Literature Review

Two Designated Pathways of Ovarian Cancer and the Crucial Implications to the Treatment

(*Dua jalur patogenesis kanker ovarium dan implikasi terhadap penatalaksanaannya*)

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Abstrak

Tujuan: Artikel ini bertujuan untuk membahas mengenai dua jalur patogenesis kanker ovarium dan implikasinya terhadap manajemen kanker ovarium.

Metode: Tinjauan pustaka

Hasil: Patogenesis kanker ovarium dapat dibagi menjadi tipe I dan tipe II berdasarkan penelitian-penelitan patologi anatomi dan molekular genetik. Kanker ovarium dengan subtipe *low-grade serous*, *mucinous*, *clear cell*, dan *endometrioid*. dikategorikan memiliki pola pertumbuhan kanker tipe I. Tipe I ini cenderung untuk berkembang perlahan, menunjukkan respons yang kurang baik pada kemoterapi platinum dan sebagian besar menunjukkan mutasi pada jalur MAPK. Kanker ovarium *subtype high-grade serous* biasanya berkembang lebih cepat dan agresif dan mengakibatkan buruknya prognosis pasien. Kanker ovarium jenis ini kemudian dikategorikan memiliki pola pertumbuhan kanker tipe II. Kanker tipe II ini banyak ditemukan mengalami mutasi pada gen TP53. Operasi yang optimal sebelum kemoterapi merupakan manajemen pilihan untuk kedua tipe tersebut sampai saat ini. Walaupun demikian, sitoreduksi optimal sangat ditekankan pada tipe II untuk meningkatkan angka *overall survival* dan *disease-free interval*. Skrining lesi minimal dengan *biomarker* untuk kanker ovarium tipe II menjadi sangat penting mengingat insepsi awalnya sangat sulit untuk dideteksi. Sementara itu skrining BRCA1/2 disertai perkembangan informasi terhadap klasifikasinya dibutuhkan sebagai metoda skrining untuk pasien-pasien dengan sindroma kanker payudara-ovarium herediter. Mutasi pada KRAS, BRAF, PTEN dan CTNNB1 terutama didapatkan pada kanker ovarium tipe I sehingga penelitan terhadap terapi inhibitor dan kemoterapi dengan target tertentu yang biasanya ditujukan kepada kanker ovarium tipe II rekuren dapat juga diarahkan pada kanker tipe I yang memiliki respons rendah terhadap kemoterapi platinum.

Kesimpulan: Strategi untuk skrining, pendekatan awal dan kemoterapi terhadap kanker ovarium dapat dikembangkan berdasarkan dua jalur tumor genesis terbaru yang memiliki pola yang berbeda.

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Kata kunci: kanker ovarium, karsinogenesis, skrining, sitoreduksi, kemoterapi

Abstract

***Objective**: To review the two designated pathways of ovarian cancer and their implications to the management of ovarian cancer.*

***Method**: Literature review*

***Result**: A proposed carcinogenesis of ovarian cancer has been developed based on a long history of pathological and molecular genetic findings. It divides ovarian cancer as having designated type I or type II pathway. Type I pathway involves ovarian carcinomas with low-grade serous subtype, mucinous, clear cell and endometrioid subtypes. They grow in a stepwise manner, shows low response toward platinum-based chemotherapy and mostly relate to MAPK pathway mutations. High-grade serous ovarian carcinomas which are often found in rapid-aggressive progression with poorer prognosis are suggested as type II pathway. Their major mutations are mainly in TP53. Optimal surgery and adjuvant chemotherapy are the treatment for both confined and advanced cancers. However, the optimal cytoreduction in type II pathway is becoming more important to increase overall survival or disease-free interval. The strategy of screening type II pathway is proposed to be shifted from detection of stage I tumors to detection of minimal ovarian carcinomas probably by biomarkers since the rapid inception is hardly found. Meanwhile the BRCA1/2 screening and classification should be improved for the hereditary breast/ovarian cancer screening. Mutations of KRAS, BRAF, PTEN and CTNNB1 occur majorly in the type I tumors. Therefore, targeted chemotherapy and inhibitor treatments which are investigated foremost in type II recurrence of ovarian malignancies may also be directed to the low response of type I pathway to platinum-based chemotherapy.*

