European Journal of Gynaecological Oncology

IMR Press

Original Research

Practice patterns for Lynch syndrome-associated endometrial cancer management in Korea

Min Kyu Kim[1,*,†], Min Chul Choi[2,*,†], Myong Cheol Lim[3], Jae-Weon Kim[4]

[1] *Division of Gynecologic Oncology, Department of Obstetrics & Gynecology, Samsung Changwon Hospital, Sungkyunkwan University of Medicine, 51353 Changwon, Republic of Korea*

[2] *Comprehensive Gynecologic Cancer Center, CHA Bundang Medical Center, CHA University, 13496 Seongnam-si, Republic of Korea*

[3] *Cancer Healthcare Research Branch, Center for Uterine Cancer, and Center for Clinical Trials, Research Institute and Hospital and Department of Cancer Control and Population Health, Graduate School of Cancer Science and Policy, National Cancer Center, 10358 Goyang, Republic of Korea*

[4] *Department of Obstetrics and Gynecology, Seoul National University College of Medicine, 03087 Seoul, Republic of Korea*

*Correspondence: minkyukim@skku.edu (Min Kyu Kim); oursk79@cha.ac.kr (Min Chul Choi)

† These authors contributed equally.

DOI:10.31083/j.ejgo4204111

Submitted: 20 May 2021 Revised: 11 June 2021 Accepted: 21 June 2021 Published: 15 August 2021

Objectives: This study aimed to investigate practice patterns for the management of LS-associated endometrial cancer among Korean gynecologic oncologists. *Material and methods*: Members of the Korean Society of Gynecologic Oncology were surveyed using a self-administered questionnaire regarding their knowledge and clinical management of LS by paper or e-mail. *Results*: Of the 49 participants, the median age was 43 years (range, 30–75). The respondents worked mainly in Seoul (25/49, 51.0%) and the capital area (16/49, 32.7%). The average score on LS knowledge assessment was 3.8 (range, 0–8) with a maximum score of 8. The following tools were used by the respondents for the identification of inherited endometrial cancer: obtaining of family history (46.7%), immunohistochemistry (IHC) test for four mismatch repair (MMR) genes (38.8%), and microsatellite instability (MSI) test (8.2%) for all endometrial cancer patients. The indications for recommending the germline MMR gene test were endometrial cancer with a family history (5/49, 10.2%), patients who met the Amsterdam II criteria (32/49, 65.3%), abnormal IHC test results (13/49, 26.5%), and abnormal MSI test results (8/49, 16.3%). Approximately half of the respondents recommended cascade testing (28/49, 57.1%) to the family of the proband and recommended risk-reducing management for MMR mutation carriers (27/49, 55.1%). *Conclusion*: Gynecologic oncologists in Korea are not aware of genetic risk assessment and patient counseling about LS. Therefore, it is necessary to educate physicians and develop guidelines in this regard.

Keywords

Endometrial neoplasms; Lynch syndrome; Practice pattern

1. Introduction

Endometrial cancer is the most common gynecologic cancer in the United States. It was estimated that 66,570 new cases of uterine cancer would occur in 2021, with 12,940 resulting deaths [1]. Endometrial cancer is the third most common gynecologic cancer in Korea. Its incidence has been increasing steadily at an annual rate of 6.9% since 1999 [2], and it is expected to become the leading gynecologic cancer with 3261 new cases being diagnosed in 2020, overtaking cervix cancer (3148 new cases) and ovarian cancer (2941 new cases) [3]. Hereditary endometrial cancer (HEC) predisposition syndromes account for up to 5% of all endometrial cancer cases [4]. Lynch syndrome (LS), previously hereditary nonpolyposis colorectal cancer, is the most common form of HEC. LS is caused by a germline mutation in one of the four DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) or the epithelial cell adhesion molecule (*EPCAM*) gene [5–10]. Individuals with LS have an increased risk of developing cancers of the colorectum, endometrium, ovary, small bowel, urothelium, biliary tract, and stomach [11]. Among women with mutations in *MLH1*, *MSH2*, *MSH6*, and *PMS2*, the lifetime risks of endometrial cancer are 20–54%, 21–49%, 16–71%, and 13–15%, respectively [12–14].

