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Implementation of Hereditary Gynecologic Cancer Clinic Utilizing Existing All Screening and Genetic Methods in Community-Based Hospital by Surgeon

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ABSTRACT

Purpose: *Hereditable cancer syndromes are mostly known by MMR(mismatch repair gene) based Lynch syndrome and BRCA gene -based hereditary breast and ovarian cancer (HBOC). There are difficulties for making selection process suitable for different groups to the final confirmation testing according to ethnicity and country. Acceptance and approval chances also are inconsistent according to cancer counseling initiation period. Our study objective was to investigate the feasibility hereditary gynecologic cancer clinic establishment using available cancer genetic counseling and tests approved by a surgeon among patients with gynecologic malignancies in Korea.*

Methods: *We included 30 patients of ovarian and endometrial cancers until refusal of genetic tests after counseling calendrically. Early cancer genetic counseling was given to patients with information of immunohistochemistry (IHC). Final genetic sequencing to prove germline mutations was done after patient consent for suspicious candidates.*

Results: *This study included 19 ovarian and 11 endometrial cancer patients. We obtained negative IHC results for MLH1, MSH2, BRCA1, and BRCA2.They were 0 (0%), 2 (7%), 14 (52%), and 3 (11%), respectively. Three patients (10%) had germline mutations (two BRCA and one MMR mutation).*

Conclusion: *Our study shows that surgeon has a favorable position to implement hereditary cancer clinic among gynecologic malignancy patients in well-equipped community hospital.*

Keywords

Lynch syndrome, BRCA mutation, Endometrial cancer, Ovary carcinoma.

Introduction

Ovarian carcinoma has a fatal mortality and ranks seventh in terms of cancer death among women, and endometrial carcinoma exceeds other malignancy with regard to incidence in the United States [1]. In Korea, approximately 247,000 new cancer cases were expected to occur in 2013. The expected incidence and mortality are 2,175 and 262 for endometrial cancer, respectively, and 2,199 and 1,003 in ovarian carcinoma [2]. The economic burden for cancer patients in the 5 years following diagnosis ranges from $5,000 US dollars (for thyroid cancer) to $20,217 US dollars (for lung cancer) in Korea. Detection of cancers at advanced stage creates enormous problems for clinicians and patients for successful treatment of cancer. Early detection and prevention are therefore more important than cancer treatment.

Two major genetic syndromes associated with ovarian and endometrial cancers are BRCA-based hereditary breast ovarian cancer (HBOC) and MMR-based Lynch syndrome related gynecologic cancer. HBOC has hereditable traits through family members mainly affecting their specific organs especially breast and the ovary. Patients with BRCA 1 and BRCA2 mutation can have chances of Breast (65% and 45%) and Ovary (39% and 11%)

cancer [3]. Among ovary cancer patients, BRCA1/2 germline mutation is reported to be 13%–15% [4,5].

Lynch syndrome, or HNPCC, is matched with error repair function named mismatch repair genes (MMR) [6-9]. Most common cancer occurring organs are colorectal and endometrium and affected individual can have about 10 percent of ovarian cancer risk [10,11].

According to existing Society of Gynecologic Oncologists [12] guidelines for HBOC, the International Collaborative group on HNPCC (Amsterdam) [13], and Bethesda guidelines [14] for Lynch syndrome, gynecological oncologists are cautiously encouraged to combine cancer risk assessments with expensive genetic tests.

The incidence of ovarian and endometrial cancers acquired due to genetic factors varies according to both country and ethnicity [15]. Among Korean ovarian cancer patients, the frequencies of BRCA mutations are 2.7% (1/37) [16] and 23.8% (15/63) [17] without information about family cancer history. In Korea, endometrial cancer risk based on Lynch syndrome was found to be at 3.5% (4/113) [18] and 11.2% (18/161) [19]. Patients with hereditary cancer may give survival and economical chance to patient and affected relative. However, the participation rate and approval rate have not been reported consistently in this population. Thus, detection of hereditary cancer syndrome patients is important in terms of decreasing economic burden and cancer incidence.

