

第 104 回日本病理学会総会コンパニオンミーティング 1

日本婦人科病理学会

平成 27 年 4 月 30 日 名古屋国際会議場 B 会場 18:40～20:10

卵巣非上皮性腫瘍 診断困難例における実際的アプローチ

オーガナイザー

福永真治（東京慈恵会医科大学附属第三病院 病院病理部）

座長

九島巳樹（昭和大学江東豊洲病院 臨床病理診断科）

松本俊治（順天堂大学附属練馬病院 病理診断科）

CM-1-1 福永真治（東京慈恵会医科大学附属第三病院 病院病理部）

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Case 1 A 66-year old female with ovarian tumor

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I have no conflicts of interests.

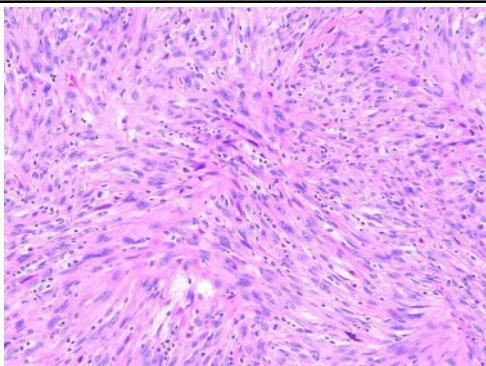
Clinical history

A 66-year-old, gravida 2, para 2, Japanese female presented with low abdominal discomfort and abnormal vaginal bleeding. Imaging analyses indicated a pelvic mass probably arising from left ovary.

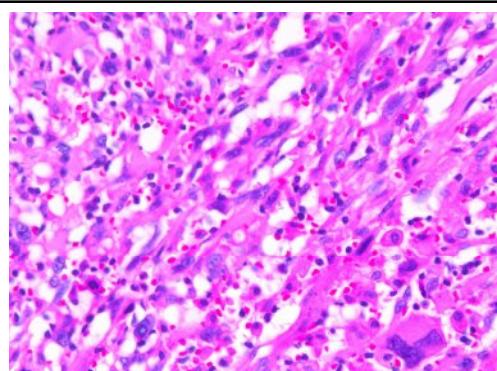
The general laboratory examinations revealed no significant abnormalities.

Under a clinical diagnosis of ovarian sarcoma, bilateral salpingo-oophorectomy and simple abdominal hysterectomy.

She had postoperative chemotherapy. The patient was well with disease at 16 months after surgery.



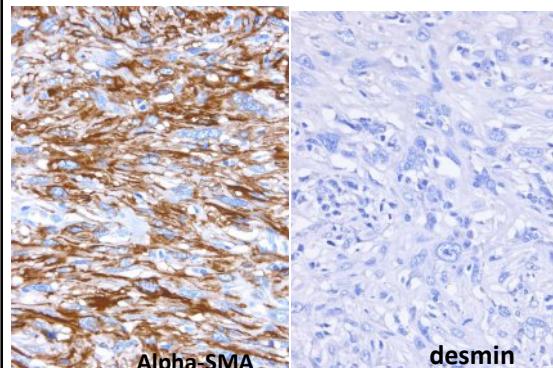
Specimen for intraoperative consultation
The predominant components show spindle cell or pleiomorphic sarcomatous features.



Sarcomatous components with marked cellular atypia and pleomorphism.



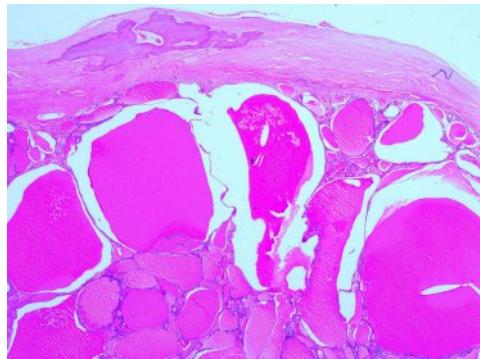
The cut surface was a fleshy and yellowish-white and solid tumor with scattered cysts containing greenish liquid and focal calcification (asterisks).



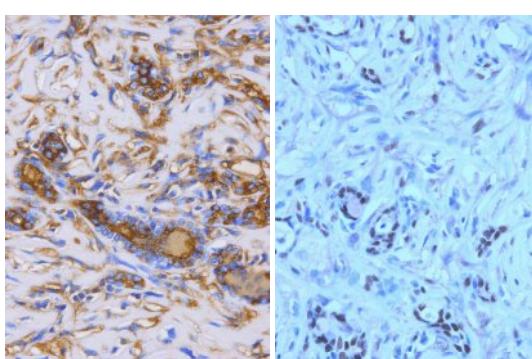
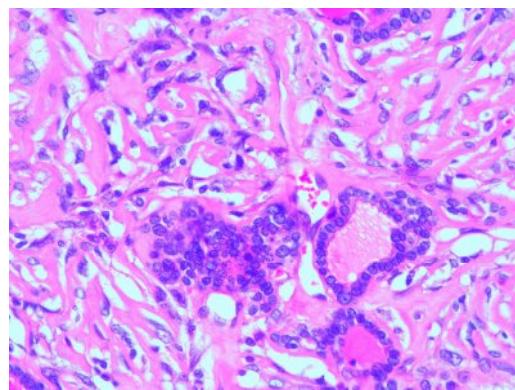
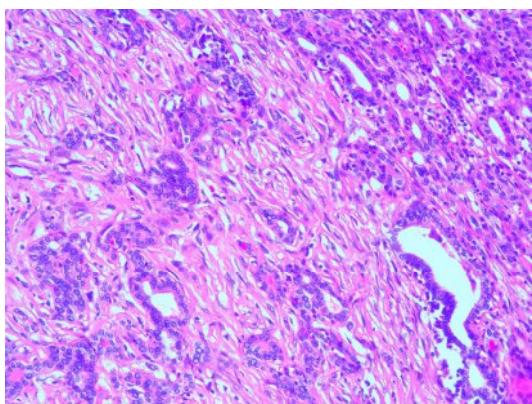
Spindle and pleomorphic cells are positive for alpha-smooth muscle actin (left) but negative for desmin (right)

**Immunohistochemistry
of the high grade spindle tumor
component**

- Vimentin (+)
- Alpha-SMA (+)
- HHF35 (+)
- CD117 (+)
- Wide keratin (+)
- Desmin (-)
- CD34 (-)
- S100 (-)
- CAM5.2 (-)
- Thyroglobulin (-)



Benign-looking thyroid component with focal calcification and ossification.



Thyroglobulin TTF-1
Follicles and spindle cells are positive for thyroglobulin (left) and TTF-1 (right).

Immunohistochemistry

Thyroid follicles

- Thyroglobulin (+)
- EMA (+)
- CAM5.2 (+)
- Wide keratin (+)
- TTF-1 (+)
- Alpha-SMA (-)
- Vimentin (-)
- HHF35 (-)

Spindle cells adjacent thyroid tissue

- Thyroglobulin (+)
- EMA (+)
- CAM5.2 (+)
- Wide keratin (+)
- TTF-1 (+)
- Alpha-SMA (+)
- Vimentin (+)
- HHF35 (+)

Microscopic features

- Predominant element
High grade spindle cell sarcomatous component without specific differentiation
- Minor component
Benign looking thyroid tissue with reactive ossification and calcification
- Mildly or moderately atypical spindle cell proliferation adjacent thyroid follicles.
- They were positive for thyroglobulin and TTF-1.
- No other teromatous elements were observed

Pathologic diagnosis

Malignant struma ovarii with a predominant component of anaplastic carcinoma

Discussion 1

- Macroscopically, the presence of green to brown color of cyst contents or lining is a clue to the correct diagnosis of struma ovarii.
- In this case the sarcomatous element could be interpreted as dedifferentiation.
- Any type of thyroid cancer can arise in struma ovarii. Papillary carcinoma is most common.

Prognosis of malignant struma ovarii

Rates of death of disease in 105 malignant struma ovarii

Histological type	Death of disease
Papillary carcinoma (53cases)	7%
Typical follicular carcinoma (31cases)	14%
Highly differentiated follicular carcinoma of ovarian origin (HDFCO) (18cases)	0%
Undifferentiated (anaplastic) carcinoma (3case)	100%

Risk factors

Low risk	High risk
Tumor size < 2cm	<ul style="list-style-type: none">Tumor size \geq 2cmThe presence of extraovarian extension.High grade histology: anaplastic carcinoma

Discussion 2

- There were three cases of malignant struma ovarii with focal anaplastic carcinomatous elements in papillary carcinoma.
- Tumors diagnosed as malignant struma ovarii on histologic grounds are rarely clinically malignant and do not require radical treatment.
- The lack of correlation between morphology and outcome in proliferative and histologically malignant struma ovarii is striking, making the behavior of these tumors particularly unpredictable.

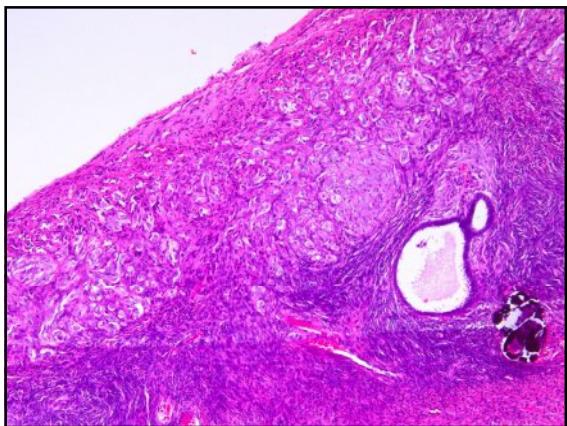
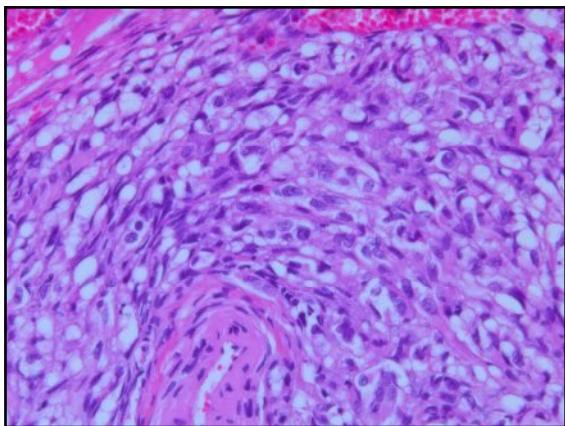
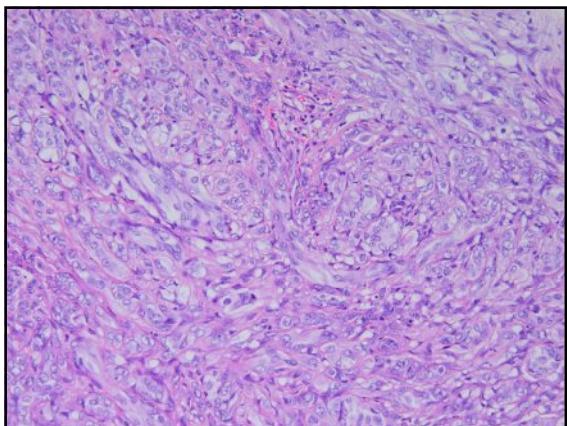
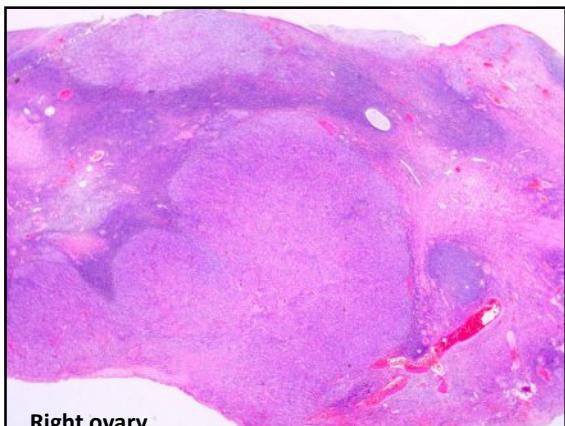
Conclusion

