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Research Article

Clinical Significance of BRCA Gene Testing in Ovarian Carcinoma Patients: Can Advanced Stage Be an Obstacle for Acceptance of Counseling?

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2. Keywords

BRCA mutation; Ovarian carcinoma; Genetic counsel-ing

1. Abstract

1.1. Objective: BRCA mutation screening is known to play an important role in terms of cancer prevention and target treatment for ovarian carcinoma patients. However, there are barriers to per-suade patients to accept genetic counseling according to adjuvant treatment and disease severity. We undertook this study to investigate the clinical significance between advanced stage patients and their acceptance rate of BRCA testing and genetic counseling by a gynecologic oncologist.

1.2. Study Design: A case and control study was done for early (I-II) and advanced (III-IV) ovar-ian carcinoma patients regarding BRCA mutation and genetic counseling acceptance.

1.3. Results: A total of 34 patients was prospectively divided into two groups classified as early stage (n=17) and advanced stage (n=17). The advanced stage group was older than the early stage group [median age: 52.53(range, 20~73) years vs. 57.77(range, 45~75) years]. Compared to theear-ly stage group, the advanced stage group had higher proportion of serous carcinoma [6/17 (35.3%) vs. 15/17 (88.2%)] and short DFS (22.27 months vs. 10.87 months). Among these34 patients, only two refused BRCA testing.In the early stage group, BRCA testing time after operation was not statistically significantly longer than that in the advanced stage group [126.38 (range, 6-981) days vs. 50.69 (range, 6-315) days, $p > 0.05$].The first 11 patients required 236days (range, 9-981 days) to accept genetic testing. Later, the time required for other groups was improved to10.8 days(range, 7-30 days) and 11.3 days (range, 6-30 days).BRCA1 was found in three patients in the advanced stage group while BRCA2 was found in one patient in the early stage group. Seven patients in the early stage group and two patients in the advanced stage group were found to have variation of un-known significance (VUS).The pathogenicity ratio of VUS was six while the benign ratio of VUS was three based on in silico analysis.

1.4. Conclusion: Genetic counseling for BRCA mutation by a gynecologic oncologist is effective even for those with advanced stage of ovarian cancer.

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3. Introduction

Ovarian carcinoma persists as a disease with poor survival rates compared to other cancers.It is often detected at an advanced stage. Treatment response varies depending on the type of cancer cells.Annual**incidence and mortality in ovarian cancer patients are expected to rise to 2600 and 1100[1]in Korea**.Furthermore, gynecologic oncologists have reported insufficientscreening test availability for early detection of ovarian carcinoma in women who seek to ascertain risk factors and take preventive measures [2, 3].

It is believed that BRCA1 and BRCA2 germline mutations account for the majority of hereditary ovarian carcinomas (HBOC) [4]. Determining the proportion and characteristics of women who have BRCA1 and BRCA2 genes is important because it may lead to earlier genetic counseling and testing to those women and their families to aid medical management [5]. BRCA mutation detection has been studied with respect to survival [6, 7]. Muta-tion carriers identified through genetic testing may benefit by re-ducing risk through prophylactic surgery [8, 9]. A previous study has found that approximately half of practicing breast surgeons provide genetic counseling and testing services to patients [10]. Physician recommendation has been found to be important for genetic counseling about BRCA testing [11]. BRCA1/2 genet-ic counseling can help women make informed decisions about their health, improve their knowledge of cancer risk, and reduce anxiety. However, the acceptance rateforgenetic testing and coun-seling remains low in women with ovarian carcinoma [12, 13]. Several reasons can explain such low acceptance rate, including cost, lack of knowledge, refusal, and procedural difficulties [14-16]. Diagnosis at an advanced stage of ovarian carcinoma has not been studied with respect to obstacles contributing to refusal of genetic testing and counseling. To address this knowledge gap, we investigated clinical significance between advanced stage and acceptance rate of BRCA testing and genetic counseling by a single gynecologic oncologist.

