Statement by the Kommission Ovar of the AGO: The New FIGO and WHO Classifications of Ovarian, Fallopian Tube and Primary Peritoneal Cancer

Stellungnahme der Organkommission Ovar der AGO: die neuen FIGO- und WHO-Klassifikationen des Ovarial-, Tuben- und primären Peritonealkarzinoms

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- FIGO stage
- ovarian cancer subtypes

Schlüsselwörter
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Abstract

More than 25 years after the last revision, in 2012 the FIGO Oncology Committee began revising the FIGO classification for staging ovarian, Fallopian tube and primary peritoneal cancers. The new classification has become effective with its publication at the beginning of 2014. Following recent findings on the pathogenesis of ovarian, Fallopian tube and primary peritoneal cancer and reflecting standard clinical practice, the three entities have now been classified uniformly. The histological subtype is included (high-grade serous – HGSC; low-grade serous – LGSC; mucinous – MC; clear cell – CCC; endometrioid – EC). Stages III and IV have been fundamentally changed: stage IIIA now refers to a localized tumor limited to the pelvis with (only) retroperitoneal lymph node metastasis (formerly classified as IIIC). Stage IV has been divided into IVA and IVB, with IVA defined as malignant pleural effusion and IVB as parenchymatous or extra-abdominal metastasis including inguinal and mediastinal lymph node metastasis as well as umbilical metastasis. A new WHO classification was published almost concurrently. The classification of serous tumors addresses the issue of the tubal carcinogenesis of serous ovarian cancer, even if no tubal precursor lesions are found for up to 30% of serous high-grade cancers. The number of subgroups was reduced and subgroups now include only high-grade serous, low-grade serous, mucinous, seromucinous, endometrioid, clear cell and Brenner tumors. The category "transitional cell carcinomas" has been dropped and the classification "seromucinous tumors" has been newly added. More attention has been focused on the role of borderline tumors as a stage in the progression from benign to invasive lesions.

Zusammenfassung

Nach über 25 Jahren hat das FIGO Oncology Committee 2012 in Rom eine Überarbeitung der FIGO-Klassifikation zur Stadieneinteilung des Ovarialkarzinoms vorgenommen. Mit der Publikation Anfang 2014 ist die neue Klassifikation gültig. Den Erkenntnissen über die Pathogenese sowie der klinischen Praxis folgend werden das Ovarial-, das Tuben und das primäre Peritonealkarzinom einheitlich klassifiziert. Der histologische Subtyp wird angegeben (high grade serös – HGSC, low grade serös – LGSC, muzinös – MC; klarzellig – CCC und endometrioid – EC). Wesentliche Änderungen beziehen sich auf die Stadien III und IV: Stadium IIIA definiert nun einen auf das Becken beschränkten Tumor mit (ausschließlich) retroperitonealen Lymphknotenmetastasen (früher IIIC). Stadium IV wird in IVA und IVB aufgeteilt: IVA definiert einen malignen Pleuraerguss, IVB parenchymatöse oder extraabdominale Metastasen, zu denen auch die inguinalen und mediastinalen Lympknoten und die Nabelmetastasen zählen. Nahezu zeitgleich wurde auch eine neue WHO-Klassifikation publiziert. Bei den serösen Tumoren wurde auf die tubare Karzinogenese des serösen Ovarialkarzinoms eingegangen, wenn auch in bis zu 30% der serösen High-Grade-Karzinome keine tubare Vorläuferläsion gefunden werden. Die Zahl der Subgruppen wurde auf High-grade seröse, Low-grade seröse, muzinöse, seromuzinöse, endometrioide, klarzellige Karzinome und Brenner-Tumoren reduziert. Das Transitionalzellkarzinom ist weggefallen, die seromuzinösen Tumoren sind neu. Der Rolle der Borderline-Tumoren als Progressionsstufe zwischen benignen und invasiven Läsionen wird mehr Raum gegeben.