We investigated the feasibility of ovarian and endometrial cancer patients in a Korean population in an attempt to understand the preventive and counseling roles of gynecologic oncologists surgeon in community hospital.

Materials and Methods

Patient selection and study algorithm

This study was approved by the institutional review board (IRB No: 2012-SCMC-028-00). The study subjects were registered by one surgeon until first refusal of any genetic tests. Changwon is a mid-sized city located in the southern part of Korea, with a population of about 1 million.

All patients in our department with ovarian or endometrial cancer were included in this study. In total, 30 women were enrolled. Clinical and pathological information including complete family history (including 1st, 2nd, and 3rd degree family) was obtained from medical records and patient interviews. Early genetic risk evaluation and counseling were offered to patients and family after pathology. Endometrial cancer patients were offered microsatellite instability (MSI) and methylation tests according to guidelines. After counseling, permission for gene sequencing was obtained, and gene sequencing was performed for approved patients. Germline mutation and variation of unknown significance (VUS) patients were recommended to obtain family counseling. Further studies (family and control study, RNA-based study) combined with in silico analysis (POLYPHEN: Polymorphism Phenotyping v2) were necessary for better hereditary risk counseling for patients with VUS (Figure 1A).

Immunohistochemical staining and evaluation as a screening test

Immunohistochemistry (IHC) was performed on all tumor specimens using monoclonal antibodies against MSH2 (Novocastra, UK), MLH1 (Novocastra, UK), MSH6 (Novocastra, UK), PMS2 (Novocastra, UK), BRCA1 (Abcam, UK), and BRCA2 (Abcam, UK). Staining procedure with the Bond-Max immunostainer (Leica Biosystems, UK) were done carefully according to written instruction. After procedure, evaluation was performed based on nuclear staining degree compared with normal stroma and infiltrating lymphocyte. Dedicated pathologist decided staining scores as number from 0(normal, strong) till 2 (abnormal, negative) (Figure 1B, C).

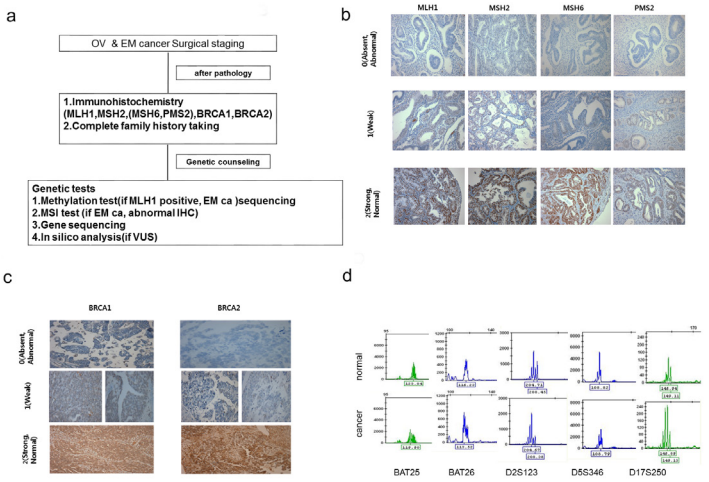

Figure 1: A Study algorithm. **B** Immunohistochemistry results for MLH1, MSH2, MSH6, and PMS2.
C Immunohistochemistry results for BRCA1 and BRCA2.
D Microsatellite instability test for patient EM-2.
MSI: microsatellite instability test, VUS: variation of unknown significance, IHC: immunohistochemistry.

Microsatellite instability test (MSI) as a screening test for Lynch syndrome

Based on National Cancer Institute Workshop guideline, MSI test is done successfully using polymerase chain reaction (PCR) amplification method. Specific primers are called Bethesda markers, and they are consisted with two mononucleotides (BAT25, BAT 26) and three dinucleotides (D17S250, D2S123, D5S346).

