Endometrioid adenocarcinoma of the ovary (EOC) accounts for 10% of ovarian carcinomas, and most are diagnosed at stage I or II. It has been suggested that a high proportion of EOC arise from endometriotic cysts, since ipsilateral ovarian and pelvic endometriosis is seen in up to 42% of cases. EOC usually occurs in perimenopausal women, and are bilateral in one third of the cases (1,2,3).

Grossly, EOC typically shows solid growth in association with an endometriotic cyst. Microscopically, EOC closely resembles its uterine counterpart. It encompasses a spectrum of neoplasms with variable histological differentiation, although the vast majority of tumors are grade 1 or 2. The well-differentiated tumors show tubular glands, some of them small, but also large or cystically dilated. The glands may be round to oval, but also show irregular or angulated profiles. Marked complexity with fusion of the glands and cribriform masses are also seen. Some tumors may show focal mucin deposition. Focal or confluent necrosis is seen, and necrotic debris may be sometimes found in gland lumens. Squamous differentiation is frequent. The appearance of the squamous component is variable. The well-differentiated tumors show typical rounded intraluminal aggregates of squamous cells (morules) that occupy the lumens of the neoplastic glands. Different patterns of invasion (expansile and destructive) have been reported. Expansile invasion has been associated with good prognosis in some series (4,5,6).

The main differential diagnosis is serous carcinoma. In the past, high grade serous carcinomas were diagnosed as high grade endometrioid or mixed serous-endometrioid carcinoma, because of the presence of glandular pattern of growth. However, numerous pathologic and molecular studies have demonstrated that the vast majority of the tumors historically interpreted as high grade endometrioid or mixed endometrioid-serous carcinomas, are indeed high grade serous carcinomas. They have frequent alterations in BRCA-1 and similar immunohistochemical profile (7,8,9,10,11). In contrast to serous carcinoma, EOC is usually negative for WT-1, only focally positive for p16, and positive for progesterone receptor, and vimentin. EOC frequently shows nuclear positive staining for beta-catenin. P53 is usually negative, but is helpful in identifying the infrequent high-grade EOC. EOC occasionally exhibits a sertoliform pattern of growth, which mimics sex cord-stromal tumors. Age, presence of hormonal symptoms, bilaterality and pattern of metastatic spread, squamous elements and adenofibromatous pattern, and presence of ovarian endometriosis or obvious endometrioid elements, are all important features in differential diagnosis. Obviously, immunohistochemistry is helpful. Occasionally, a metastatic tumor to the ovary may be misinterpreted as EOC. Presence of dirty and segmental necrosis, and obvious features of intestinal differentiation, are all helpful features, but the diagnosis can be made after performing immunostaining (progesterone receptor, vimentin, CK-20, CK-7, CDX-2). If the pathological and immunohistochemical features are not typical, gene-expression microarray analysis can be helpful (12).

The molecular alterations of EOC are similar to the uterine counterpart, as it is its expression profile (1,2,313,14). Main molecular alterations are: microsatellite instability (MI), and mutations in the PTEN, k-RAS, PIK3CA, ARID-1A and beta-catenin genes.

Microsatellite instability (MI). MI has been demonstrated in 12-20% of EOC. EOC patients from HNPCC kindreds have an inherited germline mutation in either MLH-1, MSH-2, MSH-6 or PMS-2 (“first hit”); but EOC develops only after the instauration of a deletion or mutation in the contralateral MLH-1,MSH-2, MSH-6 or PMS-2 allele (“second hit”) (15). In sporadic tumors, MLH-1 inactivation by promoter hypermethylation is the main cause of mismatch repair deficiency. The instauration of MI, the so-called mutator phenotype, in one cell has important molecular implications. The MI-associated mismatch repair deficiency leads to the accumulation of myriads of mutations in coding and non-coding DNA sequences. Short-tandem repeats, like microsatellites, are particularly susceptible to mismatch repair alterations, but they are predominantly located in non-coding DNA sequences; and the presence of subtle mutations (insertions or deletions) do not have consequences in the production of abnormal proteins. However, some small short-tandem repeats, like
mononucleotide repeats, are sometimes located within the coding sequence of some important genes; (BAX, IGFIIR, hMSH3, and hMSH6 MBD4, CHK-1, Caspase-5) and they may be potential targets in the process of tumor progression of MI+, EOC (16).

