第 103 回日本病理学会総会コンパニオンミーティング 6

日本婦人科病理学会

平成 26 年 4 月 24 日　18:00～19:20

H 会場　ANA クラウンプラザホテル広島 3 階　アカシア 2

卵巣腫瘍の病理：WHO 分類改訂の動向

オーガナイザー

九島巳樹（昭和大学医学部　臨床病理診断科）

森谷卓也（川崎医科大学　病理学 2）

CM-6-1　卵巣腫瘍の概念と分類

柳井　広之（岡山大学病院　病理診断科）

CM-6-2　現行 WHO 分類（第 3 版：2003 年）の枠組みと問題点

前田　大地（東京大学医学部附属病院　病理部）

CM-6-3　改定 WHO 分類の概要

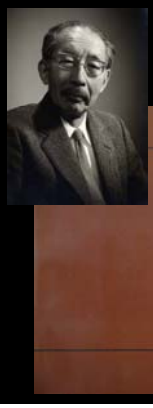
三上　芳喜（京都大学医学部附属病院　病理診断科）

2014.4.24
第103回日本病理学会総会
コンパニオン・ミーティング

卵巣腫瘍の概念と分類
-WHO 分類第2版まで-

岡山大学病院 病理診断科
柳井広之

岡山大学病院



腫瘍の分類は，ただ分けるという意味ではなく，あるprincipleによって総括することでもある。そして，その根本には，人体腫瘍についてはその腫瘍が患者に対して，いかにふるまうかを予測し，これを統御しようという医の目的にかなうことを望んでいるのである。

（牛島 宥「卵巣腫瘍」より）

卵巣腫瘍の分類の歴史

Peasleeの分類 (1873)

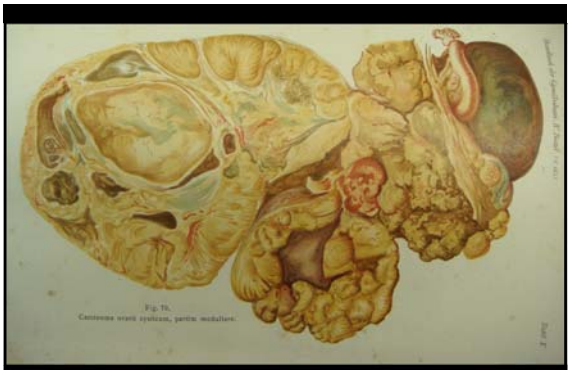
- Solid tumors
  - Enchondroma
  - Osteoma (ossification)
  - Carcinoma
  - Papilloma
  - Fibroma (of corpora lutea, of the stroma)
- Cystic tumors
  - Hydrops filliculorum
  - Cystoma ovarii
    - struma
    - oligocysts
    - polycysts
    - Dermoid cysts

Peaslee E. Randolph. Ovarian Tumors: Their Pathology, Diagnosis, and Treatment, Especially by Ovariotomy. Appleton & Company: New York, 1872.

Pfannenstielの分類 (1908)

- **Die parenchymatogenen Neubildungen**
  - **Die epithelialen Neubildungen**
    - Das Kystoma serosum simplex
    - Die Adenome
      - Papilläre Wuncherungen in Kystadenomen
      - Adenoma papillare superficiale
      - Einzelne Arten der Kystadenome
      - Das Kystadenoma pseudomucinosum, das Psudomucinkystom
      - Das Kystadenoma serosum. Das papilläre Kystom
      - Das "solide" Adenom
    - Die Karzinome
  - **Die ovulogenen Neubildungen**
    - Die Dermoidkystome
    - Die Teratome
      - Struma ovarii
    - Das Epithelioma chorioectodermale
- **Die stromatogenen Neubildungen**
  - Fibrome und Myome
  - Das Osteoma ovarii
  - Das Chondrom des Eierstockes
  - Das Myxoma ovarii
  - Die Angiome des Eierstockes
  - Die Tumoren der Sarkomgruppe
- **Die Kombinationsgeschwülste**
- **Inklusionstumoren**
- **Das Epoophoron und die Geschwülste des Nebeneierstockes**

Veit Handbuch der Gynäkologie 第2版 より



Carcinoma ovarii cysticum partim medullare

Veit Handbuch der Gynäkologie 第2版 より

Medullares Karzinom

Veit Handbuch der Gynäkologie 第2版 より

Schillerの分類 (1940)

A. Ovariogenic

1. Granulosa cell tumor
2. Fibroma
3. Lymphangioma, hemangioma, luteinoma (of other than granulosa origin)
4. Hilum cell tumor

B. Heterotopic - derived from tissues not normally present within the ovary

1. By pathologic differentiation
   - a. from surface epithelium - prosoplasia in direction of Müllerian epithelium
     - (1) serous cystoma and derivatives (tubal type epithelium)
     - (2) endometrioma (uterine type of epithelium)
     - (3) pseudomucinous cystoma and variants (uterine cervical type of epithelium)
   - b. from mesenchymal (ovarian) core by error in sex chromosomes
     - (1) arrhenoblastoma (from male-directed elements)
     - (2) disgerminoma (from nutral or germinal elements)

2. From tissues displaced
   - a. in fatal life
     - (1) early - teratoma
       immature - embryoma
       mature - dermoid
     - (2) late - from tissues in vicinity of ovary
       hypernephroma
       mesonephroma
       Brenner tumor
       ganglioneuroma
   - b. in adult life
     - (1) by implantation - endometrioma
     - (2) by metastasis - Krukenberg tumors, etc.


CONCEPTS OF A NEW CLASSIFICATION OF OVARIAN TUMORS

WALTER SCHILLER, M.D., Chicago, Illinois

Schiller,W. Surg.,Gynec. & Obst., 1940, 70, 773-782

Novakの分類（抄・1952）

Benign

- Cystic
  - Non-neoplastic
  - Neoplastic
    - Cystadenoma
      - pseudomicinous
      - serous
    - Dermoid
- Solid
  - Papilloma, fibro-adenoma, fibroma, etc.
  - Brenner tumors (rarely malignant)
  - Adrenal tumors (masculinoblastoma)
  - Hilus cell tumors (probably benign)

Malignant

- Carcinoma
  - Primary solid carcinoma
    - Adenocarcinoma
    - Embryonic or dysontogenetic (incl. granulosa cell carcinoma, thecoma, lutomea, arrhenoblastoma, dysgerminoma)
    - chorioepithelioma
  - Cystic carcinoma
- Teratoma (incl. struma ovarii)
- Melanoma

樋口の分類

A 嚢胞性腫瘍（良性）

1. 偽ムチン性嚢胞腺腫
2. 漿液性嚢胞腺腫
3. 類皮嚢胞腫

B 充実性腫瘍

I. 良性群

1. 線維腫，線維筋腫
2. Brenner型腫瘍
3. 莢膜細胞腫
4. 甲状腺腫
5. 類副腎腫
6. 門細胞腫

II. 中間群

1. 未分化胚細胞腫
2. 顆粒膜細胞腫
3. 男化腫瘍
4. 充実性奇形腫

III. 悪性群

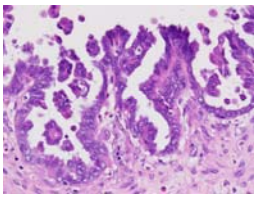
1. 単純性
   - 原発性癌
   - 続発性
     - 偽ムチン嚢胞腺腫癌
     - 漿液性嚢胞腫癌
     - 類皮嚢胞腫癌
2. 転移性癌（Krukenberg腫瘍を含む）
3. 絨毛上皮腫
4. 肉腫
5. embryonal carcinoma

A群 純型
B群 未分化胚細胞腫との合併
C群 奇形腫との合併

AFIP atlas 1st fascicleの分類 (1950's)

1. Gonadal stromal tumors
   - Granulosa-theca cell tumor
   - Arrhenoblastoma
   - Gynandroblastoma
2. Germ cell tumors
   - Dysgerminoma
   - Choriocarcinoma
   - Benign cystic teratoma
   - Malignant teratoma
   - Teratocarcinoma
3. Cystomas
   - Serous cystadenoma and cystadenocarcinoma
   - Mucinous cystadenoma and cystadenocarcinoma
   - Endometrial cystoma, benign and malignant
   - Cystadenofibroma, benign and malignant
4. Congenital rest tumors
   - Adrenal rest tumors
   - Mesometanephric rest tumor
   - Brenner tumor
   - Hilar cell tumor
5. Nonintrinsic connective tissue tumors
   - Fibroma
   - Fibrosarcoma
   - Rhabdomyosarcoma
6. Metastatic tumors

Hertig, Gore. Tumors of the Female Sex Organs. TUmors of the Ovary and Fallopian Tube. 1959



上皮性境界悪性腫瘍

Ueber die papillären Geschwülste des Eierstocks.

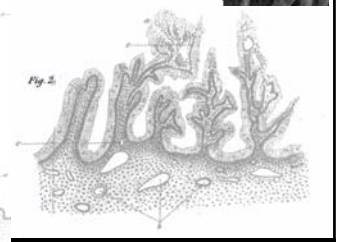
Anatomische und klinische Untersuchungen zur Klärung der Frage ihrer Malignität.

Von

Dr. **J. Pfannenstiel,**

Privatdocent in Breslau.

Adenoma papillare simplex



Adenoma papillare pseudomucinosum

204 SURGERY, GYNECOLOGY AND OBSTETRICS

MALIGNANT AND SEMIMALIGNANT TUMORS OF THE OVARY

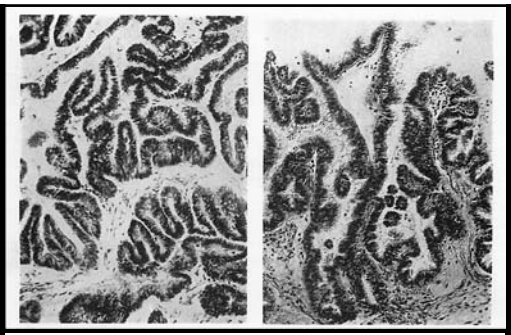
HOWARD C. TAYLOR, JR., M.D., NEW YORK CITY
From the Gynecological Service of the Roosevelt Hospital

FOR the study of the malignant tumors of the ovary, the pathological reports of the Gynecological Division of the Roosevelt Hospital were reviewed from the beginning of the year 1910 until the end of 1927, and all cases with the diagnosis of papillary cystadenoma, primary carcinoma of any variety, and sarcoma were selected, and the pathological sections re-examined as far as possible. That each of these varieties should be included in the complete survey was necessary because of the extreme variation in interpretation placed upon these terms by various surgeons and pathologists. Tumors considered by the operator or pathologist as being probably metastatic in the ovary have tumors of a faintly papillary form, but of a more adenofibromatous histology had been added to the papillary cystadenomata. That clinical reports of such heterogeneous material is useless, is self-evident, and we are, therefore, reporting results on numerous small groups and later summarizing as far as consistency permits.

CLASSIFICATION

The origin of the cells that form the ovarian tumors has been a disputed point since the first studies in cellular pathology. All observable epithelial structures found in the adult ovary, in the ovary of the embryo, and in neighboring embryological structures, such as

Taylor HC. Surg Gynecol Obstet 1929;48:204–230.



Of the hyperplastic variety, 3 were bilateral, and each of these had implants scattered diffusely over the peritoneum or in the intestine or omentum, one other had ascites and external papillae on the surface of the cyst, while a fifth had external papillae alone.

Taylor HC. Surg Gynecol Obstet 1929;48:204–230.

SantessonのLow potential malignancy (1968)

Experience has shown that *between obviously benign and obviously malignant neoplasms there exists a group of tumours that, in their clinical behaviour, resemble true carcinomas in as much as they give rise to implantationmetastases and ascites - but have quite a different course.* The general epithelial structures are maintained as in benign tumours but the epithelial cells show signs of proliferative activity, nuclear abnormalities and pathological mitosis. However, there is no visible evidence of infiltrative destructive growth in the connective tissue of the growth.

SantessonのLow potential malignancy

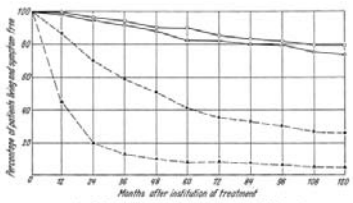
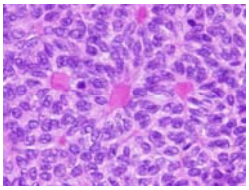
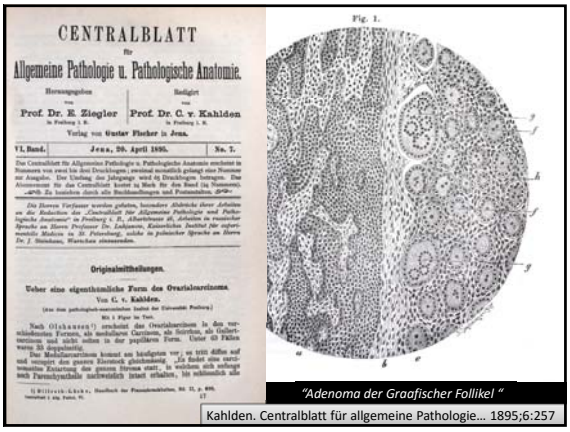


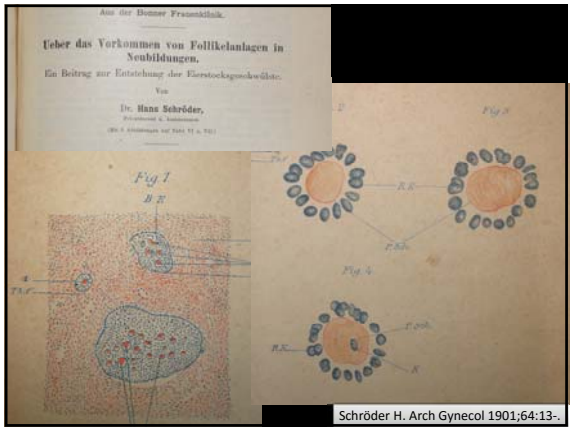
Fig. 3. Survival rate of cystomas 10year (375 cases)

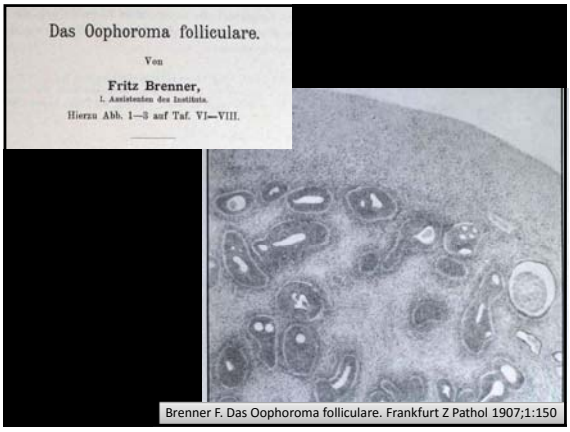
—•— Low potential malignancy: surgically completely removed (54 cases). —▲— Low potential malignancy: surgically not completely removed (75 cases). ···•··· Carcinomas: surgically completely removed (96 cases). ···▲··· Carcinomas: surgically not completely removed (150 cases)