Extracted DNA from paraffin-embedded tissue of each tumor and corresponding normal mucosa. Each area was identified on a reference hematoxylin and eosin (H&E)-stained slide and then micro dissected using a scalpel blade, ascertaining the presence of adequate neoplastic tissue. PCR analyses were performed using a DNA auto sequencer (Applied Biosystems 3130 sequencer; Applied Biosystems, Foster City, CA, USA). The mobility shift of PCR products from tumor DNA was compared with that of corresponding normal colonic mucosa. MSI was defined as a band shift in either of the two alleles or as appearance of a differently sized band in analysis of the tumor sample. Samples were classified as MSI-high (MSI-H) if instability was found at >50%

of the loci screened; MSI-low (MSI-L) if at least one but <50% of the loci showed instability; MSS (MSI-S) if all loci were stable and there was no instability at the five markers; low-frequency MSI (MSI-L), if only one of the five markers showed instability; and high-frequency MSI (MSI-H), when more than two marker are abnormal (Figure 1C).

Methylation test as a screening test to rule out germline mutation

MLH1 gene promoter methylation patterns were determined by methylation-specific PCR (MSP). MSP distinguishes unmethylated from methylated alleles of a given gene based on sequence changes after bisulfide treatment of DNA. Subsequent PCR using primers specific for sequences that correspond to either the methylated or unmethylated MLH1 gene promoter DNA were then performed. Methylation-specific PCR was also performed to detect promoter hypermethylation of hMLH1.

We used two kinds of primers to detect promoter methylation of hMLH1. One set by Herman et al, and another set by Park et al were both used to detect hMLH1 methylation associated with hMLH1 silencing. DNAs were sodium bisulfite-treated using the EZ DNA Methylation Kit (Zymo Research, Orange, CA, USA). After bisulfite modification, beta-actin was used to analyze and standardize the amount of DNA. PCR reactions were performed in a 25 ml reaction with 1.25 U of Taq polymerase. Universal unmethylated DNA (Chemicon) was used as negative control. CIMP status was recorded as negative if ≤ 1 locus was methylated, low if 2 or 3 loci were methylated, and high if ≥ 4 loci were methylated. To compare the CIMP data in this study to previously published data from studies on American patients, an additional two-tiered CIMP classification system was applied as well.29 In this two-tiered classification, negative corresponds to ≤ 1 methylated loci, and positive corresponds to ≥ 2 loci methylated among five genes (hMLH1, p16, MINT1, MINT2, and MINT31) (Figure 2A).

Sequence analysis for confirmative test

Germline mutation test is done with patient's peripheral blood using DNA from leukocyte with help of the Wizard Genomic DNA Purification Kit (Promega, WI, USA). PCRamplification using primers with Thermal Cycler 9700 (Applied Biosystems, Foster City, CA, USA) was done to check all coding exons and flanking introns of the target genes (MSH2, MLH1, BRCA1, and BRCA2). Sequencing result was acquired with application of the BigDye Terminator Cycle Sequencing Ready Reaction Kit on an ABI Prism 3130 Genetic Analyzer (Applied Biosystems). Analysis and was accurately done with the Sequencer program (Gene Codes Corporation, Ann Arbor, MI, USA) and variation detection was concluded based on information in Human Genome Variation Society (http://www.hgvs.org/mutnomen/).

In silico analysis for VUS result

We used PolyPhen-2 (Polymorphism Phenotyping v2) (Figure 2B) to estimate possible impact of an amino acid substitution on usage of a functioning protein. A mutation is evaluated qualitatively as probably damaging (probabilistic score > 0.85), possibly damaging (probabilistic score > 0.15), or benign (remaining), corresponding to the pair of false positive rate (FPR) and true positive rate (TPR) thresholds, adjusted separately for HumDiv (10% and 18% FPR, for probably and possibly damaging mutations, respectively) and HumVar (19% and 40% FPR).