The tumor suppressor gene termed PTEN, located on chromosome 10q23.3, is frequently abnormal in EOC. Somatic PTEN mutations are also common in EOC, occurring in 20% of them (14). In agreement with Knudson’s two-hit proposal, LOH at 10q23 frequently coexists with somatic PTEN mutations. The coexistence of both alterations leads to activation of the PI3K/AKT pathway, which plays a key role in the regulation of cellular homeostasis. Activated AKT modulates the expression of several genes involved in suppression of apoptosis and cell cycle progression. Mutations in PIK3CA have been described in various tumours and may contribute to the alteration of the PI3K/AKT signalling pathway in EOC. PI3K is is a a heterodimeric enzyme consisting of a catalytic subunit (p110) and a regulatory subunit (p85). The PIK3CA gene, located on chromosome 3q26.32, codes for the p110 catalytic subunit of PI3K.

The beta-catenin gene (CTNNB1) maps to 3p21. Beta-catenin appears to be important in the functional activities of both APC and E-cadherin. Beta-catenin is a component of the E-cadherin-catenin unit, very important for cell differentiation, and maintenance of the normal tissue architecture. Beta-catenin is also important in signal transduction. Increased cytoplasmic and nuclear levels of beta-catenin produce transcriptional activation through the LEF/Tcf pathway. The APC protein down regulates beta-catenin levels by cooperating with the glycogen synthase kinase 3 beta (GSK-3beta), inducing phosphorylation of the serine-threonine residues coded in exon 3 of the beta catenin gene (CTNNB 1), and its degradation through the ubiquitin-proteasome pathway. Mutations in exon 3 of beta-catenin result in stabilization of the protein, cytoplasmic and nuclear accumulation, and participation in signal transduction and transcriptional activation through the formation of complexes with DNA binding proteins. Mutations in exon 3 of CTNNB1 with nuclear accumulation of beta-catenin occur in 38-50% of EOC (14).

Mutation of the ARID1A gene and loss of the corresponding protein BAF250a has recently been described as a frequent event in clear cell and EOC (3).

Up to 20% of EOC coexist with and independent endometrioid carcinoma of the endometrium. Differential diagnosis between two independent tumors and endometrioid carcinoma of the endometrium with metastasis to the ovaries is easy in most cases. Several clinical and pathological features should be considered: Tumor sizes histological grades, bilaterality, pattern of tumor growth, tubal, myometrial, vascular invasion, and presence of endometriosis. Molecular techniques (single gene or high throughput approaches) may be used in difficult cases. Usually, independent tumors exhibit different molecular features between the two tumors. However, occasionally, similar molecular features are found in tumors unequivocally independent, raising the possibility of field effect (17,18).

References


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ENDOMETRIOID CARCINOMA OF THE OVARY

Xavier Matias-Guiu, MD, PhD
Hospital U Arnau de Vilanova. Univ Lleida. IRBLLEIDA, Spain
Summary

• Definition. Main clinical and pathological features
• Differential Diagnosis
• Molecular Features
• Endometriosis as precursor lesion
• Hereditary Non-Polyposis Cancer Syndrome
• Simultaneous endometrioid carcinomas of the endometrium and the ovaries
ENDOMETRIOID CARCINOMA OF THE OVARY (Definition)

A malignant epithelial tumor of the ovary that closely resembles the common variants of endometrioid carcinoma of the uterus

WHO, 2003
ENDOMETRIOID CARCINOMA OF THE OVARY
(Clinical Features)

- Less than 10% of ovarian cancers (15-20% in older literature)
- Perimenopausal women
- Bilateral (28%)
- Early stages
- Associated with ipsilateral or pelvic endometriosis (40%)
ENDOMETRIOID CARCINOMA 
OF THE OVARY 
(Pathology)

- Solid growth, occasionally coexisting with an endometriotic cyst or an adenofibroma
- mimic uterine counterpart
- Usually low grade (but not always)
- Squamous differentiation
- Spindle cell pattern and Sex cord like features may be present
ENDOMETRIOID CARCINOMA OF THE OVARY
(Expansile versus destructive invasion)
ENDOMETRIOID CARCINOMA OF THE OVARY
(Expansile versus destructive invasion)


