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Implementation of tumor testing for lynch syndrome in endometrial cancers at a large academic medical center

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HIGHLIGHTS

- There were no differences in age, histology, grade, stage, or BMI in patients with Lynch syndrome versus sporadic tumors.
- Universal screening in endometrial cancers is practical and eliminates the chance for missing eligible cases.
- Lynch syndrome screening in endometrial cancer is successfully implemented with collaboration among genetic counselors, gynecologic oncologists, and pathologists.

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ABSTRACT

Objectives. Lynch syndrome (LS) is a hereditary condition that increases the risk for endometrial and other cancers. Recognizing women at risk for LS based on personal/family history is burdensome and imprecise. Tumor testing using microsatellite instability (MSI) testing and immunohistochemistry (IHC) for mismatch repair protein expression can be an effective strategy for identifying potential LS in patients presenting with colorectal or endometrial cancer. Here we describe our experience implementing a screening program for endometrial cancers.

Methods. Endometrial cancers diagnosed ≤50 years or those with suspicious personal history or histopathologic features were screened with MSI/IHC, June 2009–June 2011. Criteria were later (July 2011–July 2012) expanded to patients diagnosed <60 years, or at any age with suspicious features, and finally (after August 2012) universal screening was implemented. Screening techniques began with both MSI and IHC for every tumor, and later converted to IHC for two proteins, and *MLH1* promoter methylation analysis when indicated. A genetic counselor contacted patients directly to offer genetic counseling appointments.

Results. Two hundred and forty-five endometrial cancers (average age, 57 years) were screened. Sixty-two patients (25%) had abnormal results, and 42 patients were referred for genetic counseling. Of the 42 patients, 34 underwent genetic counseling, 28 pursued genetic testing, and 11 were diagnosed with LS. When age and pathology criteria were used, 27 eligible cases were overlooked for screening and 3 cases of LS were found only because a clinician requested screening.

Conclusions. Universal screening of endometrial cancers for LS is practical and successfully implemented with collaboration among genetic counselors, gynecologic oncologists, and pathologists.

Introduction

Lynch syndrome (LS) is an autosomal dominant disorder, caused by germ line mutations in the four mismatch repair (MMR) pathway genes, *MLH1*, *MSH2*, *MSH6*, and *PMS2*, and *EPCAM* deletion (resulting in *MSH2* promoter methylation), which increase the risk of endometrial,

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colorectal, ovarian, gastric, small bowel, and other cancers. LS confers up to a 60% risk of endometrial cancer and accounts for 2%–6% of all endometrial cancers [1,2]. Nearly 50% of women with LS and multiple malignancies present with endometrial cancer as their first primary cancer [3]. It is therefore essential to identify endometrial cancer patients with LS to guide medical management and to help reduce the risk of additional cancers for the patient and relatives.

Traditional methods of identifying LS, including the Amsterdam criteria, have proven to be ineffective for endometrial cancer patients, with sensitivity <40% [1]. Tumor testing with microsatellite instability (MSI) testing and immunohistochemistry (IHC) for MMR protein expression are more sensitive methods of identifying LS. Over 90% of endometrial cancers caused by LS demonstrate MSI [1]. IHC for the MMR proteins has a sensitivity of approximately 94% and can be used alone or in conjunction with MSI to identify patients who for whom directed germ line testing is indicated [1].

Several large institutions across the United States have implemented universal screening using MSI and/or IHC in colorectal cancers due in part to the recommendation from the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group, stating that all newly diagnosed colorectal cancer patients should be offered testing for LS [4]. However, the only guidelines for MSI/IHC screening for LS in endometrial cancer state that testing should be considered for women diagnosed before the age of 50 years [5]. Since most women with LS are diagnosed with endometrial cancer after the age of 50 years and are more likely to be diagnosed with endometrial cancer than with colon cancer, there is a need for a better screening strategy in this population [6]. A few hospitals have begun screening endometrial cancers; however, the best screening criteria and methodology are not well established. Here we report on implementing and evaluating universal screening of endometrial cancers for LS at a large academic medical center.