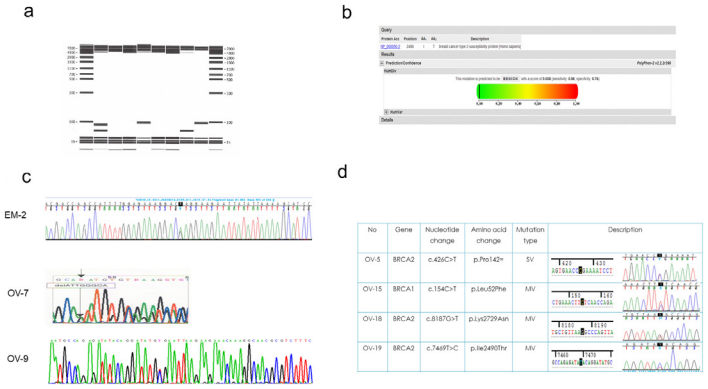

Figure 2: A Methylation test.
B POLYPHEN-2 result of OV-19.
C Gene sequencing result of germline mutation patients.
D Variation of unknown significance patients.
MV: missense variation, SV: silent variation.

Results

Median age of participating 30 patients was 56.1 year (19–79 years) (Table 1). Complete family histories were obtained from 73% (22/30) of the patients. For the remaining patients, there was either memory loss or inconsistent information between family members. Five patients (17%) had a family history of cancer, and three of these five had Lynch and HBOC in their family history (Table 1).

Characteristics	Patients, No. (range)
Median age (years)	56.1 (19~79)
<50	9
>50	21
Complete family history	22 (73%)
Family hx. of cancer	5 (17%)
Breast ca Fhx	2
Colon ca Fhx	1
Other ca Fhx	2 (Lung (1st), Stomach (2nd))
OV cancer stage	19
I~II	8 (42%)
III~IV	11 (58%)
EM cancer stage	11
I~II	7 (64%)
III~IV	4 (36%)

Table 1: Demographic characteristics (N=30). OV: Ovary cancer, EM: Endometrial cancer.

Among the 30 patients, 19 had ovarian cancer and 11 had endometrial cancer. Approximately 60% of the ovarian cancer patients had advanced stage disease (III~IV). Serous papillary pathologic type is the most common(n=13) and mucinous, transitional and

endometrioid were half of serous type (n=6(4,1,1)). Among endometrial cancer patients, 40% had advanced-stage cancer. Endometrioid pathologic type comprises half of endometrial cancer patients (6/11,54.5%).

Tumor blocks from all patients were obtained for review after consent. The numbers of patients with negative IHC staining for MLH1, MSH2, BRCA1, and BRCA2 were 0 (0%), 2 (7%), 15 (52%), and 5 (17%), respectively (Table 2). Additional IHC for MSH6 and PMS2 was performed for EM cancer patients. After counseling patients about their IHC results and family history of cancer, further genetic tests were offered. After counseling, 9 patients (31%) refused further testing. However, the refusal rate decreased with counseling time and family participation.

No	Age	Fhx	MLH1	MSH2	BRCA1	BRCA2	Result
OV-1	68	NO	2	2	0	1	N/A
OV-2	53	NO	2	2	2	1	N/A
OV-3	47	NO	2	2	1	2	Refuse
EM-1	67	NO	2	2	0	1	Refuse
EM-2	55	NO	2	0	0	2	MSH2(+), MSI-H
EM-3	74	NO	2	2	0	2	Refuse
OV-4	50	NO	2	2	0	1	N/A
OV-5	49	NO	2	2	2	2	BRCA2: VUS
OV-6	73	NO	1	2	2	1	Refuse
OV-7	52	YES	1	2	0	1	BRCA1 (+),
EM-4	55	NO	2	2	0	2	Refuse
OV-8	57	NO	2	2	0	0	N/A
OV-9	41	YES	2	2	0	0	BRCA2 (+)
OV-10	46	YES	1	2	0	1	N/A
OV-11	62	NO	1	2	0	2	N/A
OV-12	73	NO	1	1	1	1	Refuse
EM-5	62	NO	2	2	3	3	Refuse
EM-6	49	YES	1	0	0	0	MSH2: VUS, MSI-H
EM-7	78	NO	2	2	1	2	Refuse
OV-13	53	NO	1	2	0	1	N/A
EM-8	38	NO	1	2	1	2	Refuse
OV-14	52	NO	1	2	1	2	N/A
EM-9	64	YES	1	2	0	1	MLH1: VUS, MSS
OV-15	54	NO	2	2	2	2	BRCA1: VUS
OV-16	51	NO	1	1	2	2	N/A
EM-10	51	NO	1	2	1	2	MLH1: VUS, MSS
OV-17	66	NO	2	2	2	2	N/A
OV-18	19	NO	2	1	1	0	BRCA2: VUS
OV-19	45	NO	1	2	0	0	BRCA2: VUS
EM-11	79	NO	2	2	1	0	N/A