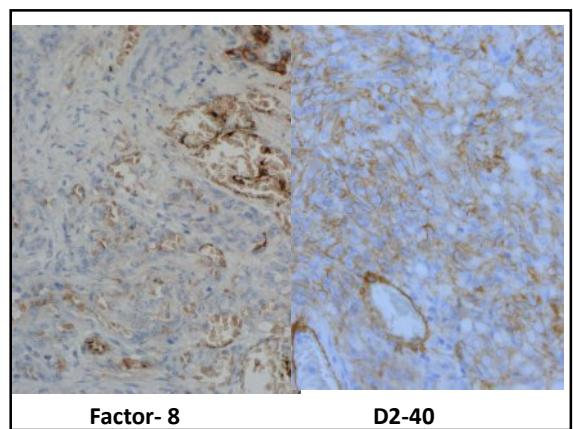
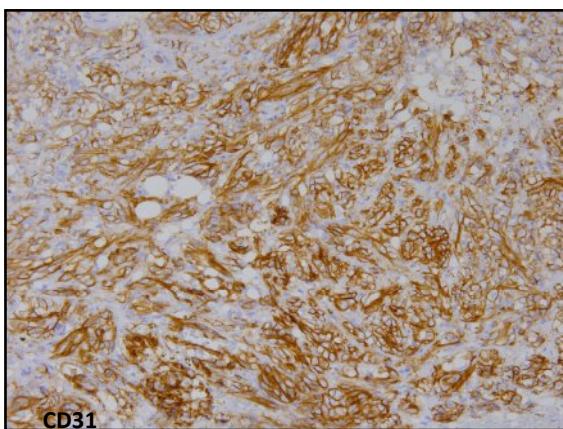
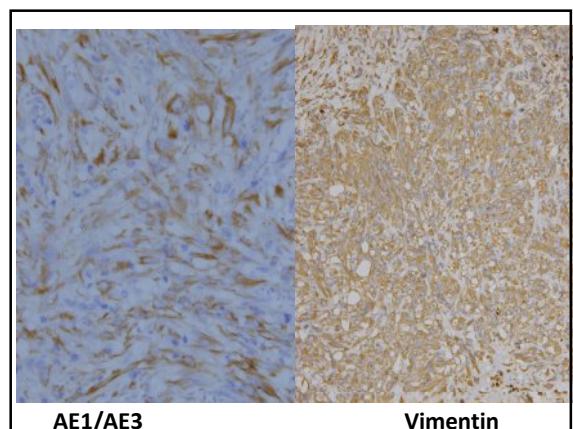
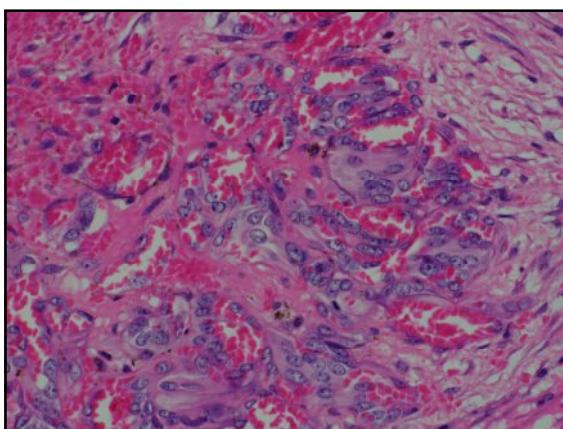
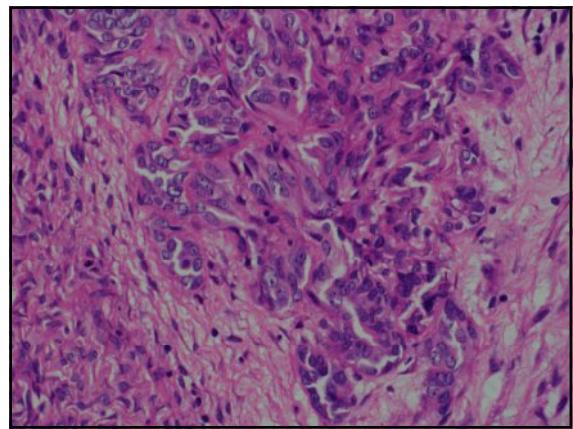
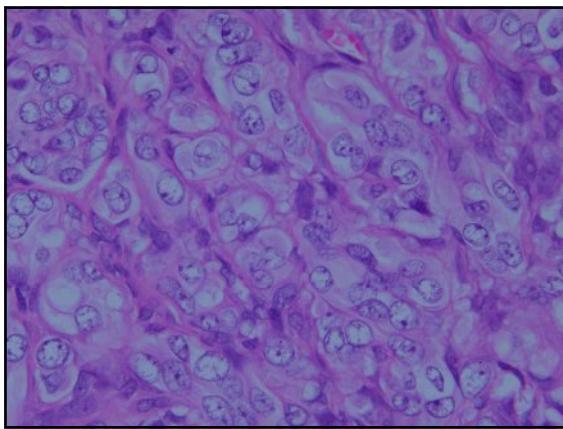
- This type of malignant struma ovarii may lead diagnostic problems, and sampling and differential diagnosis among sarcomatous ovarian tumors are important for making the diagnosis.

Case 2

A 34-year old female with ovarian and omentum tumors

- Peritoneal carcinoma with dissemination was clinically suspected.
- Metastatic lesions in lung, liver, spleen and bone (TH12) were suspected.
- Serous levels of CA125 were elevated (148U/ml, normal <35U/ml).
- Salpingoophorectomy and partial omentectomy was performed.
- Discussion points : Pathologic diagnosis

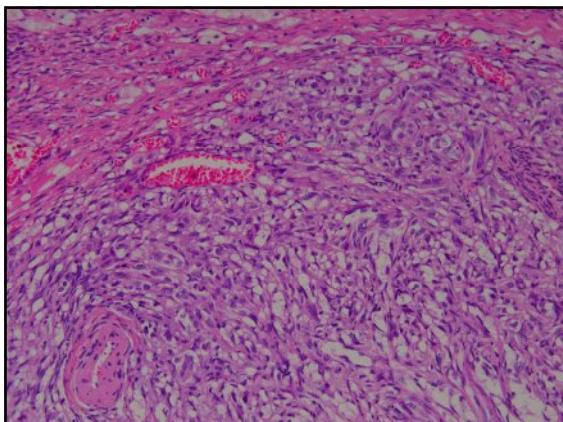




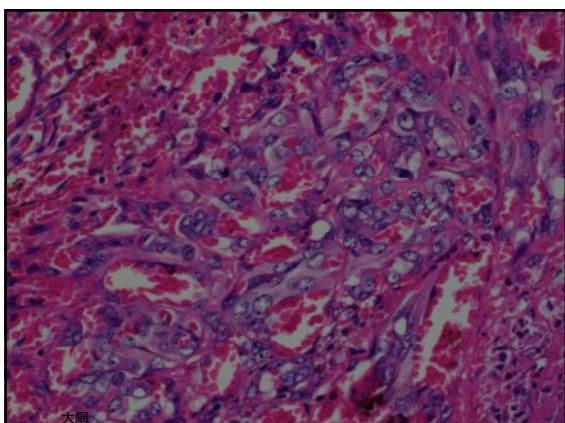
Immunostains

- Vimentin, CD31:(++)
- D2-40, p53: (+)
- AE1/AE3, CD34, factor 8: 一部(+)
- Calretinin, CEA, S100, CK7, CAM5.2, C-kit, SMA, desmin, HMB45, Melan A:(-)

Left ovary



Omentum



Diagnosis

- Epithelioid angiosarcoma
 - metastasis to bilateral ovaries.
 - Primary: Omentum, most likely

Differential diagnosis

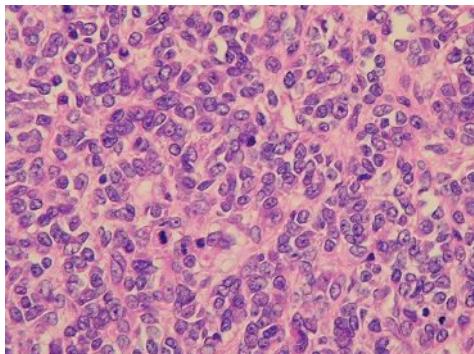
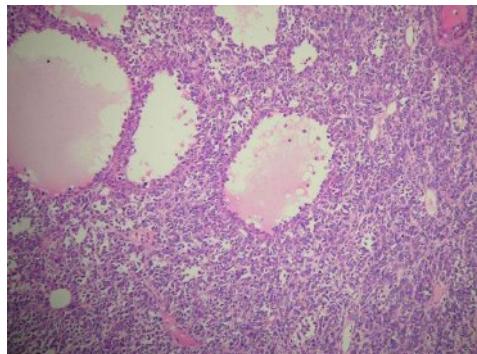
- Metastatic adenocarcinoma
- High grade serous carcinoma
- Malignant mesothelioma
- PEComa

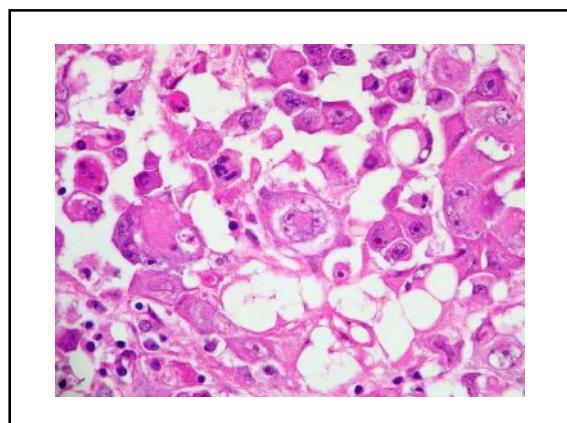
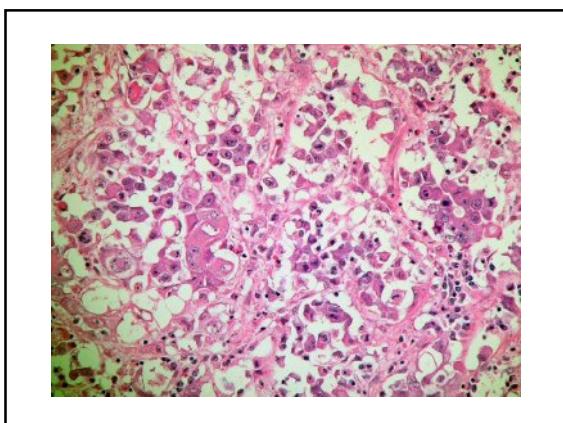
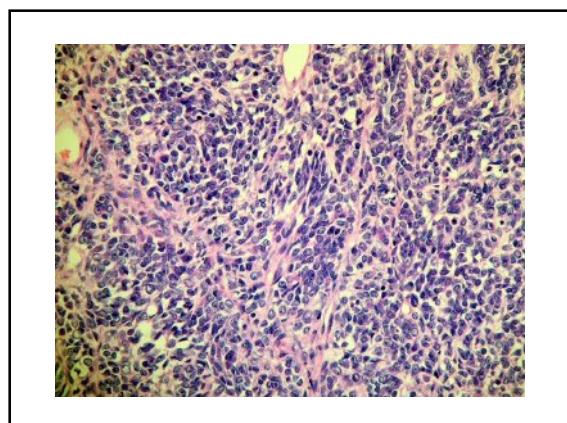
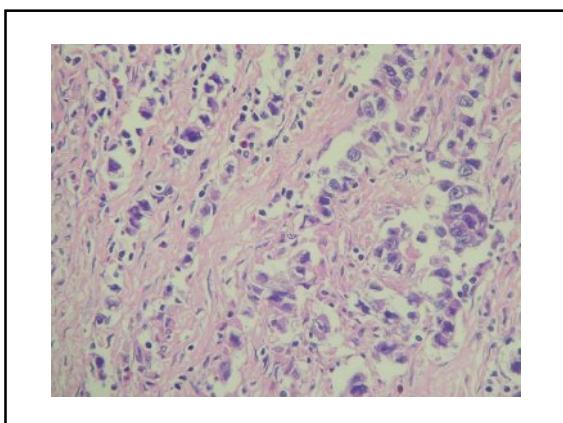
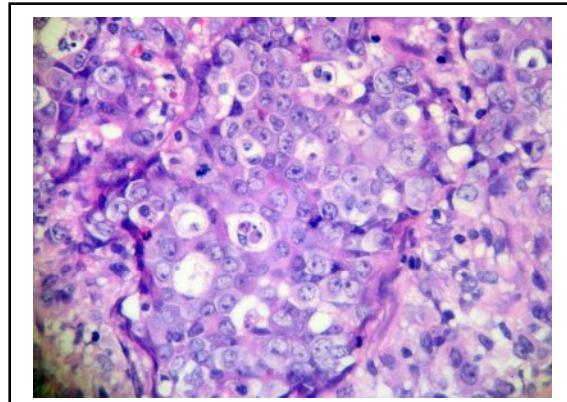
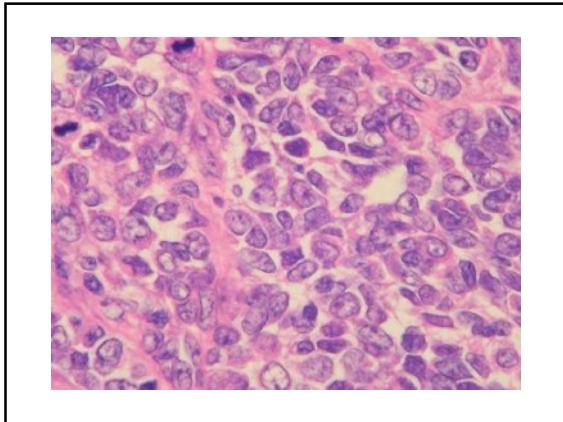
Epithelioid angiosarcoma

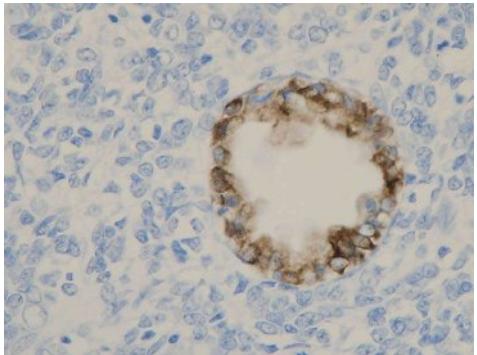
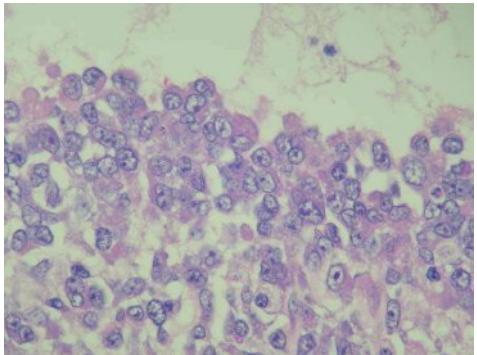
- Epithelioid, trabecular, tubular or alveolar arrangements of atypical cells
- Extensive necrosis and hemorrhage
- Positive for endothelial markers
- Epithelial markers are positive in one third of patients
- Metastasis to lung, liver, bone, lymph nodes
- Poor prognosis. One half of patients die of disease in one year.