***Conclusion**: A different strategy based on the tumorigenesis of ovarian cancer should be considered in term of screening, primary approach and following chemotherapy since there are some distinctive patterns in both pathways.*

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***Keywords**: ovarian cancer, carcinogenesis, screening, cytoreduction, chemotherapy*

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Ovarian carcinoma is the most lethal disease among all gynecological malignancies. The World Health Organization has classified ovarian tumors into some According to the origin of the cells, WHO categorized ovarian tumors as germ cells tumors, sex-cord tumors, stromal tumors and surface epithelial tumors. Ovarian tumors can also be classified as benign, low potential malignant (borderline), or malignant tumors according to certain criteria which include layer of cells, cellular proliferation, pleomorphism, and stromal invasion. Almost 90% of the malignancies are actually surface epithelial stromal type. Scarce information on initiation and progression are provided. Hereinafter the pathologist will classify epithelial type cancer into serous, clear cell, endometrioid, mucinous and other subtypes.[1-3]

The management of epithelial ovarian cancer begins with an optimal surgical staging procedure after a careful diagnosis. All subtypes of histology findings will be treated as a single entity of ovarian malignancy. Then, it is followed by the first line chemotherapy agents which are almost similar for all early stages and advanced stages; paclitaxel and carboplatin.[1] The classification of early stage and advanced stage are employed to decide the treatment approach. The chemotherapy administration for ovarian cancers stage IA and IB with well-differentiated and moderately-differentiated tumors which are considered as early stages remains controversy. Whilst the rest stages categorized as advanced stages will definitely require recommended adjuvant chemo-therapy after surgical management.[4] Recent clinicopathological and molecular studies propose two different pathways of ovarian carcinogenesis which are different in term of morphology and molecular biology.[3,5]

Model of Ovarian Tumorigenesis Based on Morphological and Molecular Genetic Analysis

A rigorous systematic microscopic and clinical analysis involving a large number of invasive and non-invasive epithelial tumors of all histological types of ovarian cancer has been conducted for almost 15 years. Despite of categorizing ovarian malignancy into different kinds of subhistopathological subtypes, a review toward advanced stage and early stage of ovarian cancer revealed differences in term of clinical behavior, morphological and molecular genetic analysis. Most of the early stages of ovarian cancer are clear cell, endometrioid and mucinous subtypes. Serous subtypes are majorly found in patients with advanced stages, only some of them were showed early growth. The serous type is divided further into high grade and low grade which follow two contrasting pathways of development.[3,6-8] Current molecular genetic studies along with histopathological and clinical findings suggest that there are two designated pathways of ovarian tumorigenesis; type I consists of low-grade ovarian cancers presenting slow progression, type II consists of high-grade ovarian cancers with rapid progression.

Type I is more likely to develop in stepwise manner supported by recognized precursors appearance (Figure 1). The clear cell, endometrioid, mucinous and low-grade serous carcinoma subtypes belong in this type. Each subtype shows a precursor state in pathological findings. Adenofibroma or atypical proliferative serous tumor develop into non invasive micropapilary serous carcinoma (MPSC) or serous borderline ovarian tumor (SBT) and in turn into invasive low grade serous carcinoma or invasive MPSC, The indolent course of MPSC may last for more than 20 years.[4,9,10]

Atypical proliferative serous tumor or SBT and MPSC show well-characterized molecular alterations as sequence mutations of KRAS and BRAF oncogenes. A study on sporadic serous ovarian malignancies demonstrated that KRAS mutations occurred in approximately 50% of SBT, MPSC, and invasive MPSC.[11] These tumors have comparable characteristics of low proliferative activity and indolent behavior. The oncogenic mutations play a critical role in the transmission of growth signals pathway and neo-