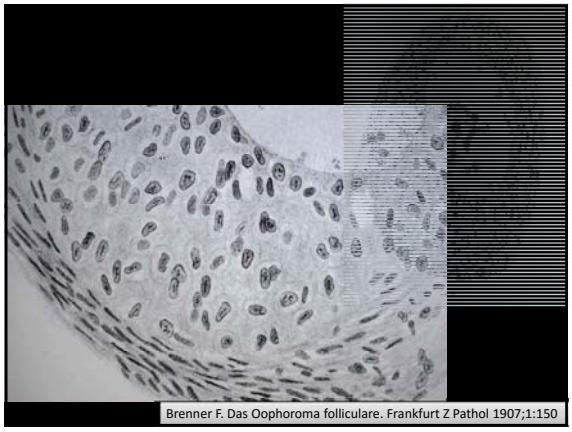


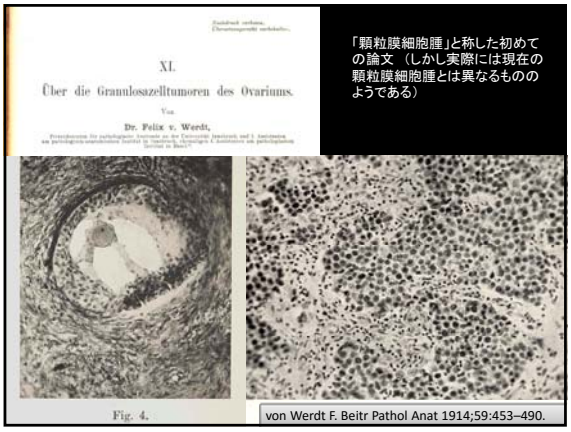
顆粒膜細胞腫をめぐって

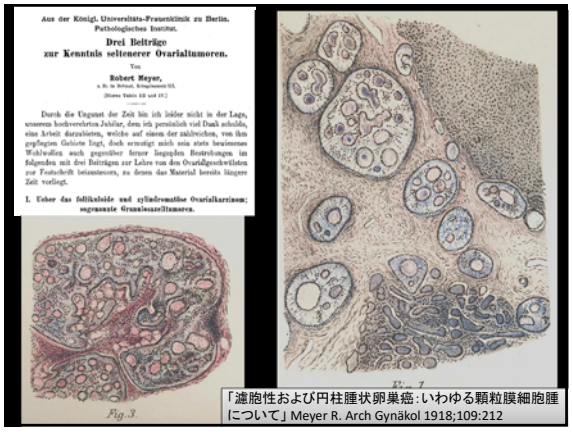

CENTRALBLATT
für
Allgemeine Pathologie u. Pathologische Anatomie.
Herausgegeben von Prof. Dr. E. Ziegler in Freiburg i. B.
Redigirt von Prof. Dr. C. v. Kahlden in Freiburg i. B.
Verlag von Gustav Fischer in Jena.
VI. Band. Jena, 20. April 1895. No. 7.
Originalmittheilungen.
Ueber eine eigenthümliche Form des Ovarialcarcinoma.
Von C. v. Kahlden.
Fig. 1.
"Adenoma der Graafischer Follikel "
Kahlden. Centralblatt für allgemeine Pathologie… 1895;6:257

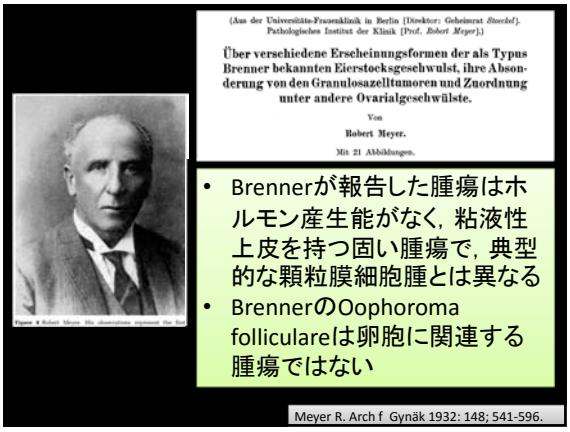

Aus der Bonner Frauenklinik.
Ueber das Vorkommen von Follikelanlagen in Neubildungen.
Ein Beitrag zur Entstehung der Eierstocksgeschwülste.
Von Dr. Hans Schröder,
Fig. 1
Fig. 3
Fig. 4
Schröder H. Arch Gynecol 1901;64:13-.

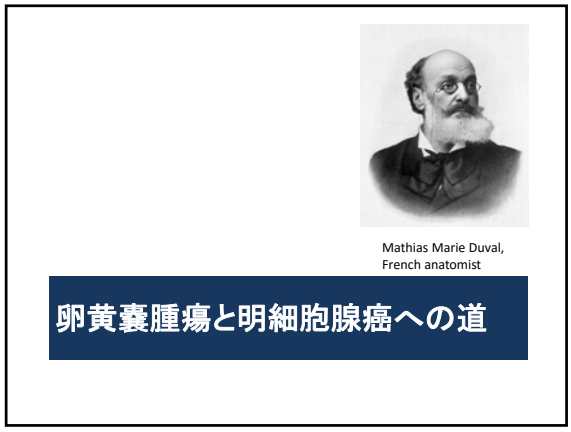

Das Oophoroma folliculare.
Von
Fritz Brenner,
I. Assistenten des Instituts.
Hierzu Abb. 1—3 auf Taf. VI—VIII.
Brenner F. Das Oophoroma folliculare. Frankfurt Z Pathol 1907;1:150

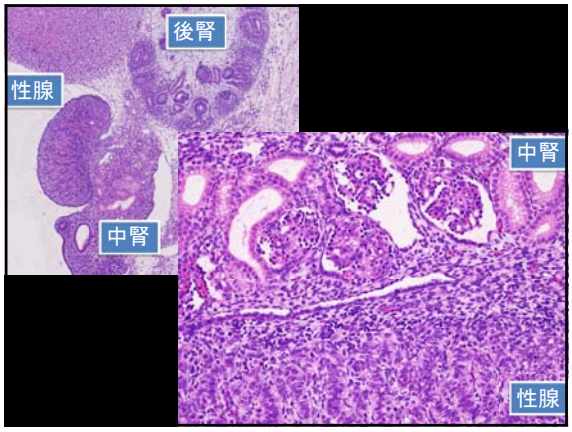

Brenner F. Das Oophoroma folliculare. Frankfurt Z Pathol 1907;1:150


XI.
Über die Granulosazelltumoren des Ovariums.
Von
Dr. Felix v. Werdt,
「顆粒膜細胞腫」と称した初めての論文 （しかし実際には現在の顆粒膜細胞腫とは異なるもののようである）
Fig. 4.
von Werdt F. Beitr Pathol Anat 1914;59:453–490.


Aus der Königl. Universitäts-Frauenklinik zu Berlin.
Pathologisches Institut.
Drei Beiträge zur Kenntnis seltenerer Ovarialtumoren.
Von
Robert Meyer,
I. Ueber das follikuloide und zylindromatöse Ovarialkarzinom; sogenannte Granulosazelltumoren.
Fig. 3.
「濾胞性および円柱腫状卵巣癌：いわゆる顆粒膜細胞腫について」Meyer R. Arch Gynäkol 1918;109:212



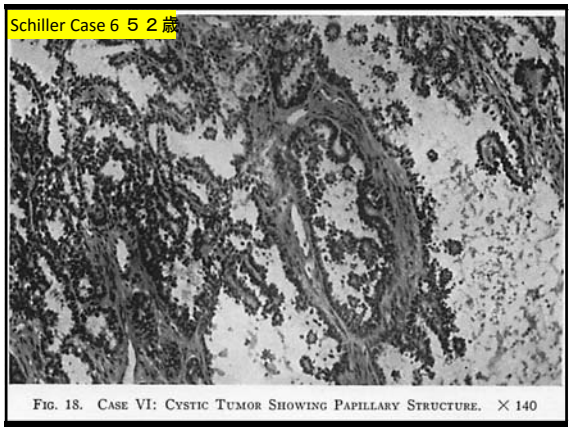




SchillerのMesonephroma

Case No.	Age	Comment
1	43歳	
2	8ヶ月	写真なし
3	20歳	
4	13歳	
5	69歳	写真はclear cell adenoca, tubulocytic typeか
6	52歳	
7	40歳	組織写真なし
8	38歳	
9	21歳	奇形腫を合併
10	26歳	dysgerminoma, embryoma (teratoma?)を合併

年齢が赤字の症例は卵黄嚢腫瘍としては年齢が高い



Schiller Case 5 69歳

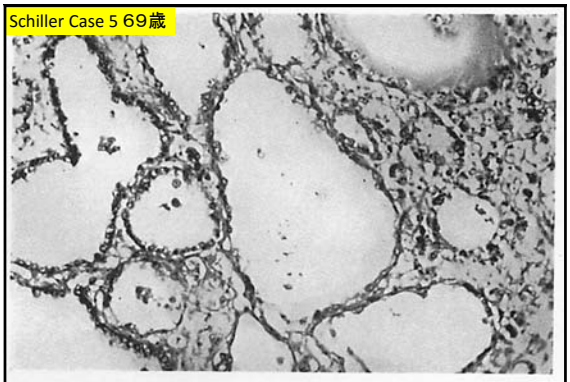
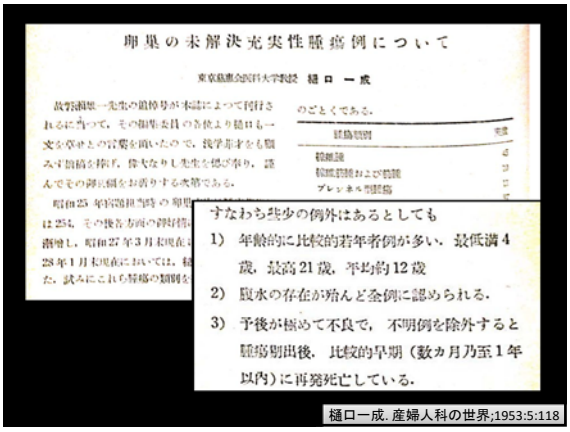


FIG. 17. CASE V: TUMOR PARENCHYMA CONSISTING OF SMALL CYSTS LINED BY ENDOTHELIAL-LIKE CELLS. × 140

Mesonephromaの別名

報告者	腫瘍名	発表年
Schiller	Mesonephroma ovarii	1939
Kazancigil et al.	Papillo-endothelioma ovarii	1940
木村，小林	Angioendothelioma	1941 日本癌学会にて
Teilum	Extraembryonic mesoblastoma	1950
樋口	未解決腫瘍	1953
Santesson, et al	Ovarian embryonal carcinoma	1957
牛島	Embryonal carcinoma	1957 日本病理学会にて
Teilum	Endodermal sinus tumor	1959



卵巣の未解決充実性腫瘍例について

東京慈恵会医科大学婦人科 樋口一成

のごとくである。

腫瘍期別	例数
腺腫	4
腺腫肉腫および肉腫	11
プレンネル腫瘍	1

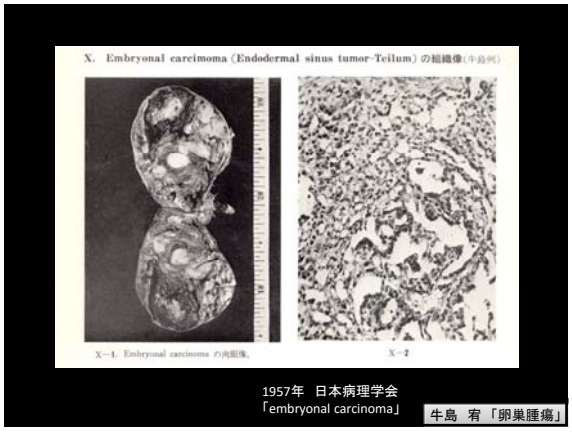
すなわち些少の例外はあるとしても

1) 年齢的に比較的若年者例が多い．最低満4歳，最高21歳，平均約12歳

2) 腹水の存在が殆んど全例に認められる．

3) 予後が極めて不良で，不明例を除外すると腫瘍剔出後，比較的早期（数カ月乃至1年以内）に再発死亡している．

樋口一成. 産婦人科の世界;1953:5:118

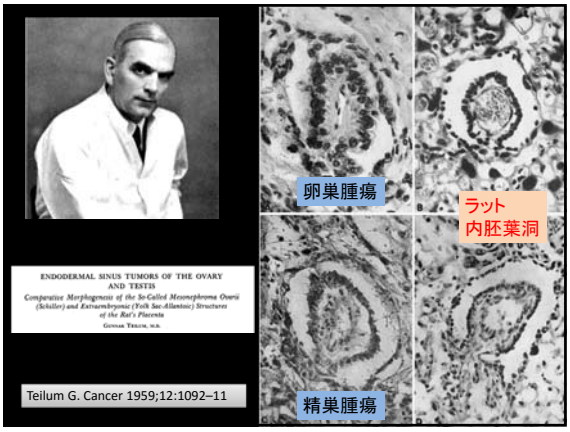


X. Embryonal carcimoma (Endodermal sinus tumor-Teilum) の組織像（牛島例）

X−1. Embryonal carcinoma の肉眼像.　　X−2

1957年　日本病理学会
「embryonal carcinoma」

牛島　宥「卵巣腫瘍」



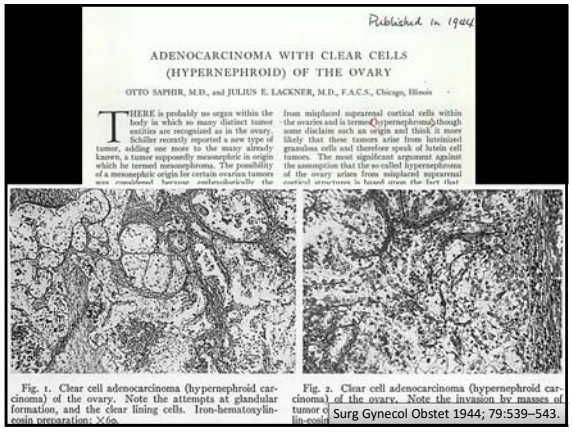
ENDODERMAL SINUS TUMORS OF THE OVARY AND TESTIS
Comparative Morphogenesis of the So-Called Mesonephroma Ovarii (Schiller) and Extraembryonic (Yolk Sac-Allantoic) Structures of the Rat's Placenta
GUNNAR TEILUM, M.D.

卵巣腫瘍

ラット
内胚葉洞

精巣腫瘍

Teilum G. Cancer 1959;12:1092–11



Published in 1944

ADENOCARCINOMA WITH CLEAR CELLS (HYPERNEPHROID) OF THE OVARY

OTTO SAPHIR, M.D., and JULIUS E. LACKNER, M.D., F.A.C.S., Chicago, Illinois

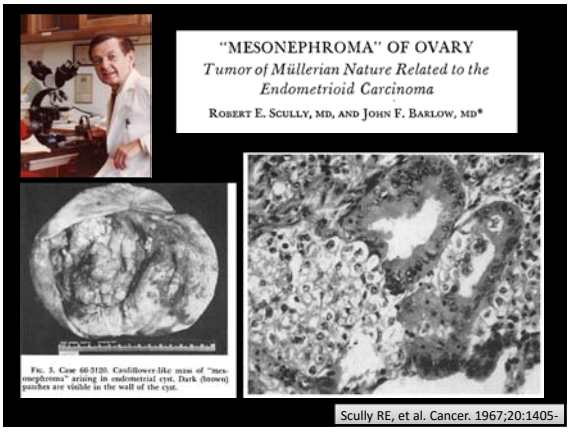
THERE is probably no organ within the body in which so many distinct tumor entities are recognized as in the ovary. Schiller recently reported a new type of tumor, adding one more to the many already known, a tumor supposedly mesonephric in origin which he termed mesonephroma. The possibility of a mesonephric origin for certain ovarian tumors was considered because embryologically the

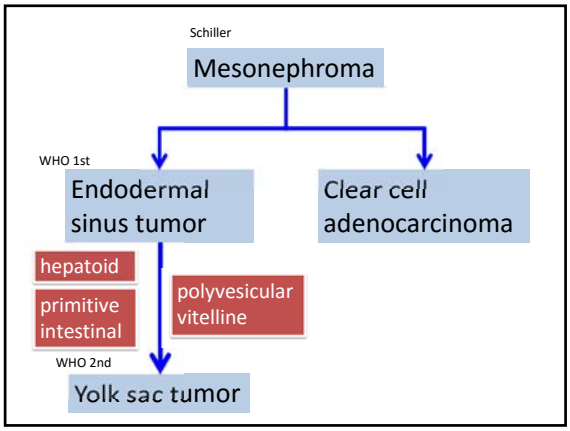
from misplaced suprarenal cortical cells within the ovaries and is termed hypernephroma, though some disclaim such an origin and think it more likely that these tumors arise from luteinized granulosa cells and therefore speak of lutein cell tumors. The most significant argument against the assumption that the so-called hypernephroma of the ovary arises from misplaced suprarenal cortical structures is based upon the fact that

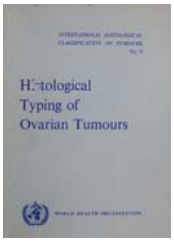
Fig. 1. Clear cell adenocarcinoma (hypernephroid carcinoma) of the ovary. Note the attempts at glandular formation, and the clear lining cells. Iron-hematoxylin-eosin preparation; ×60.

Fig. 2. Clear cell adenocarcinoma (hypernephroid carcinoma) of the ovary. Note the invasion by masses of tumor c... lin-eosin

Surg Gynecol Obstet 1944; 79:539–543.







