International Journal of Gynecology and Obstetrics 131 (2015) S127–S131

Contents lists available at ScienceDirect

International Journal of Gynecology and Obstetrics

journal homepage: www.elsevier.com/locate/ijgo

FIGO CANCER REPORT 2015

The future role of molecular staging in gynecologic cancer

Pratibha S. Binder [a], Jaime Prat [b], David G. Mutch [a]

[a] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Washington University School of Medicine, St Louis, MO, USA
[b] Department of Pathology, Hospital de la Santa Creu i Sant Pau, Autonomous University of Barcelona, Spain

1. Introduction

A cancer staging system should be explicit, practical, and should provide information required to make important decisions about prognosis and treatment. The first FIGO staging nomenclatures for gynecologic cancers were based solely on the anatomical extent of the disease determined by physical examination and a few surgical parameters. As surgical evaluation of some gynecologic cancers became feasible, the FIGO staging system was revised to include surgical and histopathologic assessment of the tumor for most gynecologic cancers. Despite modifications in staging systems, the principles and purpose of cancer staging remain the same (Box 1).

Identification of the cellular events leading to carcinogenesis provides additional information for comprehensive tumor classification and prognostication. While genetic sequencing was expensive and identifying driver mutations was laborious in the past, current technologies produce high-throughput data that makes methodical analysis of DNA, RNA, and proteins achievable. Genetic and molecular studies can be performed on blood and tumor samples obtained during the operative evaluation and treatment of cancer. A classification based on genomic and proteomic platforms is practical at this time, has minimal morbidity, and could provide essential information regarding prognosis and response to targeted therapies. The present article focuses on molecular discoveries that have been made in the last decade that should be considered in future revisions of gynecologic cancer staging systems.

2. Ovarian cancer

2.1. Classification

Shih and Kurman [1] classified ovarian cancers into two types based on genetic and histologic features. Type I is a heterogeneous group including low-grade serous, endometrioid, clear-cell, and mucinous carcinomas, which commonly arise from precursor lesions and are typically slow growing. Type II includes high-grade serous cancers, which usually present with advanced stage and metastasis at the time of diagnosis and are associated with *p53* mutations. Prat et al. [2] proposed a five-subtype classification including high-grade serous (HGSOv), low-grade serous (LGSOv), endometrioid (EOv), clear-cell (CCOv), and mucinous (MOv) carcinomas. Each subtype has distinct molecular events leading to carcinogenesis, therefore resulting in different precursor lesions, patterns of spread, prognosis, and response to adjuvant therapy. Morphologic assessment is currently the mainstay for subtype diagnosis, but immunohistochemical reactivity to Wilms tumor protein (WT-1), estrogen receptor (ER), hepatocyte nuclear factor (HNF) 1β, cancer antigen 125 (CA-125), and Ki-67 (Table 1) may be helpful [3]. Since research to detect aberrations in molecular pathways is gaining popularity, characteristic genetic profiles for each subtype have also been determined (Table 1). Since there is overlap in the histologic features and genetic profiles of different ovarian cancer subtypes, there is no clear consensus on which tests to routinely perform for accurate diagnosis.

2.2. Homologous recombination repair pathway

Germline and somatic mutations in tumor suppressor genes *BRCA1* and *BRCA2* disrupt the cell's ability to repair double strand breaks in damaged DNA (homologous recombination). The BRCA pathway is disabled in up to 50% of HGSOv. An assessment of 390 ovarian cancers showed similar mutation rates in HGSOv and non-HGSOv of 13 genes involved in homologous recombination DNA repair. The presence of a mutation was associated with a longer overall survival and improved response to platinum-based chemotherapy [4]. Poly (ADP-ribose) polymerase (PARP) inhibitors induce double strand DNA breaks that lead to genomic instability and death in cells that lack homologous recombination repair genes. This treatment is therefore being used to target BRCA1 and BRCA2 mutated tumors [5]. Determination of BRCA status is consequently valuable and satisfies the principles of cancer staging since it classifies patients into different prognostic groups and predicts response to chemotherapy and targeted PARP inhibitors.