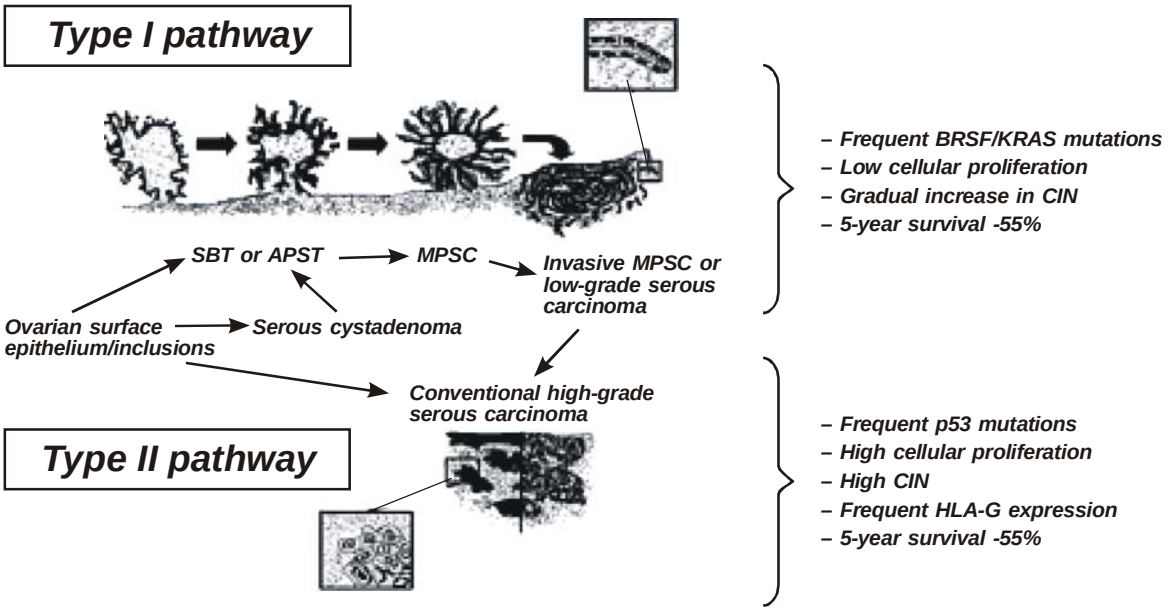

Figure 1. Schematic representation of the proposed model of tumorigenesis pathways. Abbreviation: SBT, serous borderline tumor; APST, atypical proliferative serous tumor; MPSC, micropapilary serous carcinoma (with permission from R.J. Kurman Am J Pathol 2004;164:1511-8).