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Bibliography
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Introduction

Extensive research in recent years have led to a fundamentally new understanding of the tumor biology of ovarian cancer. It is now generally accepted that the term "ovarian cancer" covers a heterogeneous group of malignant tumors which differ significantly in their etiology, pathogenesis, prognosis, pathology and molecular pathology [1]. Numerous clinical studies have identified the most important prognostic factors whose clinical relevance also affects therapeutic decisions. The FIGO Oncology Committee has revised the previous FIGO classification of 1988 over a period of several years, publishing the new classification in 2014 [2]. Since the publication of the revised classification, only the new classification is considered valid; the new categories should therefore be used in clinical and scientific practice. The currently available S3-guideline (www.ago-online.org) refers to the "old" FIGO classification (1988) [3–5]. With this statement we provide a guide which may prove useful until the S3-guideline has been officially updated.

Below we present the most important aspects of the new FIGO classification of ovarian, Fallopian tube and primary peritoneal cancer. To highlight the differences between the old and the new classification, we have compiled tables contrasting the differences.

Around 90% of all malignant tumors of the ovaries, Fallopian tubes and peritoneum are epithelial tumors (carcinomas). Morphological, genetic, epigenetic investigations and expression analyses have led to the realization that ovarian carcinomas consist of a heterogeneous group of tumors which can present as ovarian, Fallopian tube or peritoneal carcinomas. Serous carcinomas, which constitute around 80% of all tumors, are the most studied type. They are no longer graded on a continuum (i.e., G1, 2, 3). Instead they are differentiated into two basic pathological, molecular and prognostically different types – "low grade" and "high grade" – and should only be classified as such in pathology reports. Serous low-grade carcinomas are well differentiated and develop out of benign cystadenomas through serous borderline tumors and their micropapillary variants. Serous high-grade carcinomas are poorly differentiated. They have no known ovarian precursor lesions. However, there are some indications that a large number of high-grade carcinomas originate in the Fallopian tubes, as serous tubal intraepithelial carcinomas – so-called STICS – have been detected in macroscopically unremarkable Fallopian tubes in connection with high-grade carcinomas [6,7]. A tubal origin has been proven for the majority of hereditary carcinomas [8,9]. Low-grade carcinomas are associated with *KRAS, BRAF, PIK3CA, CTNNB1* and *PPP2R1A* mutations, whereas high-grade carcinomas are typically associated with *TP53* mutations, and *BRCA* mutations or inactivation (**Table 1**) [10–12].

Although still a topic of scientific study and controversially discussed, the five morphological subtypes also appear to represent the five most common subtypes of epithelial ovarian carcinoma: low-grade serous (5%): LGSC; high-grade serous (70%): HGSC; mucinous (3%): MC; endometrioid (10%): EC; clear cell (10%): CCC [13]. The new classification therefore requires that the histological subtype is included together with the stage: HGSC, EC, CCC, MC, LGSC; "other" or "cannot be classified" [2].

The findings outlined above have been reflected in the new FIGO staging system which is used to classify ovarian, Fallopiann tube and primary peritoneal carcinomas. The location of the primary tumor is also included in the classification as follows: OV for ovary, FT for Fallopian tube and P for peritoneum. The classification must include an X if the primary site cannot be determined [2]. For convenience' sake we have used the term ovarian carcinoma for all types below.

The New FIGO Classification

The meaning of all staging is to categorize tumors and patients into prognostically specific groups based on the determination of tumor stage and the stage-appropriate therapy. Ensuring the comparability of groups in scientific studies also depends on being able to classify lesions into specific groups.

Careful clinical, surgical and pathological staging is necessary to correctly classify ovarian carcinomas. Surgery consists of longitudinal laparatomy, peritoneal cytology, biopsies of both suspicious and unremarkable areas of the peritoneum, hysterectomy, bilateral salpingo-oophorectomy, (infragastric) omentectomy as well as systematic pelvic and paraaortal lymphadenectomy in patients free of macroscopic tumors or the removal of enlarged ("bulky") lymph nodes in patients with macroscopically visible tumors (S3-guideline on ovarian carcinoma, www.ago-online.org). In patients with advanced carcinoma, all visible tumor manifestations should be removed as postoperative tumor remnants are an important prognostic factor. Optimal debulking is achieved if all macroscopically visible tumor manifestations have been resected [14]. At the subsequent histopathological examination it is important to indicate the tumor grade in addition to the above-mentioned primary tumor location and histological subtype. Differentiating carcinomas into low grade and high grade is particularly important for serous carcinomas. The differentation can have an important impact on future therapy as low-grade carcinomas have a more favorable prognosis and there are also indications that – in contrast to high-grade carcinomas – low-grade tumors have only a poor response to chemotherapy [15,16]. There is no prognostically relevant grading system for mucinous tumors [17].