Table 2: Summary of notable patients. Ov: Ovary cancer, EM: Endometrial cancer, VUS: Variant of Unknown Significance, MSI: Microsatellite instability, MSI-H: Unstbale MSI, MSS: Stable MSI, 0: Negative (abnormal), 1: weak, 2: Positive, Strong (normal).

Gene analysis data indicated there were 3 patients (10%) with germline mutations (two HBOC and one Lynch syndrome) (Table 3; patients EM-2, OV-7, OV-9) (Figure 2C). Patient EM-2 was offered regular colonoscopy and genetic cancer risk evaluation by an enteroncologist, and her family was offered Lynch syndrome-related cancer screening and prophylactic surgery according to sex. There was no known family member with cancer. MSI and gene sequencing were also performed. The results indicated two unstable markers (BAT25 and BAT26), and the patient was scored MSI-H (unstable) (Figure 1D). Further gene sequencing analyses revealed one missense mutation [c.23C>T (p. Thr8Met)].

Age	Gene	Nucleotide change	Amino acid change	Zygocity	Mutation type & Effect
52	BRCA1	5470_5477del8	Ile1824AspfsX3	Hetero	FS
55	MSH2	23C>T	Thr8Met	Homo	MM
41	BRCA2	7480C>T	Arg2494X	Hetero	NM

Table 3: Germline mutation patients (N=3). FS: Frameshift mutation, MM: Missense mutation, NM: Nonsense mutation.

For patient OV-7, breast exam, mammogram, and ultrasonography were performed, and further education was offered by a general surgeon. Her family members and relatives were counseled, and those who approved were examined with sequencing. The patient remembered her parents had died of cancer but could not remember the specific type. IHC screening of mismatch repair genes (BRCA1 and BRCA2) was performed. The results showed abnormal BRCA1 (negative) staining, whereas BRCA2 staining was focal positive in intensity and proportion.

Gene sequencing showed a deletion of ATTGGGCA at codon 1824 in exon 24. Therefore, the stop codon (TGA) appears at codon 1826 [5470_5477del8 (p. Ile1824AspfsX3)], and this frame shift mutation produces a truncated protein.

For patient OV-9, breast exams were performed as had been done for OV-7. The IHC results for BRCA1 and BRCA2 were negative. Gene sequencing revealed a nonsense mutation (Arg2494X) at base 7480 of exon 15 in BRCA2. Her daughter (23 years old) consented to be tested. A test for just the mutated band in BRCA2 showed that the daughter carried the same mutation as her mother. The daughter was provided information with close surveillance, chemoprevention with oral contraceptive, and risk reducing surgery after childbearing.

Seven patients (OV-5, -15, -18, and -19 and EM-6, -9, -10) also showed VUS mutation (Table 4; Figure 2D). Although information on the link between VUS and cancer risk is limited, a physician from the Department of Laboratory Medicine and Genetics counseled patients and recommended close follow up.

Further studies (e.g., family and control study, RNA-based study) combined with in silico analysis (POLYPHEN, SIFT) are necessary for better hereditary risk counseling for VUS patients.

Age	Gene	Nucleotide change	Amino acid change	Mutation type & Effect
49	BRCA2	426C>T	Pro142=	SV
49	MSH2	1886A>G	Gln629Arg	P
64	MLH1	1151T>A	Val384Asp	MV
54	BRCA1	154C>T	Leu52Phe	MV
51	MLH1	2110G>C	Val704Leu	MV
19	BRCA2	8187G>T	Lys2729Asn	MV
46	BRCA2	7469T>C	Ile2490Thr	MV

Table 4: Notable Variant of Unknown Significance (VUS) patients (N=7). MV: Missense variation, P: Polymorphism, SV: Silent Variation.

