Discussion of posters

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Clinical significance of BRCA gene testing among ovarian carcinoma: Can advanced staging be an obstacle for acceptance of counseling?

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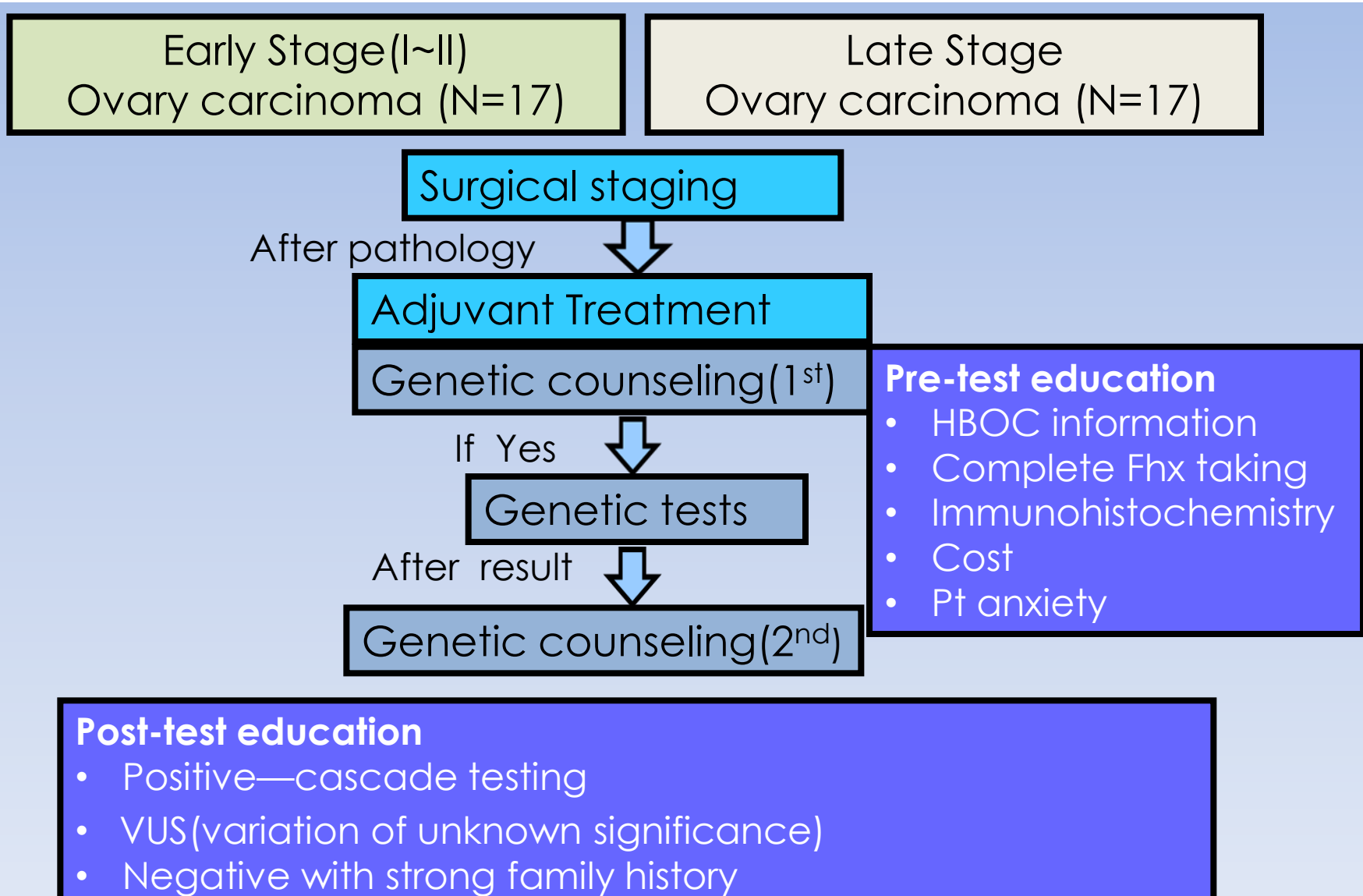
Objective

BRCA testing and genetic counseling was highly recommended **for women who had strong family history among** ovarian cancer.

There are some barriers for offering genetic counseling and acceptance according to disease severity.

We undertook this study to investigate **whether advanced staging can be a barrier in BRCA testing** and genetic counseling.