Table 2 shows the new FIGO staging system and contrasts it with the older version of 1988; **Table 3** shows the corresponding TNM stages. An update of the TNM classification is planned for 2016 [18].

Stage I

Stage I includes tumors limited to the ovary or Fallopian tube, although tumor cells may be present in peritoneal fluids. An important difference between the old and the new classification is the explicit reference to the Fallopian tubes as a potential site of

Table 1 Subtypes of ovarian carcinoma and associated genetic changes [12].

Histological subtype	High-grade serous	Low-grade serous	Endometrioid	Clear cell	Mucinous
Mutations	p53, BRCA 1/2	KRAS/BRAF, Erbb2, PIK3CA	ARID1A, CTNNB1, PTEN, PIK3CA, PPP2RIA	ARID1A, PIK3CA, ZNF217, PPP2RIA	KRAS

Table 2 FIGO staging of ovarian, Fallopian tube and primary peritoneal cancer (FIGO 2013 vs. FIGO 1988) – differences highlighted in **bold**.

FIGO (1988)	FIGO (2013)
I: tumor confined to the ovaries	I: tumor confined to the ovaries **or tube(s)***
IA: tumor confined to 1 ovary (capsule intact), no tumor on ovarian surface, no malignant cells in the ascites or peritoneal cytology	IA: tumor confined to 1 ovary **or tube** (capsule intact), no tumor on ovarian surface, no malignant cells in the ascites or peritoneal cytology
IB: tumor involves both ovaries (capsule intact), no tumor on ovarian surface, no malignant cells in the ascites or peritoneal cytology	IB: tumor involves both ovaries **or tubes** (capsule intact), no tumor on the ovarian **or tubal** surface, no malignant cells in the ascites or peritoneal cytology
IC: tumor limited to 1 or both ovaries together with one of the following: capsule rupture; tumor on ovarian surface; malignant cells in the ascites or peritoneal cytology	IC: tumor limited to 1 or both ovaries **or tube(s)** together with one of the following:
	▶ **IC1: capsule rupture intraoperatively**
	▶ **IC2: capsule rupture preoperatively or tumor on ovarian or tubal surface**
	▶ **IC3: malignant cells in the ascites or peritoneal cytology**
II: tumor in 1 or both ovaries with pelvic involvement	II: tumor in 1 or both ovaries **or tube(s)** with pelvic involvement or **primary peritoneal carcinoma****
IIA: extension and/or implant on uterus and/or Fallopian tube(s); no malignant cells in the ascites or peritoneal cytology	IIA: extension and/or implant on uterus and/or Fallopian tube(s) **and/or ovar(ies)**
IIB: extension to other pelvic tissue; no malignant cells in the ascites or peritoneal cytology	IIB: extension to other pelvic intraperitoneal tissue
IIC: IIA or IIB plus malignant cells in the ascites or peritoneal cytology	
III: tumor in 1 or both ovaries with microscopic extrapelvic peritoneal metastases and/or regional lymph node metastases	III: tumor in 1 or both ovaries **or tube(s) or primary peritoneal carcinoma** with cytologically or histologically verified peritoneal metastases outside the pelvis and/or **retroperitoneal** lymph node metastases.
IIIA: microscopic extrapelvic peritoneal metastases	
	IIIA1: positive *retroperitoneal* lymph nodes only (verified cytologically or histologically)
	▶ **IIIA1(i): metastases, maximum diameter 10 mm**
	▶ **IIIA1(ii): metastases, maximum diameter more than 10 mm**
	IIIA2: microscopic extrapelvic peritoneal metastases with or without positive retroperitoneal lymph nodes
IIIB: macroscopic extrapelvic peritoneal metastases of up 2 cm	IIIB: macroscopic peritoneal pelvic metastases of up to 2 cm, **with or without retroperitoneal lymph node metastases (including the capsule of the liver/spleen but excluding parenchymatous metastasis)**
IIIC: macroscopic extrapelvic peritoneal metastases larger than 2 cm and/or regional lymph node metastases	IIIC: macroscopic extrapelvic peritoneal metastases larger than 2 cm with or without retroperitoneal lymph node metastases (including capsule of the liver/spleen but excluding parenchymatous metastases)
IV: distant metastases excluding peritoneal metastases	IV: distant metastasis excluding peritoneal metastases
	IVA: pleural effusion with positive cytology
	IVB: parenchymatous metastases and metastases to extraabdominal organs (including inguinal lymph node metastases and extraabdominal lymph node metastases)***