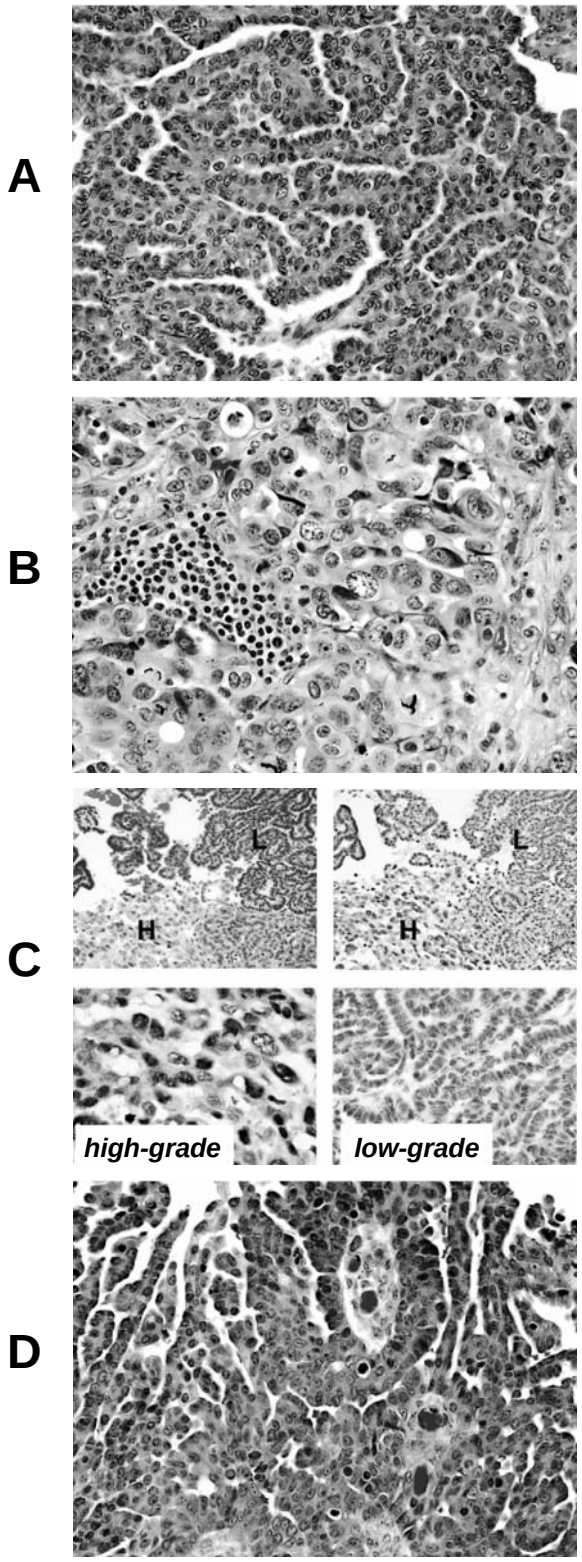

Figure 2. **A**, Invasive low grade micropapilary serous carcinoma characterized by a micropapilary architecture and grade I nuclei. **B**, High grade serous carcinoma with a solid growth patten and grade 3 nuclei or grade **C**, An unusual case of a synchronous high grade (H) and low grade (L) serous carcinoma. Antibody against Rsf-1 was used to stain high grade serous carcinoma. **D**, serous carcinoma with grade 2 nuclei (with permission from R.J. Kurman Int J of Gynecol Pathol 2008; 27:151-60).

plastic transformation through the mitogen-activated protein kinase (MAPK). Other study indicated that mutations in either codon 599 of BRAF or codons 12 and 13 of KRAS counted for 86% in MPSC and 61% in the serous borderline tumors.[12,13] A study that observed the adjacent epithelium from cystadenoma presumed as SBT precursor has showed lack of cytological epithelial; however same mutations of BRAF and KRAS occurred in the adjacent epithelial as in the SBT (seven to eight SBT had either BRAF or KRAS mutations and six of seven adjacent epithelium of cystadenoma showed the same mutations). These mutations appeared to occur very early in the development of low-grade ovarian cancer.[14]

Mucinous tumors of ovaries without any associated to either psedomyxoma peritonei (PMP) or metastatic spread from the upper gastrointestinal tract are predominantly confined within the ovaries. Mucinous cancers are often found well-differentiated with areas of borderline and mucinous cystadenomas. The invasive growth can be usually found as a focus in mucinous borderline tumors (MBT).[15] From molecular analysis, the KRAS oncogene mutations reported existing mostly in the first stage tumors in all subtypes but majorly in mucinous ovarian cancers.[16,17] Such mutations were discovered in the suggested early morphologic transition of adjacent mucinous cystadenomas into MBT and eventually mucinous carcinomas.[18]

