent germline testing of the corresponding MMR gene(s).

Recognizing the accelerated adoption of MMR testing the College of American Pathologists has stated that pathologists "need to recognize the histologic and clinical features that should prompt at least a recommendation for MMR testing."[4]

However, the most likely clinical feature encountered by the pathologist is patient age, and this criterion is controversial.[5] Morphologic criteria are not absolutely defined and although useful, are limited by interobserver variation. Germane to this review, such features in extraintestinal cancers are poorly characterized. Basing the recommendation to perform a class II laboratory test on such features is not ideal and in a recent publication we highlighted discrepant practice in this regard.[5] Finally, recommendations to test may be "overlooked" by the clinical team.[6]

These issues, in conjunction with lacklustre performance of clinical schemas and overall low referral rates have prompted recommendations of reflex testing on all incident cases of CRC and EC, with most advocating use of MMR-IHC.[7–10] These proposals are further supported by studies demonstrating acceptable cost-benefit ratios.[9] Reflex testing refers to routine testing performed by a pathologist without specific clinician request. In the proposals cited above, it is typically premised on tumor type (eg, colon, sebaceous, or EC) similar to hormone receptor testing in breast cancer, with or without a liberal age-based criterion (eg, < 70 y). Alternatively the initiating event for reflex testing may be a morphologic finding. It is difficult to include clinical criteria (other than age) in reflex testing strategies as the pathologists may not be aware of such history. Deploying reflex MMR-IHC testing represents a paradigm shift from nonlaboratory physician initiated screening to laboratory physician driven screening.

With the growing role pathologists are set to play in LS detection, it is incumbent on us to address the practical and ethical issues involved. In this article we will briefly highlight shortcomings of clinical schemas for LS EC,

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review the morphologic and age demographic features of LS EC, and thereby assess the feasibility of reflex testing strategies premised on the latter 2 criteria.

ENDOMETRIAL CANCER IN LYNCH SYNDROME

About 2% of women and 10% of women under 50 years with EC have LS. Data and in particular histology data of LS EC is limited, with interest blunted by the assumption that EC has a good prognosis and hence not clinically significant. As highlighted by Walsh et al,[11] the myriad of study designs used is also confounding. There are few studies of mutation confirmed LS EC and many of these cases have been identified through CRC registries rather than prospective EC screening programs. In the absence of germline confirmation, study cohorts include MSI-high (MSI-H) EC (with different MS markers used), MMR-IHC–deficient EC with or without methylation status and less commonly methylation status only studies. Few prospective studies have looked at an unselected EC population. Furthermore study cohorts are typically small with no or variably defined control groups.

FAMILY HISTORY

The traditional clinical schemas for LS, Amsterdam and Bethesda, are colon-centric and have been shown to perform poorly in identifying LS in patients with gynecologic malignancies.[12–14] The Society of Gynecologic Oncology (SGO) has recently proposed 2 new schemas (SGO 20% to 25% and SGO 5% to 10%) which are focused on hereditary gynecologic tumors.[15] Using detailed family pedigree data, we confirmed that these schemas are more sensitive in identifying LS in women with EC.[14] However, their specificity is untested and there are several aspects in which there is uncertainty in these schema including the lack of a specific genetic risk assessment strategy.[10,14]

Reflecting similar difficulties with LS CRC the Evaluation of Genomic Applications in Practice and Prevention Working Group recommended exclusion of family history

TABLE 1. Distribution of Cell Type From Studies With Central Pathology Review of LS EC