Discussion

In Korea, 124,122 new female cancer patients were predicted in 2013, and approximately 3.5% (4,374 and 124,122) were predicted to have ovarian or endometrial cancer. The estimated frequency of death was calculated as 4.6% (1265/27,569) [2]. The mean 5-year net costs per patient ranged from $5,647 for thyroid cancer to $20,217 for lung cancer in Korea spanning the period 2006 until 2010 [20]. Therefore, identifying patients with hereditary cancer will be advantageous because it could reduce the number of new cancer patients. Another advantage to identifying patients with hereditary cancer diseases is the associated increase in cancer prevention. Finding cancer at advanced stages increases both patient risks as well as costs. Few studies have focused on specific regional cancer centers located in central Korea. Therefore, this study can provide a foundation for examining the nationwide incidence of hereditary cancer in Korea.

After identifying hereditary cancer patients, prophylactic surgery and surveillance options were provided. Among patients with BRCA mutation, ovarian cancer risk can be reduced by almost 90 percent after risk-reducing salpingo-oophorectomy [21]. All patients had bilateral salpingectomy during the staging operation except no. 28 because she was young [19]; a fertility-sparing operation was performed. In addition, oral contraceptives and other surveillance methods will be undertaken following chemotherapy. Breast cancer risk can be lowered by 50% through this procedure [22]. Risk reducing mastectomy for affected individual gained 95% breast cancer reduction and consequently decreased breast cancer-specific mortality by 90% [23]. For patients no. 10 and 13, deep discussions were conducted with the general surgeon about risks and benefits of prophylactic surgery. For patients no. 8, 24, 28, and 29, the risks of developing breast cancer were unclear; therefore, careful screening was offered. After fertility, risk reducing surgery including uterus and ovaries has been reported reasonable option for mutation carrier [24].

Prophylactic colectomy remains controversial in the management of patients with Lynch syndrome. Therefore, total or subtotal colectomy is the operation of choice in patients with Lynch syndrome and colorectal tumors [25]. Prophylactic colectomy has also been discussed as a reasonable option in mutation carriers for whom colonoscopy is painful or difficult [26,27]. Patient no. 5 had a screening colonoscopy, and prophylactic surgery was discussed between colorectal surgeons. Patients no. 18, 23, and 26 were counseled about regular colon cancer screening after the operation.

Other surveillance and close follow up can be an alternative choice. Colonoscopy surveillance has been recommended for carriers of Lynch syndrome mutations to prevent the development of cancer. Scheduled screening also has shown incidence reduction by 10% and mortality reduction by 14% arising from colorectal cancer [28].

This study is the first study examining the incidence of genetic malignancies (HBOC and Lynch syndrome) among gynecological malignancy patients in the Korean middle town population. Our data indicate that 10% of patients have germline mutations. The staining differences found in biopsies and resections will enhance the use of IHC in the screening workup for Lynch syndrome patients [29]. Like previous study with correlation of BRCA1 IHC and gene sequencing result, IHC has values as a screening test in our study group [30]. However, our study indicates only a weak correlation between IHC results and germline mutations (Table 2). Whether this long-term cohort study will help to reduce the incidence of cancer risk in the future is still unclear. Seven patients with VUS need a longer follow up and further family study (Table 3). In genetic testing, high cost of the tests and refusal rate are the two obstacles for detection of hereditary cancer.

We hypothesize that patients refuse testing because of the guilt associated with knowledge of hereditary disease, lack of active genetic counseling, and shortage of ethnic data concerning Korean people. Increasing insurance coverage and large data sets focused on Korean cancer patients will help to identify hereditary cancer syndromes in Korea.

In conclusion, our study indicated that 10% of the enrolled patients with ovarian and endometrial cancer had germline mutations. Surgeons must provide active counseling for genetic testing to be effective in controlling cancer incidence and mortality in well-equipped community hospital.

Acknowledgments

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