Furthermore, endometriosis has been long associated as precursor of endometrioid and clear cell type ovarian cancer. The cases are mostly found in premaneopausal age and early stage cancer with possible different mechanism of carcinogenesis for both subtypes.[19,20] Endometrioid type has a long history of beta-catenin gene (CTNNB1) mutations involvement. Alterations on CTNNB1 along with PTEN were observed to a greater extent in endometrioid ovarian carcinoma and associated with endometriosis more often than in tumors without endometriosis.[21,22] A nearly constant molecular mutations and microsatellite instability of CTNNB1 are present in borderline endometrioid ovarian tumors, whereas PTEN and KRAS mutations and microsatellite instability are less frequent. It is suggesting that CTNNB1 mutations are involved in the early event of low-grade endometrioid ovarian carcinogenesis.[23] As in clear cell type of ovarian tumor, the molecular genetic changes were found in several distinctive factors. Up-regulated HNF1B (hepatocyte nuclear factor-1 beta) was found in almost 90-100% of clear cells specimens.[24,25] Some of the studies reported KRAS mutations (5-16%), microsatellite instability (13-50%), and at least 66% of TGF-β RII mutations on clear cell type but the frequency derived from limited cases.[18] But in fact, clear cell subtype do not share typical type I or type II designated pathway group. This subtype tends to be found in advanced stage although unlike type II tumors it is more genetically stable. Microsatellite instability of clear cell subtypes apply the same as in endometrioid subtype confirming endometriosis involvement as precursor.[26]

In contrast, the tumors which are categorized as having type II pathway of ovarian cancer are considered high grade at presentation. The high-grade serous carcinoma, undifferentiated carcinoma, and malignant mixed mesodermal tumors have tendency to feature the same clinicopathological patterns. Designated type II carcinomas are uncommonly associated with morphologically recognizable precursor lesions.[5,12] Higher Ki-67 nuclear labeling index in high-grade serous carcinoma compared to low-grade serous carcinoma is presumably because of rapid transit from inception as a microscopic carcinoma to a clinically diagnosed neoplasm. Type II group evolves and metastasizes aggressively. Precursor lesions are hardly elucidated presumably due to the rapid transit.[27] TP53 mutations are observed consistently in type II; at least 50-80% of advanced stage high grade serous carcinoma showed p53 mutations and approximately 37% is showed in stage I and stage II.[28,32] Similar TP53 mutations are also demonstrated in malignant mesodermal tumors advising the same pathway of carcinogenesis.[33] In efforts to reveal the rapid transit of the type II inception, the fallopian tubes derived from prophylactic bilateral salpingooophorectomies on women with BRCA1/2 mutations were analyzed. Tubal carcinoma was detected in both histologic evaluation and immunostaining in women with BRCA1/2 positive. Genomic instability, TP53 mutations, and dramatically increased proliferation marked by increased Ki-67 were observed in these early developments in fallopian tubes but not in ovarian cortical inclusion cyst. Genetic abnormalities were found in both fallopian tube mucosal and ovarian tumors. The gene copy abnormalities obtained from risk-reducing salpingectomies which showed in situ epithelial lesions suggested that the chromosomal instability is a very early event in serous carcinoma. It hypothesized that the early lesion of women with high risk of ovarian carcinoma in particular the high grade serous carcinoma happened to be aroused from the epithelium of the fimbriated end of fallopian tubes or involved the mucosal fimbriated fallopian tubes. In total of 11 articles of tubal involvement in serous ovarian cancer, 31 cases were observed over 51 cases of high risk prophylactic bilateral salpingoophorectomies.[34-39]

Table 1. Summary of precursor, molecular genetic alteration, and clinical behavior of ovarian carcinoma subtypes

	Ovarian carcinoma subtypes				
	High grade serous carcinoma	**Low grade serous carcinoma**	**Mucinous carcinoma**	**Endometrioid carcinoma**	**Clear-cell carcinoma**
Presumable precursor lesion	Fallopian tube or tubal metaplasia in inclusions of ovarian surface epithelium	Serous cystadenoma/ adenofibroma Atypical proliferative serous tumor (APST) Non-invasive micro papillary serous carcinoma (MPSC) or serous borderline tumor (SBT) Invasive MPSC	Mucinous cysta denoma Atypical proliferative mucinous tumor Intraepithelial carcinoma	Endometriosis Endometrioid adenofibroma Atypical proliferative endometrioid tumor Intraepithelial carcinoma	Endometriosis clear cell adenofibroma Atypical proliferative clear cell tumor Intraepithelial carcinoma
Molecular protein alteration	TP53 mutations (50-80%) Amplification and overexpression of HER2/neu gene and AKT2 gene (12-18%) RB1 pathway	BRAF or KRAS mutations (67%)	KRAS mutations (>60%)	Lost of heterozygocity or mutations in PTEN (20%) CTNNB1 mutations (16-54%) KRAS mutations (4-5%)	Up-regulated HNFB1 (90--100%) TGF-β RII mutations (60%) Microsatellite instability (13-50%) KRAS mutations (5-16%)
Proliferation	High	Low	Intermediate	Low	Low
Genetic risk	BRCA1/2	?	?	HNPCC	?
Clinical behavior	Rapid and aggressive growth Majorly found at advanced stage G2/G3	Indolent and slow progression Majorly found at early stage G1	Indolent and slow progression Majorly found at early stage G1-G3	Indolent and slow progression Majorly found at early stage G1-3	Indolent and slow progression Found at early and advanced stages G3
Response rate to chemo therapy	80%	26-80%	15%	?	15%
5-year survival	30-38%	51.5%	71.4%	67.1%	50.8%
Prognosis	Poor	Favorable	Favorable	Favorable	Intermediate