	Endometrioid	Serous	Clear Cell	Mixed/Other/Nonendometriod	MMMT
Broaddus et al[17] n = 50	43 (86%)	—	3	3 mixed	1
	19 grade 1 17 grade 2 7 grade 3	—	—	—	—
Palacios et al[18] n = 16	10 (62.5%)	—	—	—	—
Carcangiu et al[19] n = 23	13 (56.5%)	2	5	1 mixed	2
	3 grade 1 4 grade 2 6 grade 3	—	—	—	—
Ryan et al[14] n = 38*	29 (76.3%)	2	1	5 mixed	1
	26 grade 1 3 grade 2 0 grade 3	—	—	—	—
van den Bos et al[20] n = 6	6 (100%)	—	—	—	—
	1 low grade 5 high grade (binarized FIGO)	—	—	—	—
De Leeuw et al[21] n = 23	20 (87%)	1	—	1 mixed 1 squamous cell carcinoma	—
	12 grade 1 7 grade 2 1 grade 3	—	—	—	—
Westin et al[22] n = 10†	6 (60%)	—	—	—	—
	1 grade 1 3 grade 2 2 grade 3	—	—	—	—
Berends et al[23] n = 5‡	4 (80%)	—	—	1 NEEC	

*Identified through colon cancer registry.
†Patients with lower uterine segment tumors.
‡Patients younger than 50 years.
EC indicates endometrial cancer; LS, Lynch syndrome; MMMT, malignant mixed Mullerian tumor; NEEC, nonendometrioid endometrial carcinoma.