WHO分類第1版 (1973), 第2版 (1999)

WHO分類第1版の骨格

I. Common "epithelial" tumor
- A. Serous tumors
- B. Mucinous tumors
- C. Endometrioid tumors
- D. Clear cell tumors
- E. Brenner tumors
- F. Mixed epithelial tumors
- G. Undifferentiated carcinoma
- H. Unclassified epithelial tumors

II. Sex cord/stromal tumors
- A. Granulosa-stromal cell tumors
  - 1. Granulosa cell tumor
  - 2. Tumors of the thecoma-fibroma group
- B. Androblastomas; Sertoli-Leydig cell tumors
- C. Gynandroblastoma
- D. Unclassified

III. Lipid [lipoid] cell tumors

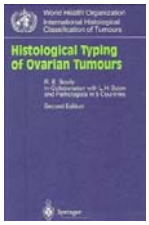
IV. Germ cell tumors
- A. Dysgerminoma
- B. Endodermal sinus tumor
- C. Embryonal carcinoma
- D. Polyembryoma
- E. Choriocarcinoma
- F. Teratomas
  - 1. Immature
  - 2. Mature
  - 3. Monodermal and highly specialized
- G. Mixed forms

V. Gonadoblastoma
- A. Pure
- B. Mixed with dysgerminoma or other form of germ cell tumor

VI. Soft tissue tumors not specific to ovary
VII. Unclassified tumors
VIII. Secondary [metastatic] tumors

WHO第2版の主な変更点

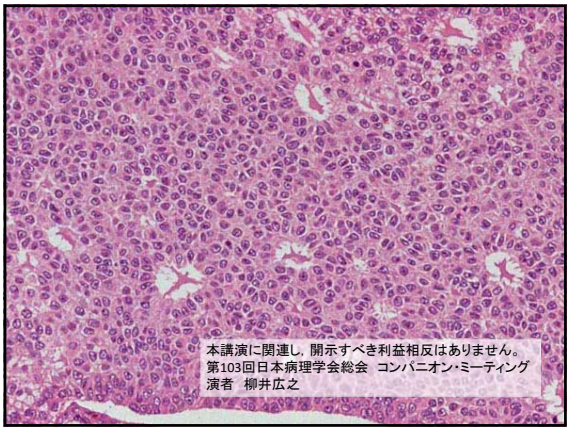
- 漿液性境界悪性腫瘍に微小浸潤を含めた
- 粘液性腫瘍をendocervical-likeとintestinal typeに
- Lipid cell tumorをSex cord-stromal tumorに包めた
- Endodermal sinus tumorをyolk sac tumorに
- 新しく認識された組織型を追加



WHO分類第2版で追加された主な腫瘍

- Juvenile granulosa cell tumor
- Sclerosing stromal tumor
- Stromal tumor with minor sex cord element
- Sex cord tumor with annular tubules
- Small cell carcinoma (hypercalcemic type)

Robert E. Scully, a giant of gynecological pathology


本講演に関連し，開示すべき利益相反はありません。
第103回日本病理学会総会　コンパニオン・ミーティング
演者　柳井広之

現行WHO分類(第3版：2003年)の枠組みと問題点

前田大地

秋田大学大学院医学系研究科器官病態学講座

- High grade serous adenocarcinomaとlow grade serous adenocarcinoma
- High grade serous adenocarcinomaと卵管病変(tubal intraepithelial carcinoma)の関連
- Intestinal-type mucinous tumorとendocervical-like mucinous tumorの区別
- Mucinous borderline tumorにおけるintraepithelial carcinoma及びmicroinvasionの位置づけ
- Transitional cell carcinomaの存在
- Adult granulosa cell tumorと*FOXL2*変異
- 卵巣腫瘍の新規疾患概念：Microcystic stromal tumorとsolid pseudopapillary neoplasm

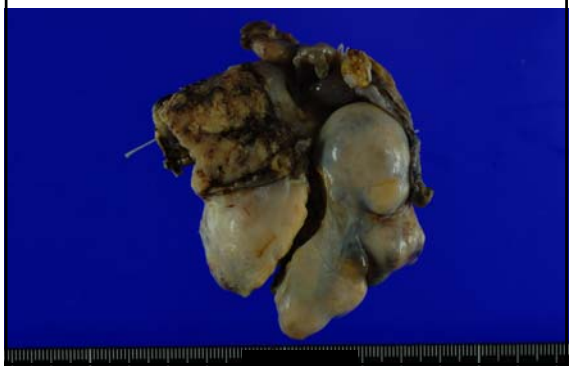
WHO 2003

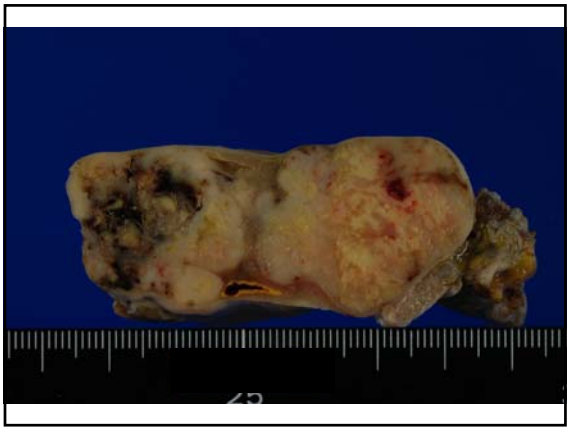
Serous tumours
- Malignant
  - Adenocarcino
  - Surface papill
  - Adenocarcino

Low grade と high gradeの区別はなされていない！

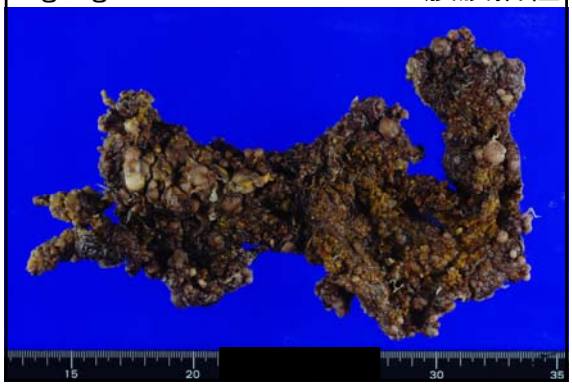
- Borderline tumor
  - Papillary cystic tumour
  - Surface papillary tumour
  - Adenofibroma, cystadenofibroma
- Benign
  - Cystadenoma
  - Papillary cystadenoma
  - Surface papilloma
  - Adenofibroma and cystadenofibroma

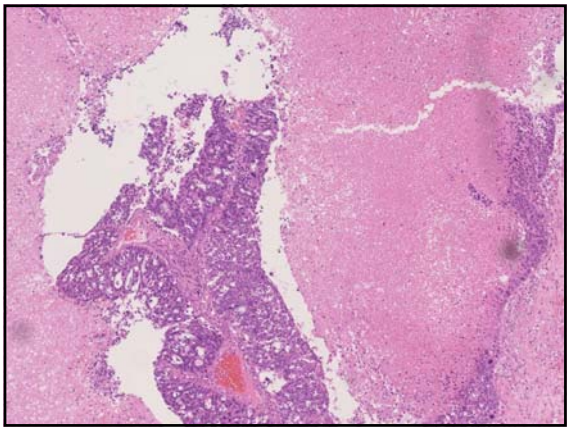
High grade serous adenoca. 例

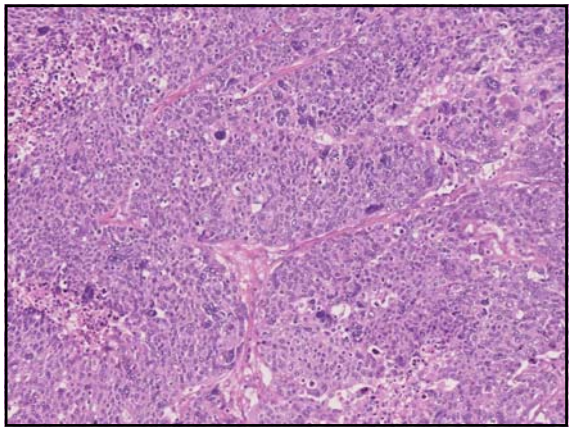


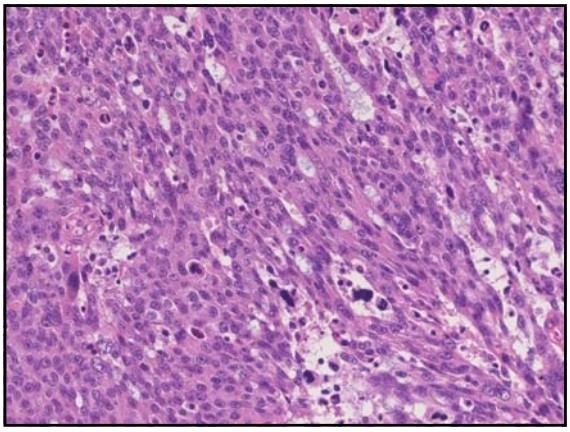


High-grade serous adenoca. 腹膜播種

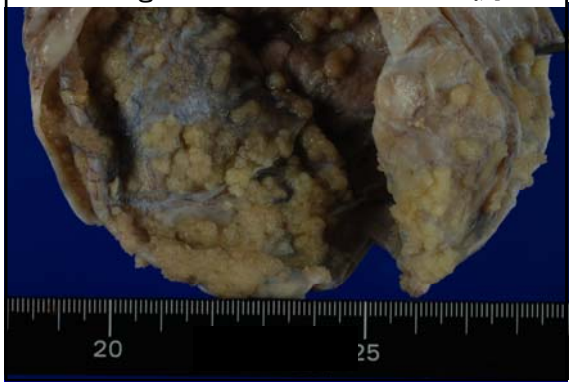


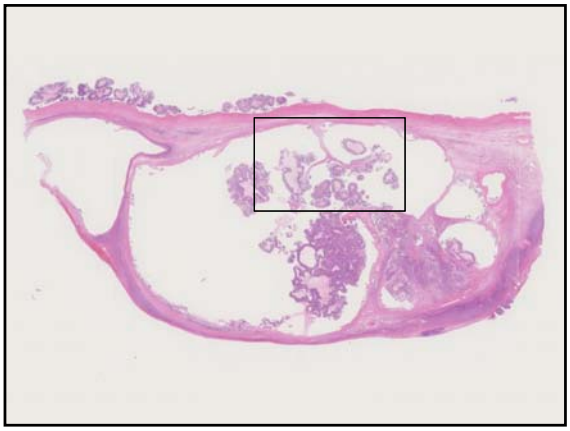




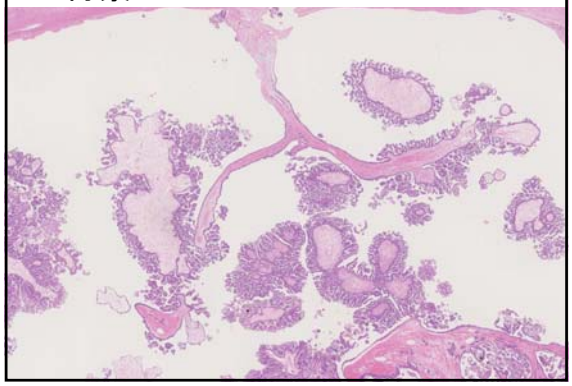


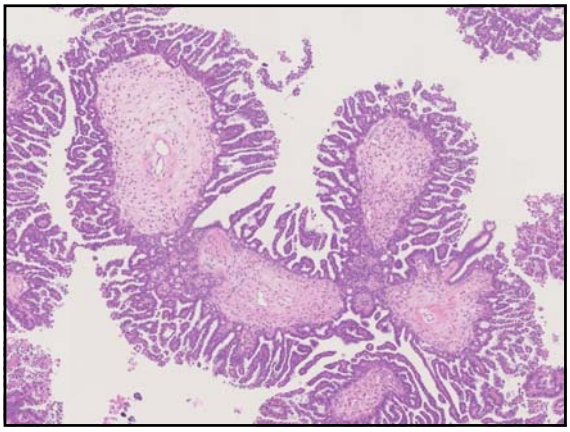
Low grade serous adenoca. 例



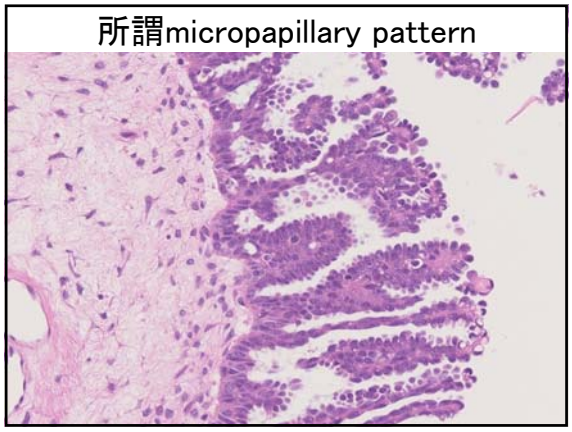


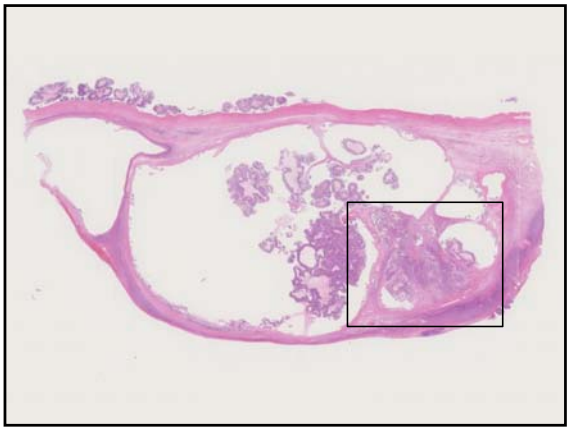
背景はserous borderline tumor



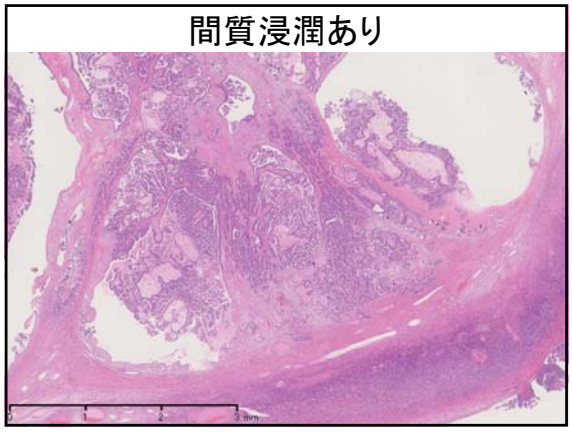


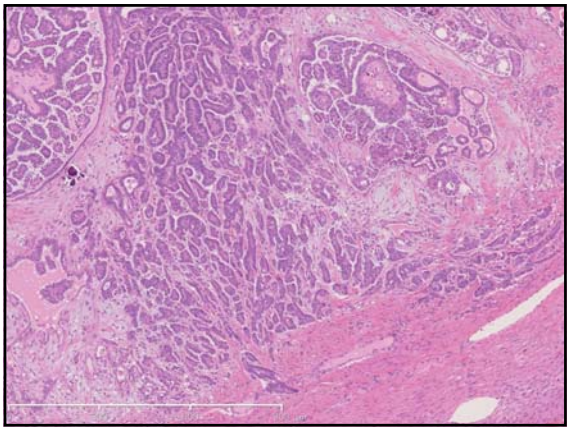
所謂micropapillary pattern



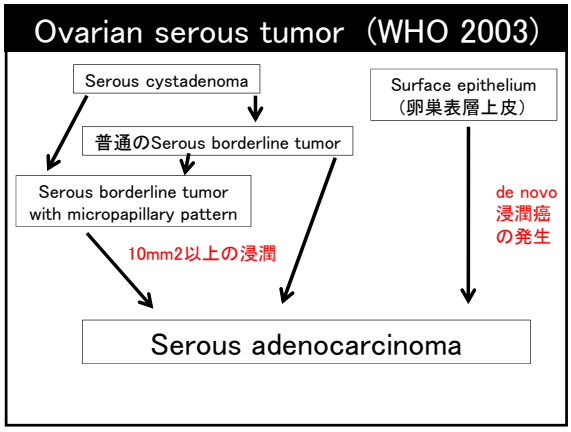


間質浸潤あり





Ovarian serous tumor （WHO 2003）



Serous adenocarcinomaをlow grade とhigh gradeの2つに分ける流れ

ORIGINAL ARTICLE

Grading Ovarian Serous Carcinoma Using a Two-Tier System

Anais Malpica, MD, Michael T. Deavers, MD,* Karen Lu, MD,† Diane C. Bodurka, MD,† Edward N. Atkinson, MD,‡ David M. Gershenson, MD,† and Elvio G. Silva, MD**

(*Am J Surg Pathol* 2004;28:496–504)

腫瘍細胞の核異型のみをもってlow grade と high gradeに分割 (high gradeは核の大小不同が3倍以上と定義）

High grade serous adenocarcinoma

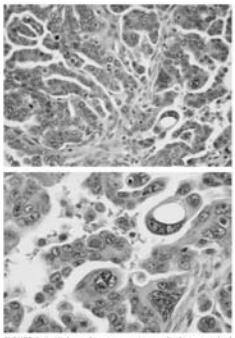


FIGURE 3. A: High-grade serous carcinoma displaying marked nuclear pleomorphism and conspicuous mitotic activity. B: Multinucleated tumor giant cells commonly seen in high-grade serous carcinoma.