***Abbreviation**: TP53, tumor protein 53; HER2/neu, human epidermal growth factor 2; AKT2, protein kinase B-2; RB1, retinoblastoma tumor suppressor; BRAF, v-raf murine sarcoma viral oncogene homologue; KRAS, Kirsten rat sarcoma viral oncogene homologue; CTNNB1, catenin (cadherin-associated protein) beta 1; HNFB1, hepatocyte nuclear factor beta-1; TGF-β RII, transforming growth factor beta receptor 2; PTEN, phosphatase and tensin homologue; BRCA1/2, breast cancer early-onset 1/2; HNPCC, heriditary nonpolyposis colon cancer; G, grade (Adapted with permission from Editorial committee of Expert Rev Mol Med. 2008;10(22) and R.J. Kurman Am J Pathol 2004;164:1511-8).*

Different Approach of Treatment Based on Suggested Designated Pathways of Ovarian Cancer

Supported by the two pathways with their distinctive attitudes, a new strategy or treatment approach of ovarian cancers could be provided. Type I tumors which are mostly confined in ovary appear mostly in early stages. Optimal surgical staging and mass removal followed by adjuvant chemotherapy have shown benefits clinically for these stages.[40,41] In addition to the confined state, type I tumors maintain to show different alterations or mutations in mitogen-activated protein kinase (MAPK) pathway. Consequently the effort of treatment should be targeted on the MAPK pathway. Inhibitor treatment and targeted immunotherapy possibly can act as a strategy for type I tumors therapy.[12] As widely known, MAPK pathway is important for signal transduction by coupling intracellular responses to the binding growth factors and cell surface which in turn responsible for cell proliferation and differentiation. Some fundamental studies towards MAPK pathway have been done both in vitro and in vivo. A research of mutated KRAS oncogene on more than 200 regulatory genes indicated that at least 79 critical genes related to the application of anchorage-independent proliferation and epithelial-mesenchymal transition using MAPK and phosphatidylinositol 3-kinase (PI3K) pathways. Reversion to the normal ovarian surface in rat model achieved by blocking MAPK or partly induced by silencing of the overexpressed transcriptional regulator Fra-1 by RNA interference.[42] MAPK phosphatase 1 (MKP-1) accounts for extracellular signal-regulated kinase (ERK1/2) deactivation is thought to be downregulated on cancer cells which lead to ERK hyperactivity. Proteosome inhibitor ZLLF-CHO or silencing ERK1/2 gene using RNA interference will hamper the cell's ability to proliferate.[43] Gonadotrophin releasing hormone-II (GnRH-II) effects on activation of p38 MAPK and ERK1/2. Activation of p38 by GnRH-II plays a role in apoptosis through activation of activator protein-1. GnRH-II might possibly be a crucial target for therapy given that the activation of ERK1/2 by GnRH-II is reversed by blocking phosphorylated Elk-1, the downstream pathway.[44,45]