2.3. KRAS/MAPK pathway

The characteristic genetic alterations in the LGSOv subtype are mutations in oncogenes *KRAS* and *BRAF*, leading to activation of the mitogen-activated protein kinase (MAPK) pathway [3]. Although LGSOv tend to be less aggressive, they are relatively non-responsive to platinum-based chemotherapy. MEK inhibitors down-regulate key enzymes in the MAPK pathway and therefore show promise in the treatment of LGSOv and other tumors with MAPK pathway aberrations. Pre-clinical research and multiple clinical trials have evaluated the use of MEK inhibitors in ovarian and other gynecologic malignancies [6]. It is important to identify cancers with MAPK pathway abnormalities as

http://dx.doi.org/10.1016/j.ijgo.2015.06.009

[Post publication notice: 13 December 2016, after issue publication: Portuguese and Spanish translations are made available in the Supporting Information].

Box 1
The purpose of cancer staging.

- To develop an accurate and universal terminology to describe the extent of disease.
- To characterize patients with cancer into different prognostic groups and enable clinicians to counsel patients about treatment options, morbidities, and mortality.
- To allow meaningful comparisons of treatment efficacy and survival outcomes when comparing treatment strategies, institutions, or geographical areas as part of clinical trials and research.

these patients may benefit from less toxic MEK inhibitors and other targeted therapies.

2.4. Vascular endothelial growth factor

Angiogenesis is important and necessary for cancer growth and metastasis. The presence of vascular endothelial growth factor (VEGF) receptors and ligands has not been associated with prognosis or clinical outcomes in ovarian cancer. However, bevacizumab, a monoclonal antibody that inactivates VEGF has been well studied and is important in the treatment of primary and recurrent ovarian cancer. While the entire cohort of patients treated with chemotherapy and bevacizumab for primary ovarian cancer only had a modest improvement in progression-free survival compared with the patients treated with chemotherapy alone, Gourley et al. [7] developed a 63-gene signature biomarker to distinguish bevacizumab responders from non-responders. Preclinical research has studied the benefit of low-dose VEGFR2 antibodies in modulating the tumor microenvironment to allow for an immune-stimulatory phenotype with improved infiltration of $CD8^+$ T-cells [8]. Now low-dose bevacizumab is being evaluated in combination with cancer vaccine therapies for breast and ovarian cancer. The search for biomarkers to help guide treatment with antiangiogenesis drugs is ongoing [9]. Appropriate identification of patients that will benefit from this targeted therapy is vital to the safe and effective use of this expensive and potentially toxic therapy.

2.5. Cancer stem-cell markers

Despite high initial response rates to cytotoxic chemotherapy, the recurrence rate for ovarian cancer remains high. The molecular features of these cancers that lead to recurrence are not clearly understood, but one theory is the presence of cancer stem cells in the original tumor. Although cancer stem cells only represent a small proportion of the tumor, they are resistant to chemotherapy and can grow rapidly, thereby repopulating tumors and leading to recurrence that is often resistant to previous chemotherapy. The detection of sensitive markers for ovarian cancer stem cells would have implications in predicting risk of recurrence and prognosis. Cell surface receptors such as CD44, CD117, and CD133 are being evaluated as markers for ovarian cancer stemness and as targets for therapeutics options against these chemo-resistant cell types [10]. Identifying cancer stem cells could be very helpful in predicting response to therapy and tumor behavior.

Table 1
Immunohistochemistry reactivity and genetic mutation profile of ovarian cancer subtypes.

Subtype	IHC reactivity	Genetic mutation profile
HGSOv	P53 +, WT-1 +, ER +, high Ki-67 index	*p53*, *BRCA1/2*, aneuploidy
LGSOv	P53-, WT-1 +, ER +, low Ki-67 index	*BRAF* and *KRAS* mutations
EOv	WT-1-, ER +	*ARID1A*, *CTNNB1*, *PTEN*, microsatellite instability
CCOv	HNF1β +, WT-1-, ER-	*ARID1A*, *PIK3CA*, *PTEN*, *KRAS*
MOv	CK7 +, CK20 +/−, CEA +/−, CA19-9 +/−, CDX2 +/−	*KRAS*, *Her2*

Abbreviations: HGSOv, high-grade serous ovarian cancer; LGSOv, low-grade serous ovarian cancer; EOv, endometrioid ovarian cancer; CCOv, clear-cell ovarian cancer; MOv, mucinous ovarian cancer.