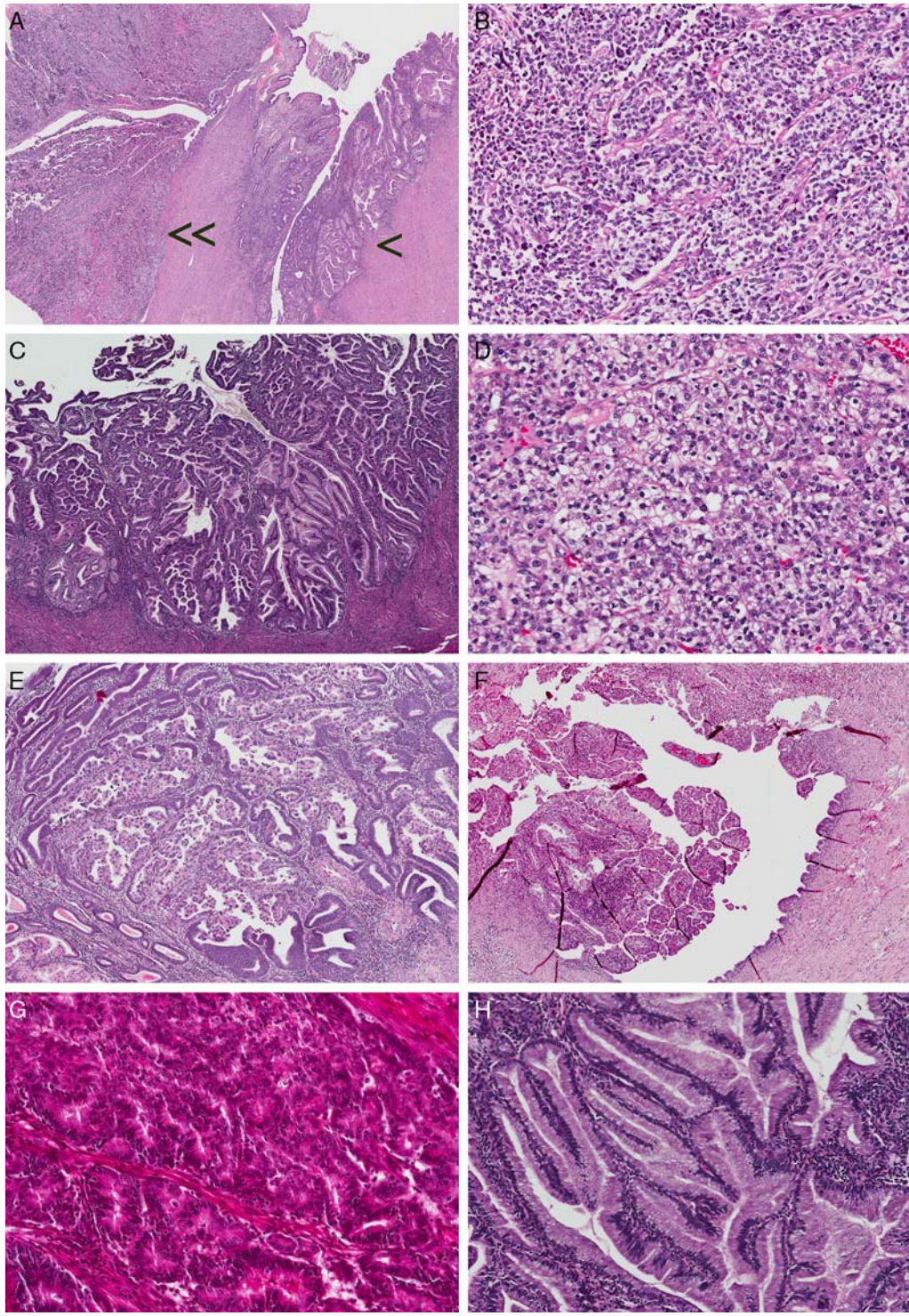

FIGURE 1. Dedifferentiated endometrioid carcinoma with juxtaposed areas of low-grade endometrioid carcinoma (arrowhead) and undifferentiated carcinoma (double arrowhead) (A) in a patient with MSH2 mutation. High power view of undifferentiated component (B) showing sheets of dyshesive round cells. Endometrial endometrioid carcinoma with mucinous differentiation (C) and synchronous ovarian clear cell carcinoma (D) in a patient with MSH2 mutation. Endometrial clear cell carcinoma (E) and synchronous endometrioid carcinoma of fallopian tube (F) in a patient with MSH2 mutation (previously reported).[28] Endometrioid carcinoma showing tumor infiltrating lymphocytes (G) in a patient with MSH6 mutation and endometrioid carcinoma with mucinous differentiation (H) in a patient with MSH2 mutation.

TABLE 2. Genotype-Cell Type Correlation

Study	MLH1	MSH2	MSH6	PMS2
*Broaddus et al[17] n = 50	3 EEC	40 EEC 3 CCC 3 USC 1 MMMT	—	—
Carcangiu et al[19] n = 23	5 EEC 2 NEEC	7 + 1 EEC 8 NEEC	—	—
*Ryan et al[14] n = 38	6 EEC 1 USC 1 CCC 2 mixed/other	20 EEC 1 USC 1 dedifferentiation 2 mixed/other	3 EEC 1 dedifferentiation	—
De Leeuw et al[21] n = 23	8 EEC	4 EEC	8 EEC 1 mixed 1 serous 1 squamous	—
Berends et al[23] n = 5	1 EEC	2 EEC 1 NEEC	1 EEC	—
Djordjevic and Broaddus[26] n = 7	—	—	—	7 EEC
Total	23 EEC 6 NEEC	73 EEC 17 NEEC	12 EEC 4 NEEC	7 EEC

CCC indicates clear cell carcinoma; EEC, endometrioid endometrial carcinoma; MMMT, malignant mixed Mullerian tumor; NEEC, nonendometrioid endometrial carcinoma; USC, uterine serous carcinoma.

as an initial screening test in CRC patients. Similarly, we would not recommend family history alone as a primary triage tool for EC.[16] If reflex testing were introduced, family history remains crucial because, it would be used to further triage those patients with MLH1-IHC–deficient tumors as this may be because of sporadic methylation. However by refining selection of such groups, family history could be taken by genetic counselors or through directed family history questionnaires.

ENDOMETRIAL CANCER CELL TYPE AND LYNCH SYNDROME

Improved reproducibility of cell type in OC, and recognition of cell type-specific associations has ensured that morphology is key in triaging patients for germline screening. In Ontario all women with invasive pelvic/peritoneal serous carcinoma are eligible for genetic testing for mutations in the BRCA1 and BRCA2 genes.