ENDOMETRIOID CARCINOMA OF THE OVARY (Differential Diagnosis)

- Serous carcinoma
- Metastatic tumors
- Sex-cord stromal tumors
ENDOMETRIOID CARCINOMA OF THE OVARY
(Differential Diagnosis with serous carcinoma)

- Low histological grade
- Round glands instead of slit-like spaces
- Squamous differentiation
- Adenofibromatous pattern
- Broad papillae
OVARIAN CARCINOMA
(BRCA-1/2)

BRCA-1 LOH and promoter hypermethylation and BRCA-2 LOH are seen in high grade serous, endometrioid, and mixed endometrioid-serous carcinomas

Endometrioid carcinomas coexpress high rates of hormone receptors ER and PR as well as CA125. Endometrioid and clear cell subtypes infrequently (<10%) expressed WT1 and p53. The median Ki-67 labelling index for endometrioid and clear cell carcinomas was similar (endometrioid 8.2%, 95% CI 0.8%–49.0%; clear cell 7.6%, 95% CI 0.5%–45.0%). Immu-
Calculator for ovarian carcinoma subtype prediction

Steve E Kalloger¹,²,⁵, Martin Köbel³,⁵, Samuel Leung¹, Erika Mehl¹, Dongxia Gao¹, Krista M Marcon¹, Christine Chow¹, Blaise A Clarke⁴, David G Huntsman¹ and C Blake Gilks¹,²

MODERN PATHOLOGY (2011) 24, 512–521

![Image](image_url)

Table 7 Marker expression across subtypes expressed as percent positive

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<td>0.883</td>
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Diagnosis of Ovarian Carcinoma Cell Type is Highly Reproducible

A Transcanadian Study

Martin Köbel, MD,* Steve E. Kalloger, BSc,† Patricia M. Baker, MD,‡ Carol A. Ewanowich, MD,§ Jocelyne Arseneau, MD,¶ Viktor Zherebitskiy, MD,‡ Soran Abdulkarim, MD,¶ Samuel Leung, MSc,† Maire A. Duggan, MD,* Dan Fontaine, MD,¶ Robin Parker, MD,§ David G. Huntsman, MD,† and C. Blake Gilks, MD, FRCPC†

(Am J Surg Pathol 2010;34:984–993)

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<th>HNF-1β (%)</th>
<th>Mammoglobin B (%)</th>
<th>Mesothelin (%)</th>
<th>MUC5 (%)</th>
<th>p16 (%)</th>
<th>p53 (%)</th>
<th>Vimentin (%)</th>
<th>WT1 (%)</th>
<th>Ki-67 (Median, 95% CI) (%)</th>
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ENDOMETRIOID CARCINOMA OF THE OVARY
(Differential Diagnosis with serous carcinoma)

- WT-1
- Estrogen and Progesterone receptor
- P53
- Beta-catenin
- P16
- Vimentin
ENDOMETRIOID CARCINOMA OF THE OVARY
(Differential Diagnosis with sex-cord stromal tumors)

- Age, and presence of hormonal symptoms
- Bilaterality and pattern of metastatic spread
- Squamous elements and adenofibromatous pattern
- Endometriosis or obvious endometrioid elements
ENDOMETRIOID CARCINOMA OF THE OVARY (Differential Diagnosis with sex cord stromal tumor)

- PAS staining
- Cytoqueratins and EMA
- Alpha-inhibin, calretinin and other sex cord stromal markers
ENDOMETRIOID CARCINOMA OF THE OVARY
(Differential Diagnosis with metastatic carcinoma)

- Bilaterality, and nodular pattern
- Infiltrative pattern with desmoplasia, and single cell infiltration
- Endometriosis and adenofibromatous areas
- Low grade and squamous elements
- Lymphovascular invasion, and extensive intraabdominal spread
Gene expression microarray-based assay to determine tumor site of origin in a series of metastatic tumors to the ovary and peritoneal carcinomatosis of suspected gynecologic origin