4. Materials and Methods

A total of 34 ovarian cancer patients underwent genetic counseling for hereditary breast and ovarian cancer in our institution. A case control study was conducted for two evenly divided groups of early (I-II) and advanced (III-IV) ovarian carcinoma patients to study the acceptance rate of BRCA mutation testing and genetic counseling.After complete surgical staging and collection of pathology results, a single gynecologic oncologist offered genetic counseling.Counseling contents includedrisk assessment based on pathology,recording family history, educating patients about the genetics of hereditary breast and ovarian cancer, explaininggenetic testing methodology, and cost and interpretation of test results. This session provided patients a foundation to discussthe benefits and risks of genetic testing and the importance of sharing testing results with family members.After obtaining informed consent,BRCA1/2 gene sequencing was completed for approved patients. BRCA-positive and VUS patients receiveda second genetic counseling session for risk management options (family counseling, risk reducing surgery, and surveillance for BRCA-associated cancer and chemoprevention).Clinical information was extracted from medical records on age, family and personal history of cancer including ovarian and breast cancer, stage at diagnosis, histology type, disease-free survival (DFS), type of genetic testing, and type of gene mutation. This study was reviewed and approved by the Institutional Review Board of Samsung Hospital. Data wereanalyzed using SPSS software version 12.0 (SPSS, Inc., Chicago, IL, USA) and R 3.1.0 (Vienna, Austria; http://www.R-project.org/). Comparison of means of variables was performed using Fisher's exact test,Independent t-test,and Mann-Whitney test. Statistical significance was considered when P value was less than 0.05.

5. Results

5.1. Patient characteristics

A groupof 34 patients was prospectively divided into early stage (n=17) and advanced stage (n=17) groups. The advanced stage group was older than the early stage group, with a median age of 52.53(range, 20~73) years vs. 57.77(range, 45~75) years,showing no significant difference (**Table 1**).Compared to the early stage group, the advanced stage group had higher proportion of serous carcinoma [6/17 (35.3%) vs. 15/17 (88.2%)].CA 125 range was higher in the advanced stage group: 1505(range, 94.76~10775) vs. 1108(range, 10.33~16000).

Table 1: Characteristics of patients enrolled in this study.

Variable	Early stage (n=17)	Advanced stage (n=17)	P-value
Mean age at diagnosis, years (range)	52.53 (20-73)	57.77 (45-75)	0.192
BRCA gene-related family history*	1 *(5.9%)	3 (17.6%)	0.601
Stage	I: 13 (76.5%) II: 4 (23.5%)	III: 10 (58.8%) IV: 7 (41.2%)	
Histology			<0.05
Serous	6 (35.3%)	15(88.2%)	
Mucinous	4(23.5%)	1(5.9%)	
Endometrioid	2(11.8%)	0(0%)	
Clear cell	1(5.9%)	0(0%)	
Others	4(23.5%)	1(5.9%)	

*BRCA gene-related family history defined as first degree (Mother, Breast, Unknown).

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5.2. Operation results

The operation time was longer for the advanced stage group compared to that for the early cancer group (353min vs. 250min). Perioperative complicationswere not significantly different between the two groups: three patients in the advanced group vs. five in the early group.Major complicationswere noted only in the advanced group. Adjuvant chemotherapy was applied at almost the same time (postoperative day 14) in both groups. Treatment regimen was three weeks or dose-dense weekly paclitaxel and carboplatin with or without addition of bevasizumab according to risk factors.Medical follow up was scheduled at 24 months. Progression-free survival was 22.27(range, 10-48) months for the early stage group and 10.87(range, 0-47) months (p<0.05) for the advanced group (**Table 2**).

Table 2: Perioperative and oncologic results.