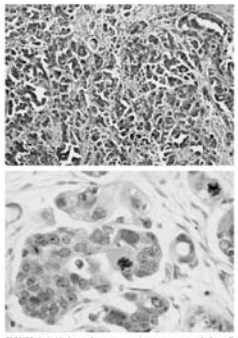


FIGURE 4. A: High-grade serous carcinoma composed of small ("micro") papillae. B: Higher magnification demonstrates mitotic activity and nuclear pleomorphism.

Low grade serous adenocarcinoma

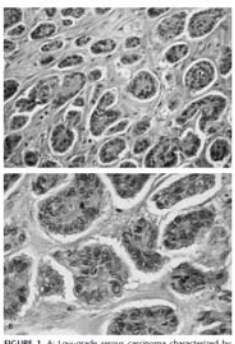


FIGURE 1. A: Low-grade serous carcinoma characterized by uniform nuclei. B: Higher magnification demonstrating uniformity of chromatin pattern.

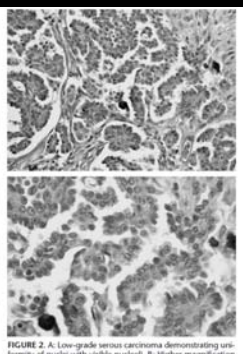
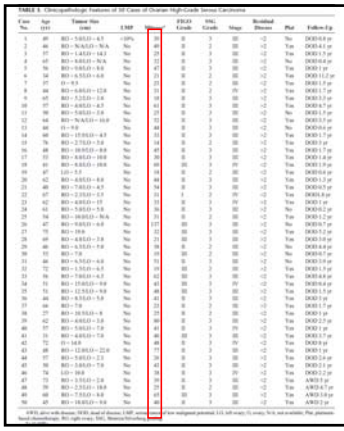


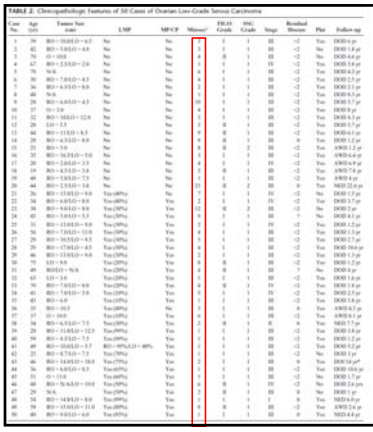
FIGURE 2. A: Low-grade serous carcinoma demonstrating uniformity of nuclei with visible nucleoli. B: Higher magnification shows mild nuclear size variation and uniform chromatin pattern.



High grade serous adenocarcinoma

・核分裂像は20/10HPF以上

・SBTの併存なし

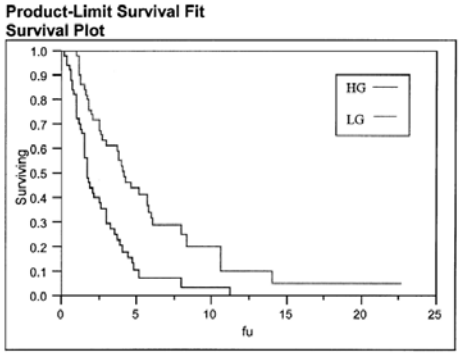


Low grade serous adenocarcinoma

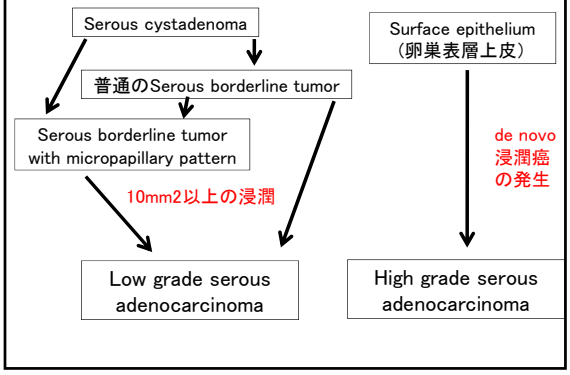
・核分裂像が12個/10HPF以下

・60%がSBTを併存

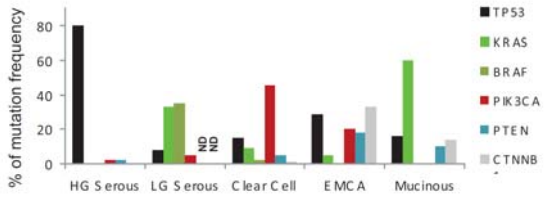
・その93%にmicropapillary patternが見られた。



Serous adenocarcinomaをlow grade とhigh gradeの2つに分ける流れ

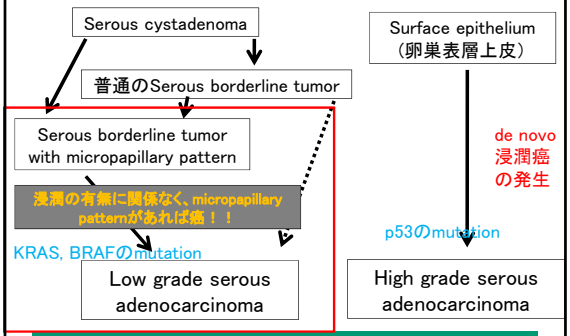


卵巣癌では組織型ごとにgenetic backgroundも異なる



Kuo et al. Am J Pathol 2009, 174; 1597-1601

Johns Hopkins学派の主張(Blaustein' sの記載)



Low-grade serousとHigh-grade serousは全く別のneoplasm!

- High grade serous adenocarcinomaとlow grade serous adenocarcinoma
- High grade serous adenocarcinomaと卵管病変(tubal intraepithelial carcinoma)の関連
- Intestinal-type mucinous tumorとendocervical-like mucinous tumorの区別
- Mucinous borderline tumorにおけるintraepithelial carcinoma及びmicroinvasionの位置づけ
- Transitional cell carcinomaの存在
- Adult granulosa cell tumorと*FOXL2*変異
- 卵巣腫瘍の新規疾患概念：Microcystic stromal tumorとsolid pseudopapillary neoplasm

卵巣癌、卵管癌、腹膜癌の定義

卵巣癌・・・・・・・・・
- 最大の腫瘍が卵巣に存在すること
- 卵巣表層のみではなく卵巣実質に腫瘍が存在すること

卵管癌・・・・・・・・・
- 最大腫瘍が卵管腔内、あるいは卵管采に存在すること
- 既存の卵管上皮から卵管上皮内癌への移行が見られること
- 卵巣表層の病変がないか、微小であること

腹膜癌・・・・・・・・・
- 最大の腫瘍が腹膜に存在すること
- 卵管、卵巣に腫瘍がないか、微小であること
- 卵巣浸潤があっても表層にとどまること

卵巣癌の中でも特にhigh grade serous adenocarcinomaは卵巣表面に増殖したり、広範な腹膜播種をきたすことが知られている。
卵巣癌とするか腹膜癌とするかが問題となる症例も多数存在する。

骨盤漿液性腺癌が卵管上皮由来であるとする説

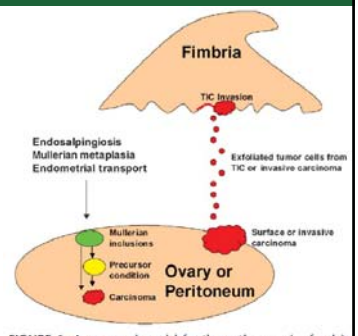


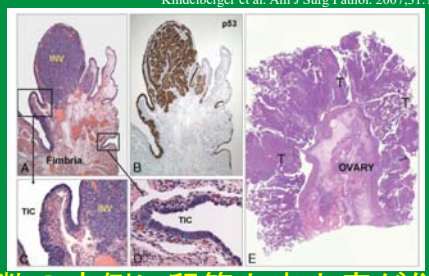
FIGURE 6. A proposed model for the pathogenesis of pelvic serous carcinoma. See text for details.

Kindelberger et al. Am J Surg Pathol. 2007;31:161

骨盤漿液性腺癌が卵管上皮由来であるとする説の根拠

一般人の卵巣漿液性腺癌、卵管漿液性腺癌、腹膜漿液性腺癌症例において、切除された卵管を全割全包埋して検討

Kindelberger et al. Am J Surg Pathol. 2007;31:161-169



多数の症例に卵管上皮内癌が併存

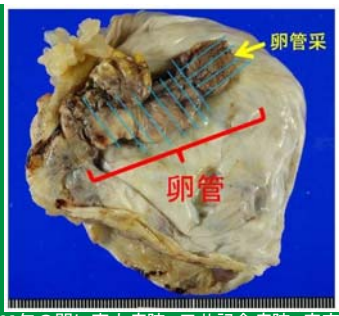
骨盤漿液性腺癌が卵管上皮由来であるとする説の根拠

・骨盤漿液性腺癌55例中29例に卵管上皮内癌 (TIC) が併存していた。そのうち27例が卵管采にTICが認められた。

・TICの併存頻度
卵巣漿液性腺癌: (20/43)
卵管漿液性腺癌: (5/5)
腹膜漿液性腺癌: (4/7)

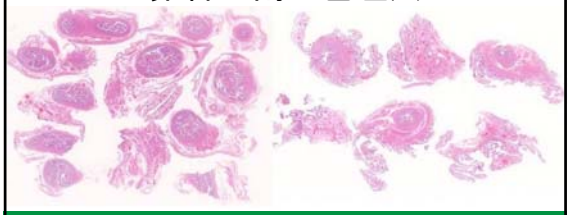
Kindelberger et al. Am J Surg Pathol. 2007;31:161-169

卵管全割全包埋法



2007年～2009年の間に東大病院、三井記念病院、帝京大学医学部附属病院で切除された卵巣癌/腹膜癌症例を対象とした。
卵管全割全包埋法が遂行可能だったのは72例中56例であった。

卵管全割全包埋法

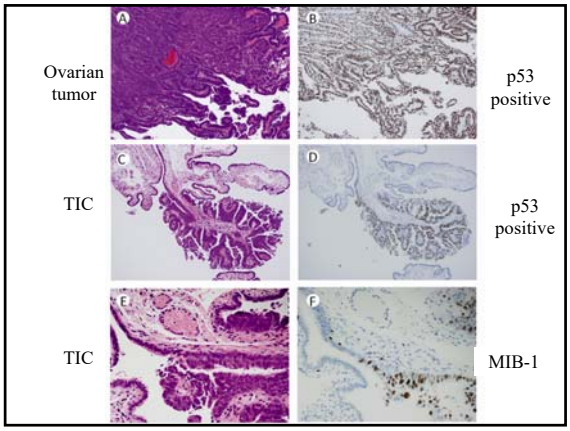


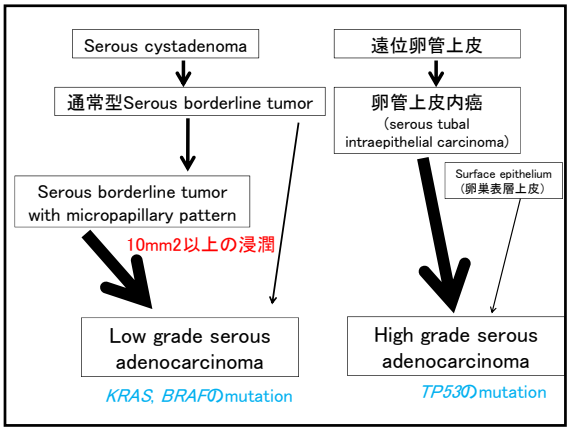
卵巣癌/腹膜癌の通常の切り出しでは各卵管につき1割面のみ標本作製が行われることが多いが、卵管全割全包埋法により卵管、卵管采の詳細な検討が可能となる

卵巣癌・腹膜癌の組織型別卵管上皮内癌 (TIC) 併存頻度

組織型	漿液性腺癌 (n=15)	非漿液性腺癌 (n=41)			
		明細胞腺癌	類内膜腺癌	粘液性腺癌	その他
症例数	15	23	9	4	5
腹膜播種を伴う例	13	7	0	1	1
TIC併存例	7	0	0	0	0

卵管上皮内癌 (TIC) は漿液性腺癌のみに併存しており、非漿液性腺癌症例には見出せなかった。
TICは7例全例で主腫瘍側の卵管采に見出された。
卵管采と卵管管状部の2カ所にTICが存在した症例が1例あった。





- High grade serous adenocarcinomaとlow grade serous adenocarcinoma
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- Adult granulosa cell tumorと*FOXL2*変異
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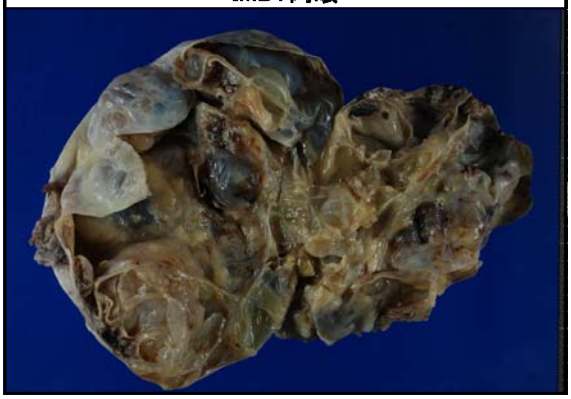
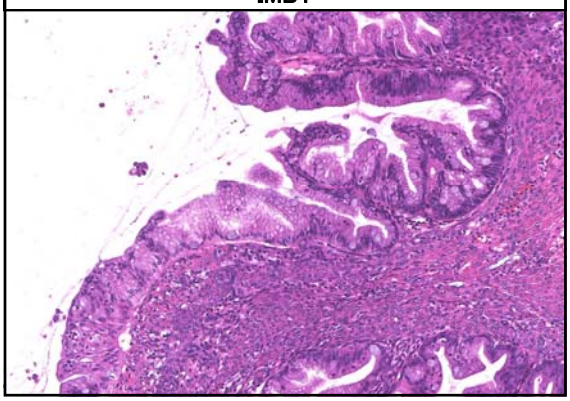
WHO 2003

Mucinous tumours
- Malignant
  - Adenocarcinoma
  - Adenocarcinofibroma
- Borderline tumor
  - Intestinal type
  - Endocervical-like
- Benign
  - Cystadenoma

