

第13回京都乳癌コンセンサス会議
ミニレクチャー「特殊型乳癌の病理」

第4回

Metaplastic carcinoma
化生癌

三上芳喜

京都大学医学部附属病院病理診断部

化生癌

Metaplastic carcinoma

- 非腺上皮、あるいは非腺上皮と間葉系細胞の表現型を示す多彩な浸潤性乳癌の一群
 - 扁平上皮細胞
 - 紡錘形細胞、軟骨細胞、骨細胞など

特殊型乳癌

乳癌取扱い規約第16版
(2008年)

- 粘液癌
- 髓様癌
- 浸潤性小葉癌
- 腺様嚢胞癌
- 扁平上皮癌
- 紡錘細胞癌
- アポクリン癌
- 骨・軟骨化生を伴う癌
- 管状癌
- 分泌癌(若年性癌)
- 浸潤性微小乳頭癌
- 基質産生癌
- その他

乳腺腫瘍のWHO分類(2003)

- Epithelial tumors
 - Invasive ductal carcinoma
 - Invasive lobular carcinoma
 - Tubular carcinoma
 - Invasive cribriform carcinoma
 - Medullary carcinoma
 - Mucinous carcinoma and other tumors with abundant mucin
 - Neuroendocrine tumors
 - Invasive papillary carcinoma
 - Invasive micropapillary carcinoma
 - Apocrine carcinoma
 - **Metaplastic carcinoma**
 - Lipid-rich carcinoma
 - Secretory carcinoma
 - Oncocytic carcinoma
 - Adenoid cystic carcinoma
 - Acinic cell carcinoma
 - Glycogen-rich clear cell carcinoma
 - Sebaceous carcinoma
 - Inflammatory carcinoma
 - Lobular neoplasia
 - Lobular carcinoma in situ
 - Intraductal proliferative lesions
 - UDH, FEA, ADH, DCIS
 - Microinvasive carcinoma
 - Intraductal papillary neoplasms
 - Benign epithelial proliferations

● 純粹型上皮性化生癌

- 扁平上皮癌
- 紡錘細胞化生を伴う腺癌
- 腺扁平上皮癌
- 粘表皮癌
- 低悪性度腺扁平上皮癌(浸潤性汗管腺腫)

● 上皮・間葉系混合型化生癌

- 骨化生を伴う癌腫
- 軟骨化生を伴う癌腫
- 基質産生癌
- 癌肉腫(癌腫成分と肉腫成分の混在)

乳癌の各組織型の頻度

| | |
|--------------------|--------|
| In situ carcinoma | 15-30% |
| 非浸潤性乳管癌 | 80% |
| 非浸潤性小葉癌 | 20% |
| Invasive carcinoma | 70-85% |
| 乳管癌(非特殊型) | 79% |
| 小葉癌 | 10% |
| 管状癌 / 篩状癌 | 6% |
| 粘液癌 | 2% |
| 髓様癌 | 2% |
| 乳頭癌 | 1% |
| 化生癌 | <1% |

Modified from; Robbins and Cotran Pathologic Basis of Disease, Professional Edition, 8th Edition

化生癌

Metaplastic carcinoma

●MMG

- 非特異的
- 腫瘍径大
- 周囲境界明瞭、石灰化なし⇒一見良性
- 上皮成分は spiculated mass
- 骨形成がある場合は不透過影
- 扁平上皮分化がある場合は嚢胞形成

化生癌

Metaplastic carcinoma

- MRI

- T2強調画像で高信号

Choi BB et al. Acta Radiol Feb 1;53(1):5-11.

化生癌

Metaplastic carcinoma

- 紡錘細胞(肉腫樣)癌(29例)
 - 年齡: 40-96歲(median、68歲)
 - 腫瘍徑: 1.5-15 cm(median、4 cm)

Carter MR et al. Spindle cell (sarcomatoid) carcinoma of the breast. AJSP 2006: 30: 300-309.