Case 3: A 37-year-old female with a right ovarian tumor

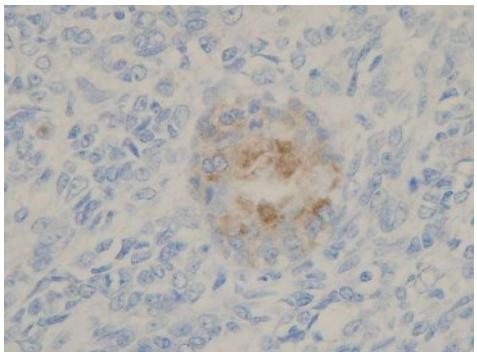
The patient presented with lower abdominal pain. Physical examination, CT and MRI indicated a right ovarian tumor. Abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and pelvic lymph node dissection were performed. Serum calcium levels were within normal range. She died of the spread disease 4 months after surgery.







CAM5.2



EMA

Immunohistochemical study

- CAM5.2 (+) (follicular areas)
- CK7(+) (follicular areas)
- EMA(+) (follicular areas)
- LCA (-)
- Inhibin-alpha(-)
- Calretinin (-)
- CD99(-)
- Chromogranin A (-)
- Synaptophysin (-)
- Inhibin-alpha (-)
- INI 1(-)



Omentum involvement

Diagnosis

Small cell carcinoma of the ovary,
hypercalcemic type

With extraovarian involvement:
omentum, subserosa of the uterus.

*She died of the spread disease 4 months
after the surgery.*

Differential diagnosis of small cell carcinoma of ovary, hypercalcemic type

- Granulosa cell tumor, adult and juvenile types
- Small cell (neuroendocrine) carcinoma, pulmonary type
- Dysgerminoma
- Secondary involvement ; malignant lymphoma, malignant melanoma, intraabdominal desmoplastic small cell tumor
- Primary or secondary primitive neuroectodermal tumor (PNET)

Summary of small cell carcinoma of the ovary, hypercalcemic type

- Young adults (mean age, 24 years)
- About 60% of the tumors are accompanied with hypercalcemia. It may be related to PTHrp in tumor cells.
- About 50% of the tumors have spread beyond the ovary at the time of laparotomy
- Diffuse sheet-like, follicle-like, cord-like arrangements of small closely packed epithelial cells.
- EMA, WT-1, calretinin positivity, inhibin and INI 1 negativity
- Differential diagnoses are wide.
- Poor prognosis: Most pts with high stage tumor have died of disease, usually within 2 years.
- Uncertain histogenesis.

*Thank you very much
for your attention.*



千船 病理学会(名古屋)

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日本婦人科病理学会

卵巣非上皮性腫瘍
診断困難例における実際的アプローチ

CM-1-2
社会医療法人 愛仁会 千船病院 病理診断科
名方 保夫

2015.4.30.

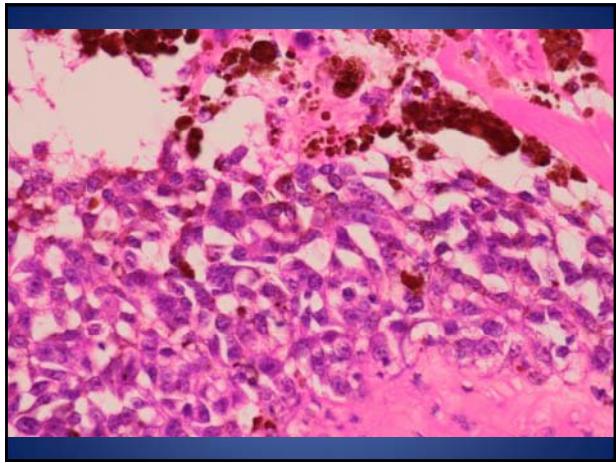
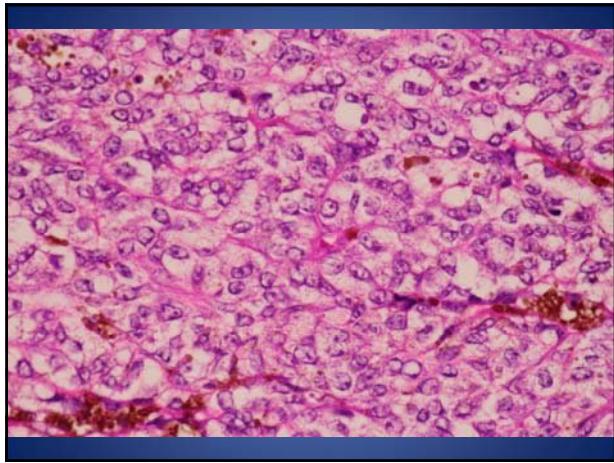
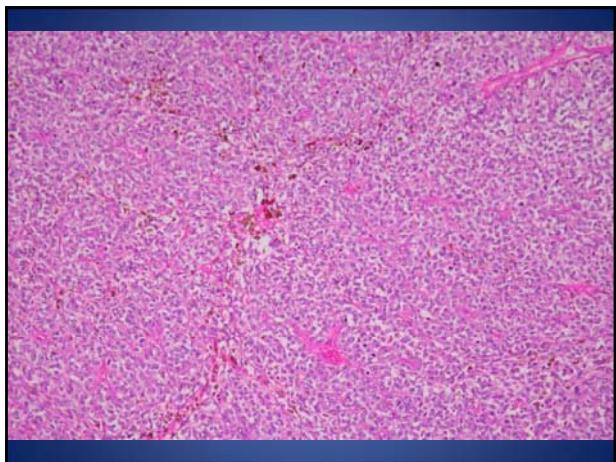
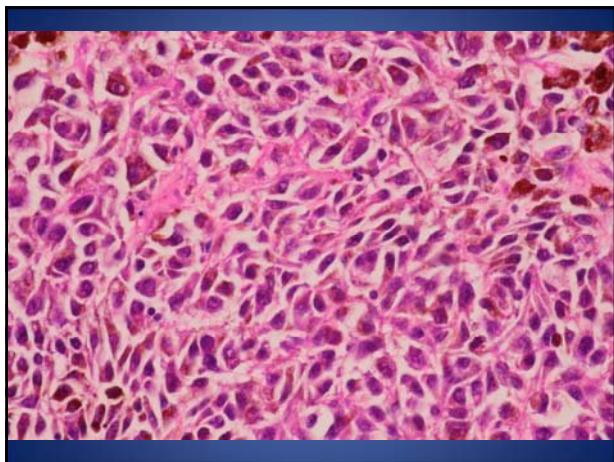
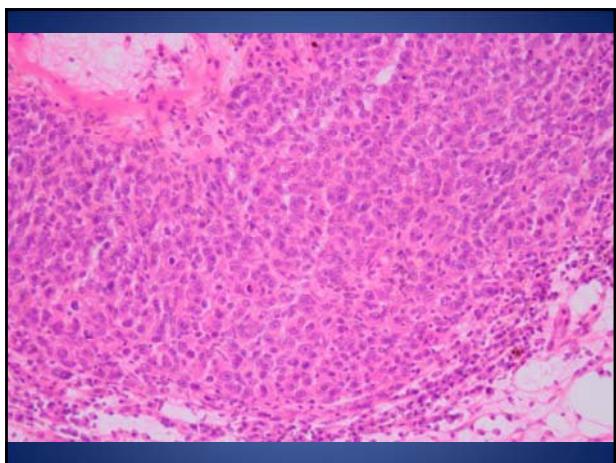
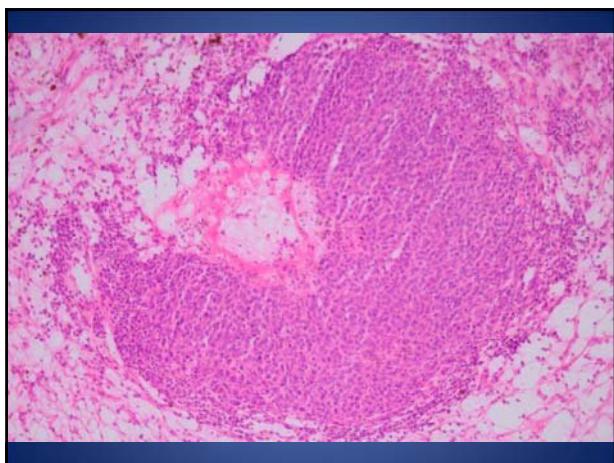
- ① 卵巣転移性悪性黒色腫 (原発巣 皮膚)
- ② 卵巣未熟奇形腫 (未熟成分の解釈、診断)

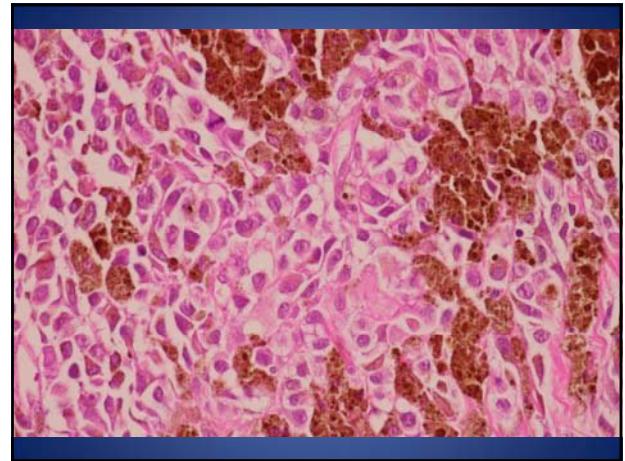
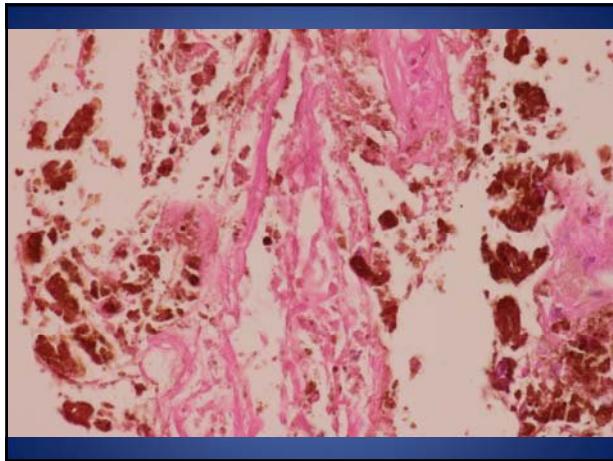
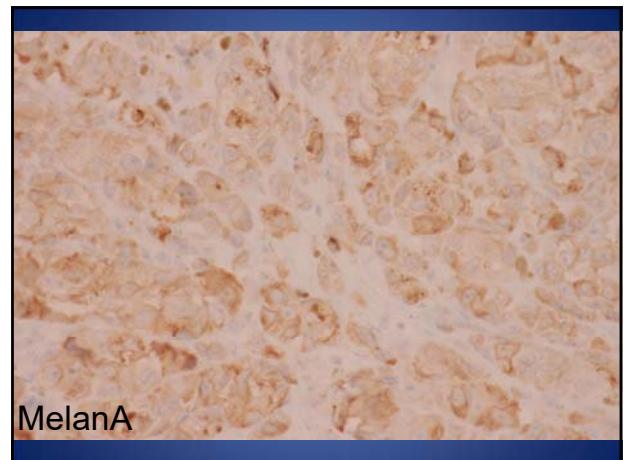
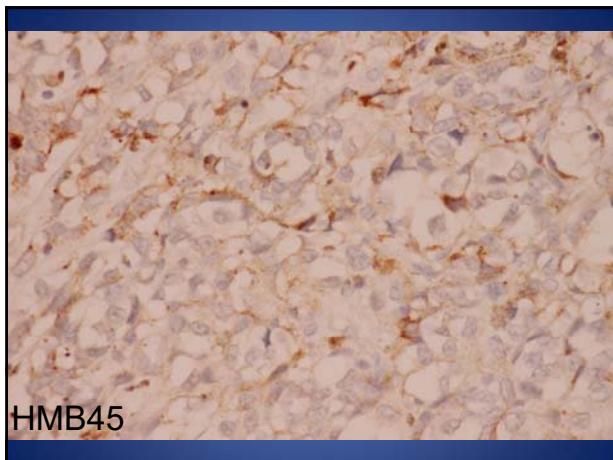
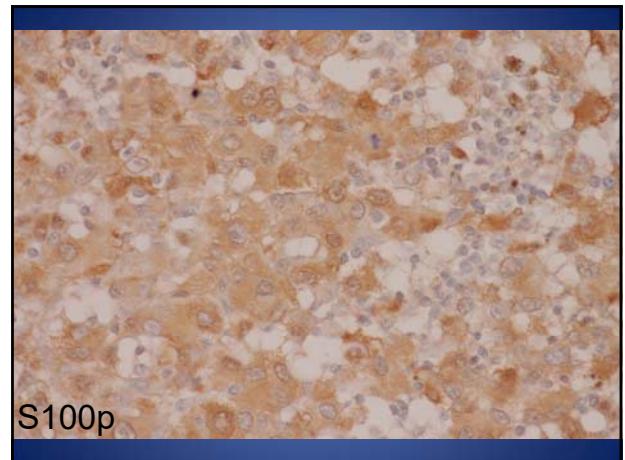
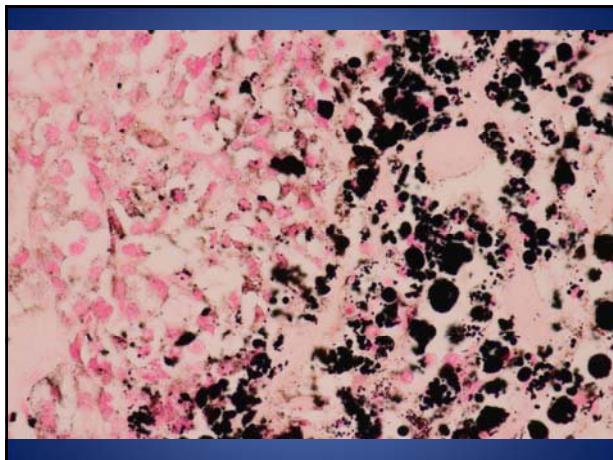
卵巣転移性悪性黒色腫
Metastatic malignant
melanoma of the ovary.
原発巣 皮膚
Primary site; Skin.