Among Korean endometrial cancer patients, the mutation frequency (limited to *MLH1* and *MSH2*) is known to be 1.2–4.4% [15, 16], similar to that reported previously in a Western country [17]. Detecting LS in patients with endometrial cancer is an important step in its clinical management. It allows for cascade testing to diagnose family members who may also have the disease. Furthermore, timely LS diagnosis allows for follow-up to prevent the occurrence of other LS-related cancers. The National Comprehensive Cancer Network guideline recommends the LS screening pathway for all newly diagnosed endometrial cancer patients, referred to as universal screening [18]. Universal screening pathways utilize tumor-based testing, such as immunohistochemistry (IHC) for MMR protein loss, microsatellite instability (MSI) testing, or *MLH1* promoter methylation testing to triage individuals to undergo further germline genetic testing for MMR genes.

Table 1. Characteristics of respondents (n = 49).

	No. of respondents	%
Type of hospital where the respondent worked		
University hospital	43	87.8
General hospital	3	6.1
Cancer-specialized hospital	3	6.1
Hospital location		
Seoul	25	51.0
Regional metropolitan city	5	10.2
Capital area (Gyeonggi-do)	16	32.7
Local area	3	6.1
No. of endometrial cancer surgeries performed annually		
0	0	
<10	8	16.3
11–50	22	44.9
51–100	8	16.3
≥101	11	22.4

Studies on LS among patients with endometrial cancer have been reported to be limited in Korea [15, 16, 19, 20]. To the best of our knowledge, there have not yet been any reports on the practice patterns of HEC management in Korea. Therefore, the present study aimed to investigate how gynecologic oncologists are managing LS in clinical practice in Korea using a questionnaire.

2. Material and methods

The present survey of practice patterns regarding HEC was performed to the attendants (n = 115) at the Hereditary Gynecologic Cancer Symposium (November, 2019) by paper, and members of the Korean Society of Gynecologic Oncology (n = 205) by e-mail. Duplicate responses were checked using the last 4 digits of the supplied telephone number. The survey was conducted using a self-administered questionnaire. The questionnaire assessed the following: (1) respondent characteristics (5 questions), (2) LS knowledge (8 questions), (3) genetic counseling and universal screening test for detecting LS (5 questions), and (4) risk management and cascade testing for the family of the proband (2 questions). 104 responses were submitted and 49 complete questionnaires considered valid for inclusion in the analysis. The present study was approved by the institutional review board.

3. Results

The information of respondents is summarized in Table 1. Most respondents worked in large organizations that specialized in the treatment of gynecologic cancer. Regarding the province in which the hospitals were situated, the respondents worked mainly in Seoul (25/49, 51.0%) and capital areas (16/49, 32.7%). All respondents were specialized in gynecologic oncology. At the hospitals in which most respondents (41/49, 83.7%) worked, more than 10 cases of endometrial cancer surgery were performed annually. The respondents were predominantly male (77.6%, 38/49), and the median age was 43 years (range, 30–75).

The average score on LS knowledge assessment was 3.8 points (range, 0–8) out of a possible maximum of 8 points. The 8 questions used in assessing LS knowledge and the correct response rate for each question are listed in **Supplementary Table 1**.

The distribution of practice patterns related to genetic counseling and universal screening are shown in Fig. 1. The following response rates were recorded among respondents: obtaining of family history for all endometrial cancer patients (46.7%, 23/49), IHC test for the four MMR genes among all endometrial cancer patients (38.8%, 19/49), MSI test for all endometrial cancer patients (8.2%, 4/49), and recommending MMR genetic tests to all endometrial cancer patients (12.2%, 6/49) (Fig. 1). Fig. 2 shows the responses to proper indications for recommending germline MMR genetic tests: all endometrial cancer patients (6.1%, 3/49), all patients with endometrial and ovarian synchronous or metachronous cancer (18.4%, 9/49), endometrial cancer patients with a family history of any type of cancer (10.2%, 5/49), endometrial cancer patients who meet the Amsterdam II criteria (65.3%, 32/49), patients with abnormal IHC test results (26.5%, 13/49), and patients with abnormal MSI test results (16.3%, 8/49).