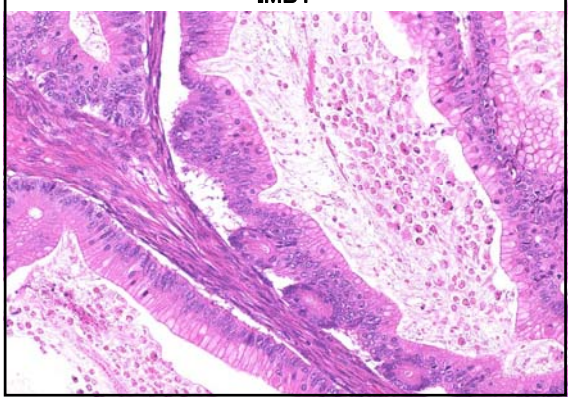
IMBT肉眼



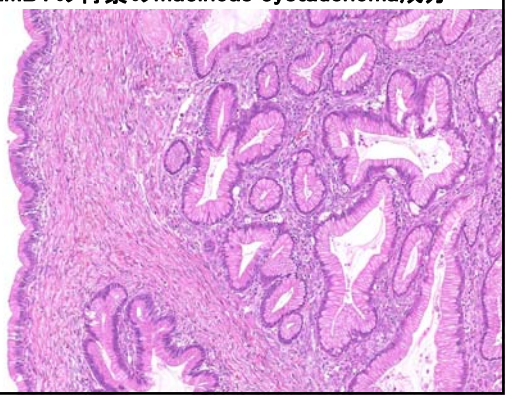
IMBT



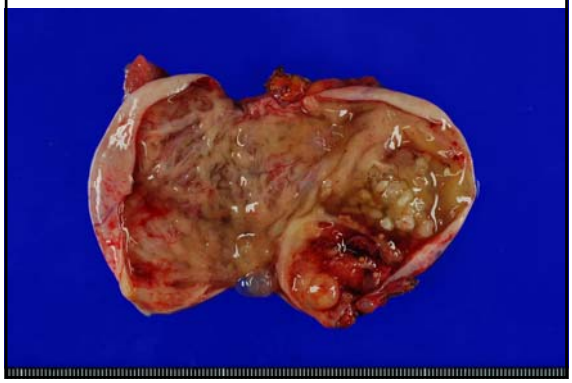
IMBT



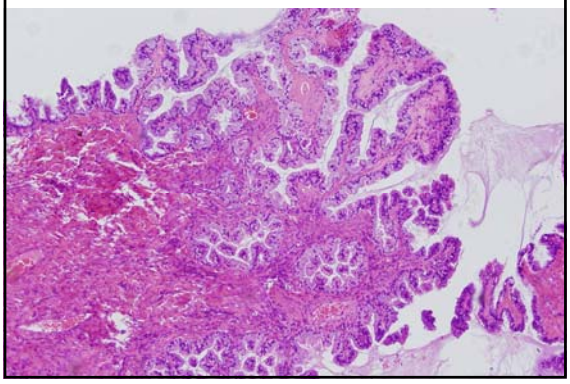
IMBTの背景のmucinous cystadenoma成分

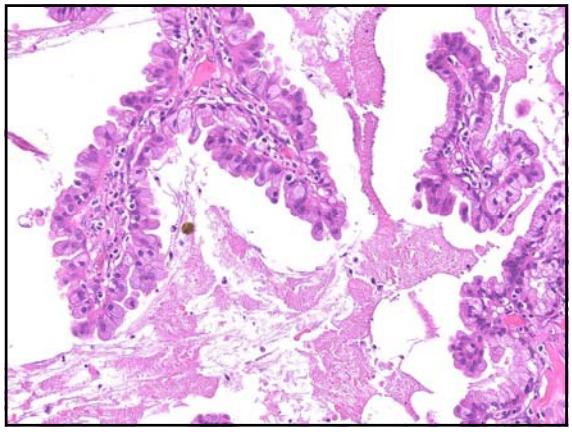


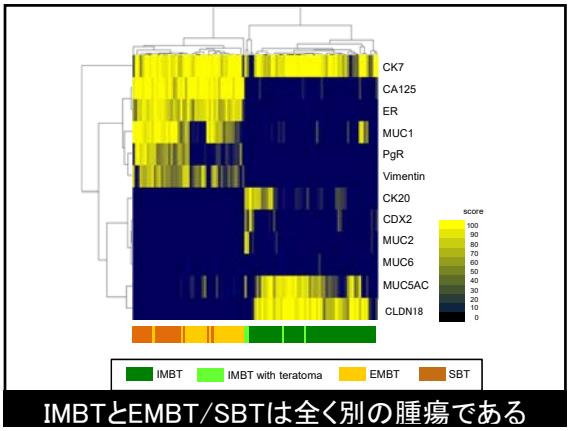
EMBT



EMBT







IMBTとEMBT/SBTは全く別の腫瘍である

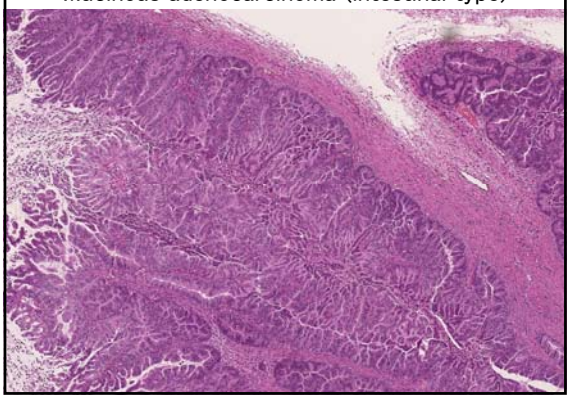
WHO 2003

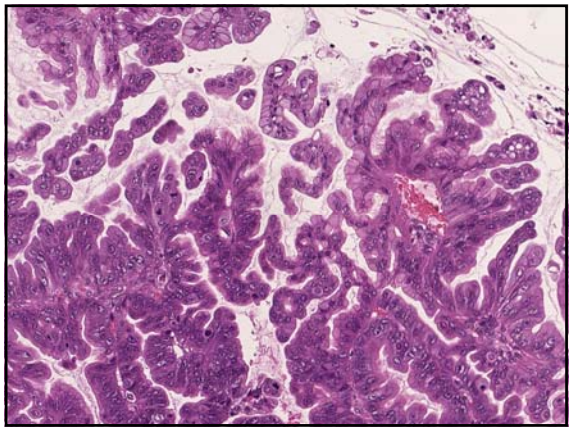
Mucinous tumours
- Malignant
  - Adenocarcinoma
  - Adenocarcinofibroma

→ 大多数は intestinal type

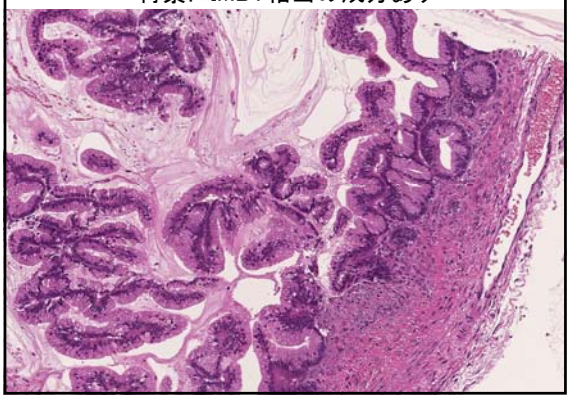
- Borderline tumor
  - Intestinal type
  - Endocervical-like
- Benign
  - Cystadenoma

Mucinous adenocarcinoma (intestinal type)

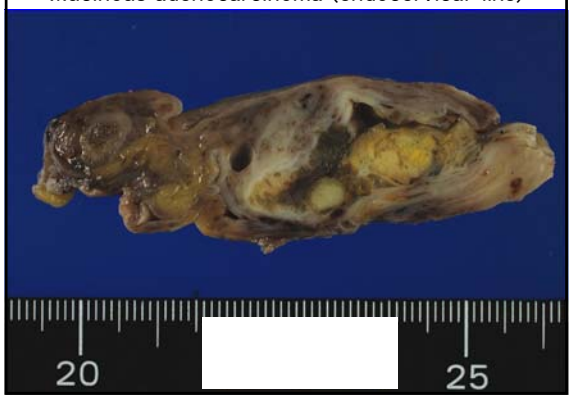


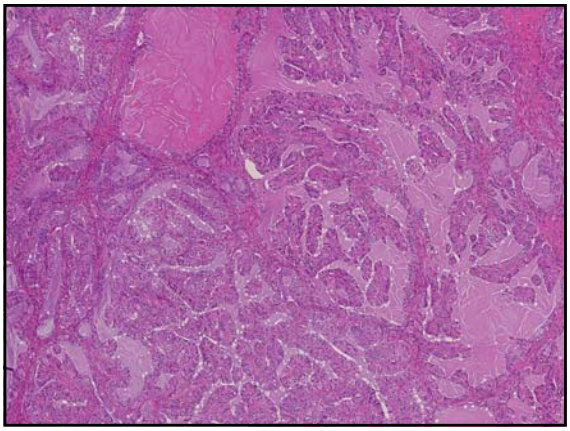


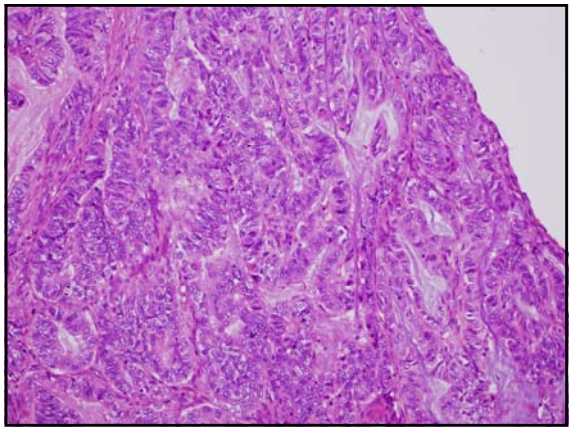
背景にIMBT相当の成分あり

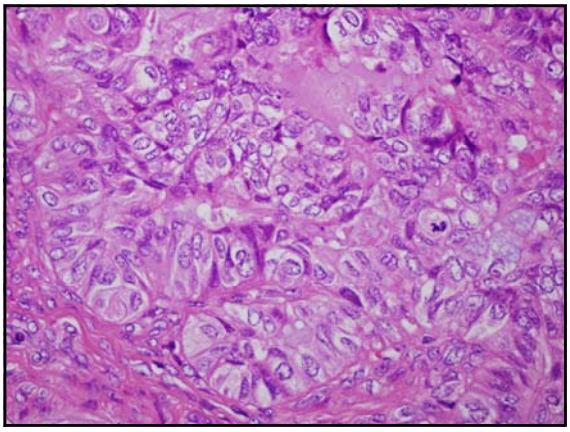


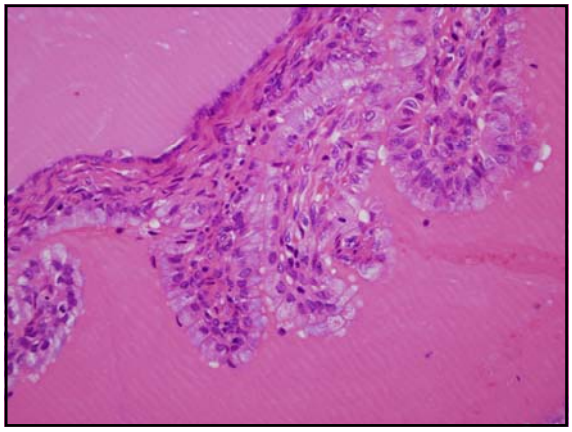
Mucinous adenocarcinoma (endocervical-like)

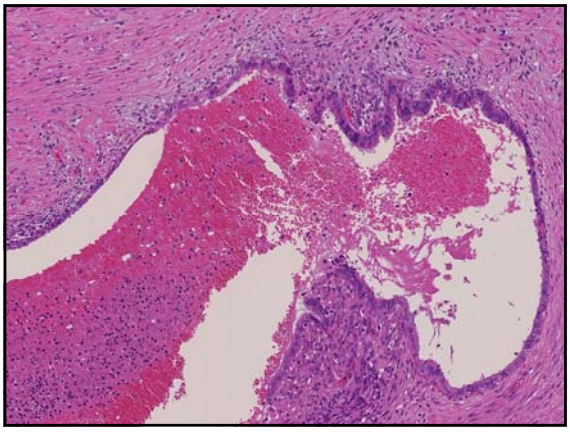


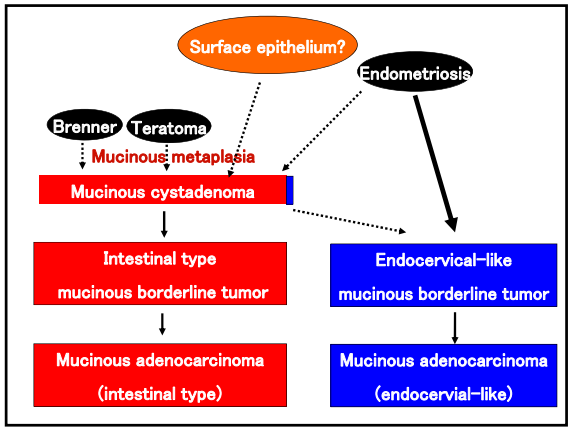












WHO 2003

Mucinous tumours
- Malignant
  - Adenocarcinoma → ・Intestinal type ・Endocervical-like
  - Adenocarcinofibroma
- Borderline tumor
  - Intestinal type
  - Endocervical-like
- Benign
  - Cystadenoma

粘液性腫瘍：Carcinomaとする際の基準

中等度までの異型⇒浸潤なし⇒mucinous borderline tumor

一部に高度の異型⇒浸潤なし⇒mucinous borderline tumor with intraepithelial carcinoma

中等度までの異型⇒浸潤10mm^{2}未満⇒mucinous borderline tumor with microinvasion

一部に高度の異型⇒浸潤10mm^{2}未満⇒ mucinous borderline tumor with microinvasion? microinvasive carcinoma?

異型度は様々⇒浸潤10mm^{2}以上⇒mucinous carcinoma

・High grade serous adenocarcinomaとlow grade serous adenocarcinoma

・High grade serous adenocarcinomaと卵管病変(tubal intraepithelial carcinoma)の関連

・Intestinal-type mucinous tumorとendocervical-like mucinous tumorの区別

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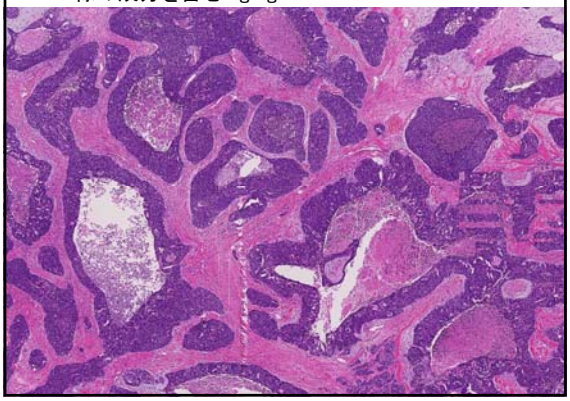
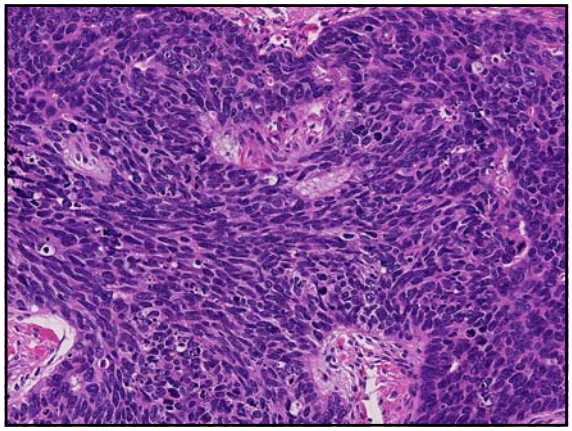
・卵巣腫瘍の新規疾患概念：Microcystic stromal tumorとsolid pseudopapillary neoplasm

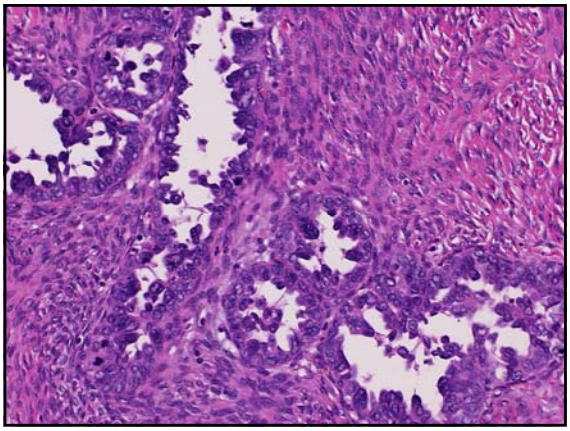
WHO 2003

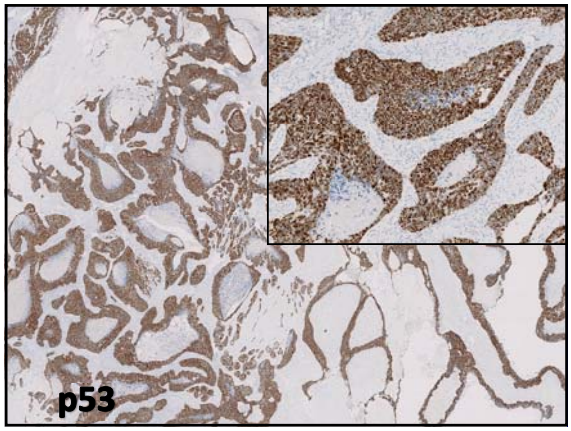
Transitional cell tumours
- Malignant
  - Transitional cell carcinoma (non-Brenner type)
  - Malignant Brenner tumour
- Borderline tumor
  - Borderline Brenner tumour
    - Proliferative variant
- Benign
  - Brenner tumour

TCC様の成分を含むhigh grade serous adenocarcinoma





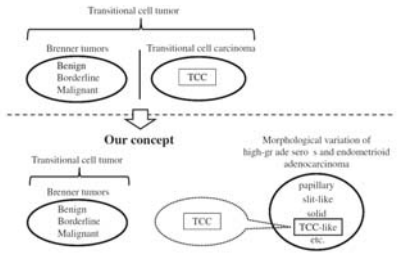




Ovarian Transitional Cell Carcinoma Represents a Poorly Differentiated Form of High-grade Serous or Endometrioid Adenocarcinoma

Tadahisa Takeuchi, MD, Yoshihiro Ohishi, MD, PhD,*† Hiroko Imamura, MD,* Murasaki Aman, MD, PhD,* Kaai Shida, MD,* Hiroaki Kobayashi, MD, PhD,‡ Kiyoko Kato, MD, PhD,‡ and Yoshinao Oda, MD, PhD**

Am J Surg Pathol 2013;37:1091–1099



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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

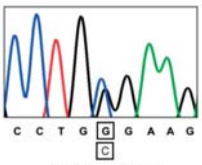
Mutation of *FOXL2* in Granulosa-Cell Tumors of the Ovary

N Engl J Med 2009;360:2719-29.