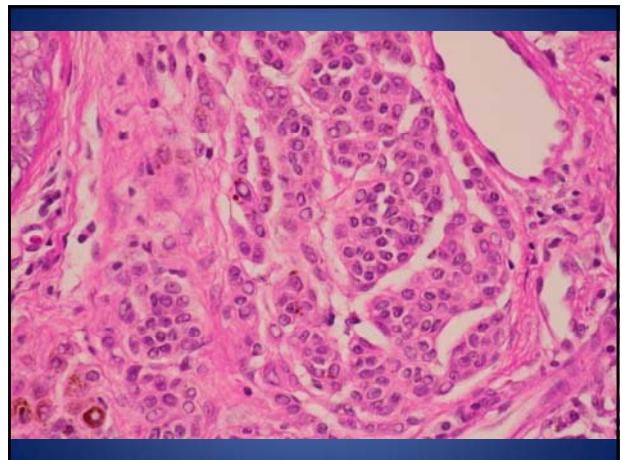
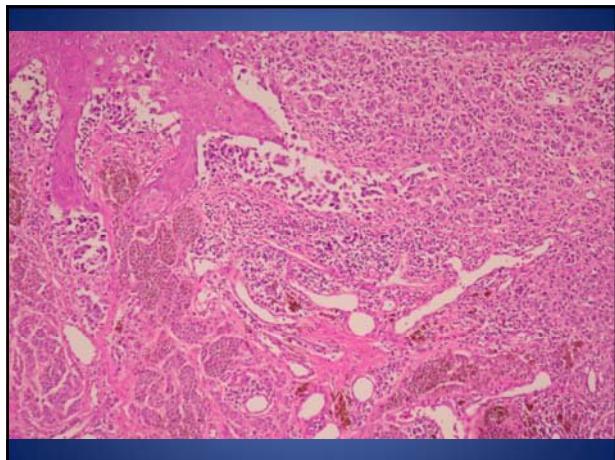
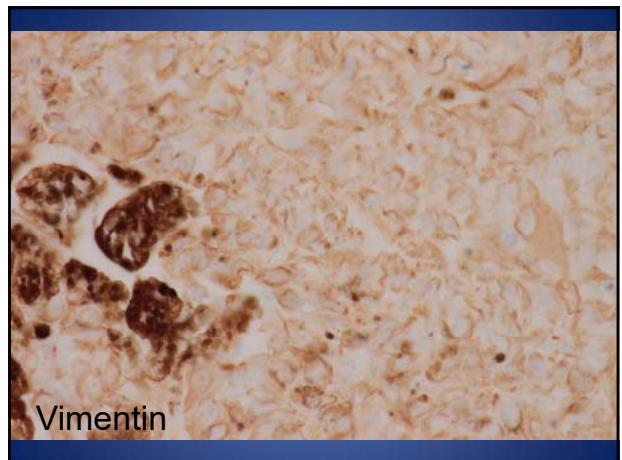
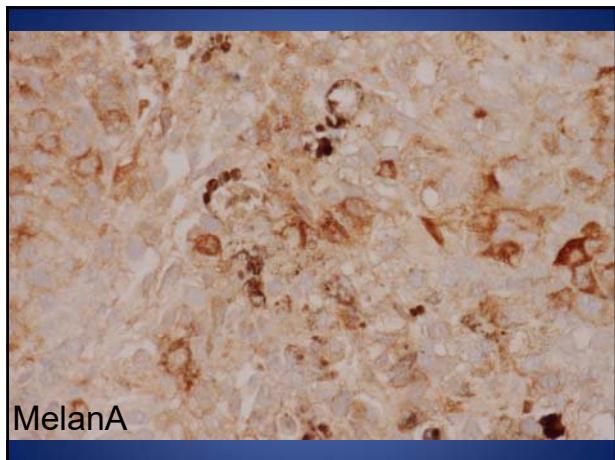
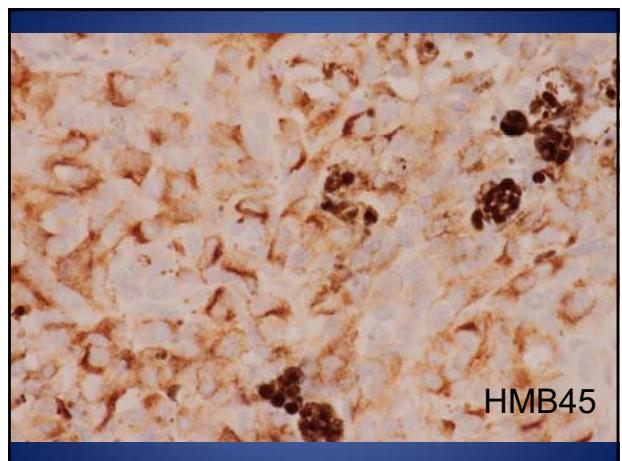
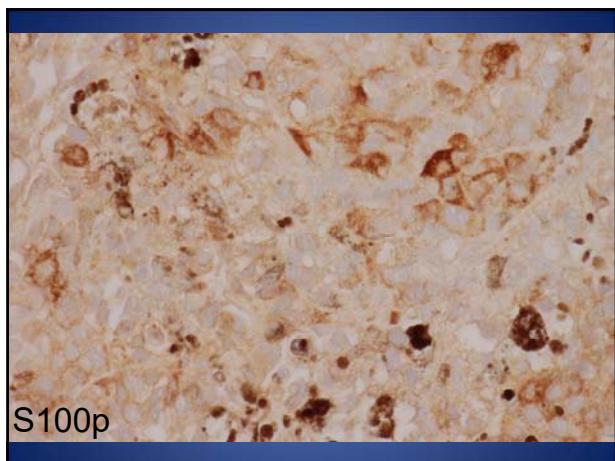
症例; 40歳代後半、女性

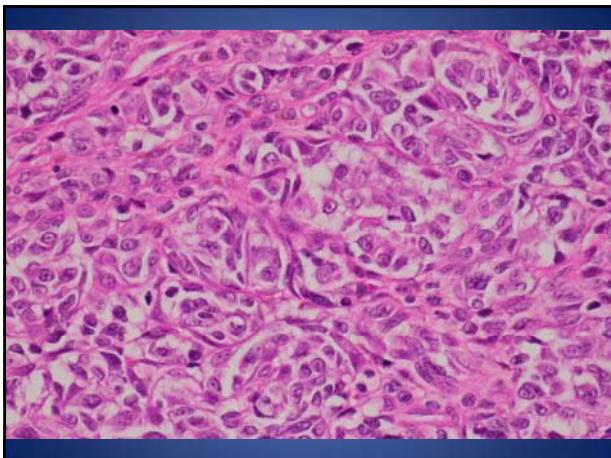
- 1、左腋窩リンパ節腫大 →→外科
左側胸皮膚に4X5cm大の黒色病変(生下時から)
- 2、骨盤腔から右腎門レベルにまで達する20cm程度の
巨大腫瘍 →→婦人科
- 3、前頭葉正中底部に転移巣 PET-CT





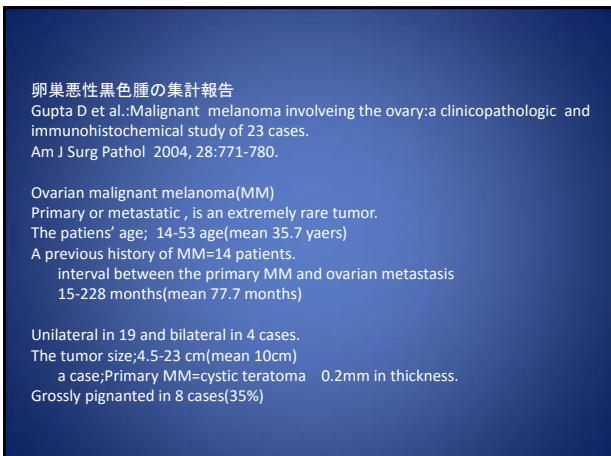






卵巣転移性悪性黒色腫の報告

- 1) Remadi S et al:Ovarian metastatic melanoma. A diagnostic pitfall in histopathologic examination. Arch Anat Cytol Pathol 1997, 45: 43-46.
- 2) Oliver R et al:Ovarian malignant melanoma:unusual presentation of a solitary metastasis. Gynecol Oncol 2005, 99:412-414.
- 3) Sbitti Y et al:Diagnostic challenge for ovarian malignant melanoma in premenopausal women: primary or metastatic?. World J Surg Oncol 2011, 9;65.
- 4) Berisavac M et al:Metastatic malignant ovarian melanoma—a case report. Vojnosanit Pregl 2013, 70:229-232.



The architectural pattern

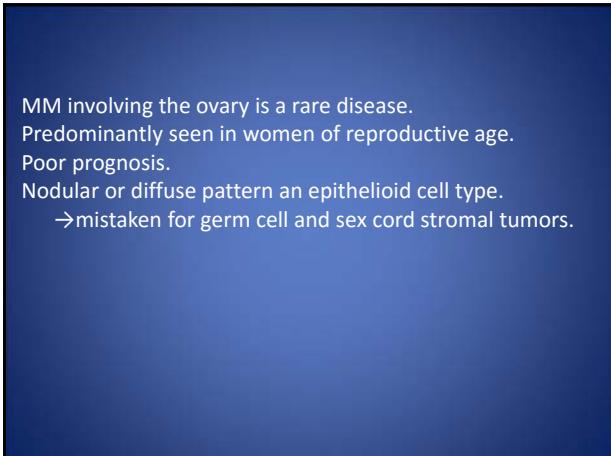
nodular 8, diffuse 6, nodular and diffuse 5, nested 3,
lentiginous arising in a teratoma 1. (*)
(*)one was the patient with arising within a teratoma.

The tumor cell type

epithelioid 19, spindled 2, mixed epithelioid and spindled 1,
small cell 1.

In 8 cases,

initial diagnosis included
sex cord stromal tumor.
grem cell tumor.
sarcoma.
undifferentiated carcinoma.



卵巣原発悪性黒色腫の報告

- 1) McCluggage WG et al:Primary malignant melanoma of the ovary :a report of 9 definite or probable cases with emphasis on their morphologic diversity and mimicry of other primary and secondary ovarian neoplasms. Int J Gynecol Pathol 2006, 25: 321-329.

→ all the primary tumors likely are of teromatous origin.

- 2) Hyun HS and Mun ST:Primary malignant melanoma arising in a cystic teratoma. Obstet Gynecol Sci 2013, 56:201-204.
- 3) Lee J et al:Primary malignant melanoma of the ovary arising in a cystic teratoma;case report and review of the literature. Dermatol Online J 2014, 20:

卵巣未熟奇形腫
(Immature teratoma of the ovary)

未熟成分の解釈、診断

奇形腫 Teratoma
1. 2胚葉性あるいは3胚葉性奇形腫 Biphasic or triphasic teratoma
a. 未熟奇形腫 Immature teratoma
b. 成熟奇形腫 Mature teratoma
1) 充実性 Solid
2) 囊胞性 Cystic {皮様囊腫 Dermoid cyst}
3) 胎児型 Fetal {こびと型 Homunculus}

卵巣腫瘍取扱い規約 第2版 2009.