Approximately half of the respondents recommended cascade testing (28/49, 57.1%) to the family of the proband and recommended risk-reducing management of LS-related cancers for MMR mutation carriers (27/49, 55.1%). Genetic counseling was predominantly provided by special consultants (or teams) (75.5%, 37/49) (specialist, 25; laboratory medicine specialist, 3; genetic counselor, 4; clinical research nurse, 1; multidisciplinary team, 4) rather than the gynecologic oncologist (12.2%, 6/49).

4. Discussion

The approach to identifying individuals at risk for LS is referred to as universal screening [18]. When screening with only clinical criteria, such as the Amsterdam II criteria, based on a personal history of cancer, a considerable number of LS

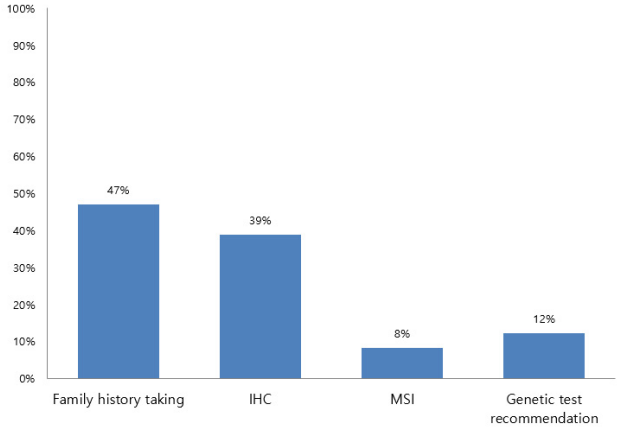

Fig. 1. Practice pattern related to genetic risk assessment (n = 49). IHC, immunohistochemistry for the four mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*); MSI, microsatellite instability test; Genetic test recommendation, germline MMR genetic testing.

patients may be missed. Approximately 50% of families who meet the Amsterdam II criteria have a mutation in an MMR gene [21]. However, these criteria are very stringent and lead to missing as many as 68% of patients with LS [22, 23]. In universal screening, tumor testing with IHC and/or MSI assessment is used as the primary approach to all individuals newly diagnosed with endometrial or colorectal cancer. IHC refers to a process in which tumor tissue is stained for protein expression of the four MMR genes and loss of protein expression by IHC in any one of the MMR genes guides further genetic testing of the gene whose protein expression was not observed. An MSI-high tumor refers to one with a proportion of alterations in a predetermined panel of microsatellite repeat markers that indicates the loss of MMR activity. If there is a high clinical suspicion for LS, even with a normal tumor-based screening test result, genetic testing could also be performed. More than 90% of LS tissues are MSI-high and/or show loss of expression in at least one MMR protein on IHC [24]. This approach of universal screening yields a sensitivity of 100% and a specificity of 93.0% in identifying individuals with LS in colorectal cancer [25]. Therefore, universal screening is recommended for all patients with endometrial and colorectal cancers to maximize sensitivity for LS detection and simplify the screening process.

In this regard, according to the results of the present questionnaire survey, a small number of respondents among gynecologic oncologists in Korea performed tumor test-based universal screening for all endometrial cancer patients. Only 38.8% of respondents indicated that the IHC test for four MMR genes was performed for all patients with endometrial cancer, and 8.2% of respondents performed the MSI test (Fig. 1). In addition, we found that genetic testing for MMR genes through tumor-based universal screening was not performed frequently, except when the Amsterdam II criteria were met as an indication for the germline MMR gene test. When faced with an abnormal IHC test result, 26.5% of respondents indicated that genetic testing would be performed thereafter and when faced with an abnormal MSI test result, 16.3% indicated that genetic testing would be performed (Fig. 2). In the same context, it could be confirmed that there is a lack of knowledge about LS-related endometrial cancer among Korean gynecologic oncologists. The average score for questions on knowledge assessment about LS was 3.8 out of 8 points (**Supplementary Table 1**).