Table 1 summarizes 8 studies which centrally reviewed EC cell type in LS patients.[14,17–23] Study cohort ranged from 5 to 50 patients and in total 77% (131 of 171) were endometrial endometrioid carcinoma (EEC). In the study by Broaddus et al, cell type distribution in the LS cohort was similar to the general EC patient population. The LS group did have more nonendometrioid endometrial carcinoma (NEEC) tumors compared with the MLH1 methylated group and the sporadic under 50 years group, but this was not significant.[17]

Our study and the work by de Leeuw and colleagues showed a similar distribution of cell type.[14,21] However, 2 studies highlighted a significantly higher incidence of NEEC [37.5% ($P < 0.05$) and 43.5% ($P < 0.0001$)] in their LS cohort compared with control groups.[18,19] Furthermore in the study by Westin and colleagues looking specifically at lower uterine segment (LUS) tumors, 40% (4/10) of LS cases were NEEC. This is in contrast to the previous MD Anderson study in which only 14% (7/50) of LS EC were NEEC.[17,22]

TABLE 3. Mean Age at Presentation of Lynch Syndrome Endometrial Cancer: Overall and According to Cell Type

	Total Cohort	EC Mean Age and Range	NEEC Mean Age and Range
Broaddus et al[17] n = 50	46.8 y	—	46.4 y
Carcingau et al[19] n = 23	46.2 y R: 30-67 y	47.8 y R: 30-67 y	44.2 y R: 35-54 y
Ryan et al[14] n = 76	47.1 y R: 31-65 y	46.8 y R: 31-65 y	48.1 y R: 40-61 y
Palacios et al[18] n = 16	44.9 y	—	—
Van den Bos et al[20] n = 6	44 R: 38-53 y	44 R: 38-53 y	NA

NA indicates not applicable; R, range.

TABLE 4. Mean Age According to Gene Mutated

	All	MLH1	MSH2	MSH6	PMS2
Ryan et al*[14] n = 76	47.3 y R: 31-73 y	49.3 y (18 cases) R: 36-61 y	46 y (50 cases) R: 31-73 y	50.6 y (8 cases) R: 34-61 y	—
Hampel et al[12,13] n = 13	54.9 y	39 (1 case)	46.3 (3 cases) R: 44-50 y	59.5 y (9 cases) R: 47-69 y	—
De Leeuw et al[21] n = 23	48 y	49.5 (8 cases)	41 (4 cases)	55.5 y (11 cases)	—
Berends et al[23] MSH6 only n = 9	—	—	—	52.2 y (9 cases) R: 45-65 y	—
Goodfellow et al[29] MSH6 only n = 7	—	—	—	54.9 y (7 cases) R: 45 to 71 y	—
Djordjevic and Broaddus[26] PMS2 only n = 7	—	—	—	—	64.6 y R: 51-87 y

*Ryan et al, total of 76 patient pedigree's available.
R indicates range.

Some studies suggest that tumor heterogeneity or the presence of mixed carcinoma may be associated with MSI-H/LS EC, citing dedifferentiated endometrioid carcinoma as the prototypic example (Figs. 1A, B).[24,25]

Studies are limited and reproducibility of cell type in EC is not as established as OC. Broadly, a spectrum of cell types is encountered in LS similar to the general population but with some studies suggesting a higher incidence of NEEC. Therefore restricting screening to a specific subtype does not seem feasible.

GENOTYPE-CELL TYPE CORRELATION

Table 2 summarizes studies showing "genotype" and cell type correlation. Not all presented studies had central pathology review or germline confirmation.

SYNCHRONOUS OVARIAN CARCINOMA

Patients with LS are also at risk for OC. Synchronous endometrioid carcinoma of ovary and endometrium is common and only those with appropriate family history should be investigated.[27] It has been suggested that EC with synchronous ovarian clear cell carcinoma should raise suspicion (Figs. 1C, D).[24] Synchronous endometrial and tubal carcinoma have also been reported (Figs. 1E, F).[28]

AGE-BASED SCREENING CRITERIA

Table 3 summarizes the mean age and range of patients with LS EC. Where possible we have presented the demographic data of the entire cohort and according to cell type (EEC vs. NEEC).