* There is no stage I peritoneal carcinoma.

** Thick adhesions with histologically verified tumor metastases require upstaging from stage I to II.

*** Extraabdominal metastases includes transmural intestinal infiltration and umbilical metastases.

Table 3 FIGO stages and TNM stages.

FIGO stage	T	N	M
IA	T1a	N0	M0
IB	T1b	N0	M0
IC	T1c	N0	M0
IIA	T2a	N0	M0
IIB	T2b	N0	M0
IIIA	T3a	N0	M0
	T3a	N1	M0
IIIB	T3b	N0	M0
	T3b	N1	M0
IIIC	T3c	N0	M0
	T3c	N1	M0
IVA	Any T	Any N	M1 (malignant pleural effusion)
IVB	Any T	Any N	M1 (parenchymatous and extraabdominal metastases)*

* Extraabdominal metastases includes transmural intestinal infiltration and umbilical metastases as well as inguinal lymph node metastases and extraabdominal lymph node metastases.

origin and the differentation of stage IC to indicate the time and cause of capsule rupture into intraoperative (IC1), preoperative (IC2) or atypical cells in ascites or rinse cytology (IC3). It is important to avoid intraoperative rupture, although it is not possible to definitively state that this will worsen prognosis. This is an issue that will require further scientific study. The new classification clearly categorizes iatrogenic rupture of what is actually FIGO stage IA as FIGO stage IC1, and treatment needs to be adjusted accordingly [19]. If tumor cells are detected in adhesions in a patient with presumed stage I carcinoma, then the patient must be upstaged to stage II [2]. The IC1–IC3 classification does not yet have any therapeutic relevance. A consistent subdivision of stage I is the prerequisite for developing further risk-adapted therapeutic strategies.

Stage II

Stage II includes the small group of tumors whose spread is limited to the pelvis below the pelvic brim. Sigma metastasis and infiltration of the sigma in the pelvis are also included in stage II. All malignant peritoneal metastases of the lesser pelvis are classified as stage II. There are therefore no stage I peritoneal carcinomas. The stage formerly known as stage IIc no longer exists [2].

Stage III

Stage III is the largest group of advanced cancers and includes tumors outside the pelvis in the peritoneum, the omentum, the renal fascia, the hepatic capsule, the splenic capsule (excluding parenchymatous metastases) and/or lymph node metastases. The prognosis for patients with isolated (paraaortal) lymph node metastases is better when the tumor is limited to the pelvic cavity compared to intraperitoneal tumor sites outside the pelvis. This has lead to a new subdivision of stage III: stage IIIA1 includes pelvic tumors with retroperitoneal lymph node metastases up to 1 cm (IIIA1i) or larger than 1 cm (IIIA1ii). Stage IIIA2 includes microscopically visible tumors outside the pelvis irrespective of the presence or absence of lymph node metastases. Stage IIIB includes tumors < 2 outside the pelvis with or without retroperitoneal lymph node metastases. In the old classification, all tumors with retroperitoneal lymph node metastases were classified as stage IIIC, meaning that tumors previously staged as IIIC may now correspond to stage IIIA ("only positive lymph nodes") or IIIB (tumors < 2 cm). it is important to be aware of this when considering the indication for therapy with bevacizumab (approved for stages IIIB–IV in the old FIGO classification, which correspond to stages IIIA–IV in the new FIGO classification). It may be necessary to explain to health insurance companies that current stage IIIA was formerly classifed as stage IIIC and that approval is based on the old classification. Enlarged lymph nodes detected on palpation alone are not sufficient for classification as metastasis; lymph node metastases must be verified cytologically or histologically [2].