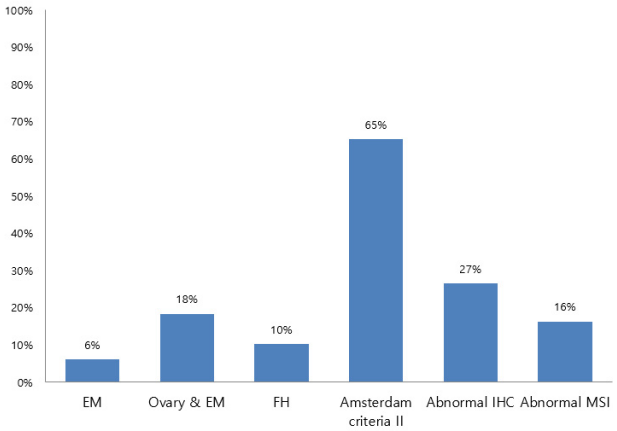

Fig. 2. Indications for germline MMR gene testing (n = 49) (allowed duplicate selection). EM, endometrial cancer; Ovary & EM, endometrial and ovarian synchronous or metachronous cancer; FH, family history of any type of cancer; IHC, immunohistochemistry for the four mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*); MSI, microsatellite instability test.

Several reasons for the results obtained in the survey are given as follows. First, the incidence of HEC is as low as less than 5% of all endometrial cancers; accordingly, physicians and the general public are less interested in it. Second, the insurance coverage for tumor testing and MMR gene testing for endometrial cancer patients in Korea are unclear. Third, guidelines for genetic and tumor testing for identifying LS-associated endometrial cancer have not yet been presented in Korea.

Identification of LS is important both for individuals with cancer and their families because LS exhibits an autosomal dominant form of inheritance. After identifying LS, surveillance offers an opportunity for early detection and prevention of other cancers among mutation carriers. Moreover, endometrial cancer is considered a sentinel cancer of LS, which may help in detecting other LS-related cancers. Approximately half of the patients were diagnosed with endometrial or ovarian cancer first preceding the development of colon cancer among LS patients [17]. Improving the detection rate of LS among these women increases the probability of reducing their subsequent risk of colorectal cancer. It is imperative that gynecologic physicians recognize the association between these cancers and LS. In this sense, it is encouraging that more than half of the respondents recommended risk reducing management for other LS-related

cancers among mutation carriers (27/49, 55.1%) and recommended cascade testing (28/49, 57.1%) to the family of the proband. However, the question remains to those who responded that they would not recommend those efforts, as to why they would not perform these tests. This is the reason for calls for the need for continuous and systematic education among physicians.

New anticancer agents, particularly immune checkpoint inhibitors, have shown promising results among patients with specific molecular markers such as MMR deficiency or MSI-high tumors [26, 27]. Treatment with the pembrolizumab, one of the immune checkpoint inhibitors, in patients with advanced MMR-deficient cancers showed objective and complete response rates of 53% and 21%, respectively [28]. Endometrial cancer is a representative cancer with a high rate of MMR deficiency of 17–33% [26], and has been in the spotlight as an excellent candidate for these inhibitors.

Based on the above reasons and the expansion of the clinical application of genetic testing through next generation sequencing testing in Korea, the clinical need for universal screening tests for detecting LS in endometrial cancer is becoming increasingly important. Therefore, it can be said that clinical efforts at actively detecting LS patients are essential for gynecologic oncologists, who primarily treat and manage patients with endometrial cancer. In addition, the release of clinical guidelines on this issue is needed urgently in Korea.