Overall, LS patients present with EC at a younger age compared with the general population, perhaps more striking in those patients with NEEC.

However, imposing an age criteria for screening may select certain genotypes.

Table 4 summarizes studies looking at age of onset of EC in LS EC carriers according to specific gene mutated.

Consistently, studies have shown that EC in patients with MSH6 mutations tend to occur at an older age (typically above 50 years) compared with MLH1 and MSH2 mutation carriers. This is particularly relevant to EC as the cumulative lifetime risk for EC in MSH6 mutation carriers was reported as being 71% at 70 years although a recent

TABLE 5. Correlation Between MSI Status, Findings in Adjacent Endometrium, and Prognostic Factors

	High Grade	Atrophy	Hyperplasia	Depth	LVI	Advanced Stage
Honore et al[35]	0.0006* 0.0182†	0.0057	—	0.021	0.0004	—
Van den Bos et al[20]	0.018%	—	—	—	0.002	—
Hirasawa et al[33]	0.0468*	—	0.9999	0.0241	0.0915	0.0241
Parc et al[36]	0.025†	—	—	—	—	0.037
Catasus et al[37]	—	—	—	—	—	No correlation
Shia et al[25]	—	0.82	0.03	—	—	—
Fiumicino et al[38]	—	—	—	0.31	—	0.003
Toledo et al[39]	No correlation percentage	—	—	—	No correlation	No correlation
Walsh et al[11]	0.045*	—	—	$P = 0.016$	> 0.05	0.029

Values listed are *P* values.
*Grades 1 and 2 versus grade 3.
†Grade 1 versus grades 2 and 3. Percentage not specified.
MSI indicates microsatellite instability; LVI, lymphovascular invasion.

TABLE 6. Correlation of MSI-H Features in EC and Honore-defined Host Response to Tumor as: Targeted Lymphoid Response Within the Tumor and at the Tumor Myometrium Interface

	TILS	Peritumoral	Mucinous
Honore et al[35]	0.4864	0.4864	0.4864
Van den Bos et al[20]	0.002	0.001	—
Parc et al[36]	0.102	—	0.046
Catasus et al[37]	—	—	No correlation
Shia et al[25]	0.002	0.004	—
Toledo et al[39]	>0.05	—	>0.05
Walsh et al[11]	0.004	>0.05	—

EC indicates endometrial cancer; MSI-H, microsatellite instability-high; TILS, tumor infiltrating lymphocytes.

multicenter review estimated cumulative risk for such women at 70 and 80 years to be 26% (95% confidence interval, 18%-36%) and 44% (95% confidence interval, 30%-58%).[30,31]

A recent abstract, representing the largest series of MSH2 IHC-deficient EC, suggests a similar profile, with the mean age of 7 patients being 64.6 years with age range of 51 to 87.[26] An age-based screening criterion for EC will need to be more liberal than most current proposals.

ANATOMIC LOCATION OF TUMOR: LOWER UTERINE SEGMENT

As with the predilection for right-sided location of colon cancers, location of EC in the LUS is strongly correlated with LS. In the seminal study, Westin et al[22] showed the prevalence of LS to be 29% (10/35) among women with LUS EC compared with 2% of the general EC population and 9% of young EC patients (< 50 y). These tumors were higher stage with a greater median depth of invasion ($P \leq 0.001$) compared with tumors in the uterine corpus but with no difference in cell type or endometrioid grade. There were no distinguishing features between LS-LUS EC and sporadic LUS EC. In our study of 38 LS EC, only 2 (5.3%) were located in the LUS.[14]

HISTOLOGIC FEATURES

The morphologic features used in colon scoring schemas such as MsPath are essentially histologic correlates of MSI.[32] Studies of EC have typically used this reasoning despite MSH6 alteration being associated with intermediate MSI.