Germ cell tumours
Dysgerminoma
Yolk sac tumour
Embryonal carcinoma
Non-gestational choriocarcinoma
Mature teratoma
 Mature cystic teratoma = dermoid cyst
 Mature solid teratoma
Immature teratoma
 Grade 1
 Grade 2
 Grade 3
 Giant cell tumor
Mixed germ cell tumor

WHO組織分類 第4版 2014.

未熟奇形腫のgrade 分類 その1
第1度 Grade 1
未熟な成分がわずかに認められる。核分裂像は乏しい。
第2度 Grade 2
未熟な成分が中等度に認められる。核分裂像を散見する。
第3度 Grade 3
未熟な成分が広範囲に存在する。核分裂像が目立つ

神経膠腫(腹膜神経膠腫症) = 第0度 Grade 0

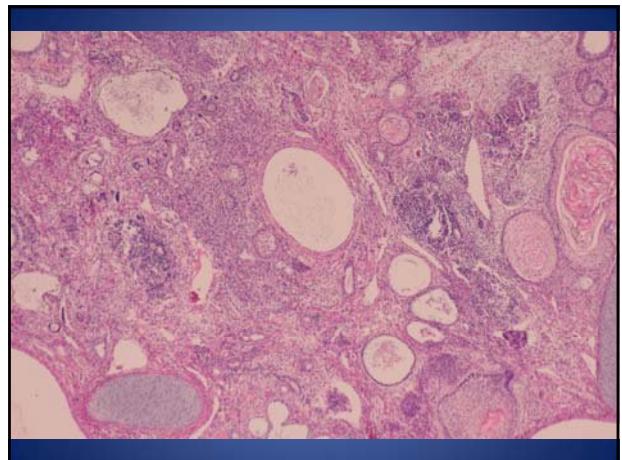
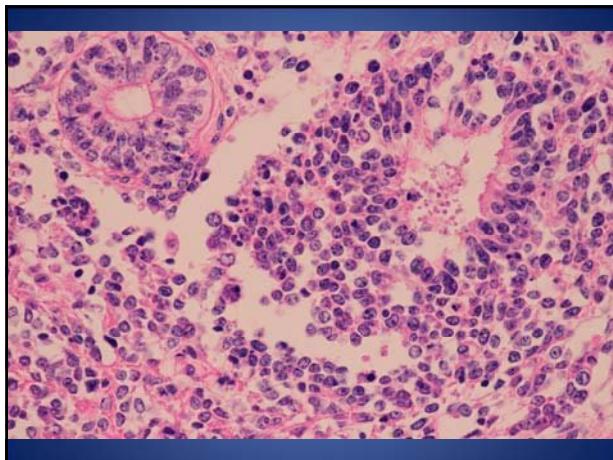
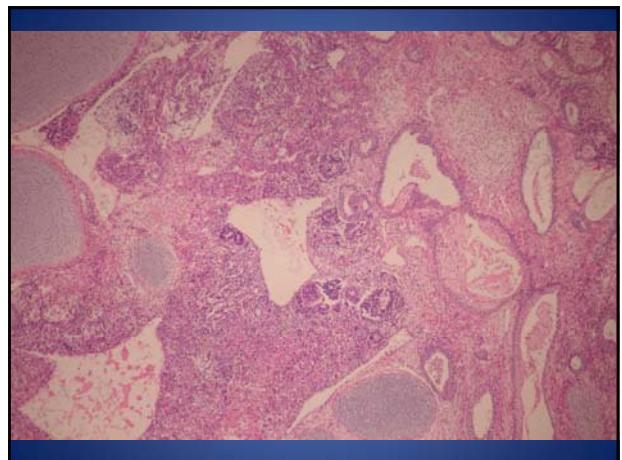
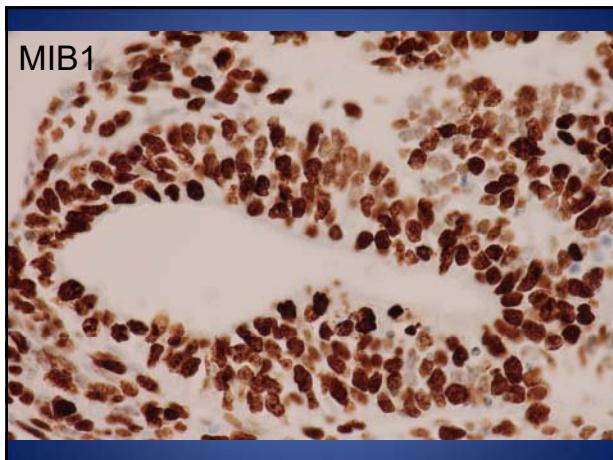
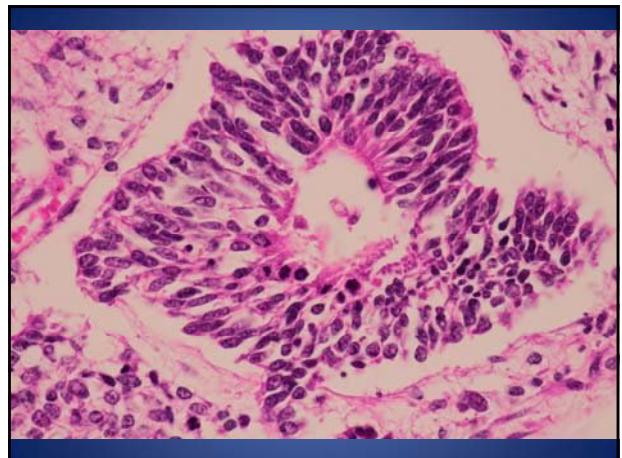
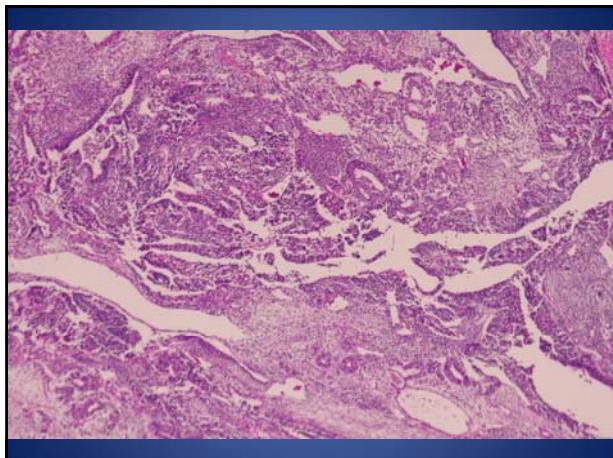
卵巣腫瘍取扱い規約 第1版 1990

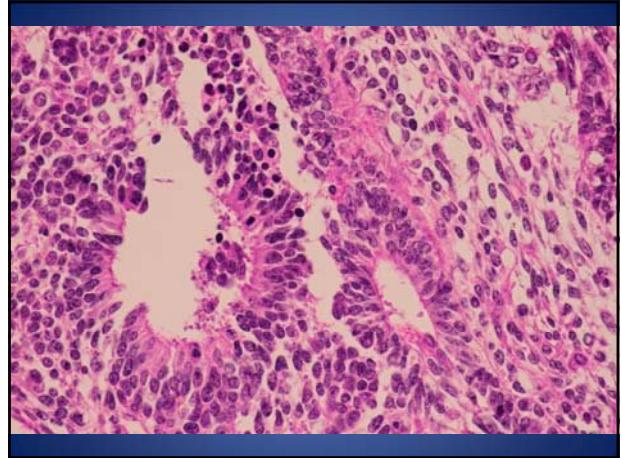
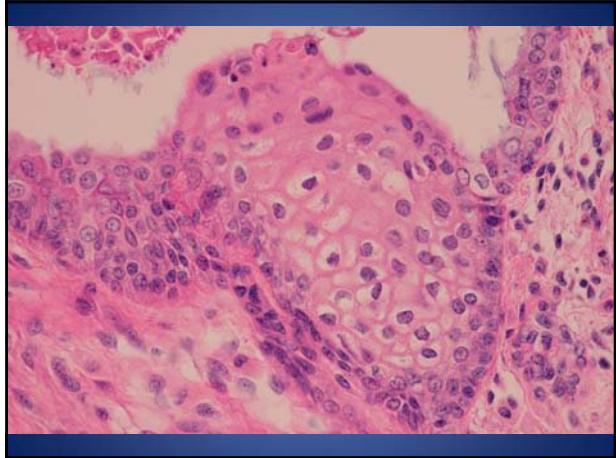
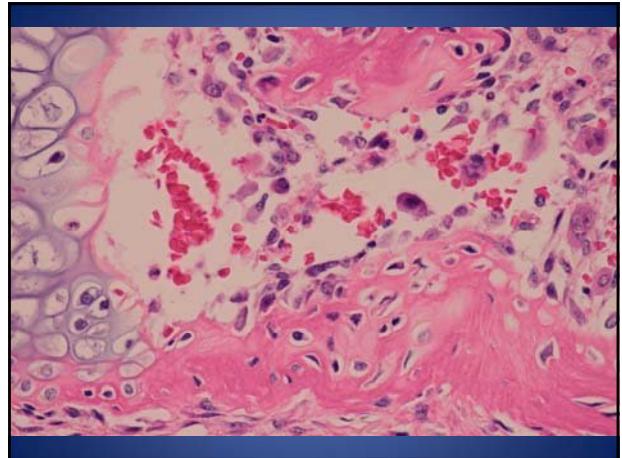
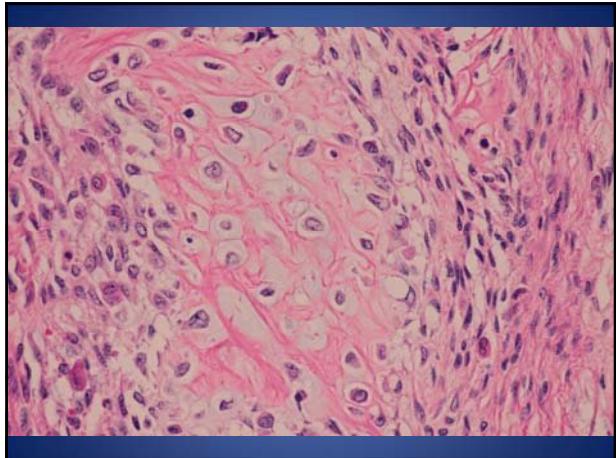
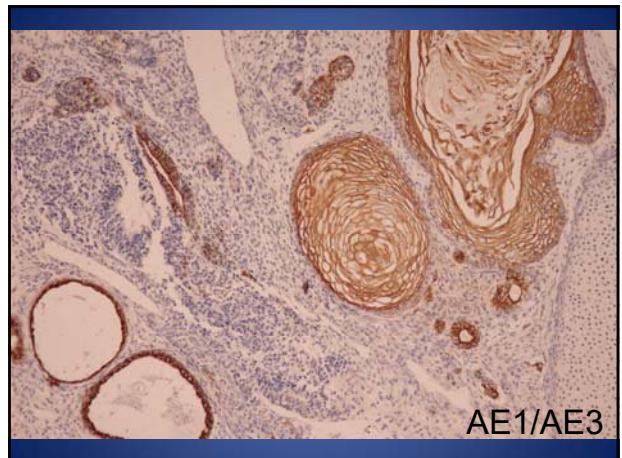
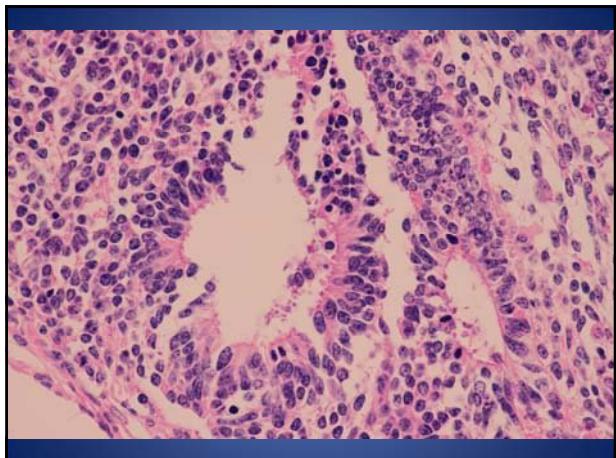
未熟奇形腫のgrade分類 その2
Grade 0:すべての成分が成熟した組織よりも
Grade 1:未熟組織が少量みられ、成熟組織と混在する。核分裂像は少ない。未熟な神経上皮成分は、標本あたり低倍率(対物 X4)で1視野を超えない。
Grade 2:未熟な成分が中等量みられ、核分裂がかなりみられる。未熟な神経上皮成分は、標本あたり低倍率(対物 X4)で3視野を超えない。
Grade 3:未熟組織と未熟神経上皮が広範囲に存在する。未熟な神経上皮成分は、標本あたり低倍率(対物 X4)で4視野あるいはそれ以上存在する。
稀に神経上皮成分よりも細胞成分に富む未熟な間葉成分が主体を占める例もあり、その場合は神経上皮以外の未熟成分の割合で異型度判定される。