Stage IV

Stage IV includes all tumors with distant metastases – with the exception of peritoneal metastasis which is included in stages II and III. Stage IV is subdivided into stages IVA and IVB. Stage IVA only includes malignant pleural effusion. Stage IVB includes parenchymatous metastases or extra-abdominal metastases (including lymph nodes outside the abdominal cavity, tumors of the umbilicus or umbilical wall, intestinal infiltration with mucosal involvement). In the new classification, inguinal lymph nodes are no longer classified as stage IIIC but as stage IVB, although the usefulness of this classification has not been conclusively demonstrated in scientific studies. The question whether resectable tumors of the umbilicus, the intestinal mucosa and the liver or spleen should, in future, be classified as stage IIIC is still controversially discussed. They are currently classifed as FIGO IVB. The differentiation of FIGO IV into IVA and IVB also remains controversial [2].

With its new classification the FIGO Oncology Committee has attempted to take account of recent clinical and translational studies. The first studies have been published comparing the old and the new classifications with regard to disease-free and overall survival. The studies showed that, overall, the new classification results in a better differentiation between prognostically different (sub-)stages [20, 21].

The New WHO Classification

While the FIGO classification focuses on the differentiation into tumor stages, the WHO classification indicates the histopathological and molecular tumor type. Both aspects – tumor stage and tumor type – are already important criteria as they form the basis of a differentiated therapeutic approach.

The following sections provide an overview of the changes in the WHO classification, which was also published in 2014 and is therefore also already valid [22].

In the old classification, the chapter on ovarian cancers focused on the mesothelial layer of the ovary as the place of origin for epithelial ovarian tumors. This has been abandoned in the new classification. Instead, the tubal carcinogenesis of ovarian cancers is already addressed in the introduction to serous tumors, even though no tubal precurson lesions have been found in up to 30% of serous high-grade carcinomas; the originally assumed pathogenesis would therefore still appear to apply for a certain percentage of serous cancers. The new classification also emphasizes that reliable determination of the place of origin of advanced serous carcinomas is often not possible. The new classification (**Table 4**) has become more consistent due to the reduction in the number of subgroups. The term "transitional cell carcinoma" has been dropped; the classification "seromucinous tumor" has been added. The role of borderline tumors as a progression stage between benign and invasive lesions in various histological subtypes has been addressed in more detail. The sections below summarize the most important changes in the classification of serous, mucinous, seromucinous, endometrioid, clear cell and Brenner tumors [22].

Serous tumors

The difference between adenomas and borderline tumors (SBOTs) has become more sharply demarcated in the new WHO classification. Cystic serous tumors with > 10% BOT structures are classified as SBOT. If the BOT percentage in the lesion is below 10%, the term "serous cystadenoma with focal epithelial proliferation" is used to describe the entity. The diagnostic criteria for SBOT have largely remained the same. The lack of p53 mutations and the absence of diffuse p16-staining in SBOTs is emphasized. The incidence of KRAS/BRAF mutations is reported to be 50%. The progression from SBOT to LGSC is given as 5%. The micropapillary SBOT variant is expressly mentioned and described in detail. The higher risk of peritoneal disease associated with micropapillary SBOT (27 compared to 13% for the conventional type) and the 50% probability that the peritoneal origin of a micropa-

Table 4 Previous and new WHO classification.