The present study had several limitations. There were only 49 respondents; this number was too small for the results to be subjected to statistical analysis. As the working places of the respondents were mostly located in Seoul and the capital areas (83.7%) (Table 1), the results of the present study may not be generalizable or considered as being representative of domestic practice patterns in the management of HEC in Korea. There might also be selection bias as the data were collected via a self-administered questionnaire. In addition, no comparable studies have been conducted in Korea. Nonetheless, the present study serves as a starting point for the development of HEC education programs and clearly demonstrates the need and desire for such programs. This is the first study, to the best of our knowledge, to investigate practice patterns regarding the management of LS-associated endometrial cancer among Korean gynecologic oncologists.

5. Conclusions

In conclusion, gynecologic oncologists in Korea are not aware of genetic risk assessment and patient counseling about LS-related HEC. Education of physicians and the development of simple and cost-effective guidelines based on evidence from the Korean population are warranted.

Author contributions

Conceptualization: all authors. Data curation: MKK. Formal analysis: MKK. Supervision: MCL, JWK. Writing—original draft: MKK, MCC. Writing—review & editing: all authors. Approval of final manuscript: all authors.

Ethics approval and consent to participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of institutional review board (CHA IRB 2018-05-022).

Acknowledgment

We would like to thank the respondents.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://ejgo.imrpress.com/EN/10.31083/j.ejgo4204111.

References

[1] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA: A Cancer Journal for Clinicians. 2021; 71: 7–33.

[2] Lim MC, Won YJ, Ko MJ, Kim M, Shim SH, Suh DH, *et al.* Incidence of cervical, endometrial, and ovarian cancer in Korea during 1999-2015. Journal of Gynecologic Oncology. 2019; 30: e38.

[3] Jung K, Won Y, Hong S, Kong H, Lee ES. Prediction of Cancer Incidence and Mortality in Korea, 2020. Cancer Research and Treatment. 2020; 52: 351–358.

[4] Hinchcliff EM, Bednar EM, Lu KH, Rauh-Hain JA. Disparities in gynecologic cancer genetics evaluation. Gynecologic Oncology. 2019; 153: 184–191.

[5] Fishel R, Lescoe MK, Rao MR, Copeland NG, Jenkins NA, Garber J, *et al.* The human mutator gene homolog MSH2 and its association with hereditary nonpolyposis colon cancer. Cell. 1993; 75: 1027–1038.

[6] Papadopoulos N, Nicolaides NC, Wei YF, Ruben SM, Carter KC, Rosen CA, *et al.* Mutation of a mutL homolog in hereditary colon cancer. Science. 1994; 263: 1625–1629.

[7] Leach FS, Nicolaides NC, Papadopoulos N, Liu B, Jen J, Parsons R, *et al.* Mutations of a mutS homolog in hereditary nonpolyposis colorectal cancer. Cell. 1993; 75: 1215–1225.

[8] Bronner CE, Baker SM, Morrison PT, Warren G, Smith LG, Lescoe MK, *et al.* Mutation in the DNA mismatch repair gene homologue hMLH1 is associated with hereditary non-polyposis colon cancer. Nature. 1994; 368: 258–261.

[9] Hendriks YMC, Jagmohan-Changur S, van der Klift HM, Morreau H, van Puijenbroek M, Tops C, *et al.* Heterozygous mutations in PMS2 cause hereditary nonpolyposis colorectal carcinoma (Lynch syndrome). Gastroenterology. 2006; 130: 312–322.

[10] Tutlewska K, Lubinski J, Kurzawski G. Germline deletions in the EPCAM gene as a cause of Lynch syndrome - literature review. Hereditary Cancer in Clinical Practice. 2013; 11: 9.

[11] Lin KM, Shashidharan M, Thorson AG, Ternent CA, Blatchford GJ, Christensen MA, *et al.* Cumulative incidence of colorectal and extracolonic cancers in MLH1 and MSH2 mutation carriers of hereditary nonpolyposis colorectal cancer. Journal of Gastrointestinal Surgery. 1998; 2: 67–71.