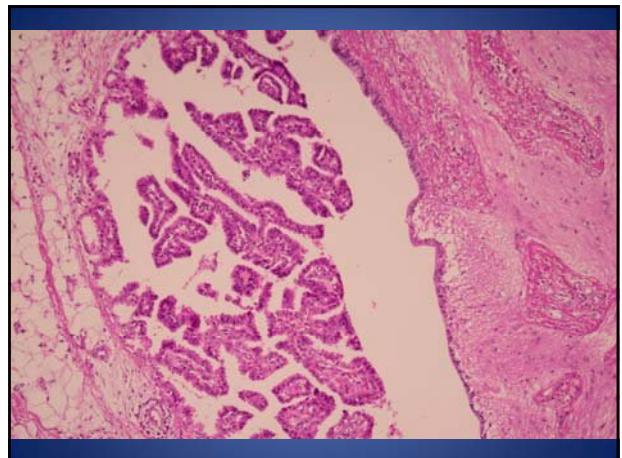
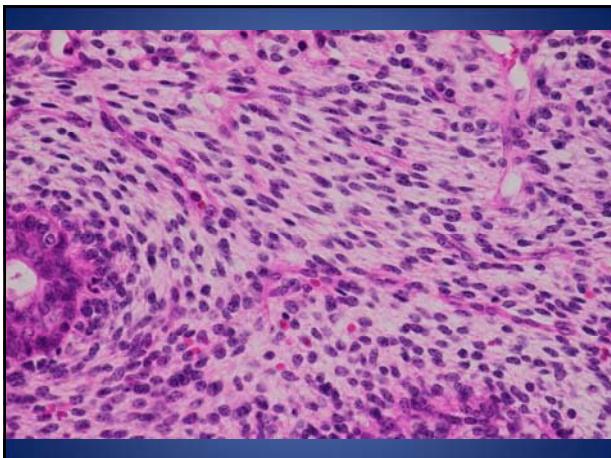
卵巣腫瘍取扱い規約 第2版 2009

未熟奇形腫のgrade分類 その3
Grade 1; Tumours with rare foci of immature neuroepithelial tissue that occupy <1 low power field(40X) in any slide(low-grade).
Grade 2; Tumours with similar elements, occupying 1-3 low power fields(40X) in any slide (high-grade).
Grade 3; Tumours with large amount of immature neuroepithelial tissue occupying >3 low power fields(40X) in any slide (high-grade).

WHO組織分類 2014



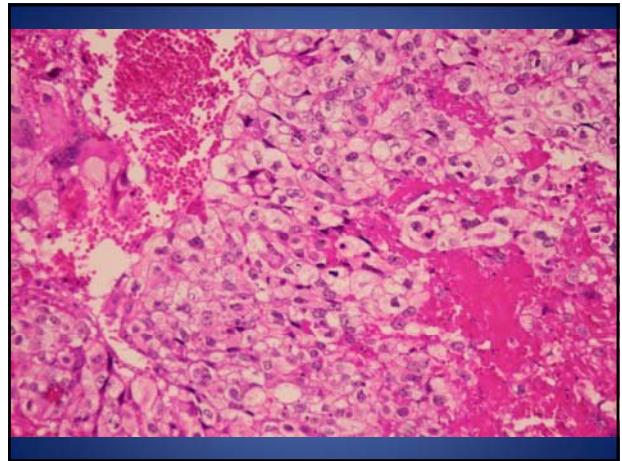


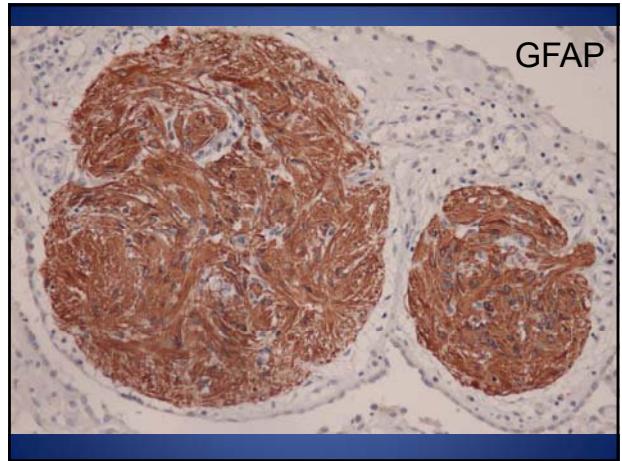
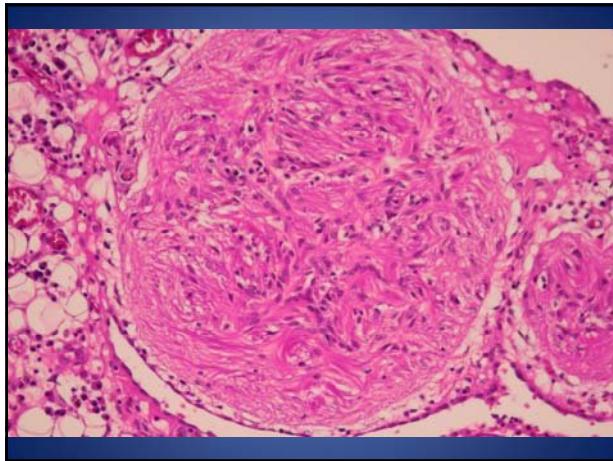
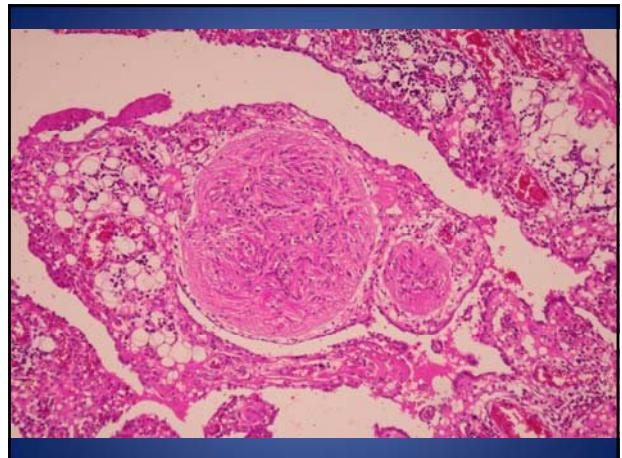
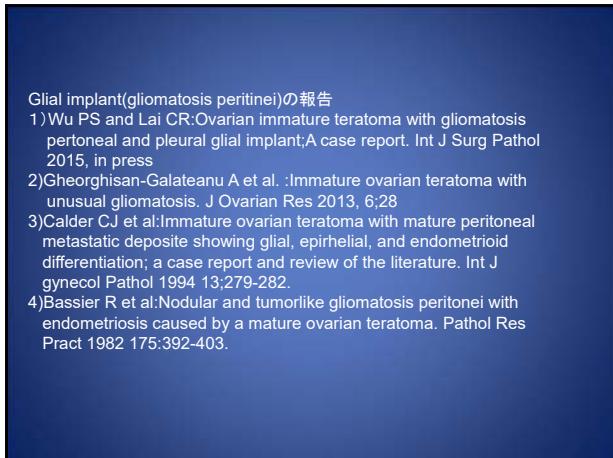
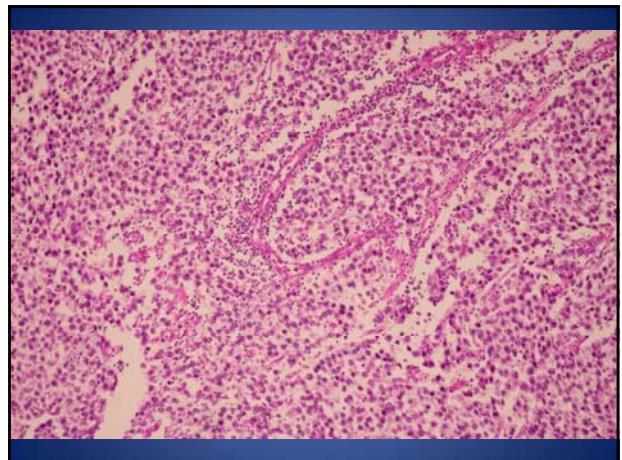
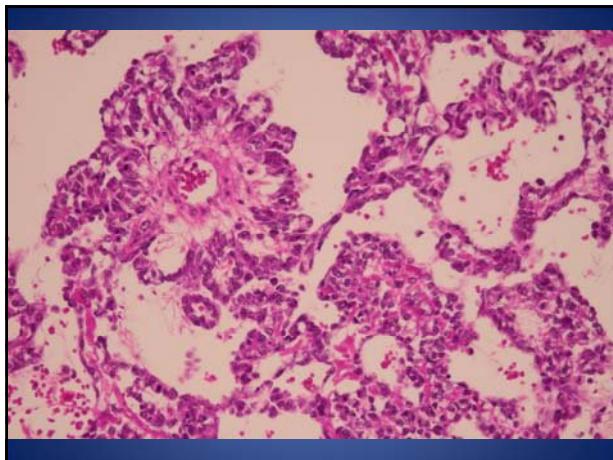


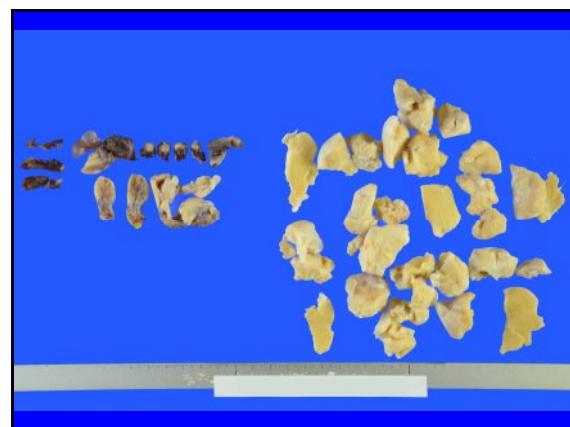
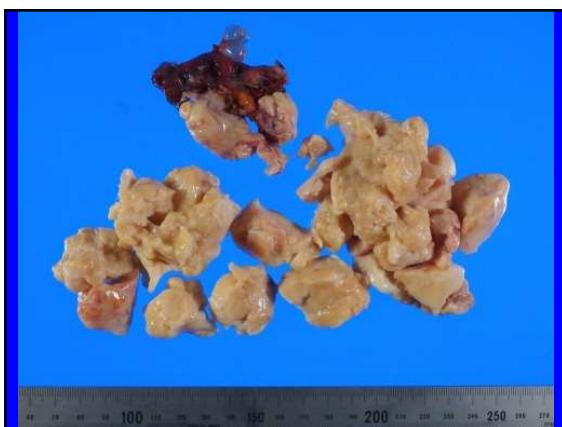
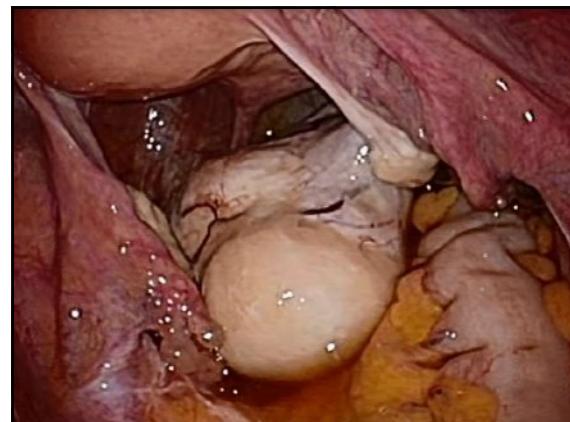
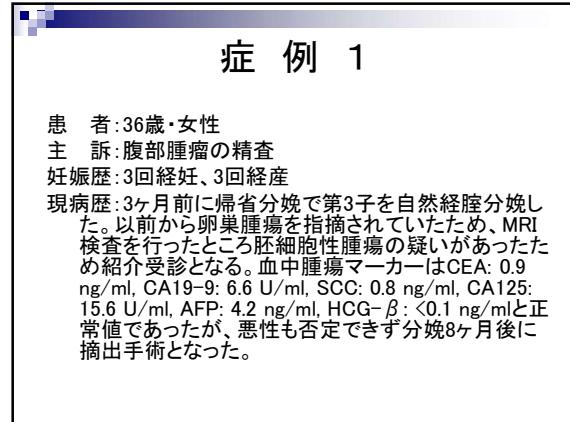
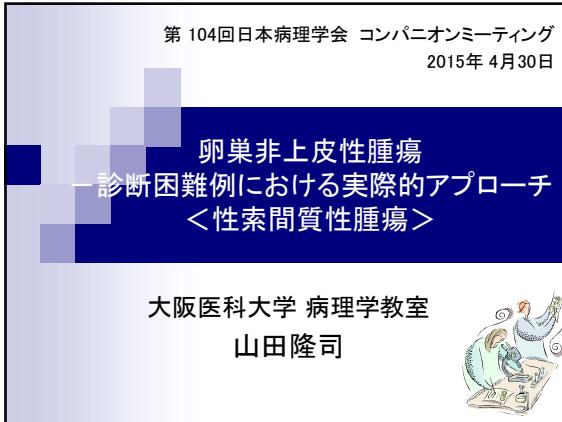
Assessments of grade were based on the overall extent of immature neuroepithelium. In retrospect, the selection of neuroepithelium as the barometer of malignancy was due to fact that this tissue was the most recognizable and increased reproducibly in the grading system.
→tumor grading systems used in the past have been tailored to estimate the amount of immature tissue in the teratoma.