Previous	New (2014)
Serous tumors	
Benign type	
Cystadenoma	cystadenoma
Papillary cystadenoma	adenofibroma
Surface papilloma	surface papilloma
Adenofibroma and cystadenofibroma	
Borderline (SBOT)	
Papillary cystic BOT	serous BOT/ atypical proliferating tumor
Papillary surface BOT	SBOT, micropapillary type/ non-invasive, serous low-grade carcinoma
Adenofibromatous and cystadenofibromatous BOT	
Malignant type	
Adenocarcinoma	serous low-grade carcinoma
Papillary surface carcinoma	serous high-grade carcinoma
Adenocarcinofibroma	
Mucinous tumors	
Benign type	
Cystadenoma	cystadenoma
Adenofibroma and cystadenofibroma	adenofibroma
Mucinous cystic tumor with mural nodules	
Mucinous cystic tumor with pseudomyxoma peritonei	
Borderline (MBOT)	
Intestinal type	mucinous BOT/atypical proliferating mucinous tumor
Endocervical type	
Malignant type	
Adenocarcinoma	mucinous carcinoma
Adenocarcinofibroma (malignant adenofibroma)	
Endometrioid tumors	
Benign type	
	endometriosis cyst
Cystadenoma	endometrioid cystadenoma
Adenofibroma & cystadenofibroma	endometrioid cystadenofibroma
Borderline (EBOT)	
Cystic tumor	endometrioid EBOT/atypical proliferative endometrioid tumor
Adenofibroma and cystadenofibroma	
Malignant type	
Adenocarcinoma NOS	endometrioid carcinoma
Adenocarcinofibroma (malignant adenofibroma)	
Malignant Müllerian mixed tumor (carcinosarcoma)	
Adenosarcoma	
Endometrioid stromal sarcoma (low-grade)	
Undifferentiated ovarian sarcoma	
Clear cell tumors	
Benign type	
Cystadenoma	cystadenoma
Adenofibroma and cystadenofibroma	
Borderline (KBOT)	
Cystic tumor	CBOT/atypical proliferating clear cell tumor
Adenofibroma and cystadenofibroma	
Malignant type	
Adenocarcinoma	clear cell tumor
Adenocarcinofibroma (malignant adenofibroma)	
Transitional cell tumors	**Brenner tumors**
Benign type	
Brenner tumor	Brenner tumor
Metaplastic type	
Borderline	
Borderline Brenner tumor	borderline Brenner tumor/ atypical proliferating Brenner tumor
Proliferative type	
Malignant type	
Transitional cell carcinoma	
Malignant Brenner tumor	malignant Brenner tumor
	seromucinous tumors
	benign tumors
	seromucinous cystadenoma
	seromucinous adenofibroma
	borderline tumors
	seromucinous borderline tumor/ atypical proliferating seromucinous tumor
	malignant disease
	seromucinous carcinoma
Squamous epithelial tumors	
Mixed epithelial tumors	
Undifferentiated and unclassifiable tumors	**Undifferentiated carcinoma**

pillary SBOT corresponds to that of serous low-grade carcinoma are emphasized. Micropapillary SBOTs have the same incidence of KRAS/BRAF mutation as normal SBOTs but their gene expression profile is different and resembles that of serous low-grade carcinomas.

If invasive implants are present, the tumor is referred to as serous low-grade carcinoma. However, this change of classification is based exclusively on pathological and morphological criteria. There are currently no clinical data which suggest that this step is necessary. In these cases it is suggested that pathological reports also include the old classification on which the current recommendations for clinical management are based.

The definition of SBOT with microinvasion is limited to single lesions with a maximum diameter of 5 mm. Analogously to the FIGO classification, the continuous grading of serous carcinoma into G1–G3 has been dropped and replaced by the subdivision into low-grade und high-grade carcinoma. Immunohistochemical staining for p53 is recommended for the morphological differentiation of tumors on the border to high-grade carcinoma.

Transitional cell carcinoma of the ovary no longer exists as a separate entity in the new classification. The corresponding histological growth pattern is now described as a variant of serous or (more rarely) endometrioid carcinoma (high-grade or G3) [22].

Mucinous tumors

The differentiation of mucinous borderline tumors (MBOT) into intestinal type and endocervical type has been abandoned. What was formerly classified as an endocervical MBOT is now part of

the newly created category of seromucinous tumors; the current definition of MBOT corresponds to the former intestinal type MBOT. In particular, the new classification highlights the importance of considering metastasis if an MBOT is present, even if no primary (extragenital) tumor has been identified. Bilateral MBOT, small tumor size and peritoneal foci are particularly suspicious for metastasis of an extragenital (gastrointestinal) malignancy. The definition of MBOT to include intraepithelial carcinoma was retained, along with the terms "microinvasive MBOT" and "microinvasive mucinous carcinoma". Nevertheless, the new classification does not offer a satisfactory resolution of the problem of defining invasion for mucinous carcinoma. The subdivision of mucinous carcinomas into expansile type and infiltrative-invasive type was retained [22].