Materials and Methods



Results

- Time from operation to counselling 126 days (6-981) in Early Stage and 50 days (6-315) in advanced stage patients
- **Refusals 6% in both groups**
- Counselling time~ 35 minutes (30-60)

Results

- 4 patients with BRCA mutations(3 A1; 1 A2)
- **10(29.4%)** VUS - **8(51%)** in early stage ; 2 in advanced stage
- Advanced Stage- 88% HGSOC
- Early Stage

Serous 35%
Mucinous 25%
Endometrioid 11%
Clear Cell 6%
Other 25%

1 BRCA2 mutation

Specific comments

- Small study but……..
- Findings in keeping with larger studies
- Demonstrates high uptake for BRCA testing in Korean women
- No difference in uptake between Early and Advanced Stage patients
- Proximity to diagnosis and start of treatment not a barrier to testing
- Supports the role of a Gynaecological Oncologist in providing initial counselling- gatekeeper

Additional comments

- High number of VUS in Early Stage –

  (only 35% serous – grade not provided)
- Raises questions about testing mucinous/ low grade serous and endometrioid /others
- VUS – Myriad 3%
- VUS – POW Clinic 5-6%
- VUS- ~ 13% in Asians

BRCA1/2 mutation frequency and patterns of treatment response in Asian women with ovarian, primary peritoneal or fallopian tube carcinoma: experience from an Asian cancer centre

V Heong[1], PY Ong[1], YW Lim[1], SE Lim[1], SC Lee[1], DS Tan[1]

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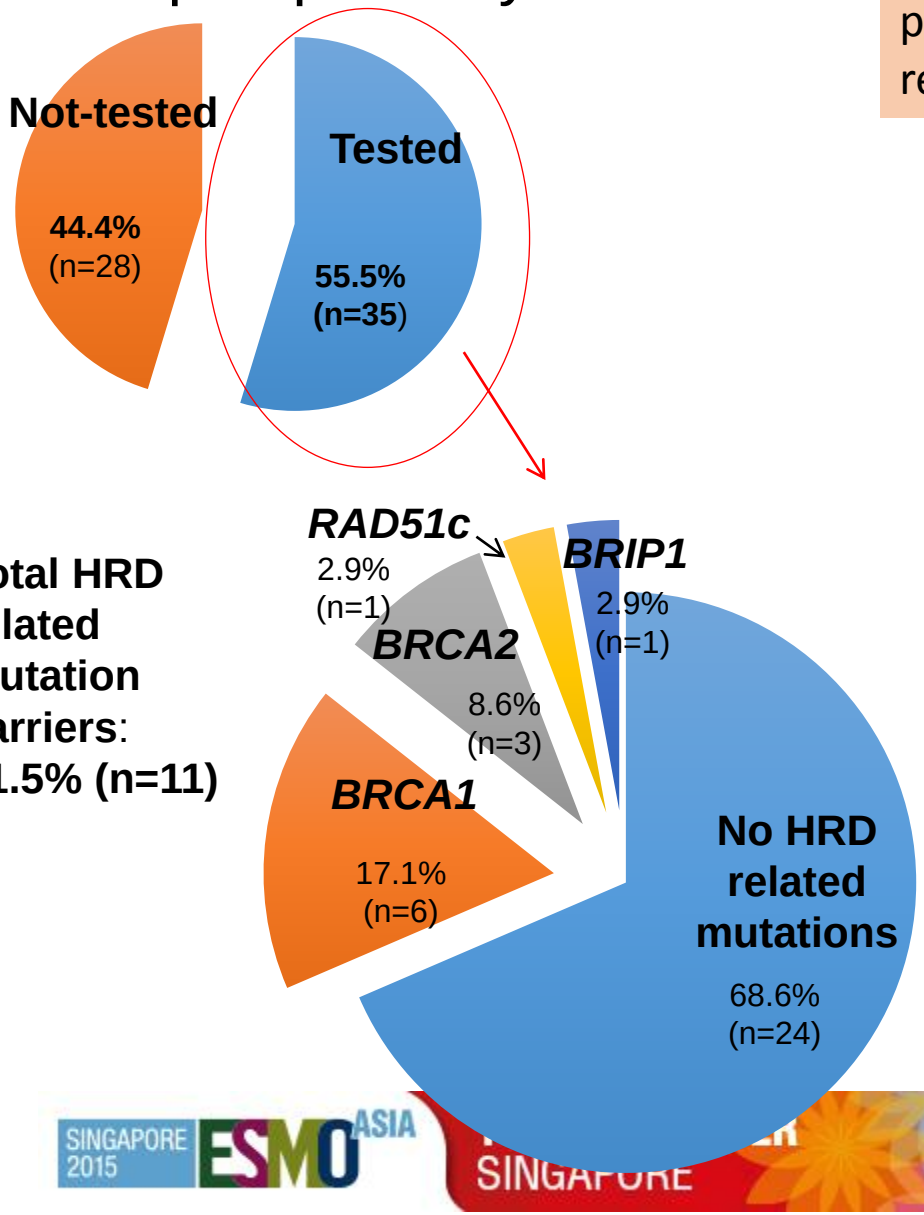
Frequency of germ-line mutations in DNA repair pathway