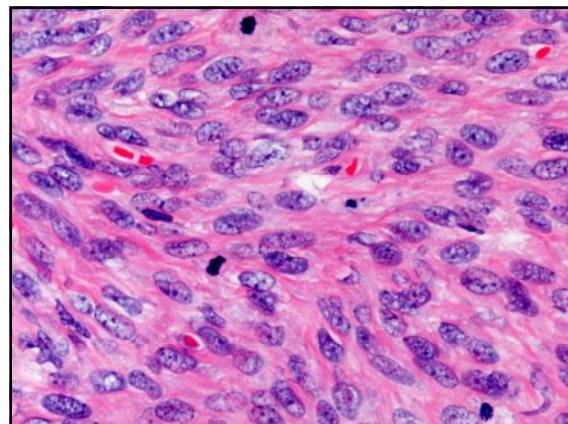
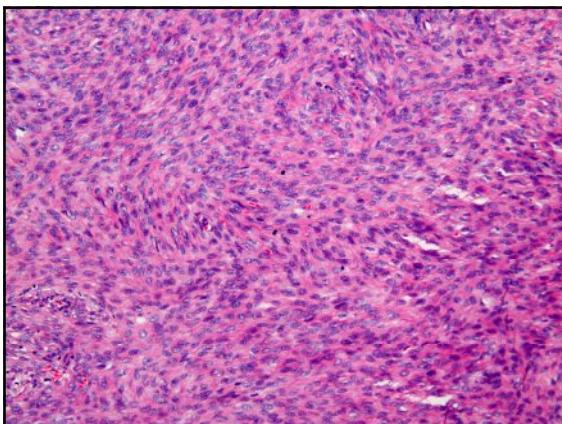
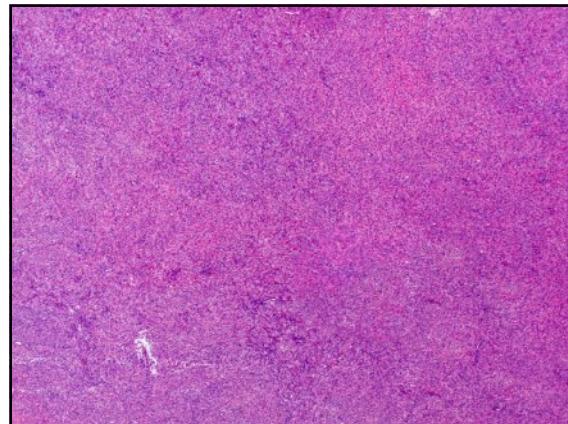
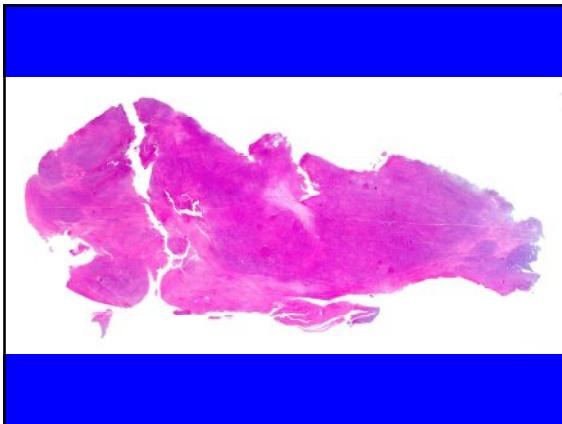
Differential diagnosis.
1, Mature solid teratomas with minimal immaturity.
→Such tumors are not classified as immature teratomas.
2, Thurlbeck and Scully showed that immature cartilage and developing cortex were not sufficient because these elements were present after fetal life.
3, Carcinosarcoma contain a mixture of primitive-appearing tissues, but these do not organize into coordinated tissue units with recognizable embryonal or fetal structures.

Differential diagnosis
4, In mixed germ cell tumors, exclusion of other elements is important, as they may contribute to recurrences, particularly in the pediatric age group.
Heifetz et al. observed that central pathology review of immature pediatric teratomas uncovered subtle patterns such as hepatoid and lung or intestinal-like glandular differentiation in yolk sac tumors. Exclusion of these subtle components of mixed germ cell tumor was important from a prognostic perspective.









病理診斷

Rt-ovarian tumor
(fibrothecoma)

鑑別診斷

- ✓ Fibroma
- ✓ Adult granulosa cell tumor
- ✓ Sclerosing stromal tumor
- ✓ Steroid cell tumor
- ✓ Smooth muscle neoplasm

診断のポイント

Rt-ovarian tumor (fibrothecoma)

- 臨床情報

10年前から指摘され、3回の妊娠出産を経ても大きさは変わっていない。腫瘍は右卵巣の正常部分を有しながら発育していた。

- 肉眼所見 割面の色・性状・硬さ
- 術式の変更
腹腔鏡下手術(摘出範囲)
- 追加治療の必要性

症例 2

患者: 75歳・女性

主訴: 不正性器出血

妊娠歴: 5回経妊、3回経産

既往歴: 23歳: 虫垂切除、63歳: 狹心症、74歳: 胆石で胆囊摘出

現病歴: 約8年前から少量の不正性器出血がみられていたため当院受診したところ、細胞診・組織診の結果からatypical endometrial hyperplasiaの診断となり、悪性も否定できないことから腹式単純子宮全摘出十両側付属器摘出手術となった。術前の血中腫瘍マーカー・ホルモン値は測定されていなかった。

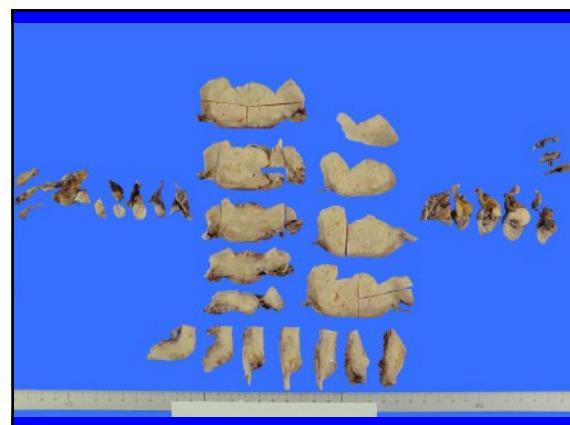
血液所見(術翌日)

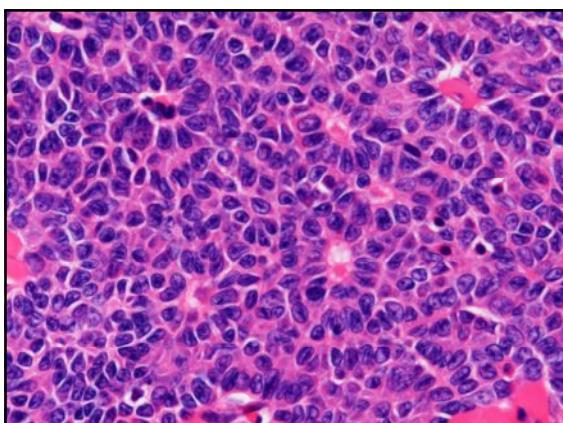
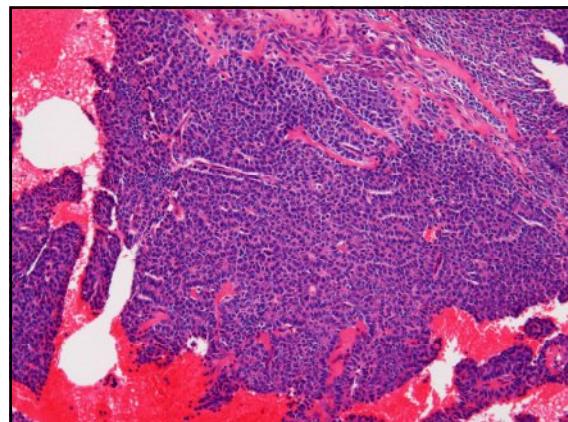
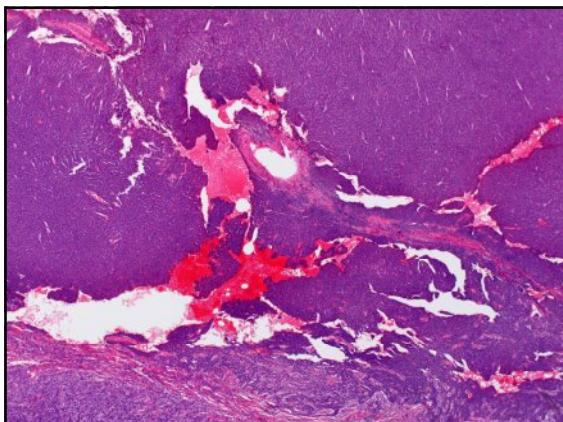
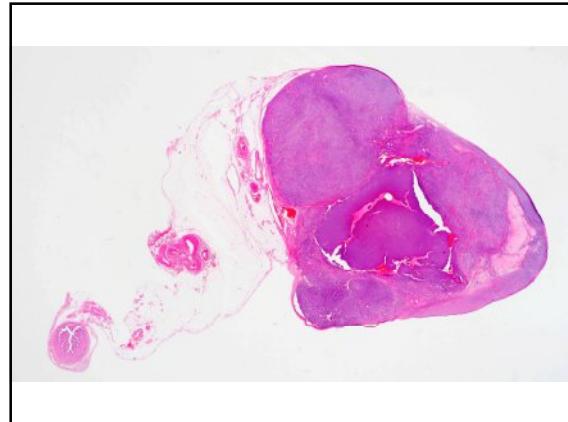
CEA:	1.4	ng/ml,
CA19-9:	23.3	U/ml,
SCC:	2.1	ng/ml,
CA125:	33.1	U/ml,
LH:	34.3 ↓	mIU/ml
FSH:	27.1 ↓	mIU/ml
E2:	30.6 ↑	pg/ml



MRI

画像診断:
LEGH-like
Adenomyosis
Leiomyoma(susp) △

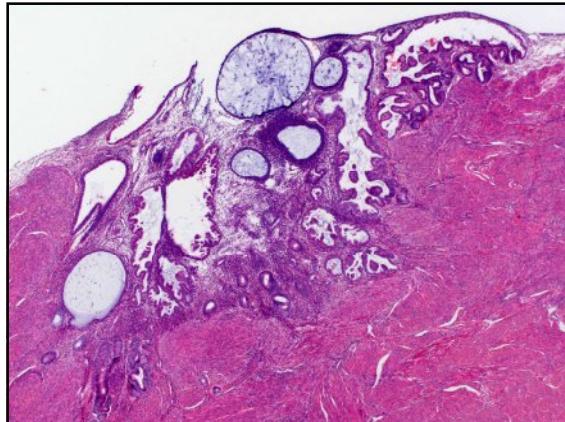
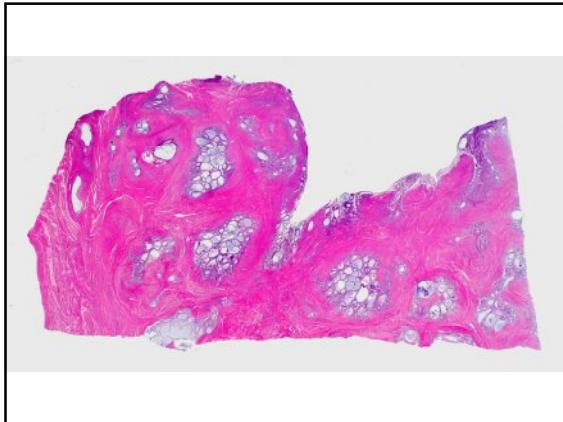




免疫染色

陽性
 α -inhibin, vimentin, α SMA

陰性
AE1/AE3, desmin



病理診断

Lt-ovarian tumor
(adult granulosa cell tumor)
Endometrial hyperplasia, complex,
Adenomyosis

鑑別診断

- ✓ Endometrioid adenocarcinoma with sex cord-like differentiation
- ✓ Carcinoid tumor
- ✓ Fibroma/thecoma/fibrothecoma
- ✓ Sex cord-stromal tumor with annular tubules
- ✓ Endometrial stromal sarcoma

診断のポイント

- 高齢者の女性ホルモンの影響
子宮頸部：頸管腺の発達・扁平上皮の肥厚
細胞診で表層系の細胞出現
子宮内膜：肥厚
- 女性ホルモン産生部位（腫瘍）
- 女性ホルモンの補充（療法）
- 画像所見の確認（放射線科医）