[12] Barrow E, Hill J, Evans DG. Cancer risk in Lynch Syndrome. Familial Cancer. 2013; 12: 229–240.

[13] Senter L, Clendenning M, Sotamaa K, Hampel H, Green J, Potter JD, *et al.* The clinical phenotype of Lynch syndrome due to germline PMS2 mutations. Gastroenterology. 2008; 135: 419–428.
[14] Dominguez-Valentin M, Sampson JR, Seppälä TT, Ten Broeke SW, Plazzer JP, Nakken S, *et al.* Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. Genetics in Medicine. 2020; 22: 15–25.
[15] Lim MC, Seo S, Kang S, Seong M, Lee B, Park S. Hereditary nonpolyposis colorectal cancer/Lynch syndrome in Korean patients with endometrial cancer. Japanese Journal of Clinical Oncology. 2010; 40: 1121–1127.
[16] Yoon SN, Ku J, Shin Y, Kim K, Choi J, Jang E, *et al.* Hereditary nonpolyposis colorectal cancer in endometrial cancer patients. International Journal of Cancer. 2008; 122: 1077–1081.
[17] Lu KH, Dinh M, Kohlmann W, Watson P, Green J, Syngal S, *et al.* Gynecologic Cancer as a "Sentinel Cancer" for Women with Hereditary Nonpolyposis Colorectal Cancer Syndrome. Obstetrics & Gynecology. 2005; 105: 569–574.
[18] NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Genetic/Familial High-Risk Assessment: Colorectal. version 1.2021-May 11. 2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf (Accessed: 12 May 2021).
[19] Lee HJ, Choi MC, Jang J, Jung SG, Park H, Joo WD, *et al.* Clinicopathologic characteristics of double primary endometrial and colorectal cancers in a single institution. Journal of Obstetrics and Gynaecology Research. 2018; 44: 944–950.
[20] Song T, Kim MK, Lee Y, Choi CH, Kim T, Lee J, *et al.* Women with double primary cancers of the colorectum and endometrium: do they have Lynch syndrome? European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2016; 199: 208–212.
[21] Vasen HF. Clinical diagnosis and management of hereditary colorectal cancer syndromes. Journal of Clinical Oncology. 2000; 18: 81S–92S.
[22] Barnetson RA, Tenesa A, Farrington SM, Nicholl ID, Cetnarskyj R, Porteous ME, *et al.* Identification and survival of carriers of mutations in DNA mismatch-repair genes in colon cancer. New England Journal of Medicine. 2006; 354: 2751–2763.
[23] Samadder NJ, Smith KR, Wong J, Thomas A, Hanson H, Boucher K, *et al.* Cancer Risk in Families Fulfilling the Amsterdam Criteria for Lynch Syndrome. JAMA Oncology. 2017; 3: 1697–1701.
[24] Hendriks YMC, de Jong AE, Morreau H, Tops CMJ, Vasen HF, Wijnen JT, *et al.* Diagnostic approach and management of Lynch syndrome (hereditary nonpolyposis colorectal carcinoma): a guide for clinicians. CA: A Cancer Journal for Clinicians. 2006; 56: 213–225.
[25] Moreira L, Balaguer F, Lindor N, de la Chapelle A, Hampel H, Aaltonen LA, *et al.* Identification of Lynch syndrome among patients with colorectal cancer. Journal of the American Medical Association. 2012; 308: 1555–1565.
[26] Marabelle A, Le DT, Ascierto PA, Di Giacomo AM, De Jesus-Acosta A, Delord JP, *et al.* Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. Journal of Clinical Oncology. 2020; 38: 1–10.
[27] Petrelli F, Ghidini M, Ghidini A, Tomasello G. Outcomes Following Immune Checkpoint Inhibitor Treatment of Patients with Microsatellite Instability-High Cancers: A Systematic Review and Meta-analysis. JAMA Oncology. 2020; 6: 1068–1071.
[28] Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, *et al.* Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017; 357: 409–413.