2.6. Genetic profiling in ovarian cancer

The Cancer Genome Atlas (TCGA) research network performed mRNA analysis on 489 HGSOv cancers and noted *p53* mutations in 96% of cases [11]. While *p53* is pivotal in HGSOv cancers, it is important to note that not all *p53* mutations are the same and further research needs to be performed to determine the prognosis of different mutations in the p53 pathway. Anti-mutant p53 drugs are now available and their ability to restore wild-type p53 properties to p53 mutant cancers is being studied [12]. In the future, determination of *p53* mutation and type should be fruitful in determining prognosis and possibly response to anti-mutant p53 therapy. Results from the TCGA HGSOv cohort are also being used to develop genetic and promoter methylation profiles for chemotherapy responders versus non-responders [13]. Profiling of large cohorts of ovarian cancers based on genomic and proteomic platforms is still required to determine the prognostic ability of different *p53* mutations and other genes that are mutated at a lower but significant frequency.

3. Endometrial cancer

3.1. Classification

The first description of endometrial cancer subtypes was by Bokhman in 1983 [14]. He distinguished between type I and type II endometrial cancer based on patient phenotype, tumor histology, clinical behavior, and survival rates. Today, pathologists assign a histologic type to type I (low-grade endometrioid) and type II (high-grade endometrioid, serous, clear cell, or carcinosarcoma) endometrial cancer based on tumor morphology and a tumor grade (1: well differentiated; 2: moderately well differentiated; or 3: poorly differentiated), based on glandular architecture and nuclear grade. Through genetic profiling of different histologic types, we now know that these tumors differ in the early driver mutations that lead to carcinogenesis. The key mutations responsible for carcinogenesis are different in endometrioid endometrial cancers (EECs) and non-EECs (serous carcinomas and clear-cell carcinomas [CCCs]) (Table 2), although there may be some overlap in genetic profiles since progression from endometrioid to non-endometrioid carcinoma may occur [15].

In addition to a high frequency of mutations in *PTEN*, *CTNNB1*, *KRAS*, *FGFR-2*, *ARID1A*, and *PIK3CA*, EECs often express estrogen and progesterone receptors and have microsatellite instability. The presentation, clinical behavior, and prognosis of EECs differ dependent on tumor

Table 2
Key mutations and useful biomarkers in the classification of endometrial cancer subtype.

Histologic type	Biomarker	Mechanism	Frequency
Endometrioid	PTEN	Mutation/deletion	50%–80%
	EGFR	Overexpression	40%–45%
	KRAS	Mutation	10%–40%
	CTNNB1	Mutation	10%–45%
	FGFR2	Mutation	16%
	MLH1	Promoter methylation	20%
Serous	TP53	Mutation/overexpression	80%–90%
	HER2/neu	Amplification/overexpression	30%–40%
	PIK3CA	Amplification	45%
	E-cadherin	Loss of function	40%–90%
	EGFR	Overexpression	35%–60%
Clear cell	PIK3CA	Mutation	
	PTEN	Mutation	
	ARID1A	Mutation/loss of function	
	HNF1β	Overexpression	

grade. Catasus et al. [15] suggested that some high-grade EECs might have significant overlap with serous carcinomas. Whereas low-grade EECs have a higher frequency of *PTEN*, *KRAS*, and *CTNNB1* (beta-catenin) mutations, high-grade EECs often have *p53* and *PIK3CA* mutations [3,15]. Now we will discuss a few of the targetable pathways involved in endometrial carcinogenesis and associated targeted therapies (Table 3).