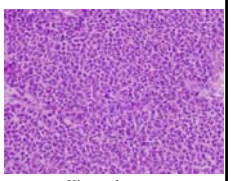
Adult type granlosa cell tumorの97%に*FOXL2*遺伝子の402C→G (C134W)変異がある

Table 1. *FOXL2* p.C134W mutations in 1353 tumours

Organ	Type of tumour	No of tumours	*FOXL2* codon 134 Mutation	Mutation (%)
Ovary	Adult GCT	56	53	94.6
	Juvenile GCT	5	0	0
	Thecoma	16	2	12.5
	Fibrothecoma	3	0	0
	Fibroma	12	0	0
	Sertoli–Leydig cell tumour	4	0	0
	Sex cord tumour with annular tubules	1	0	0
	Sclerosing stromal tumour	4	0	0
	Serous adenocarcinoma	40	0	0
	Mucinous adenocarcinoma	25	0	0
	Endometrioid adenocarcinoma	20	0	0



FOXL2 c.402C>G



Kim et al.
Journal of Pathology
J Pathol 2010; **221**: 147–152

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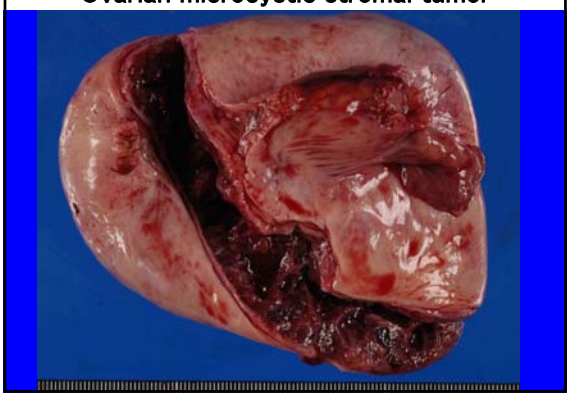
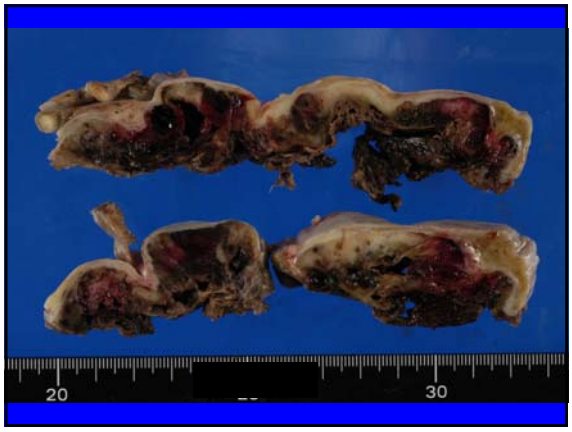
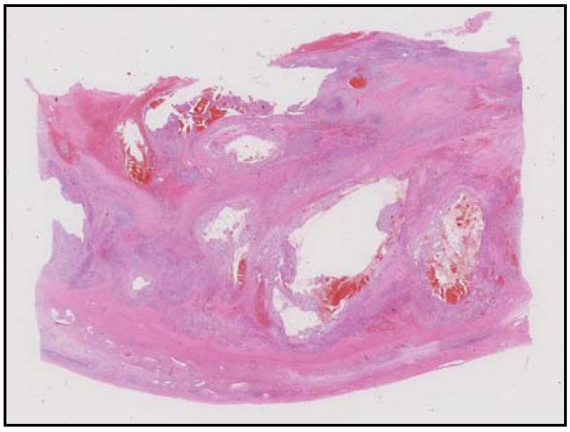
卵巣腫瘍の新規疾患概念
Microcystic stromal tumorとsolid pseudopapillary neoplasm

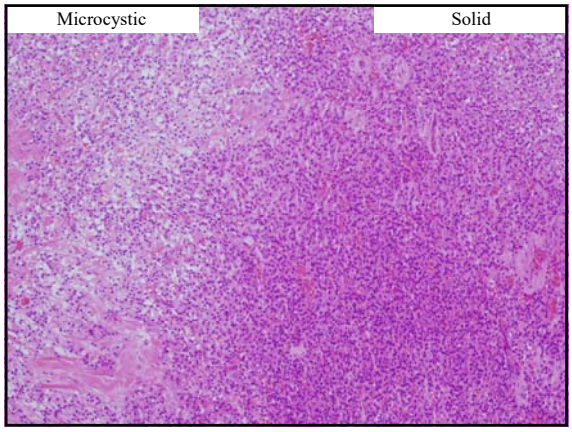
- Microcystic stromal tumorは2009年にHarvardから16例のcase seriesとして報告された。
- Thecoma様の特異的な像を呈する(sex cord-) stromal tumor.
- 振る舞いは良性
- その後蓄積された日本の症例は8例
⇒孤発例ではβ-cateninの変異が証明されており、FAP/Gardner症候群に生じた家族例もあることから、wnt/β-catnin経路の異常によって生じるdistinct entityと考えられている
- Wnt/β-cateninの異常で生じる腫瘍として2010年にsolid pseudopapillary neoplasm of the ovaryも報告された (3例).

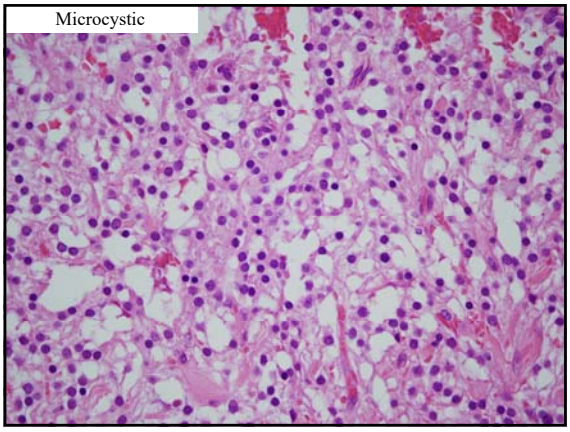
Ovarian microcystic stromal tumor

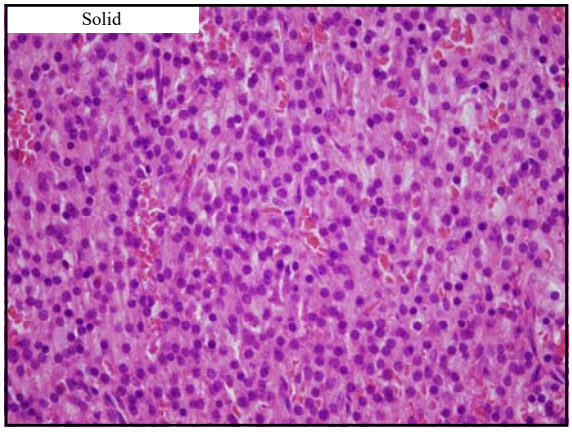






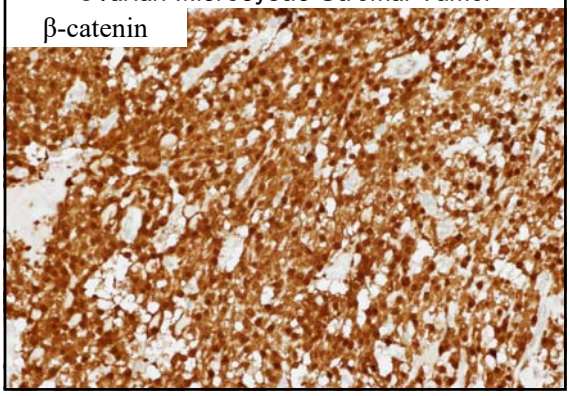




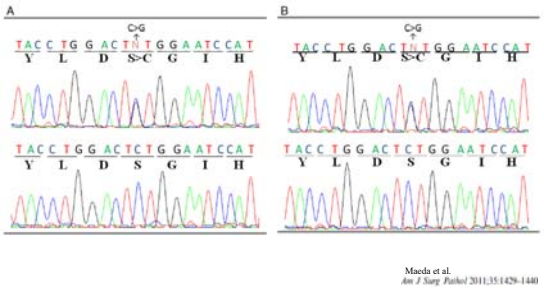


Ovarian Microcystic Stromal Tumor

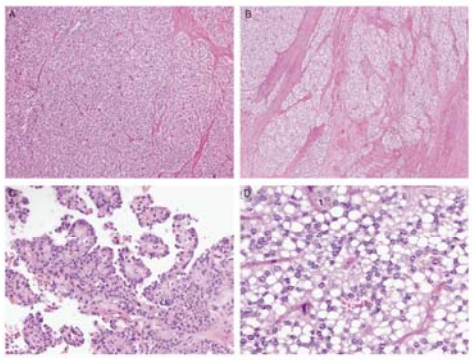
β-catenin



β-catenine Exon 3にmutationあり（33番目のS＝＞C）



Ovarian solid pseudopapillary neoplasm



日本病理学会学春期総会　コンパニオンミーティング
平成26年4月24日

卵巣腫瘍の病理

改訂WHO分類（第4版）の概要

三上芳喜
熊本大学医学部附属病院　病理診断科（病理部）
Kumamoto University Hospital, Department of Diagnostic Pathology

WHO 2014 Consensus

Borderline

↓

Atypical proliferative / borderline

WHO 2014 Consensus

Tumor of the Ovary

↓

Tumor of the tube, ovary and peritoneum

WHO分類第3版（2003）の課題

- 漿液性腺癌のグレード
- 漿液性腺癌と卵管上皮内癌の関連
- 粘液性腺癌における腸型と内頸部様の区別
- 粘液性境界悪性腫瘍における上皮内癌とその微小浸潤の位置づけ
- 移行上皮癌の存在
- 分子生物学的新知見
  - 成人型顆粒膜細胞腫における*FOXL2*遺伝子変異
- 新疾患・概念：
  - Microcystic stromal tumor
  - solid pseudopapillary neoplasm

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WHO 2014 (DRAFT)

Surface

- Epithelial-stromal tumours – Serous Tumours
  - Benign
    - Adenofibroma and cystadenofibroma
    - Serous surface papilloma
    - Serous adenofibroma
    - Papillary cystadenoma
  - Borderline
    - Adenofibroma
    - Serous borderline tumor
    - Papillary cystic tumor
    - Surface papillary tumor
  - Malignant
    - Low-grade serous adenocarcinoma, invasive
    - High-grade serous adenocarcinoma
    - Surface papillary adenocarcinoma
    - Adenocarcinofibroma (malignant adenofibroma)

1-1C. Serous tumours, malignant

1-1C-i. Low grade serous adenocarcinoma, invasive

Change to Low-grade serous carcinoma?

Definition:
A papillary tumor resembling fallopian tube epithelium and showing low-grade cytological atypia. The tumor may be noninvasive or invasive

ICD-O code:
8460/3

Synonyms: Micropapillary serous carcinoma, noninvasive and invasive; serous borderline tumor, micropapillary type

Epidemiology:
LGSCs account for about nearly 10% of all serous carcinomas {20407318}. Prior to age 40 years, incidence rates for low grade tumors are higher, but at older ages, rates for high-grade tumors increase more rapidly and predominate {19622723}, suggesting possible etiological differences. Analyses of risk factors for low-grade tumors are limited by case numbers and diagnostic reproducibility {23378140}.

Clinical features:
Patients with LGSC present approximately one decade earlier than patients with high-grade serous carcinoma (HGSC) {19700937}. Ovarian masses can be symptomatic or detected incidentally. With advanced stage, ascites and other features similar to HGSC may be present, yet the volume of disease is

7

1-1C. Serous tumours, malignant

低悪性度漿液性腺癌、浸潤性

Change to Low-grade serous carcinoma?

定義：卵管上皮に類似し、異型が軽度である乳頭状の腫瘍．浸潤性の場合と非浸潤性の場合がある．

ICD-O code:
8460/3

同義語：浸潤性、非浸潤性微小乳頭状漿液性（腺）癌、微小乳頭型漿液性境界悪性腫瘍

Epidemiology:
LGSCs account for about nearly 10% of all serous carcinomas {20407318}. Prior to age 40 years, incidence rates for low grade tumors are higher, but at older ages, rates for high-grade tumors increase more rapidly and predominate {19622723}, suggesting possible etiological differences. Analyses of risk factors for low-grade tumors are limited by case numbers and diagnostic reproducibility {23378140}.

Clinical features:
Patients with LGSC present approximately one decade earlier than patients with high-grade serous carcinoma (HGSC) {19700937}. Ovarian masses can be symptomatic or detected incidentally. With advanced stage, ascites and other features similar to HGSC may be present, yet the volume of disease is

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1-1C-ii. High grade serous adenocarcinoma

Change to High-grade Serous Carcinoma?

Definition:
A noninvasive or invasive carcinoma composed of epithelial cells displaying papillary, glandular and solid patterns with high grade nuclear atypia and displaying molecular genetic alterations of *TP53*. In glandular and cribriform patterns, characteristic features of endometrioid adenocarcinoma of the uterine corpus are absent.

ICD-O code:
Adenocarcinoma 8441/3
Poorly differentiated adenocarcinoma 8461/3

Synonyms:
Serous carcinoma, serous carcinoma with transitional features;

Epidemiology:
High-grade extrauterine serous carcinomas may arise from the fallopian tube or the ovary but by the time of detection, the site of origin is often obscured by bulky disease. Accordingly, tumors diagnosed as ovarian serous carcinoma might be viewed as an amalgamation of primary pelvic carcinomas [22940485]. Nonetheless, these tumors are characterized by common epidemiological features and clinical behavior. At present, there is no effective screening test {21642681}.
Annually, there are about 225,000 newly diagnosed ovarian carcinomas and 140,000 related deaths worldwide, the majority of which demonstrate serous histology {21351269}. Serous carcinomas disproportionately affect women in western nations {21351269} with cumulative lifetime risks in the

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高悪性度漿液性腺癌

Change to High-grade Serous Carcinoma?