GRADE OF ENDOMETRIOID CARCINOMA IN LYNCH SYNDROME

When analyzing studies of grade of EEC encountered in LS one needs to be cognizant of 2 issues: few studies have distinguish between LS MSI-H EEC and sporadic cases attributable to MLH1 methylation; although clinical convention is to binarize the FIGO grading system into low grade (grades 1 and 2) versus high grade (grade 3) not all studies have used this convention, many have been vague not specifying binarization convention, or used terms like "higher" grade.

Broaddus et al[17] noted that grade of EEC in LS was similar to the general population but that the sporadic MLH1 methylated group had significantly fewer grade 1 tumors and more grade 3 tumors ($P = 0.009$). In our review of LS EEC, 26 of 29 cases (90%) were grade 1 and 3 (10%) grade 3.[14] The latter contention by Broaddus is supported by Hirasawa et al[33] in which MSI-H EEC (92% of which were methylated) were significantly more likely to be high grade (grade 3 vs. grades 1 and 2). The data are uncertain. Zighelboim claims that MSI phenotype (MSI +) was strongly associated with higher FIGO grade ($P = 0.0001$) comparing 147 MSI + EEC to 299 microsatellite stable (MSS) tumors. However, if binarized as low grade (grades 1 and 2) versus high grade (grade 3) there is no significant association between MSI + and high grade. Rather, there is a positive association between the MSI + phenotype and low-grade tumors ($P = 0.04$). Furthermore, when subdividing MSI + according to MLH1 methylation status, the methylated cases show a trend toward a higher incidence of low-grade tumors ($P = 0.07$).[34] Similarly, van den Bos et al and Carcangiu and colleagues showed a significantly higher frequency of poor differentiation/high grade in LS EEC compared with control groups ($P = 0.018$ and 0.0368).[19,20] Table 1 summarizes grade of EEC in LS in studies in which centrally pathology review was performed.

TABLE 7. Other Histologic Features in Studies of LS EC

				P		
	Ryan et al[14]	Palacios et al[18]	Van den Bos et al[20]	Ryan et al[14]	Palacois et al[18] ≤50 y (n = 28)	Van den Bos et al[20] 15 Controls >45 y
Lynch						
TILS	2 (5.3%)	8 (50%)	6 (100%)	NA	< 0.05	0.002
Peritumoral	13 (34.2%)	7 (46%)	6 (100%)	NA	< 0.05	0.001
Dediff	2 (5.3%)	NA	NA	NA	NA	NA
LUS	2 (5.3%)	NA	NA	NA	NA	NA
Controls						
TILS	NA	3 (10.7%)	5 (33%)	—	—	—
Crohns	NA	5 (17.8%)	1 of 8	—	—	—
Dediff	NA	NA	—	—	—	—
LUS	NA	NA	—	—	—	—

Dediff, dedifferentiation; EC indicates endometrial cancer; LS, Lynch syndrome; LUS, lower uterine segment; NA, not applicable; TILS, tumor infiltrating lymphocytes.

MICROSATELLITE INSTABILITY STATUS AND PROGNOSTIC FACTORS: GRADE, LYMPHOVASCULAR INVASION, DEPTH OF INVASION, AND STAGE

Table 5 summarizes studies comparing the frequency of a number of findings in MSI-H EC compared with MSS EC.[11,20,25,33–39] One of the few studies to compare MSI-H MLH1 methylated cancers to LS EC, showed that the former group were significantly more likely to have lymphovascular invasion (0.041).[17] Although most studies in Table 5 have shown correlation between MSI-H status and high grade, advanced stage, and depth of invasion, there are exceptions. The lack of distinction between MSI-H LS EC and sporadic MSI-H MLH1 methylated cases may account for some of the discrepant results. Overall, we need to be cautious in applying these findings to LS EC.