3.2. PTEN-PI3K-AKT-mTOR pathway

Mutations in the tumor suppressor gene *PTEN* and oncogene *PIK3CA* lead to direct activation of the anti-apoptotic PI3K-AKT pathway. *PTEN* mutations are more commonly seen in low-grade EECs, but loss of PTEN protein expression can lead to up-regulation of the PI3K-AKT pathway and inhibition of apoptosis, which is a poor prognostic maker in EECs [15]. *PIK3CA* mutations are more common in high-grade EECs and mixed histology endometrial cancers. PI3K/AKT/mTOR inhibitors are being evaluated in pre-clinical and clinical trials [16]. While the results of single therapy mTOR inhibitors in phase II trials have been modest, there seems to be more potential when used in combination with chemotherapy or other targeted inhibitors of angiogenesis or the MAPK pathways. Unfortunately, the response to treatment with PI3K-, AKT-, or mTOR-inhibitors does not correlate with *PTEN* mutations or phosphorylated downstream targets (AKT, mTOR, S6). Therefore, we must continue to search for biomarkers that predict response to these targeted therapies.

3.3. KRAS-MAPK pathway

Mutated KRAS GTPase protein up-regulates the MAPK pathway and can also bind the PIK3CA protein leading to activation of the PI3K-AKT-mTOR pathway. *KRAS* mutations are mostly seen in EECS, rarely in non-EECs, and are associated with longer disease-free survival [17]. Pre-clinical trials of MEK inhibitors as single therapy and in combination with PI3K/AKT/mTOR inhibitors are promising and a clinical trial evaluating the response of the MEK inhibitor trametinib alone or in combination with an AKT inhibitor is underway.

3.4. Tyrosine kinase receptors

Tyrosine kinase receptors (TKRs) are a family of transmembrane glycoproteins that are usually activated by a variety of growth factors. The important TKRs involved in endometrial carcinogenesis include HER2 (Erb-B2), EGFR (Erb-B1), FGFR2, and VEGFR.

Table 3
Targeted therapies in treatment of endometrial cancer.

Target	Drug	Research status
PI3K	GDC-0941	Preclinical
AKT	GSK2141795	Phase II active
mTOR	Temsirolimus	Phase II completed
	Everolimus	Phase II completed
	Ridaforolimus	Phase II completed
	AZD8055	Preclinical
PI3K/mTOR	GDC-0980	Preclinical
MEK	Trametinib	Phase II active
	PD98059	Preclinical
	PD0325901	Preclinical
HER2	Trastuzumab	Phase II completed and active
	Pertuzumab	Phase II completed
EGFR	Erlotinib	Phase II completed
	Gefitinib	Phase II completed
	Pertuzumab	Phase II completed
HER2/EGFR	Lapatinib	Phase II completed
FGFR2	Ponatinib	Phase I active
	PD173074	Preclinical
VEGF	Bevacizumab	Phase II completed and active
FGFR2/VEGF	Brivanib	Phase II completed
	Nintedanib	Phase II completed

3.4.1. HER2

Overexpression of the HER2/neu protein is common in uterine papillary serous cancers (UPSCs) and leads to cell proliferation, differentiation, and migration by activation of both the PI3K-AKT-mTOR and MAPK pathways. HER2/neu RNA amplification and protein overexpression are ideal biomarkers as they predict survival and response to chemotherapy as well as PI3K and mTOR inhibitors [18]. Trastuzumab and pertuzumab are monoclonal antibodies against HER2 receptors that are approved for the treatment of HER2-positive breast cancer. They are currently being evaluated in the treatment of HER2-positive UPSCs.

3.4.2. Epidermal growth factor receptor

Epidermal growth factor receptor (EGFR) overexpression is seen in both EECs (low-grade and high-grade) and UPSCs [18]. EGFR activation leads to the activation of many cellular pathways including PI3K-AKT-mTOR and MAPK pathways. EGFR inhibitors gefitinib and erlotinib did not improve survival in phase II trials of advanced endometrial cancer and response rates were not associated with EGFR overexpression [19]. Translational studies of the lapatinib (dual EGFR and HER inhibitor) phase II trial identified one previous unreported EGFR mutation that was present and associated with objective tumor response in one patient [20]. Further studies need to be performed to validate the value of this mutation in predicting response to lapatinib.