Seromucinous tumors

This group represents a new entity among the epithelial ovarian tumors in the new WHO classification. Basically, this group of tumors includes cancers formerly classified as endocervical-type mucinous BOT, although the WHO requires at least two degrees of Müllerian differentiation for a diagnosis. The structures of seromucinous BOTs resemble those of SBOTs; however, up to one third of them are associated with endometriosis, and because of ARID1A mutations their molecular structures suggest that they are closer to endometrioid tumors than to serous tumors. This category includes both microinvasive and micropapillary BOTs and – in contrast to SBOTs – BOTs with intraepithelial carcinoma. As the findings for this tumor group are still limited, their clinical importance remains to be seen [22,23].

Endometrioid tumors

ARID1A and PIK3CA mutations and PTEN loss of heterozygosity (LOH) occur with similar frequency in endometriosis cysts and endometrioid cystadenomas, suggesting they may share a pathogenic connection. Similar mutations are also found with endometrioid ovarian carcinomas. Atypical lesions of endometriosis are also associated with the development of endometrioid (but also clear cell) ovarian carcinomas [24,25].

Because ARID1A and PIK3CA mutations and LOH of PTEN occur with the same incidence in endometriosis cysts as in endometrioid cystadenomas, the new WHO classification places endometriosis cysts in a neoplastic context. The endometrioid borderline category has been broken down further, differentiating between adenofibromatous (originating from an endometrioid adenofibroma) und intracystic (originating from an endometrioid cystadenofibroma/from an endometrioid cyst) EBOTs. In analogy to MBOTs, the diagnostic addendum "with intraepithelial carcinoma" is recommended when describing EBOTs with high-grade nuclear atypia. As with mucinous tumors, the problem of differentiating these entities from carcinomas in the differential diagnosis has not yet been satisfactorily resolved. There are many types of endometrioid carcinomas (with squamous differentiation, with secretory changes, with mucinous differentation, oxyphile type or with similar patterns to germ cell-stromal tumors). It is important to consider the possibility of metastasis when evaluating lesions presenting as endometrioid tumors [22].

Clear cell tumors

The new WHO classification has not resulted in any significant changes in the classification of clear cell tumors. Clear cell BOTs are very similar to clear cell adenomas and parts of both entities are usually present in tumors. In contrast, clear cell carcinomas are irregular, with papillary structures, solid parts with desmoplastic hyalinized stroma, and high-grade nuclear atypia [22]. Clear cell carcinomas may be associated with Lynch syndrome but also with endometriosis and are the most common ovarian carcinoma with paraneoplastic symptoms (thromboembolism and hypercalcemia) [24,25].

Brenner tumors

The former chapter on transitional cell tumors is now entitled "Brenner tumors". Around 25 % of Brenner tumors are associated with other epithelial tumors. Brenner tumors consist of cell nests of varying sizes and can be differentiated immunohistochemically from transitional cell tumors. The differentiation between Brenner tumors and borderline tumors is not defined precisely or in terms of size. Epithelial proliferation in Brenner BOTs is significantly higher, resulting in considerably larger lesions (mean diameter 18 cm) with a significantly higher epithelial percentage. This BOT category also includes a subgroup "intraepithelial carcinoma". Malignant Brenner tumors are characterized by destructive stromal invasion of unspecified morphology. These tumors additionally present with focal, high-grade nuclear atypia [22].