Ainara Azueta MD\textsuperscript{a}, Oscar Maiques BsC\textsuperscript{a}, Ana Velasco MsC\textsuperscript{a}, Maria Santacana MsC\textsuperscript{a}, Judith Pallares MD\textsuperscript{a}, Anna Novell MSc\textsuperscript{a}, Antonio Llombart-Cussac MD, PhD\textsuperscript{a}, Xavier Gonzalez-Tallada MD, PhD\textsuperscript{a}, Ana Mozos MD\textsuperscript{b}, Jaime Prat MD, PhD\textsuperscript{b}, Raji Pillai PhD\textsuperscript{c}, Manuel Mata PhD\textsuperscript{d}, Xavier Matias-Guiu MD, PhD\textsuperscript{a,}\textsuperscript{a}

Human Pathology (2013) 44, 20–28

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MOLECULAR FEATURES OF ENDOMETRIOID CARCINOMA OF THE OVARY

Similar to its far more common uterine counterpart
Gene Expression Profiles of Serous, Endometrioid, and Clear Cell Subtypes of Ovarian and Endometrial Cancer

Kristin K. Zorn,1 Tomas Bonome,1 Lisa Gangi,2 Gadisetti V.R. Chandramouli,1 Christopher S. Awtrey,3 Ginger J. Gardner,1 J. Carl Barrett,1 Jeff Boyd,5 and Michael J. Birrer1


Histologic Type, Organ of Origin, and Wnt Pathway Status: Effect on Gene Expression in Ovarian and Uterine Carcinomas

Kerby A. Shedden,1 Malti P. Kshirsagar,2 Donald R. Schwartz,2 Rong Wu,2 Hongfeng Yu,2 David E. Misek,3 Samir Hanash,3 Hidetaka Katabuchi,6 Lora Hedrick Ellenson,7 Eric R. Fearon,2,4,5 and Kathleen R. Cho2,4,5

Clinical Cancer Research Vol. 11, 2123–2131, March 15, 2005

Patterns of Gene Expression in Different Histotypes of Epithelial Ovarian Cancer Correlate with Those in Normal Fallopian Tube, Endometrium, and Colon

Rebecca T. Marquez,1 Keith A. Baggerly,2 Andrea P. Patterson,1 Jinsong Liu,5 Russell Broaddus,5 Michael Frumovitz,3 Edward N. Atkinson,2 David I. Smith,6 Lynn Hartmann,6 David Fishman,7 Andrew Berchuck,8 Regina Whitaker,8 David M. Gershenson,3 Gordon B. Mills,4 Robert C. Bast, Jr.,1 and Karen H. Lu3

Molecular Genetic Alterations in Endometrioid Carcinomas of the Ovary: Similar Frequency of Beta-Catenin Abnormalities but Lower Rate of Microsatellite Instability and PTEN Alterations Than in Uterine Endometrioid Carcinomas

LLUIS CATASÚS, PhD, ELENA BUSSAGLIA, PhD, INGRID RODRÍGUEZ, MD, ALBERTO GALLARDO, MD, CRISTINA PONS, PhD, JULIE A. IRVING, MD, AND JAIME PRAT, MD, FRCPATH
MOLECULAR FEATURES OF ENDOMETRIOID CARCINOMA

ENDOMETRIUM

- PIK3CA: 30%
- MI: 20-30%
- K-RAS: 10-30%
- ADID 1A: 30%
- PTEN: 30-60%
- FGFR2: 10-20%
- β-catenin: 28-35%

OVARY

- MI: 12-19%
- ARID 1A: 40%
- K-ras: 10-30%
- β-catenin: 16-54%
- PTEN: 20%
- PIK3CA: 20%
ENDOMETRIOID CARCINOMA OF THE OVARY
(MOLECULAR FEATURES)
Microsatellite Instability

• Germline mutation + somatic mutation in MSH-2, MLH-1, PMS-2, MSH-6 (Lynch Sd cancers)

• MLH-1 promoter hypermethylation (sporadic cancers)
Random Methylation Errors

Active Gene

Reduced Expression

Clonal Selection of Cells

Further Random Methylation Errors

Silenced Gene
Microsatellite Instability, MLH-1 Promoter Hypermethylation, and Frameshift Mutations at Coding Mononucleotide Repeat Microsatellites in Ovarian Tumors