3.4.3. FGFR2

Mutations in this oncogene are more common in low-grade EECs, but it is associated with chemo-resistance and with poor progression-free survival and overall survival [17]. Pre-clinical studies show that the FGFR2 inhibitor PD173074 has a synergistic effect on apoptosis when combined with cytotoxic chemotherapy [19]. In phase II clinical trials, treatment of recurrent endometrial cancer with brivanib or nintedanib resulted in a progression-free interval of at least 6 months in 30% and 22% of patients, respectively [21,22].

3.4.4. Vascular endothelial growth factor

As with ovarian cancer, there is no clear consensus on whether VEGF overexpression is associated with prognosis or response to angiogenesis inhibitors in endometrial cancer. While bevacizumab alone had a modest response rate in recurrent endometrial cancer, the combination with mTOR inhibitor temsirolimus improved response rates but was also more toxic [23]. The efficacy and toxicity of bevacizumab with cytotoxic chemotherapy for advanced endometrial cancer is being evaluated in phase II trials. Since combination treatments can be expensive and toxic, it is important to focus future research on biomarkers that predict response to antiangiogenic drugs so that this treatment can be limited to patients who would benefit from treatment.

3.5. Genetic profiling in endometrial cancer

The 2013 TCGA cooperative study on endometrial carcinoma has expanded the dualistic clinicopathologic classification (types I and II) to four molecular genetic categories: (1) *POLE* ultramutated; (2) microsatellite instability hypermutated, corresponding to type I; (3) copy-number low (*CTNNB1* mutated); and (4) copy-number high (*TP53* mutated), corresponding to type II [24]. Although categories 2 and 3 included mainly EECs and category 4 had predominantly serous carcinomas, 25% of high-grade EECs showed a genetic profile similar to serous carcinomas and were re-classified. Despite overlapping of the molecular genetic findings, there was some association between separate categories and prognosis. The novel *POLE* ultramutated category consisted of 7% of tumors (type I and type II) and was characterized by mutations in the gene *POLE* that is important for DNA replication and repair. *POLE* mutations predicted favorable prognosis, particularly in high-grade tumors. In another endometrial cancer cohort of 535 EECs, *POLE* mutations were found in 5.6% (70% were high-grade EEC)

and were mutually exclusive of tumors with inherited microsatellite instability genotypes [25]. Therefore, classification as *POLE* ultramutated provides information regarding prognosis and would preclude the need for Lynch screening in these tumors.

4. Cervical cancer

Among gynecologic malignancies, cervical cancer has the highest incidence and mortality rate worldwide. Numerous biomarkers are under investigation to predict progression of pre-invasive lesions to invasive disease, as well as to predict prognosis and response to treatment of invasive cervical cancer.

4.1. Proliferation markers

Proliferation markers such as p16, p53, and Ki-67 index are seen in advanced stage and metastatic disease but they are not proven independent predictors of survival since almost all these patients will succumb to their disease. However, the presence of p16 and Ki-67 by immunohistochemistry had a higher sensitivity and specificity in detecting clinically significant pre-invasive lesions (CIN2, CIN3, and adenocarcinoma in situ) than high-risk HPV testing [26]. IHC for p16 and Ki-67 may be incorporated into cervical cancer screening to identify and treat pre-invasive lesions that are likely to progress to invasive disease.

4.2. Biomarkers predicting advanced disease and prognosis

High expression of angiogenesis markers like HIF-1α and VEGF are associated with poor prognosis in cervical cancer. HIF-1α expression allows the proliferation and metastasis of cancer cells in an oxygen- and nutrient-poor environment, and high IHC reactivity to HIF-1α predicts lower survival in cervical squamous cell carcinoma (SCC) and adenocarcinomas. VEGF expression has been correlated to lymph node metastasis and poor survival [27]. While most cervical cancers are positive for HRHPV, HPV-negative status was associated with an increased risk of recurrence and death [28]. A high level of the serum biomarker SCC antigen correlates with lymph node metastasis and advanced disease visible by FDG-PET imaging and this information may guide treatment strategies for individual patients [29].