ADDITIONAL MORPHOLOGIC FEATURES OF MICROSATELLITE INSTABILITY-HIGH ENDOMETRIAL CANCER—TUMOR INFILTRATING LYMPHOCYTES, PERITUMORAL INFLAMMATION, AND MUCINOUS DIFFERENTIATION

Results (*P* values) from control-cohort studies assessing the presence of tumor infiltrating lymphocytes (Fig. 1G), peritumoral inflammation, and mucinous differentiation (Fig. 1H) in MSI-H EC compared with MSS EC are shown in Table 6.[11,20,25,35–37,39] Again the association of these features with MSI-H EC has not been consistently demonstrated. Although this may be attributable to different definitions used for these features and inter-observer variation, if such features are to be used clinically, there is a need for additional work to ensure robustness and to determine reproducibility. Furthermore many studies of such features have only included EEC. Because there may be a higher incidence of NEEC in LS, it is not certain if such findings can be extrapolated to other cell types.

Table 7 summarizes findings of tumor infiltrating lymphocytes, peritumoral inflammation, dedifferentiation and LUS location in 3 studies of LS EC.[14,18,20] In our study such features were present in only minimal cases with the exception of peritumoral inflammation which was seen in one third of cases. The inflammatory response findings were higher in the other 2 studies which also included control groups highlighting a significant association with LS.

MICROSATELLITE INSTABILITY VERSUS MISMATCH REPAIR IMMUNOHISTOCHEMISTRY AS PRIMARY TRIAGE TEST IN ENDOMETRIAL CANCER

MSH6 alteration may be associated with intermediate MSI.[21,23,29,40] Because the cumulative lifetime risk for EC in patients with MSH6 mutations may be as high as 70%, MSI testing may not be the ideal triage tool in EC.[31] Furthermore, whereas in CRC the presence of somatic BRAF mutation is quite robust in excluding LS as the cause of MSI, such a test is lacking in EC.

Because MMR-IHC is more akin to germline testing some groups prefer MSI analysis as a primary triage tool. Although we agree with Chubak et al[41] that MMR-IHC should not be considered a germline test, consensus or guidelines on this are required by the pathology community. A quality assurance review highlighted an 11.8% discordance rate in MMR-IHC with MSI results cautioning against the sole use of MMR-IHC as a screening test.[42] However in a recent MMR-IHC proficiency test using tissue microarrays of carcinomas of known germline MMR status, overall sensitivity for the 4 markers, among 14 participating laboratories, was 96% to 100% (B.A.C. and K.C., unpublished data, 2011).

SCREENING PROPOSALS

In the report from the Jerusalem Workshop on LS, Dr Chapelle of Ohio State University proposed that all incident case of EC be screened for LS, using MMR-IHC, because this is more accessible, inexpensive, and directs mutation analysis unlike MSI analysis.[7]

At Sloan Kettering all patients less than 50 years with EC are screened using MMR-IHC. In patients older than 50-year suggestive tumor morphology, LUS location, personal/family history (exact criteria not specified), and synchronous clear cell carcinoma of ovary are listed as features warranting screening with MMR-IHC. MSI analysis is only performed in discordant cases of high clinical suspicion but intact MMR-IHC. Methylation studies are used for those cases with MLH1 IHC loss.[24]

Kwon et al[43] (British Columbia and MD Anderson) recommended MMR-IHC triage of women with EC at any age with at least 1 first-degree relative with a LS-associated cancer.

CONCLUSIONS

Despite well-established clinical-based and morphology-based schemas to identify LS/MSI-H CRC there is an emerging standard of care of reflex testing of all or most CRCs with MMR-IHC and/or MSI testing.[44] Clinical schemas to address EC are only recently established, are untested and in some aspects lack clarity. MSI-H/LS morphologic features are less well defined in EC as is acknowledged in the College of American Pathologists uterine cancer checklist, and as evidenced by this review. In light of the experience in CRC and cognizant of the less established clinical and morphologic schemas in EC, adoption of reflex testing of all/most newly diagnosed EC for LS should be considered.

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