Variable	Early stage (n=17)	Advanced stage (n=17)	P-value
CA-125 *pre-op (U/ml)*	1108(10.33-16000)	1505(94.76-10775)	<0.05
Post-op (U/ml)	69.1(4.5-434.5)	682(101.8-4046)	
Operation time (min)	250(105-370)	353(199-492)	<0.05
Peri-op complication (%)	5(29%)	3(18%)	
Major	0	2*	
Minor	5 **	2 ***	
Adjuvant treatment	13(76%)	17(100%)	
Method (Patient No.)	DD-TC(2) 3W-TC(11)	DD-TC(1) 3W-TC(16) +BV (3)	
Time from operation (days)	14(7-31)	14(8-46)	<0.05
Follow up (months, mean, range)	24(8-48)	23(6-47)	
DFS (months, mean, range)	22.27 (10-48)	10.87 (0-47)	<0.05
Death with disease	0(0%)	3(18%)	0.103

*Hematoma, Colostomy, **Pneumonia, wound resuture, ***Ileus, wound resuture

5.3. BRCA counseling and testing

Two patients refused BRCA testing.BRCA-related family history was present in one (1/17, 5.9%) patient in the early stage group and three (3/17, 17.6%) in the advanced stage group.BRCA testing time after operation in the early stage group was longer than that in the advanced stage group [126.38 (range, 6-981) days vs. 50.69 (range, 6-315) days, p >0.05] (**Table 3**), although the difference was not statistically significant.Postoperative time to acceptance of genetic counseling by patients became shorter as surgeon gained more counseling experience. The first 11 patients needed an average of 236days (range, 9-981 days) to accept. However, the time laterwas improved to 10.8(range, 7-30) and 11.3(range, 6-30) days (Figure 1).Counseling session time was 38.13 min in the early stage group and 35.63min (p=0.224) in the advanced stage group. BRCA1 was found in three patients in the advanced stage group while BRCA2 was found in one patient in the early stage group. Eightpatients in the early stage group and two patients in the advanced stage group were found to have variation of unknown significance (VUS). The pathogenicity ra-tio of VUS was six while the benign ratio of VUS was three based on in silico analysis.

Table 3: Genetic counseling results.

Variable	Early stage (n=17)	Advanced stage (n=17)	P-value Result
Refusal rate	1(5.9%)	1(5.9%)	
Time from operation (days, mean, range)	126.38 (6-981)	50.69(6-315)	0.809
Result of BRCA testing			<0.05
Positive (Germline mutation)	1*	3**	4(12%)
VUS***	8	2	10(29%)
Negative	7	11	18(59%)
Counseling time (minutes, mean, range)	38.13 (30-60)	35.63 (30-60)	0.224

*One BRCA2, ** Three BRCA1***VUS: Variation of Unknown Significance.

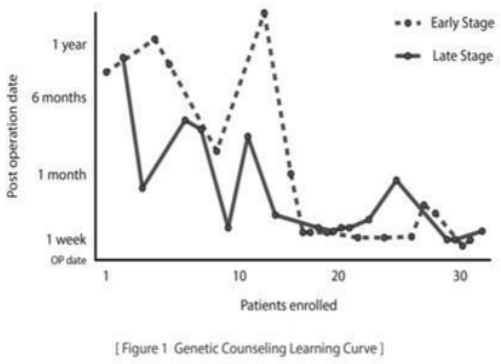

Figure 1: Genetic counseling learning curve.

6. Discussion

This study addressesthe importance of BRCA genetic testing and counseling in advanced ovarian carcinoma patientsby a surgeon and counselor as a gatekeeper for BRCA mutation-related can-cer prevention and screening. Comprehensive cancer counseling including pathology reports and genetic testing is desirable at the commencement of adjuvant treatment. Therefore, advanced stage patients may not be an obstacle for early counseling by the surgeon regarding BRCA mutation. The learning curveshowst-hat about 20 patients are needed to achieve a high acceptance rate of genetic counseling and testing approval in advanced stage patients.Comprehensive care and enhanced recovery in addition to early genetic counseling are equally important services that should be offered by the gynecologic oncologist.