Total HRD related mutation carriers: **31.5% (n=11)**

63 Asian patients with non-mucinous ovarian, primary peritoneal or fallopian tube carcinoma referred for genetic testing

Barriers to genetic testing	N = 28 (%)
Cost	**8 (28.6)**
Family objection	1 (3.6)
Perceived negative impact of genetic testing	**5 (23.8)**
Overwhelmed; requiring additional time for consideration	**12 (42.3)**
Reason not given	1 (3.6)
Not available	1 (3.6)

Patterns of treatment response in Asian women with germline mutation in DNA repair pathway

Characteristics	HRD related mutation positive patients
Median age at diagnosis	49 yrs
Family history (%)	73%
Primary treatment: Platinum based treatment (%) Median PFS Median PFI	 100% 17.5 mths 13 mths (range: 5 – 45 mths)
Number of subsequent platinum based treatment at relapse: RR to 2nd line platinum treatment(%) Median PFS to 2nd line platinum treatment (mths)	2 (range: 1 – 4) **71.4%** **≥ 12 mths**
RR to 3rd line platinum treatment(%) Median PFS to 3rd line platinum treatment (mths)	**50%** **≥ 11.5 mths**

PFI – platinum free interval

BRCA mutations in EOC

AOCS Allsop et al 2012- unselected population based study 1001 patients

VOLUME 30 · NUMBER 21 · JULY 20 2012
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

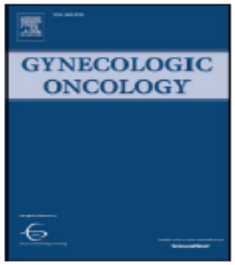
- 14.1 % BRCA mutations in EOC
- 22% High grade serous
- 44% of mutation carriers –NO Family History

- Limited data available in Asian population- 11-13% BRCA1 and 2-3% BRCA 2 in Hong Kong* and Pakistan**

*Khoo US et al Hum Mutat 2000: 16;88

**Liede A et al Am J Hum Genet 2002;71:595

Accepted Manuscript



Evaluation of germline *BRCA1* and *BRCA2* mutations in a multi-ethnic Asian cohort of ovarian cancer patients

Hanis Nazihah Hasmad, Kah Nyin Lai, Wei Xiong Wen, Daniel Jonathan Park, Tú Nguyen-Dumont, Peter Choon Eng Kang, Eswary Thirthagiri, Mahirah Ma'som, Boon Kiong Lim, Melissa Southey, Yin Ling Woo, Soo-Hwang Teo

PII: S0090-8258(15)30173-6
DOI: doi: 10.1016/j.ygyno.2015.11.001
Reference: YGYNO 976090

- Hospital based cohort in Malaysia
- 218 women with invasive ovarian cancer
- BRCA1 in 8% (17) and BRCA2 in 3%(7)
- Same age as non carriers Mainly HGSOC
- Indian predominance 23% (8/35) vs 7% in Chinese BRCA m
- **Offering testing based on FH – would have missed 35% (6/17) BRCA1 and 57%(4/7) BRCA 2**
- 11(2.5%) VUS

Comprehensive spectrum of *BRCA1* and *BRCA2* deleterious mutations in breast cancer in Asian countries

Ava Kwong,[1,2,3,5] Vivian Y Shin,[1] John C W Ho,[1,4] Eunyoung Kang,[6] Seigo Nakamura,[7] Soo-Hwang Teo,[8,9] Ann S G Lee,[10,11,12] Jen-Hwei Sng,[13] Ophira M Ginsburg,[14] Allison W Kurian,[3] Jeffrey N Weitzel,[15] Man-Ting Siu,[1] Fian B F Law,[2,4] Tsun-Leung Chan,[2,4] Steven A Narod,[14] James M Ford,[3] Edmond S K Ma,[2,4] Sung-Won Kim[6]

Kwong A, *et al*. *J Med Genet* 2016;**53**:15–23.

Future directions

Despite our understanding of the *BRCA1*/*BRCA2* mutations, there remain many unanswered questions. A large number of VUS still need to be classified as pathogenic or not, and due to their low frequencies of occurrence, some variants will probably never be classified. There are also increased reports of *BRCA1*/*BRCA2* missense mutations, particularly in the less tested ethnicities, some of which have already been classified as pathogenic. Such reports are likely to increase when more genetic tests are being performed in different ethnic groups. Characterising VUS in familial breast cancers will be the future direction of the ABRCA Consortium group and will be included in the separated study.