定義：高度の核異型を示し、p53遺伝子の異常を伴う浸潤性ないし非浸潤性の腫瘍で、乳頭状、管状、あるいは充実性パターンを示す上皮細胞で構成される．管状、篩状パターンを示す領域では子宮体部類内膜腺癌の特徴的なパターンは認められない．

ICD-O code:
Adenocarcinoma 8441/3
Poorly differentiated adenocarcinoma 8461/3

漿液癌、移行上皮癌類似のパターンを示す漿液性癌

Epidemiology:
High-grade extrauterine serous carcinomas may arise from the fallopian tube or the ovary but by the time of detection, the site of origin is often obscured by bulky disease. Accordingly, tumors diagnosed as ovarian serous carcinoma might be viewed as an amalgamation of primary pelvic carcinomas [22940485]. Nonetheless, these tumors are characterized by common epidemiological features and clinical behavior. At present, there is no effective screening test {21642681}.
Annually, there are about 225,000 newly diagnosed ovarian carcinomas and 140,000 related deaths worldwide, the majority of which demonstrate serous histology {21351269}. Serous carcinomas disproportionately affect women in western nations {21351269} with cumulative lifetime risks in the

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or display surface nodules of tumor smaller than 1 cm (these have been classified as "primary peritoneal" serous carcinomas). Tumors are often bilateral, exophytic and demonstrate solid and papillary growth and fluid-filled cysts. The solid regions are tan-white, and typically contain extensive necrosis and hemorrhage. The fallopian tube may be macroscopically involved and not readily identifiable or a small firm, sometimes polypoid lesion may be seen at its fimbriated end. The fimbriae may be splayed over the tumor surface.

Histopathology:
The vast majority of HGSC at diagnosis is invasive and typically composed of solid masses of cells with slit-like spaces (Fig. 18). In addition, papillary, glandular and cribriform areas are common. Necrosis is nearly always present. Nuclei are large, hyperchromatic and pleomorphic, often with large bizarre or multinucleated forms. Nucleoli are usually prominent and may be very large and eosinophilic. Mitoses are numerous and often atypical. A papillary pattern closely resembling papillary urothelial carcinoma (transitional cell carcinoma) may be present and occasionally predominates. A small proportion of HGSC lack invasion and in the past have erroneously been classifed as "borderline" tumors. These tumors display marked nuclear atypia and high mitotic activity similar to their invasive counterpart.
HGSCs are CK7 positive and usually CK20 negative. CAM 5.2, OC-125, EMA and BER-EP4 are frequently expressed. WT1 {21993272} and PAX8 {20414098} are positive, while calretinin is negative. ER and PR may be focally positive {23103384}. The p53 protein is frequently overexpressed; strong and diffuse positivity indicates that the tumor very likely has a *TP53* mutation {15644779}. Tumors in which the p53 immunostain is completely negative in all likelihood harbour a *TP53* mutation that results in a truncated protein that is not identified by the antibody. Staining for p16 is often diffuse {19700937} and the Ki-67 proliferation index is usually high.

Histogenesis:
HGSC is the prototypic type II carcinoma. Based on complete sectioning of the ovaries and fallopian

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or display surface nodules of tumor smaller than 1 cm (these have been classified as "primary peritoneal" serous carcinomas). Tumors are often bilateral, exophytic and demonstrate solid and papillary growth and fluid-filled cysts. The solid regions are tan-white, and typically contain extensive necrosis and hemorrhage. The fallopian tube may be macroscopically involved and not readily identifiable or a small firm, sometimes polypoid lesion may be seen at its fimbriated end. The fimbriae may be splayed over the tumor surface.

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核は大型で、クロマチン増量、多形性を示し、奇怪な大型核、多核がしばしばみられる．核小体は明瞭で、大型、好酸性であることもある．核分裂が多数認められ、異常核分裂もしばしば認められる．尿路上皮癌（移行上皮癌）に類似した乳頭状構造を示すことがあり、ときにこれが大部分を占める．

tumors display marked nuclear atypia and high mitotic activity similar to their invasive counterpart.
HGSCs are CK7 positive and usually CK20 negative. CAM 5.2, OC-125, EMA and BER-EP4 are frequently expressed. WT1 {21993272} and PAX8 {20414098} are positive, while calretinin is negative. ER and PR may be focally positive {23103384}. The p53 protein is frequently overexpressed; strong and diffuse positivity indicates that the tumor very likely has a *TP53* mutation {15644779}. Tumors in which the p53 immunostain is completely negative in all likelihood harbour a *TP53* mutation that results in a truncated protein that is not identified by the antibody. Staining for p16 is often diffuse {19700937} and the Ki-67 proliferation index is usually high.

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- 粘液性腺癌における腸型と内頸部様の区別
- 粘液性境界悪性腫瘍における上皮内癌とその微小浸潤の位置づけ
- 移行上皮癌の存在
- 分子生物学的新知見
  - 成人型顆粒膜細胞腫における*FOXL2*遺伝子変異
- 新疾患・概念：
  - Microcystic stromal tumor
  - solid pseudopapillary neoplasm

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tubes in women at high risk of developing ovarian cancer, prophylactic salpingo-oophorectomy specimens have revealed, small noninvasive and invasive carcinomas much more commonly in the fallopian tube rather than the ovary {11688463; 11745677; 16434898}. The noninvasive intramucosal tumors have been designated serous tubal intraepithelial carcinoma (STIC). They have cytological features identical to HGSC, and also show *TP53* mutation/aberrant protein expression, high-proliferation indicies, and marked genomic instability {16434898; 18597838}. It has also been shown that STICs are present in the fallopian tube in 25-60% of women with HGSCs that would have been considered to be ovarian or primary peritoneal tumors based on formerly used criteria {17255760; 18597838; 20861711; 22317864}. The fallopian tube is completely obliterated by tumour in an additional 20% of cases, and may be the primary site in these cases as well. The STICs in cases of advanced stage HGSCs harbour identical *TP53* mutations as the disseminated tumour, establishing that they are clonal {21990067;11294827}, and comparison of telomere length in matched STIC and ovarian tumour pairs suggest that the STICs are indeed the earlier lesion, antedating the ovarian tumor {20431479}. In approximately 15-30% of cases of HGSC, however, the fallopian tubes are normal, with neither STIC nor invasive carcinoma present despite total histopathological assessment {20861711; 18597838}. Some have argued that they are derived from cortical inclusion cysts which may have developed from implanted tubal epithelium. A report of aneuploidy in inclusion cysts supports this proposal {20436685}. There is some molecular evidence suggesting that tubal-type secretory cells are the cell of origin of HGSC.

Although there is much excitement and an impending paradigm shift based on these observations, it must be emphasized that definitive proof of a tubal origin for most HGSC is lacking. The best evidence is in *BRCA1* mutation carriers who constitute no more than 10-12% of patients. Whether *BRCA2*-associated and sporadic HGSC arise from the tubes is highly likely but less clear and a firm conclusion awaits further investigation and confirmation.

In any event, the molecular genetic features of HGSCs (see below) are distinct from those detected in LGSC {22102435; 19383911} indicating that these tumors develop along distinctly different and

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tubes in women at high risk of developing ovarian cancer, prophylactic salpingo-oophorectomy specimens have revealed, small noninvasive and invasive carcinomas much more commonly in the fallopian tube rather than the ovary {11688463; 11745677; 16434898}. The noninvasive intramucosal tumors have been designated serous tubal intraepithelial carcinoma (STIC). They have cytological features identical to HGSC, and also show *TP53* mutation/aberrant protein expression, high-proliferation

従来の診断基準で卵巣あるいは腹膜原発であると考えられた高悪性度漿液性腺癌を有する女性の25～60％でSTIC（卵管上皮内癌）が、存在することが示されている.

22317864}. The fallopian tube is completely obliterated by tumour in an additional 20% of cases, and may be the primary site in these cases as well. The STICs in cases of advanced stage HGSCs harbour identical *TP53* mutations as the disseminated tumour, establishing that they are clonal {21990067;11294827}, and comparison of telomere length in matched STIC and ovarian tumour pairs

しかし、全体を組織学的に検索しても高悪性度漿液性癌の15～30％では卵管は正常で、STIC、浸潤癌のいずれも認められない.

have argued that they are derived from cortical inclusion cysts which may have developed from

卵管の分泌細胞が高悪性度漿液性癌の細胞起源であることを示す分子生物学的証拠がある.

以上の知見に基づいて、今まさに興奮すべき概念の変革（パラダイムシフト）が迫っているといえるが、殆どの高悪性度漿液性腺癌が卵管由来であることを示す決定的な証拠はないということは強調される必要がある.

awaits further investigation and confirmation.

In any event, the molecular genetic features of HGSCs (see below) are distinct from those detected in LGSC {22102435; 19383911} indicating that these tumors develop along distinctly different and

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- 新疾患・概念：
  - Microcystic stromal tumor
  - solid pseudopapillary neoplasm

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WHO 2014 (DRAFT)

Epithelial-stromal tumours – Mucinous Tumours

- Benign
  - Cystadenoma
  - Cystadenoma and cystadenofibroma
- Borderline
  - Mucinous borderline tumour, gastrointestinal type
  - Mucinous borderline tumour with intraepithelial carcinoma
  - Mucinous borderline tumour with stromal microinvasion/microinvasive carcinoma
  - Mucinous borderline tumour, endocervical-like ⇒ **削除**
- Malignant
  - Mucinous carcinoma
  - Mucinous tumor associated with mature cystic teratoma
  - Mucinous cystic tumours with mural nodules

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WHO 2014 (DRAFT)

Epithelial-stromal tumours – Mullerian tumours of mixed cell type

- Benign
  - Mullerian mixed cell type
- Borderline
  - Borderline mullerian tumours of mixed cell type
- Malignant

Adenocarcinoma ?

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1-2. Epithelial-stromal tumours - Mucinous tumours

1-2A. Mucinous tumours, benign

1-2A-i. Mucinous cystadenoma, cystadenofibroma

Definition:
Benign tumor lined by gastrointestinal type epithelium.

ICD-O code:
Mucinous cystadenoma 8470/0
Mucinous adenofibroma and cystadenofibroma 9015/0

Synonyms:
Mucinous cystadenoma; mucinous adenofibroma

Epidemiology:
Mucinous cystadenomas account for approximately 80% of all primary ovarian mucinous tumors. Mucinous adenofibromas are uncommon {15626914; 1996729}.

Clinical features:
These tumors are seen in patients with a wide age range. Mean age is 50 years. The most common

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1-2. Epithelial-stromal tumours - Mucinous tumours

1-2A. Mucinous tumours, benign

1-2A-i. Mucinous cystadenoma, cystadenofibroma

Definition:
胃腸型上皮（杯細胞、パネート細胞、幽門腺上皮、腺窩上皮など）で被覆された良性腫瘍

ICD-O code:
Mucinous cystadenoma 8470/0
Mucinous adenofibroma and cystadenofibroma 9015/0

Synonyms:
Mucinous cystadenoma; mucinous adenofibroma

Epidemiology:
Mucinous cystadenomas account for approximately 80% of all primary ovarian mucinous tumors. Mucinous adenofibromas are uncommon {15626914; 1996729}.

Clinical features:
These tumors are seen in patients with a wide age range. Mean age is 50 years. The most common

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1-2B. Mucinous tumours, borderline

1-2B-i. Mucinous borderline tumour, gastrointestinal type

Definition
Tumors composed of mildly-to-moderately atypical gastrointestinal-type mucin-containing epithelial cells that show proliferation greater than that seen in benign mucinous tumors. Such proliferative areas must comprise greater than 10% of the epithelial volume of the tumor. Stromal invasion is absent, except for very small areas of invasion that fulfill the criteria for stromal "microinvasion".

ICD-O code
? 8472/1 TBD

Synonyms
Atypical proliferative mucinous tumor
Mucinous borderline tumor
Mucinous tumor of low malignant potential

Epidemiology
These tumors are the second most common type of atypical proliferative/borderline tumor in North America and Europe, comprising 30-50% of such tumors, but are the most common form in Asia making up about 70% of atypical proliferative/borderline tumors {21464732}.

Clinical features
The tumors occur across a wide age range from 13 to 88 years, with a mean age of 40-49 years {8600070; 21464732; 17414101; 11075847; 10366144}. Patients most often present with an abdominal

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1-2B. Mucinous tumours, borderline

粘液性境界悪性腫瘍-胃腸型

Definition
軽度から中等度の異型を示す胃腸型の粘液含有上皮細胞で構成される腫瘍で、良性粘液性腫瘍でみられるよりも高度の増殖を示す．そのような増殖は腫瘍を構成する上皮の10％を超える領域を占める必要がある．間質浸潤は認められないが、微小浸潤の診断基準を満たす小浸潤巣はこの限りではない．

ICD-O code
? 8472/1 TBD

Synonyms
Atypical proliferative mucinous tumor
Mucinous borderline tumor
Mucinous tumor of low malignant potential

Epidemiology
These tumors are the second most common type of atypical proliferative/borderline tumor in North America and Europe, comprising 30-50% of such tumors, but are the most common form in Asia making up about 70% of atypical proliferative/borderline tumors {21464732}.

Clinical features
The tumors occur across a wide age range from 13 to 88 years, with a mean age of 40-49 years {8600070; 21464732; 17414101; 11075847; 10366144}. Patients most often present with an abdominal

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APMT with microinvasion is defined as either small foci of stromal invasion measuring less than 5 mm in greatest linear extent or 10 square mm, with no requirement regarding the number of such foci allowed in a given tumor {7922984; 8666359; 9850171; 10366144; 12090592; 11075847; 11812936; 21464732}. It is characterized by single cells, glands, or small clusters/nests of mucinous epithelial cells within the stroma or as small foci of confluent glandular or cribriform growth within the stroma. *Two forms of microinvasion* have been recognized: (1) *stromal microinvasion*, which consists of small foci of stromal invasion by cytologically low-grade cells similar to the borderline mucinous tumor, and (2) *microinvasive carcinoma* which consists of small foci of invasion displaying higher-grade cytologic features similar to mucinous carcinoma {15297962}. Some tumors with microinvasion also have intraepithelial carcinoma (see below). Based on limited data, the recurrence rate for mucinous tumors with microinvasive carcinoma is 5% and the tumor-related death rate is less than 5% with adverse behavior restricted to FIGO stage IC tumors {17414101}.

APMT with intraepithelial carcinoma displays features of APMT and in addition has foci with marked nuclear atypia. A cribriform pattern or epithelial stratification of greater than three cell layers in absence of severe atypia does not qualify {15297962; 15626914; 21464732; 20737216}.

Immunoprofile
CK7 is typically diffusely positive whereas CK20 displays variable positivity (usually less extensive than CK7 expression). CDX2 ranges from negative to positive and PAX8 is nearly always negative as is ER and PR {16980943; 16931958; 16294196}.

Histogenesis
These tumors appear to arise from benign mucinous cystadenomas, although some are undoubtedly of

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微小浸潤を伴う粘液性境界悪性腫瘍（異型増殖性粘液性腫瘍）は径 5 mm 未満、ないし 10 mm^2 未満の小浸潤巣の存在によって定義され、浸潤巣の数は問わない

21464732}. It is characterized by single cells, glands, or small clusters/nests of mucinous epithelial cells

微小浸潤には2つの様式がある：(1)細胞学的に粘液性境界悪性腫瘍と同様の軽度(low-grade)の異型を示す細胞による間質内小浸潤巣で構成される間質微小浸潤(**stromal microinvasion**)、(2)粘液性腺癌と同様の高度(high-grade)の細胞異型を示す小浸潤巣で構成される微小浸潤癌(**microinvasive carcinoma**)

intraepithelial carcinoma (see below). Based on limited data, the recurrence rate for mucinous tumors with microinvasive carcinoma is 5% and the tumor-related death rate is less than 5% with adverse behavior restricted to FIGO stage IC tumors {17414101}.

上皮内癌を伴う粘液性境界悪性腫瘍（異型増殖性粘液性腫瘍）は（典型的な）境界悪性腫瘍の形態に加えて、著明な核異型を示す領域を伴う．篩状パターンあるいは細胞3層を超える上皮の重積がみられても、高度の細胞異型がみられない場合は上皮内癌とはしない．

Immunoprofile
CK7 is typically diffusely positive whereas CK20 displays variable positivity (usually less extensive than CK7 expression). CDX2 ranges from negative to positive and PAX8 is nearly always negative as is ER and PR {16980943; 16931958; 16294196}.

Histogenesis
These tumors appear to arise from benign mucinous cystadenomas, although some are undoubtedly of

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1-6B. Müllerian tumours of mixed cell type, borderline

1-6B-i. Borderline müllerian tumours of mixed cell type

Definition
A noninvasive proliferative epithelial tumour composed of more than one epithelial cell type most often serous and endocervical-type mucinous, sometimes endometrioid, and less often clear cell, transitional or squamous.