Beside MAPK pathway, there are some other targets of potential interest such as epidermal growth factor receptor (ErbB) family. Erlotinib, cetuximab, and gefitinib are drugs which inhibit overexpression of ErbB. Clinical trial of erlotinib combine with the standard chemotherapy of ovarian cancer is still on going. A phase Ib clinical trial of erlotinib with docetaxel/carboplatin showed more benefits as maintenance therapy in particular.[46] Cetuximab combined with standard chemotherapy does not give additional advantage on phase II trial in advanced stage patients; no prolongation of progression free survival and association with rash as hypersensitivity reactions in majority patients.[46,47] The gefitinib experience of phase II study reported that the patients needed to be screened for activating mutations in the epidermal growth factor receptor (EGFR) in order to increase the response rate to gefitinib on patients with recurrent ovarian or primary peritoneal carcinoma.[48] Other target therapy is vascular endothelial growth factor (VEGF) which well-known inhibitor is bevacizumab. Bevacizumab in combination with standard chemotherapy has demonstrated excellent efficacy for the treatment of recurrent ovarian cancer. It is reported to be well-tolerated in phase II trial by Gynecology Oncology Group (GOG) as the second line or third line treatment. Unfortunately the benefits have come with a serious complication if bowel perforations making a slower progression in clinical practice.[49-51] Nevertheless, there are no data on early stage patients with these drugs, possibly because the survival is quite good with standard chemotherapy and chemotherapy is aiming majorly to advanced stages with cases of chemoresistance.

The vast majority of ovarian cancers exhibit the characteristics of those which are suitable to designated type II pathway; extremely aggressive and advanced stage at presentation. They are mainly high grade serous carcinoma, account for 70% of all ovarian carcinomas and are found almost 90% at stage III or IV.[7,52] Rapid transit accompanied by unidentifiable precursor lesion hinders any efforts of early detection. The early detection strategy might be useful for slow-growing tumors but not for the type II tumors. A meta-analysis showed that improving prognosis of advanced ovarian cancer has involved the optimal cytoreduction surgery; each 10% increase in maximal cytoreduction amplifies the median survival time for at least 5.5%. Surgical techniques have evolved the constitution of optimal cytoreduction. It has shifted from less than 2 cm to less than 1.5 cm and finally to less then 1 cm. Therefore, the proposed strategy of screening type II pathway is detection of minimal ovarian carcinoma define as microscopic to 1 cm lesions which could be detected ultimately by biomarkers because of the lack of recognizable precursors. Treatment of type II pathway depends on maximal primary cytoreduction like the type I pathway. Hence consistent referral of patients with apparent advanced ovarian cancer to gynecology oncology centers for primary surgery might be the best approach currently available to improve overall survival.[18,53]

Besides the importance of optimal cytoreduction to reach minimal size of tumor mass, two important issues that also deprive attention are genetic risk and protein mutations affected, TP53. BRCA1 and BRCA2, carried by patients with hereditary breast/ovarian cancer, are mainly high-grade serous carcinoma. The mutations could happen in one allele of either BRCA1 or BRCA2. BRCA1/2 germline mutations are exclusively existed in high-grade serous carcinoma, which suggested having designated type II pathway.[53,54] Granting only 16-20% of all histology subtypes of ovarian cancer associated with BRCA1/2 mutations, some studies reported that the BRCA1/2-associated group had a longer recurrence-free and longer overall

survival compare to non-associated group. It also showed that BRCA1 mRNA levels were related to the overall survival in sporadic ovarian cancers even though the mechanisms are not clear yet.[55-58] The routine screening of BRCA1/2 among positive hereditary breast-ovarian cancer failed to show benefit in increasing overall survival. Despite of reduction of breast and gynecological cancer incidence among carriers after mastectomy and prophylactic gynecological surgery including bi- or unilateral oophorectomy, a systematic review of research reported flaws in screening efficiency of familial breast-ovarian malignancy conducted in 1996-2005.[59] Developing strategy for BRCA1/2 as critical predictor for ovarian cancer is considerable because mainly the BRCA1/2 associated ovarian cancers manifest as high grade serous subtype. Regardless the screening which could possibly only be accounted for one fifth of all incidences, improvement of BRCA1/2 status detection and further classification is necessary to be applicable in clinical daily use.