Our study was limitedby the small sample sizefor investigating the survival effect between the early acceptance group and the late acceptance group.A high portion of VUS population should be corrected through NGS techniques.Cost may be an additional obstacle.

Identifying BRCA mutation in ovarian cancer patients requires

several factors: 1) acost effective screening method forthe general population or according to ethnicity (fonder mutation) [17-19];2) therapeutic effects of chemotherapy for mutation-carrying patients [20, 21];3)changes in chemoprevention, screening, and risk reducing surgery for mutation-positive family members through cascade testing [22];and 4) preventive strategies for sec-ondary cancer in ovarian cancer patients [23]. There are conflict-ing results of BRCA mutation in individuals regarding survival [6, 7, 24]. Their staging characteristics have not been fully inves-tigated yet.

There are several known means through which a healthcare provider can educate patients with respect to genetic testing. The surgeon,the first person who knows the diagnosis, can be the initial counselor to educate patient about genetic information of BRCA mutation.This study has emphasized the gatekeep-ing role of the surgeon regarding BRCA mutation, especially for advanced stage cancer patients. Patients are often loath to seek genetic counseling and testing because of a poor prognosis, with higher refusal as timeelapses.Refusal of counseling and testing may skew the prevalence data of BRCA mutationsin ovarian can-cer patients.

Our study was limitedtoa specific ethnicity and VUS rate. In addition to BRCA mutation status, the characterization of VUS will be increasingly important in treatment decisions and prognosis. In addition, there is a considerable difference in acceptance of BRCA testing due to cultural background and cost.Government insurance support for BRCA testing has been an issue for ovarian cancer patients.

Goals of genetic counseling are to determine the risk of HBOC and educate patients regarding risks, advantages, and limitations of genetic testing. Counseling also aims to assist patients in mak-ing a voluntary decision by providing a clear explanation of the risk of hereditary disease and its treatment method.In addition, specialized genetic counselingenhancesa patient's level of knowl-edge of HBOC, thereby decreasing anxiety and increasing the rate of participation in genetic testing. The complexity of genetic counseling content is an obstacle for an individual who attempts to gain a thorough understanding of the risk and necessity for testing. In this study, a single gynecologic oncologist made an ef-fort to increase the patient's level of knowledge about HBOC and reduce anxiety or fear by using personalized genetic counseling. This played a crucial role in increasing the rate of participation in genetic testing. In addition, to encouragepatients to share results with family members, we provided every patient who was identified to have a *BRCA* mutation or VUSwith a detailed counseling sessionwhich consisted of basic information about HBOC and the necessity of genetic test for family members who might be possible carriers.Earlier studies have indicated a lack of information regarding BRCA genetic testing and counseling among ovarian carcinoma patients [25]. Genetic testing and counseling should be encouraged, considering an individual's risk factors [26, 27].

There are many barriers that prevent women with advanced stage ovarian carcinoma from obtaining genetic testing. However, this study showed a high acceptance rate of genetic testing in an advanced group of patients. We attribute this result to ouroffering of systematic genetic counselingand short-term follow-up for reassurance. Furthermore, the cost of genetic testing was low compared to that in other countries where refusal rate was low. Although limitations of this study included a small sample size and a single surgeon, this study showed that proper genetic counsel-ing by the surgeon influenced patientsto readily and voluntarily accept genetic testing even in those with advanced stage ovarian carcinoma. Our results will be valuable for counseling women diagnosed with ovarian cancer. Long-term follow up of the early acceptance group is needed. In addition, future studies need to include a larger number of patients.

In our study, factors influencing participation in genetic test included age (40 years or less) and family history of breast cancer. Our results revealed that advanced stage of ovarian carcinoma did not affect the decision to undergo a genetic testwith recommendation ofsystematic genetic counseling.Cooperative counseling by the pathologist and geneticist along with the gynecologic oncologist is desirable. Further development of a comprehensive program for patient education and a cost-effective means to complete cascade testing could help manage patient anxiety and fear.

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