ICD-O code
8323/1

Synonyms
Endocervical-type mucinous borderline tumour, seromucinous borderline tumour, müllerian mucinous borderline tumour, mixed müllerian tumour, atypical proliferative (borderline) müllerian tumour

Epidemiology
This is an uncommon tumor and accounts for approximately 1% of ovarian atypical proliferative tumours. In the past they have been considered a subset of mucinous tumors (endocervical type), and therefore of all mucinous atypical proliferative (borderline) tumors, they account for 4-15% of cases {3334969}.

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1-6B. Müllerian tumours of mixed cell type, borderline

1-6B-i. Borderline müllerian tumours of mixed cell type

定義
2種類以上の上皮細胞で構成される非浸潤性の増殖性上皮性腫瘍で、**殆どは漿液性および内頸部型粘液細胞が混在**する．ときに類内膜細胞で構成され、頻度は低いものの明細胞、移行上皮細胞、扁平上皮細胞がみられる．

ICD-O code
8323/1

同義語
内頸部様粘液性境界悪性腫瘍、漿粘液性境界悪性腫瘍、ミューラー管型粘液性境界悪性腫瘍（MMBT）、混合型ミューラー管腫瘍、異型増殖性（境界悪性）ミューラー管腫瘍

Epidemiology
This is an uncommon tumor and accounts for approximately 1% of ovarian atypical proliferative tumours. In the past they have been considered a subset of mucinous tumors (endocervical type), and therefore of all mucinous atypical proliferative (borderline) tumors, they account for 4-15% of cases {3334969}.

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- 新疾患・概念：
  - Microcystic stromal tumor
  - solid pseudopapillary neoplasm

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WHO 2014 (DRAFT)

Epithelial-stromal tumours – Transitional cell tumours
- Benign
  - Brenner tumours
- Borderline
  - Borderline Brenner tumours
- Malignant
  - Malignant Brenner tumours

Transitional cell carcinoma

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ICD-O code
9000/3
Malignant Brenner tumours account for less than 5% of Brenner tumours {5074634;5040741;2321577}.

Clinical features
These tumors occur in women over 50 years of age. Patients present with an abdominal mass or pain. Some may have abnormal vaginal bleeding. {3570630;4005816}.

Macroscopy
The tumours are usually large with a median size of 16-20 cm. They may be solid or cystic with mural nodules. Typically, they exhibit a benign Brenner tumour component which may be fibromatous and calcified. Malignant Brenner tumours are bilateral in 12% of cases {3570630}. About 80% of cases are confined to the ovary (stage 1) at the time of diagnosis.

Histopathology
The tumor is composed of irregularly shaped masses of malignant transitional-type cells. Cystic areas within the tumor are lined by multilayered epithelium exhibiting hyperchromatic and pleomorphic nuclei and prominent mitotic activity. Invasion may be difficult to detect because of the densely fibromatous background of the tumor but desmoplastic stromal reactions are helpful features in identifying unequivocal stromal invasion. Rarely the invasive component appears to arise directly from a benign Brenner tumour, without an atypical proliferative component {23202779}. Mucinous glandular elements and, more rarely, mucinous adenocarcinoma may coexist with the Brenner component. Lack of a benign or atypical proliferative Brenner component should raise the possibility of high-grade serous or endometrioid carcinomas with transitional cell-like differentiation. No convincing examples of a malignant Brenner tumour completely lacking a benign or atypical proliferative component have been reported {23018212;23108017}.

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良性あるいは増殖型（境界悪性）ブレンナー腫瘍が認められない場合は、移行上皮に類似した分化（移行上皮癌類似のパターン）を示す高悪性度の漿液性あるいは類内膜腺癌である可能性を考慮する必要がある．

malignant Brenner tumour completely lacking a benign or atypical proliferative component have been reported {23018212;23108017}.

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  - ➢solid pseudopapillary neoplasm

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(SF-1), WT1 and CD56 {21378549}{19033865}{15754297}. Granulosa cell tumors are vimentin positive and most are keratin negative. Occasional tumors show focal or diffuse staining for the low molecular weight cytokeratins 8 and 18. Granulosa cell tumor is negative for epithelial membrane antigen (EMA). There is positive staining for smooth muscle actin in most tumors, there is membrane staining for CD99 in up to 70 %, and about 50 % are positive for S-100 protein.

Histogenesis
Granulosa cell tumor develops from the granulosa cells of ovarian follicles.

Genetic profile
Granulosa cell tumor cytogenetics have not been extensively studied; the most common abnormalities reported have been trisomy 12, trisomy 14, monosomy 16 or deletion of 16q and monosomy 22 {15790439}{22200085}. There is a missense somatic point mutation in the FOXL2 gene (402 C to G) in more than 90% of adult granulosa cell tumors {19516027}{20198651}{20693978}.

Prognosis and predictive factors
Standard treatment is total abdominal hysterectomy and bilateral salpingo-oophorectomy. Unilateral salpingo-oophorectomy is appropriate treatment for stage IA tumors in young women who wish to retain their fertility. The recurrence rate is 10–15 percent for stage IA tumors and 20–30 percent overall. Granulosa cell tumors grow slowly and metastases are often detected more than 5 years after initial treatment, sometimes after intervals of more than 20 years. It is difficult to predict the prognosis but unfavorable factors include large size (> 15cm), bilaterality, tumor rupture and spread beyond the ovary. The stage is the single most powerful prognostic indicator. There is no correlation between the microscopic pattern and the clinical outcome.

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WHO分類第3版（2003）の課題

- 漿液性腺癌のグレード
- 漿液性腺癌と卵管上皮内癌の関連
- 粘液性腺癌における腸型と内頸部様の区別
- 粘液性境界悪性腫瘍における上皮内癌とその微小浸潤の位置づけ
- 移行上皮癌の存在
- 分子生物学的新知見
  - ➢成人型顆粒膜細胞腫における*FOXL2*遺伝子変異
- **新疾患・概念：**
  - ➢Microcystic stromal tumor
  - ➢Solid pseudopapillary neoplasm

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WHO 2014 (DRAFT)

Sex-cord stromal tumours – Pure stromal tumours
- Fibroma
- Thecoma, typical
- Thecoma, luteinzing
- Fibrosarcoma
- Sclerosing stromal tumour
- Signet-ring cell stromal tumour
- Microcystic stromal tumor

Mixed sex-cord stromal tumours
- Adult granulosa cell tumour
- Juvenile granulosa cell tumours

Sex-cord stromal tumours – Sertoli cell, Sertoli-Leydig cell and Steroid cell tumours
- Sertoli cell tumour
- Sertoli-Leydig cell tumour
- Sex cord tumour with annular tubules
- Sex-cord stromal tumor, NOS
- Leydig cell tumor
- Steroid cell tumor, NOS

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1-7G. Microcystic stromal tumour

Definition:
A rare benign ovarian tumour which is probably of stromal origin and characterised by the presence of distinctive microcystic architecture.

ICD-O code:
TBD

Clinical features:
In the only reported series of 16 cases, the patients ranged from 26 to 63 (mean 45) years of age and typically presented with symptoms referable to a pelvic mass{18971779}. Hormonal manifestations were possibly present in 2 patients. Seven patients with available follow-up were without evidence of disease at a mean of 4.25 years from the time of initial diagnosis {18971779}.

Macroscopy:
All tumours in the only reported series of 16 cases were unilateral with a mean size of 8.7cm (range 2 to 27cm) and none exhibited evidence of extraovarian spread {18971779}. The tumours were solid-cystic (11 cases), solid (3 cases), or predominantly cystic (2 cases). The solid component was usually firm and tan or white-tan, but in 1 case was yellowish; soft foci were present in 3 cases and small foci of haemorrhage, necrosis, or both, in 3.

Histopathology:
On microscopic examination, the appearance varies according to the relative prominence of the 3 fundamental components: microcysts, solid cellular regions and fibrous stroma. Microcysts usually, but not always, predominate. The microcystic pattern is characterized by small rounded to oval cystic

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Histopathology:
On microscopic examination, the appearance varies according to the relative prominence of the 3 fundamental components: microcysts, solid cellular regions and fibrous stroma. Microcysts usually, but not always, predominate. The microcystic pattern is characterized by small rounded to oval cystic spaces, in areas coalescing to larger irregular channels; intracytoplasmic vacuoles are also frequently present. The solid cellular areas are usually focally intersected by fibrous bands and hyaline plaques. The cells contain a moderate amount of finely granular, lightly eosinophilic cytoplasm, with generally bland, round to oval or spindle-shaped nuclei with fine chromatin and small indistinct nucleoli. Foci of bizarre nuclei are present in some cases. Mitotic activity is low. These neoplasms are usually positive with CD10 and vimentin while inhibin and calretinin are typically negative {18971779}. Cytokeratins are sometimes focally positive while epithelial membrane antigen is negative {18971779}. WT1 nuclear immunoreactivity has been described, as has aberrant nuclear staining of β-catenin {21881488}.

Histogenesis:
These are presumed to be of ovarian stromal origin, although the histogenesis is not firmly established.

Genetic profile:
Mutation analysis in 2 cases revealed the presence of an identical point mutation, c.98C>G, in exon 3 of β-catenin (CTNNB1) {21881488}. This is an oncogenic mutation that causes replacement of serine with cysteine at codon 33, leading to the loss of a phosphorylation site in the β-catenin protein. This suggests that dysregulation of the Wnt β-catenin pathway plays a fundamental role in the pathogenesis of ovarian microcystic stromal tumour.

Prognosis and predictive factors:
Malignant behaviour or extraovarian spread has not been reported in any of these neoplasms.

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Reference list:

18971779: Dr JA. Irving, Dr RH. Young. PubDate:Mar 2009. Microcystic stromal tumor of the ovary: report of 16 cases of a hitherto uncharacterized distinctive ovarian neoplasm. The American journal of surgical pathology. Volume: 33, Issue:3, p 367-75.

21881488: Dr D. Maeda, Dr J. Shibahara, Dr T. Sakuma, Dr M. Isobe, Dr S. Teshima, Dr M. Mori, Dr K. Oda, Dr S. Nakagawa, Dr Y. Taketani, Dr S. Ishikawa, Dr M. Fukayama. PubDate:Oct 2011. F-catenin (CTNNB1) S33C mutation in ovarian microcystic stromal tumors. The American journal of surgical pathology. Volume: 35, Issue:10, p 1429-40.

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Miscellaneous tumours
- Tumours of rete ovarii
  - Adenoma
  - Adenocarcinoma
- Wolfian tumour
- Small cell carcinoma, hypercalcemic type
- Small cell carcinoma, pulmonary type
- Wilms tumor
- Paraganglioma
- Solid peudopapillary neoplasm

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1-13G. Solid pseudopapillary neoplasm

Definition:
Tumour morphologically identical to the neoplasm of the same name in the pancreas.

Synonyms:
Solid and pseudopapillary tumour.

Epidemiology:
Rare

Clinical features:
The patients have ranged from 17 to 57 years and presented with non-specific symptoms related to the ovarian mass { 20871224; 21979589}.

Macroscopy:
Tumours are often large (>10 cm). They have a solid and cystic cut surface, the former being friable and yellow to tan { 20871224; 21979589}.

Histopathology:
The tumour is usually well circumscribed. The neoplastic cells grow in sheets and nests, and less frequently in cords and pseudopapillae. The nests and sheets are surrounded by septa that may be hyalinized and contain a delicate vascular network. The pseudopapillae have myxoid or myxohyaline cores and are lined by one to several cell layers. Microcysts filled with colloid-like material may be present. Cells have moderately abundant pale (sometimes foamy) to bright eosinophilic cytoplasm often containing paranuclear vacuoles and intracellular (as well extracellular) eosinophilic globules. Nuclei are uniform and round, may contain grooves and have dispersed chromatin and typically rare to absent

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その他の変更点・議論

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卵巣癌の Grading

Grading The grading of endometrioid carcinoma of the ovary is the same as for endometrial adenocarcinoma of the uterus (see chapter X). Most ovarian endometrioid carcinomas are well-differentiated, and show low-grade nuclei. Thus, nuclear grade is the best discriminator. Poorly differentiated endometrioid carcinomas are predominantly solid with focal microglandular areas. Mitotic activity is high (up to 5 or more mitoses per HPF) and squamous or secretory change is rare. Hemorrhage and/or necrosis are prominent. Most high-grade carcinomas with these features are currently classified as serous based on recent IHC studies which show an immunoprofile more consistentent with HGSC (See below). {20505499}. Rarely, ovarian carcinomas with a predominantly

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卵巣癌の Grading

卵巣類内膜腺癌のグレーディングは子宮体部の類内膜腺癌と同様である.

differentiated, and show low-grade nuclei. Thus, nuclear grade is the best discriminator. Poorly differentiated endometrioid carcinomas are predominantly solid with focal microglandular areas. Mitotic activity is high (up to 5 or more mitoses per HPF) and squamous or secretory change is rare.

High-grade の類内膜腺癌は、同様の免疫組織化学的表現型を示すことから、漿液性腺癌と同様にⅡ型腫瘍、あるいは漿液性腺癌そのもの、である.

- Grading(Grade-1~3)について明記されているのは類内膜腺癌のみ
- 漿液性、粘液性、明細胞については定義なし

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Epithelial-stromal tumours – Clear cell tumours
- Benign
  - Adenofibroma (and cystadenofibroma)
- Borderline
  - Clear cell borderline tumour ➡ 削除？
- Malignant
  - Clear cell adenocarcinoma

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WHO 2014 (DRAFT)

Epithelial-stromal tumour – Endometrioid and Endometiroid stromal tumours
- Benign
  - Cystadenoma
  - Cystadenoma and cystadenofibroma
- Borderline
  - Cystic tumor
  - Adenofibroma and cystadenofibroma
- Malignant
  - Variant with squamous differentiation
  - Ciliated variant
  - Oxyphilic variant
  - Secretory variant
- **Endometrioid stromal tumours**
  - Low grade endometrioid stromal sarcoma
  - High grade endometrioid stromal sarcoma
  - Undifferentiated endometrial stromal sarcoma

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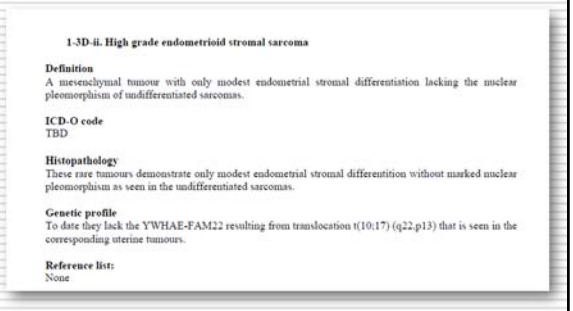

1-3D-ii. High grade endometrioid stromal sarcoma

Definition
A mesenchymal tumour with only modest endometrial stromal differentiation lacking the nuclear pleomorphism of undifferentiated sarcomas.

ICD-O code
TBD

Histopathology
These rare tumours demonstrate only modest endometrial stromal differentiation without marked nuclear pleomorphism as seen in the undifferentiated sarcomas.

Genetic profile
To date they lack the YWHAE-FAM22 resulting from translocation t(10;17) (q22.p13) that is seen in the corresponding uterine tumours.

Reference list:
None

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WHO 2014 (DRAFT)

Mixed mullerian mesenchymal tumours
- Benign
  - Adenofibroma
- Malignant
  - Adenosarcoma
  - Malignant mullerian mixed tumor (carcinosarcoma)

内膜腫瘍より分離・独立

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TAKE HOME

- ✓漿液性腺癌を高悪性度、低悪性度に2分
- ✓漿液性腺癌と卵管上皮内癌(STIC)の関連を明記
- ✓腸型と内頸部様粘液性腫瘍を分離
- ✓粘液性境界悪性腫瘍における上皮内癌とその微小浸潤を明確に定義
- ✓移行上皮癌⇒消滅
- ✓分子生物学的新知見を記載
  - ➢ 成人型顆粒膜細胞腫における*FOXL2*遺伝子変異など

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TAKE HOME

- ✓新疾患・概念の導入
  - ➢Microcystic stromal tumor
  - ➢solid pseudopapillary neoplasm
  - ➢High-grade ESS
- ✓Atypical proliferative terminology
- ✓卵巣腫瘍を“卵管・卵巣・腹膜”腫瘍として一括
- ✓上皮間質混合腫瘍(腺肉腫、癌肉腫)を内膜腫瘍から分離・独立

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