ENDOMETRIOID CARCINOMA
Mononucleotide repeat microsatellite (genes)

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ENDOMETRIOID CARCINOMA

### Table: MLH-1 methylation and expression of related genes

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</tr>
<tr>
<td>16</td>
<td>+</td>
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<tr>
<td>23</td>
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<tr>
<td>204</td>
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<td></td>
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<td>+</td>
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</tbody>
</table>
Cell Proliferation and Survival
PTEN Mutation

MUTATION

ET-47

TTTTTGTTAAAA

TTTTTTGTTAAA

LOH

PROMOTER METHYLATION

N

T
b-CATENIN/CTNNB1 MUTATION IN OVARIAN ENDOMETRIOID CARCINOMA

Ser(TCT)33(TGT)Cys
b-CATENIN/CTNNB1 MUTATIONS IN OVARIAN CANCER

<table>
<thead>
<tr>
<th>Type</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrioid</td>
<td>44</td>
</tr>
<tr>
<td>Clear Cell</td>
<td>1</td>
</tr>
<tr>
<td>Serous</td>
<td>1</td>
</tr>
<tr>
<td>Mucinous</td>
<td>1</td>
</tr>
</tbody>
</table>

GSK3β

β-catenin

29-SYL-D-S-G-IH-S-GAT-T-TAP-S-L-SG-48

%  
16 16 14 33 14 3.5 3.5
β-CATENIN/CTNNB1 MUTATIONS IN ENDOMETRIOID CARCINOMA OF THE OVARY

β-CATENIN/CTNNB1 MUTATION

BORD 8/9 (88%)
EC grade I 21/36 (58.3%)
EC grade II 1/36 (2.7%)

(Gamallo et al, 1999; Wright et al, 1999; Zhai et al, 2002; Oliva et al, 2004)
**ENDOMETRIOSIS AS THE PRECURSOR LESION**

**MOLECULAR ALTERATIONS**

<table>
<thead>
<tr>
<th>Gene</th>
<th>LOH</th>
<th>MUTATION</th>
<th>DECREASED EXPRESSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTEN</td>
<td>56%</td>
<td>20%</td>
<td>15%</td>
</tr>
<tr>
<td>LOH</td>
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<tr>
<td>Mutation</td>
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<tr>
<td>Decreased Expression</td>
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<tr>
<td>MSI</td>
<td>10%</td>
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<tr>
<td>K-RAS</td>
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<tr>
<td>TP53</td>
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<tr>
<td>b-CATENIN</td>
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<td>?</td>
</tr>
<tr>
<td>ARID 1A</td>
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</tbody>
</table>
Contents of Endometriotic Cysts, Especially the High Concentration of Free Iron, Are a Possible Cause of Carcinogenesis in the Cysts through the Iron-Induced Persistent Oxidative Stress

Ken Yamaguchi,1 Masaki Mandai,1 Shinya Toyokuni,2 Junzo Hamanishi,1 Toshihiro Higuchi,1 Kenji Takakura,1 and Shingo Fujii1, 3

Ovarian cancer in endometriosis: molecular biology, pathology, and clinical management

Fig. 4. Hypothetical pathogenesis of malignant transformation of endometriosis
HEREDITARY NON-POLYPOSION COLON CANCER SYNDROME (OVARIAN CANCER)

• HNPPC patients have a life time risk of 8 – 15%

• 2% of ovarian cancers are HNPCC-related

• HNPCC is infrequent (7%) in patients with synchronous endometrioid carcinomas of the endometrium and the ovaries.
HNPCC-related cancers

- Colon ca
- Endometrial Ca
- Gastric Ca
- Small bowell ca
- Ovarian Ca
- Pancreas /Biliar Tract
- Urinary Tract
- CNS
- Skin tumors