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References

1 *Meinhold-Heerlein I, Hauptmann S.* The heterogeneity of ovarian cancer. Arch Gynecol Obstet 2014; 289: 237–239
2 *Prat J; FIGO Committee on Gynecologic Oncology.* Staging classification for cancer of the ovary, fallopian tube, and peritoneum. Int J Gynaecol Obstet 2014; 124: 1–5
3 *Shepherd JH.* Revised FIGO staging for gynaecological cancer. Br J Obstet Gynaecol 1989; 96: 889–892
4 *Pecorelli S, Benedet JL, Creasman WT et al.* FIGO staging of gynecologic cancer. 1994–1997 FIGO Committee on Gynecologic Oncology. International Federation of Gynecology and Obstetrics. Int J Gynaecol Obstet 1999; 65: 243–249
5 *Pecorelli S, Benedet JL, Creasman WT et al.* FIGO staging of gynecologic cancer. 1994–1997 FIGO Committee on Gynecologic Oncology. International Federation of Gynecology and Obstetrics. Int J Gynaecol Obstet 1999; 64: 5–10
6 *Przybycin CG, Kurman RJ, Ronnett BM et al.* Are all pelvic (nonuterine) serous carcinomas of tubal origin? Am J Surg Pathol 2010; 34: 1407–1416
7 *Zeppernick F, Meinhold-Heerlein I, Shih IeM.* Precursors of ovarian cancer in the fallopian tube: serous tubal intraepithelial carcinoma–an update. J Obstet Gynaecol Res 2015; 41: 6–11
8 *Benedet JL, Bender H, Jones H 3rd et al.* FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. Int J Gynaecol Obstet 2000; 70: 209–262
9 *Piek JM, van Diest PJ, Zweemer RP et al.* Dysplastic changes in prophylactically removed Fallopian tubes of women predisposed to developing ovarian cancer. J Pathol 2001; 195: 451–456
10 *Meinhold-Heerlein I, Bauerschlag D, Hilpert F et al.* Molecular and prognostic distinction between serous ovarian carcinomas of varying grade and malignant potential. Oncogene 2005; 24: 1053–1065
11 *Shih IeM, Kurman RJ.* Ovarian tumorigenesis: a proposed model based on morphological and molecular genetic analysis. Am J Pathol 2004; 164: 1511–1518
12 *Kurman RJ, Shih IeM.* Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer–shifting the paradigm. Hum Pathol 2011; 42: 918–931

13 *Prat J.* New insights into ovarian cancer pathology. Ann Oncol 2012; 23 (Suppl. 10): x111–x117
14 *du Bois A, Reuss A, Pujade-Lauraine E et al.* Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). Cancer 2009; 115: 1234–1244
15 *Gershenson DM, Sun CC, Bodurka D et al.* Recurrent low-grade serous ovarian carcinoma is relatively chemoresistant. Gynecol Oncol 2009; 114: 48–52
16 *Gershenson DM, Sun CC, Iyer RB et al.* Hormonal therapy for recurrent low-grade serous carcinoma of the ovary or peritoneum. Gynecol Oncol 2012; 125: 661–666
17 *Hauptmann S, du Bois A, Meinhold-Herlein I et al.* [Histological grading of epithelial ovarian cancer. Review and recommendation]. Der Pathologe 2014; 35: 497–503
18 *Hohn AK, Einenkel J, Wittekind C et al.* [New FIGO classification of ovarian, fallopian tube and primary peritoneal cancer]. Der Pathologe 2014; 35: 322–326
19 *Vergote I, De Brabanter J, Fyles A et al.* Prognostic importance of degree of differentiation and cyst rupture in stage I invasive epithelial ovarian carcinoma. Lancet 2001; 357: 176–182
20 *Paik ES, Lee YY, Lee EJ et al.* Survival analysis of revised 2013 FIGO staging classification of epithelial ovarian cancer and comparison with previous FIGO staging classification. Obstet Gynecol Sci 2015; 58: 124–134
21 *Suh DH, Kim TH, Kim JW et al.* Improvements to the FIGO staging for ovarian cancer: reconsideration of lymphatic spread and intraoperative tumor rupture. J Gynecol Oncol 2013; 24: 352–358
22 *Kurman RJ, Carcangiu ML, Herrington CS et al.* WHO Classification of Tumours of female reproductive Organs. In: Kurman RJ, Carcangiu ML, Herrington CS et al., eds. WHO Classification of Tumours. 4th ed. Lyon: WHO Press; 2014
23 *Hauptmann S.* Die neue WHO-Klassifikation des Ovarial-, Tuben- und primären Peritonealkarzinoms. 2015
24 *Chene G, Ouellet V, Rahimi K et al.* The ARID1A pathway in ovarian clear cell and endometrioid carcinoma, contiguous endometriosis, and benign endometriosis. Int J Gynaecol Obstet 2015; 130: 27–30
25 *Wiegand KC, Shah SP, Al-Agha OM et al.* ARID1A mutations in endometriosis-associated ovarian carcinomas. N Engl J Med 2010; 363: 1532–1543