症例 3

患者：44歳・女性
主訴：腹部腫瘤感覚
妊娠歴：0回経妊娠、0回経産
既往歴：26歳：虫垂切除
現病歴：約4年前から不妊治療中であったが、腹部腫瘤感覚があり、前医受診したところ画像で8cm大の多胞性腫瘍がみられたため、当院紹介受診となった。画像所見・血液所見から悪性が強く疑われたため、開腹手術が施行された。

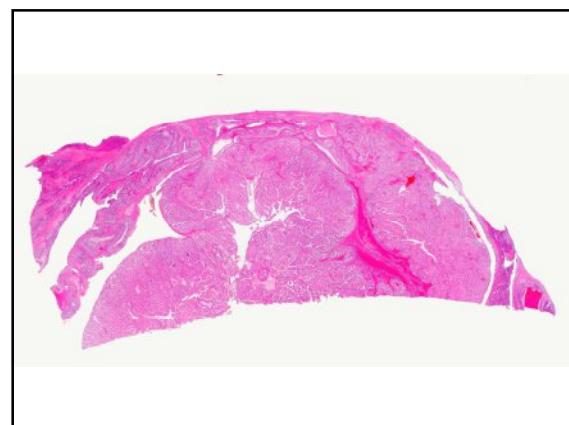
血液所見(術前)

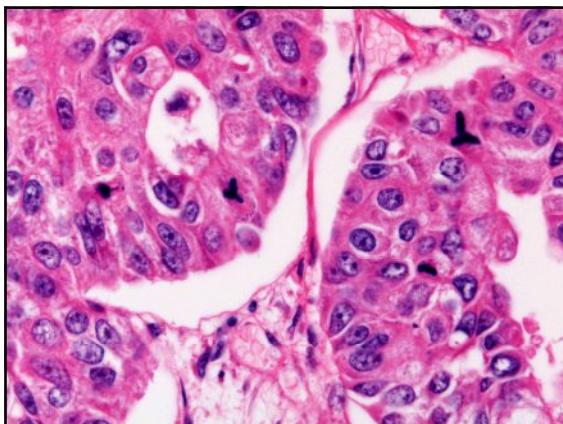
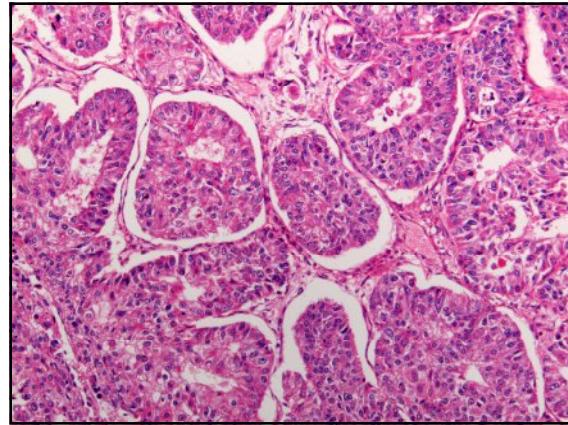
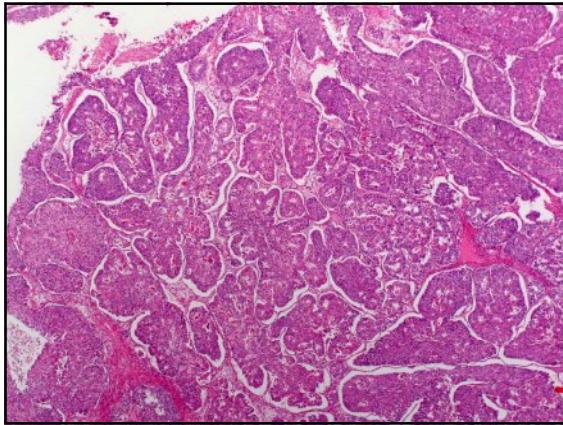
CEA:	15.0 ↑ ng/ml
CA19-9:	1696.0 ↑ U/ml
SCC:	0.9 ng/ml
CA125:	303.4 ↑ U/ml
LH:	17.5 ↓ mIU/ml
FSH:	16.4 ↓ mIU/ml
E2:	167.4 ↑ pg/ml
TS:	1.11 ↑ pg/ml (0.11–0.47)



MRI

画像診断:
malignant ovarian tumor





免疫染色

陽性

EMA, vimentin, AE1AE3, CK7,
PgR, ER

陰性

CEA, CK20, AFP, CD30,
 α -inhibin

病理診斷

Lt-ovarian tumor
endometrioid adenocarcinoma

鑑別診斷

- ✓ Sertoli-Leydig cell tumor
- ✓ Adult granulosa cell tumor
- ✓ Metastatic adenocarcinoma (colon, breast, uterus)
- ✓ High-grade serous carcinoma
- ✓ Female adnexal tumor of probable Wolffian origin
- ✓ Carcinoid tumor, insular or trabecular

診断のポイント

- 女性ホルモンの高値
- 男性ホルモンの軽度高値
- 免疫染色
 α -inhibinが陰性
 上皮系マーカーが陽性

症例 4

患者: 67歳・女性
 主訴: 腹部膨満感
 妊娠歴: 0回経妊、0回経産
 既往歴: 36歳:C型肝炎、42歳:子宮内膜症、
 67歳: 痛風・高血圧
 現病歴: 腹部膨満感があり、近医受診したところCT
 検査で、腹部腫瘍と両側水腎症がみられたため、
 当院に紹介受診となった。水腎症については両
 側尿管にステント挿入で腎機能が改善されたこと
 と腫瘍が悪性の可能性が考えられたことから開
 腹手術となつた。

血液所見(術前)

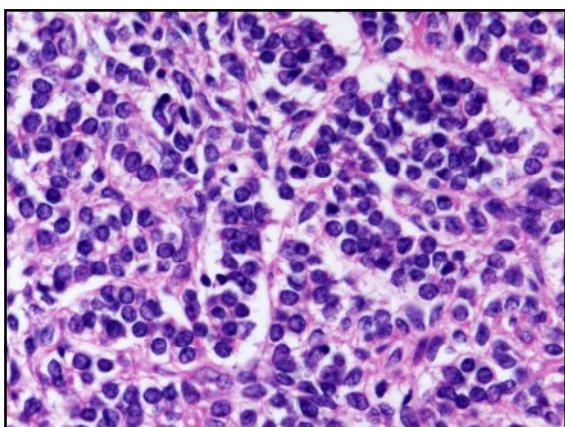
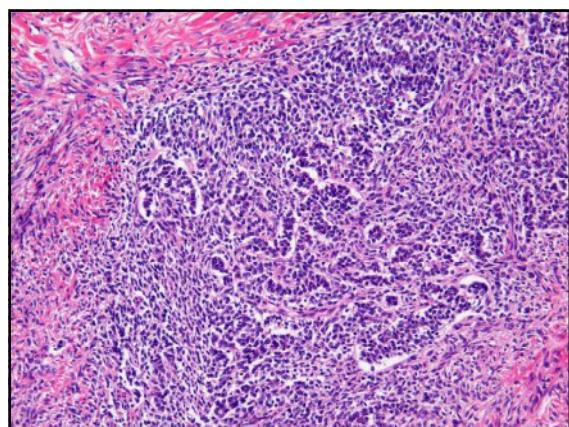
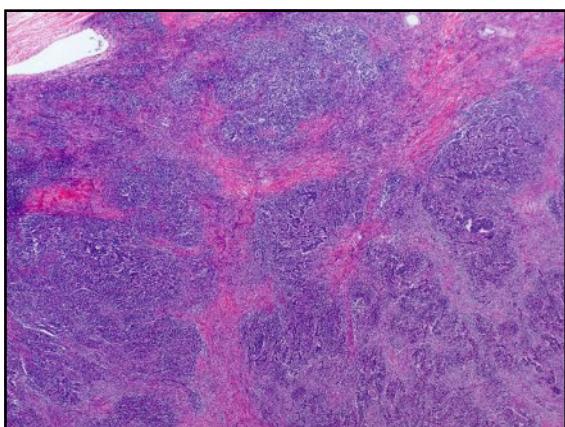
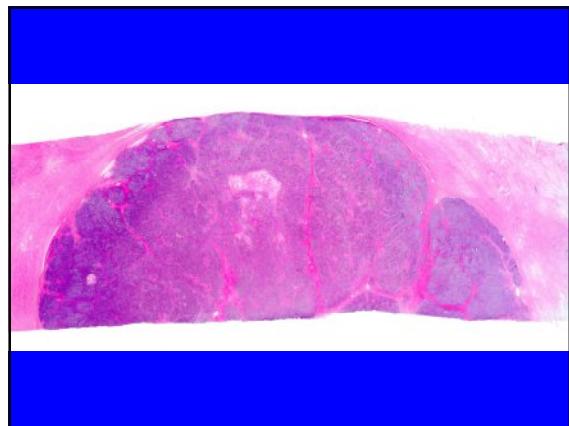
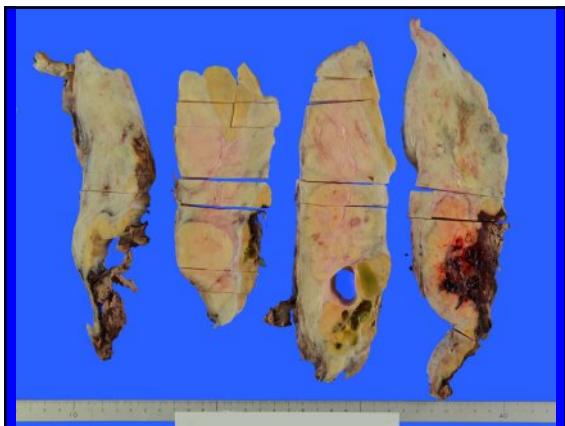
CEA:	8.8	ng/ml
CA19-9:	<0.6	U/ml
SCC:	2.5 ↑	ng/ml
CA125:	28.7	U/ml
LH:	7.5	mIU/ml
FSH:	0.2	mIU/ml
E2:	163.6 ↑	pg/ml
TS:	5.63 ↑	pg/ml (0.11-0.47)



MRI

画像診断:
 Malignant tumor
 (endometrioid
 carcinoma from
 adenofibroma)
 鑑別診断:
 Malignant Brenner
 否定的
 Fibrothecoma
 Granulosa cell tumor

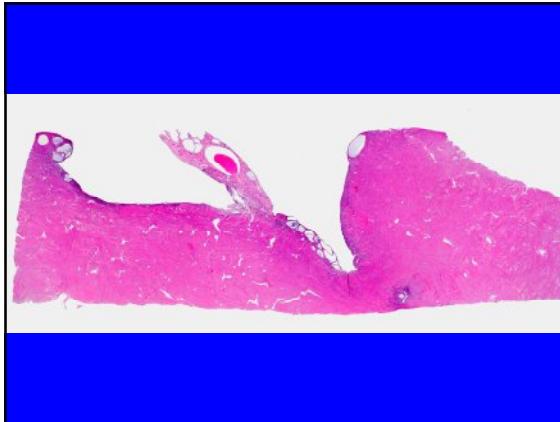




免疫染色

陽性
 α -inhibin

陰性
EMA, CEA, vimentin, AE1AE3,
CK7, CK20, AFP, CD30, ER, PgR



病理診断

Rt-ovarian tumor

Sertoli-Leydig cell tumor of intermediate differentiation

Endometriosis

Endometrial polyp

鑑別診断

- ✓ Sertoli cell tumor
- ✓ Adult granulosa cell tumor
- ✓ Endometrioid adenocarcinoma
- ✓ Serous borderline tumor

診断のポイント

- 男性ホルモン産生腫瘍
女性ホルモンも産生
- 臨床症状
男性化徵候
- 術中迅速診断では要注意
術式が決定される(良性～悪性)

ホルモン産生卵巣腫瘍

Causes	Hyperandrogenism	Hyperestrogenism
Ovarian disorders		
Sex cord-stromal tumors		
Sertoli stromal tumors		
Sertoli-Leydig cell tumor	Yes	Rarely
Stromal cell tumors		
Leydig cell tumor	Yes	Rarely
Stromal luteoma	Yes	Yes
Stromal cell tumor not otherwise specified	Yes	Rarely
Granulosa stromal tumors		
Granulosa cell tumor	Rarely	Yes
Thecoma	Rarely	Yes
Sclerosing stromal tumor	Yes	Yes
Sex cord tumor with annular tubules	No	Yes
Gynandroblastoma	Yes	No
Germ cell tumors		
Carcinoid (classified as a monodermal teratoma)	Yes	No
Gonadoblastoma	Yes	No
Surface epithelial tumors		
Serous tumors	No	Yes
Mucinous tumors	No	Yes
Endometrioid tumors	No	Yes
Brenner tumor	Yes	No
Secondary (metastatic tumor)	Yes	Yes

Tanaka YO, et al. Radiographics 2004; 24 Suppl 1:S147-166.

まとめ

臨床情報は重要(可能な限り得る)

- 症状
- 血液検査
- 画像所見
- 手術所見
- 腫瘍の所見(剖面・内容液の性状)