Methods

Patients

MSI/IHC screening was performed for patients with endometrial cancer diagnosed at the Cleveland Clinic Main Campus based on provider request (surgeon or genetic counselor [GC]), or automatic screening criteria as outlined below. Cleveland Clinic gynecologic oncologists perform surgeries at Main Campus, as well as two regional hospitals, the latter with pathology departments that do not perform MSI/IHC. Screening criteria and methodology were determined by the Department of Anatomic Pathology and were modified over time. Data collected from the medical record included age at diagnosis, tumor characteristics, body mass index (BMI), and family history of cancer. This study was approved by the Cleveland Clinic Institutional Review Board.

Time frame 1

Beginning in June 2009, endometrial cancers in patients ≤50 years who underwent hysterectomy at the Cleveland Clinic main campus were screened for MSI with reflex to IHC for the MMR proteins MLH1, MSH2, MSH6, and PMS2 (Fig. 1). Microsatellite stable (MSS) tumors were also screened with IHC for MSH6 due to previous reports showing some MSS tumors deficient in MSH6 [1]. Individuals with a prior history of colon cancer or dedifferentiated/undifferentiated endometrial cancers regardless of age were also screened [7]. Beginning in January 2011, screening was also performed for endometrial cancers in patients <60 years old with certain pathological features previously described in LS (tumor infiltrating lymphocytes, isthmic tumor, synchronous endometrial carcinoma and ovarian clear cell carcinoma, ambiguous histology, mixed histology, and high grade tumors) [7]. In May 2011, screening was switched to an IHC-only approach, whereby eligible tumors were screened with IHC for MSH6 and PMS2. This technique is possible since MMR proteins function as heterodimers. PMS2 requires binding by MLH1, and MSH6 requires MSH2 as its binding partner. It has been shown that intact results for PMS2 and MSH6 alone confirms that all four mismatch repair proteins are intact in at least 95% of cases, while reducing testing costs [8]. If PMS2 or MSH6 were absent, additional IHC for MLH1 or MSH2 was performed, respectively.

Time frame 2

Screening criteria were expanded to all patients younger than 60 years who underwent hysterectomy at the Cleveland Clinic Main Campus July 2011–July 2012. Patients 60 years or older with pathology features as described above were also screened. Beginning in late July 2012, tumors deficient in MLH1/PMS2 were analyzed for *MLH1* promoter methylation.

Time frame 3

Starting in August 2012, all endometrial cancers diagnosed at Cleveland Clinic Main Campus were screened with IHC for MSH6 and PMS2. Data were captured until the end of December 2012.

A database search of all endometrial cancers diagnosed at the Cleveland Clinic since June 2009 was performed by the Department of Anatomic Pathology to determine the number of cases that were not screened despite meeting criteria.

MSI and IHC

MSI was performed as previously described [9]. The following antibodies were used to perform IHC: MLH1 (clone G168.15, 1:20

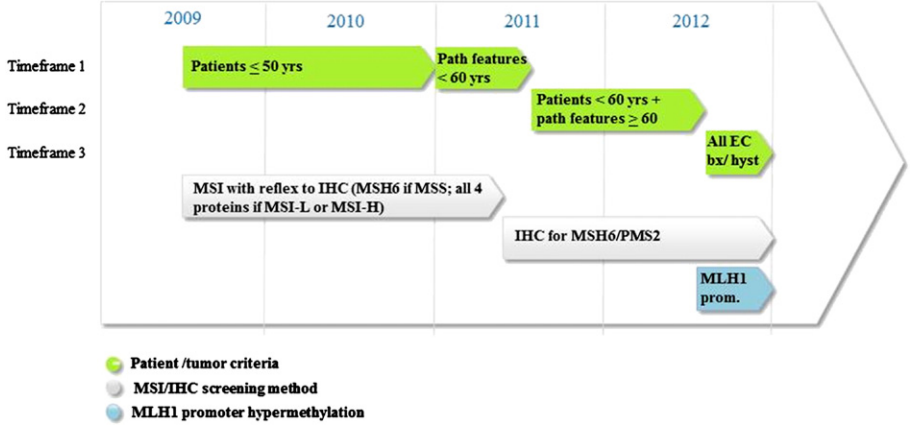

Fig. 1. Timeline of evolving criteria and methodology for Lynch syndrome screening in endometrial cancers. Path = pathology; MSI = microsatellite instability testing; IHC = immunohistochemistry; EC = endometrial cancer; bx = biopsy; hyst = hysterectomy.