<table>
<thead>
<tr>
<th></th>
<th>MLH1</th>
<th>MSH2</th>
<th>MSH6</th>
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<tr>
<td>Colon ca</td>
<td>50-65%</td>
<td>39-68%</td>
<td>18-39%</td>
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<tr>
<td>Endometrial Ca</td>
<td>27%</td>
<td>40%</td>
<td>71%</td>
</tr>
<tr>
<td>Gastric Ca</td>
<td>6%</td>
<td>5%</td>
<td>?</td>
</tr>
<tr>
<td>Small bowell ca</td>
<td>3-6%</td>
<td>3-6%</td>
<td>?</td>
</tr>
<tr>
<td>Ovarian Ca</td>
<td>6%</td>
<td>12%</td>
<td>?</td>
</tr>
<tr>
<td>Pancreas /Biliar Tract</td>
<td>4%</td>
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</tr>
<tr>
<td>Urinary Tract</td>
<td>2%</td>
<td>9-20%</td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>1,7%</td>
<td>2,5%</td>
<td></td>
</tr>
<tr>
<td>Skin tumors</td>
<td>42%</td>
<td>44%</td>
<td></td>
</tr>
</tbody>
</table>
Ovarian Cancer (Suspected HNPCC)

Microsatellite Instability and/or Immunohistochemistry (MLH-1/MSH-2/MSH-6/PMS-2)

Sequencing
Simultaneous endometrioid carcinomas of the endometrium and the ovaries
Simultaneous endometrioid carcinomas of the endometrium and the ovaries

- 15-20% ovarian endometrioid carcinomas, and 5% of endometrial carcinomas
- Usually favourable outcome suggest independent origin, but may be metastatic or uncertain
Simultaneous endometrioid carcinomas of the endometrium and the ovaries (Criteria)

- Tumor sizes
- Histological grades
- Bilaterality
- Pattern of tumor growth
- Tubal, myometrial, vascular invasion
- Presence of endometriosis
Simultaneous endometrioid carcinomas of the endometrium and the ovaries (Techniques)

- Immunohistochemistry
- Flow Cytometry
- LOH analysis
- Single gene approaches
- High throughput genomic approaches (cDNA, aSNP)
Use of gene expression profiles to stage concurrent endometrioid tumors of the endometrium and ovary

Alfied Guirgis a, Esther Elishaev b, Sung-Hee Oh c, George C. Tseng c, Kristin Zorn a, Julie A. DeLoia a,∗

a Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh, PA, USA
b Department of Pathology, University of Pittsburgh, PA, USA
c Department of Biostatistics, University of Pittsburgh, PA, USA

Received 5 July 2007

Fig. 3. Hierarchical unsupervised clustering of all samples in both the training and test sets using the SAM-generated 163 gene list. E= primary endometrial cancer; O= primary ovarian cancer; PME= primary metastatic endometrial cancer; PMO= primary metastasis to the ovary; DPO= dual primary ovarian cancer; DPE= dual primary endometrial cancer.
Original contributions

Synchronous endometrioid carcinomas of the uterine corpus and ovary: alterations in the β-catenin (CTNNB1) pathway are associated with independent primary tumors and favorable prognosis

Julie A. Irving MD, FRCPC¹, Lluis Catasús PhD, Alberto Gallardo MD, Elena Bussaglia PhD, Marisa Romero BSc², Xavier Matias-Guiu MD³, Jaime Prat MD, FRCPath*
MOLECULAR FEATURES OF ENDOMETRIOID CARCINOMA

ENDOMETRIUM

- PIK3CA: 30%
- MI: 20-30%
- K-RAS: 10-30%
- ADID 1A: 30%
- PTEN: 30-60%
- FGFR2: 10-20%
- β-catenin: 28-35%

OVARY

- MI: 20%
- ARID 1A: 40%
- K-ras: 10-30%
- PIK3CA: 30%
- PTEN: 20%
- β-catenin: 16-54%
CTNNB1 S33Y
TCT-TAT

ENDOMETRIAL

OVARIAN
Summary

• Definition. Main clinical and pathological features
• Differential Diagnosis
• Molecular Features
• Endometriosis as precursor lesion
• Hereditary Non-Polyposis Cancer Syndrome
• Simultaneous endometrioid carcinomas of the endometrium and the ovaries
ENDOMETRIOID CARCINOMA OF THE OVARY

Xavier Matias-Guiu, MD, PhD
Hospital U Arnau de Vilanova. Univ Lleida. IRBLLEIDA, Spain