Functional studies of *BRCA1* and *BRCA2* can provide valuable information on their roles in cancer development. Regardless of entering the era of next-generation high-throughput sequencing, many mutations in *BRCA1* and *BRCA2* to date still remain unclassified in terms of their pathogenicity, and much work would need to be done to better understand the mutations of these genes, particularly in different ethnic populations. The establishment of an Asian registry of *BRCA1*/*BRCA2* mutation carriers would allow more organised research work to be done on this population.

Prevalence of BRCA mutations in Asians similar to Caucasians

Common mutations in some ethnic groups

Wide variations in selection criteria, genetic Testing methods, availability and cost

Discussion Points – Early testing

- **Treatment focused genetic counselling and testing** – qualitative study*

Australian women with ovarian cancer strongly endorsed genetic testing around the time of their diagnosis if it were to provide more information about their cancer treatment, with little indication that this would generate undue distress.

- The main motivator for TFGT was to increase treatment options and for potential risk reduction in family members
- Women included in the study were predominantly well-educated and of Caucasian background
- Significant cultural and ethnic variations with respect to acceptance of genetic testing as well as surgical risk reducing strategies in carriers
- High uptake in Korea 90% (728/804) of patients with ?HBOC and 88% of probands #

*Gynecol Oncol. 2012 Jan;124(1):153-7

Japanese JCO 2015:45;527

Cultural /Ethnic attitudes to testing

- Attitudes to cancer genetic testing are strongly influenced by the cultural context
- Individuals of Chinese background are more likely to take familial issues into account when making decisions about genetic testing for cancer risk
- Ethnographic study exploring culture-specific beliefs about kinship and cancer among Chinese Australians found that identification of a mutation in an individual is likely to be perceived as a ‘weakness in the line’ which will negatively impact the carrier's marriage prospects

Soc Sci Med, 59 (2004), pp. 235–248

Table 3. Characteristics of the Myriad Genetic Laboratories* *BRCA1/2* Testing Database (n = 10,000)

Characteristic	No.	%
Total population size	10,000	100
Sex, female	9,090	90.9
Age, years		
Median	49	
Range	6-97	
Race/ethnicity		
Western European	4,073	41
Ashkenazi Jewish	3,022	30
Central European	1,041	10
Latin American/Caribbean	229	2.3
Native American	218	2.2
African	163	1.6
Asian	112	1.1
Near/Middle Eastern	91	0.9
Deleterious mutation	1,720	17.2

NOTE. Adapted from Frank TS.[4]
*Salt Lake City, UT.

Hall and Olopande J Clin Oncol 2006;24:2197

CHEMOTHERAPY RESPONSE IN BRCA m carriers

TABLE 1. Overall Response Rates following Chemotherapy in Patients with BMOC

Chemotherapy Regimen	ORR in Platinum-Sensitive BMOC	ORR in Platinum-Resistant BMOC	References
Platinum-Based Chemotherapy	First Line		
	87%[a] *BRCA1* (83 patients)	-	Vencken et al[9]
	92%[a] *BRCA2* (13 patients)	-	Vencken et al[9]
	96%[b] (21/22 patients)	-	Tan et al[8]
	Recurrent		
	65%[c] (48 patients)	80%[c] (8/10 patients)	Alsop et al[5]
	92%[b] (11/12 patients, second line)	-	Tan et al[8]
	100%[b] (7/7 patients, third line)	-	Tan et al[8]
	100%[d] (6/6 patients)	-	Leunen et al[20]
Paclitaxel Monotherapy	60%[b] (9/15 patients)	27%[b] (3/11 patients)	Tan et al[21]
Pegylated Liposomal Doxorubicin	57%[d] (13/23 patients)	77%[d] (10/14 patients)	Adams et al[22]
	39%[d] (13/33 patients) in relapsing disease < 12 months after most recent platinum-based chemotherapy	-	Kaye et al[23]
Trabectedin	41%[b] (36/88 patients)	-	Lorusso et al[24]
Topotecan	-	0% (0/9 patients)	Hyman et al[25]
Mitomycin C	33%[e] (2/6 patients)	66%[e] (4/6 patients)	Moiseyenko et al[26]
Melphalan	-	CR in 1 patient	Osher et al[27]

Conclusions

- Both papers raise important points regarding BRCA testing
- Important due the limited data from Asia
- Urgent need to determine penetrance and risk in Asian mutation carriers as well as characterize VUS
- Frequency of BRCA mutations similar to Caucasians
- Illustrate big differences in uptake of BRCA testing
- Test all patients with EOC irrespective of FH
- BRCA mutation status will be increasingly important in treatment decisions
- Oncologists as initial gatekeepers – initial counselling and BRCA testing – refer mutation +ve and VUS to genetics

Questions

- Dr Kim-Can you comment on the high % of patients with VUS and what the reasons for this are ?
- Dr Heong- what do you think could /should be done to increase uptake of BRCA testing –can the barriers be broken in Singapore ?