As the protein affected, mutations in TP53 could reach between 50-80% of all invasive ovarian cancers.[29,32,60] TP53 is the gene mostly responsible for cell cycle regulation including apoptosis and resolving DNA damage. Gene mutations contribute to the loss of cell regulation and lead to an excessive cell proliferation and dysfunction. The type of mutation is mainly missense mutations that allow a genetic change involving the substitution of one base in the DNA for another which in turn change one amino acid in a polypeptide for another.[32] Mutation in TP53 appears to develop very early in the genesis of type II neoplasia in the fimbriated part of fallopian tubes of BRCA-positive patients.[39] Regarding correlation of TP53 with the early detection, there have to be a better of identification other than immunohisto-chemistry staining in order to offer useful method of screening. The correlation of the mutations to the prognosis or chemotherapy sensitivity remains unclear. Some data suggest that the loss of function of p53 tend to have more favorable clinical response to chemotherapy. It was supporting a model whereby p53 mediated cell-cycle-arrest/DNA repair served as a barrier to optimal chemotherapy.[61-63] Other data implicate that mutated p53 are more responsive to taxane-based or taxane-platinum-based chemotherapy than platinum standard chemotherapy which addressed chemoresistancy than chemosensitivity.[64,65] It is also crucial to further investigate TP53 mutations since they are inherited during cancer evolution and contribute to the transformed state. New technologies such is BEAM-ing which detect small amounts of mutations or highly sensitive mass spectrometry or even specific capture enzyme-linked immunosorbent assay (ELISA) could be utilized to detect expression products of the mutant marker genes.[18,66]

CONCLUSION

A new model of ovarian tumorigenesis is developed based on rigorous studies of pathology and molecular genetics. Two proposed pathways are designated type I and type II. Type I tumors are characterized by indolent behavior and slow progression while type II have the opposite characters, rapid and aggressive growth. Type I tumors include low-grade serous, mucinous; clear cell and endometrioid ovarian carcinoma while high-grade serous subtypes are dominant in type II tumors. Type I tumors are known previously through precursor lesions which develop in stepwise manner. It is recommended that low grade serous ovarian cancers are developed from adenofibroma or atypical proliferative serous tumor into non invasive MPSC then finally into invasive MPSC. The process could take almost 20 years to be invasive. Regarding therapy, optimal surgery prior to adjuvant chemotherapy is still the best strategy to type I pathway which is usually confined in the ovary. Mutations of MAPK pathways such as KRAS, BRAF, PTEN, and CTNNB1 are expressed mostly in type I group along with the low response to platinum-based chemotherapy. Efforts to strengthen the chemotherapy effect by looking at MAPK pathway as target are put forward in the future directions. Some inhibitor treatment and targeted immunotherapy should also develop toward not only advanced stages but early stages with low response.

The quest into finding the rapid transient pre-lesion which is presented the high grade serous ovarian cancer comes across the findings of presumably pre-lesion in epithelial or mucosal of fimbriated fallopian tubes among BRCA1/2-associated hereditary breast/ovarian cancer patients. Meanwhile, the type II tumors best approach should possibly be shifted from stage I detection into detection of minimal ovarian carcinoma which only be recognized by biomarkers. Consistent referral to gynecology oncology center would give valued in term of optimal surgical cytoreduction. Type II tumors also showed more p53 mutations and more associations with hereditary BRCA1/2 syndrome with problem of high recurrences after first chemotherapy. In spite of the roles of p53 mutations remain more explanations in clinical practice, TP53 could be correlated to chemo-resistance toward platinum based therapy and sensitivity to taxane therapy. Mutations of TP53, found coherently in fimbriated fallopian tubes of BRCA1/2 hereditary-associated ovarian cancer, could possibly act as a starting point toward type II ovarian cancer screening while improving the BRCA1/2 status screening and bilateral salpingo-oophorectomies could be retained as screening strategy in the breast/ovarian cancer hereditary group.

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