4.3. Biomarkers predicting response to therapy

Hypoxic tumor environments prevent degradation of HIF-1α proteins and also increase resistance to chemotherapy and radiation [27]. Therefore HIF-1α expression may be a marker of resistance to primary chemo-radiation therapy, but further research needs to be conducted to validate this theory. In a systematic review, IHC reactivity to EGFR/HER2 and COX-2 was associated with resistance to chemo- and/or radiation-therapy [30]. Two large cohorts showed EGFR overexpression and co-expression of EGFR and HER2 was associated with poor progression-free survival and overall survival in patients treated with primary chemoradiation therapy. COX-2 is associated with angiogenesis, inhibition of apoptosis, and resistance to radiation therapy. This makes COX-2 an attractive target and preclinical studies already show that COX-2 inhibition improves cervical cancer response to radiation.

4.4. Future of biomarkers in cervical cancer

Biomarkers such as high-risk HPV testing and IHC for p16 and Ki-67 index score have been tested in large cohorts and will soon be implemented in guidelines for screening and treating pre-invasive lesions. Many biomarkers have shown promise in predicting the risk of recurrence and response to chemo- and radiation-therapy (Table 4) but they have not moved into clinical practice because of the lack of prospective data with large cohorts. Future research should be focused on validating the prognostic values of candidate biomarkers including cell cycle regulators (p16, p21, p27, cyclin A/D/E), receptor tyrosine kinases (EGFR, HER2), metastatic or stem cell markers (CD44, cathepsin D), and apoptotic markers (p53, Bcl-2, Bax) [30].

Table 4
Important biomarkers and predictive ability in cervical cancer.

Predictive value	Biomarkers
Associated with prognosis	HIF-1α
	VEGF
	SCC Ag
	CEA
	HR-HPV and type
Associated with chemotherapy sensitivity	HIF-1α
	EGFR
	CD44v6
Associated with radiosensitivity	COX-2
	HIF-2α

5. Vulvar cancer

Accurate evaluation of the prognostic potential of biomarkers in vulvar cancer is difficult because most studies involve small case series. Biomarkers evaluated in SCC of the cervix have also been evaluated in small series of vulvar cancer. Similar to cervical SCC, biomarkers p16, p21, VEGF, CD44, EGFR, and HER2 may correlate to clinical outcomes in vulvar SCC [31]. High VEGF expression was associated with poor survival outcome in a series of 25 vulvar cancers, however multivariate analysis was not performed owing to the small size of the cohort [32]. Clinical trials evaluating treatment of antiangiogenesis drugs and other targeted therapies are also difficult owing to the low incidence of disease.

Unlike cervical cancer, multiple small studies report conflicting data about the association of high-risk HPV and prognosis of vulvar cancers. Most of the data does not show a significant association between HPV and prognosis, while another reports favorable clinical outcomes in HPV positive vulvar cancers when compared with HPV-negative vulvar cancers [31].

Matrix metalloproteinase 2 (MMP-2) is a protein biomarker present in approximately 50% of vulvar cancers and the degree of IHC reactivity is higher in invasive carcinomas when compared with pre-invasive precursor lesions [33]. IHC reactivity of MMP-2 was associated with shorter survival after adjusting for tumor size, depth of invasion, and patient age in a multivariate analysis of 75 vulvar cancers [34]. When MMP-2 expression exceeded 50%, there was a significant reduction in five-year overall survival from 72.3% to 40%. Nafamostat mesilate is a synthetic inhibitor of MMP-2 that was evaluated in preclinical studies of SCC of the vulva and the head and neck [35]. Nafamostat decreased proliferation rates in vulvar cancer cell lines but it did not cause cell death and did not reduce tumor burden in tumor-bearing mice.

6. Conclusion

Considerable progress has been made in the identification and validation of molecular markers for gynecologic cancers in the past decade. However, this progress has not been accompanied by the introduction of universal molecular marker testing in clinical practice. Genomic and proteomic profiling of large cohorts of gynecologic cancers will generate a large amount of data regarding early mutation events in carcinogenesis. Now, expert committees need to be assembled to reach a consensus on which biomarkers should be incorporated into classification and staging of gynecologic cancers.

Conflict of interest

The authors have no conflicts of interest to declare.

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