化生癌

Metaplastic carcinoma

●臨床病理学的特徴

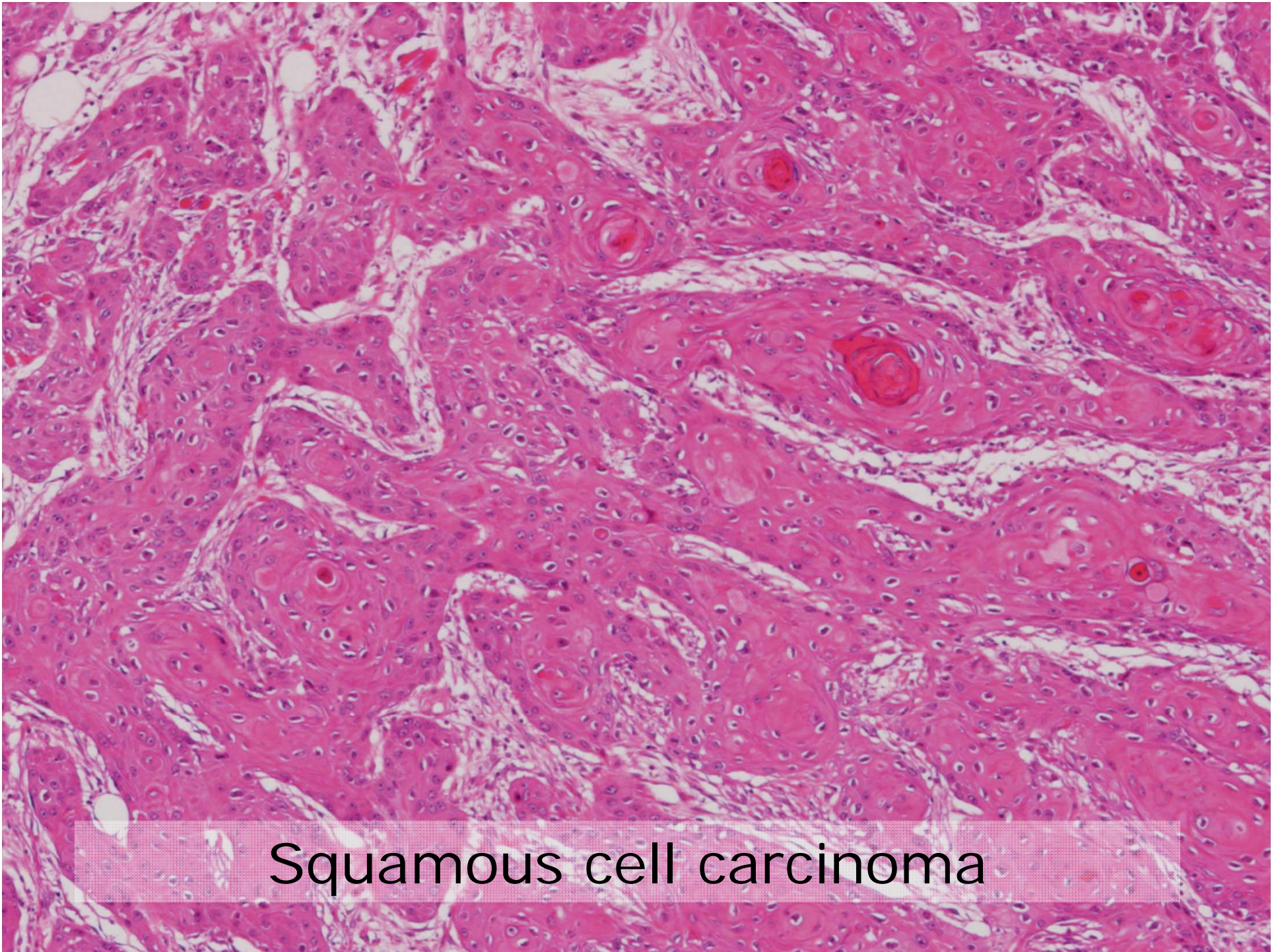
- 腫瘍径大
- リンパ節転移の頻度が低い
- 進行例が多い
- 悪性度（grade）が高い
- ER陰性例が多い

Pezzi CM et al. Ann Surg Oncol 2007; 14: 166-73.

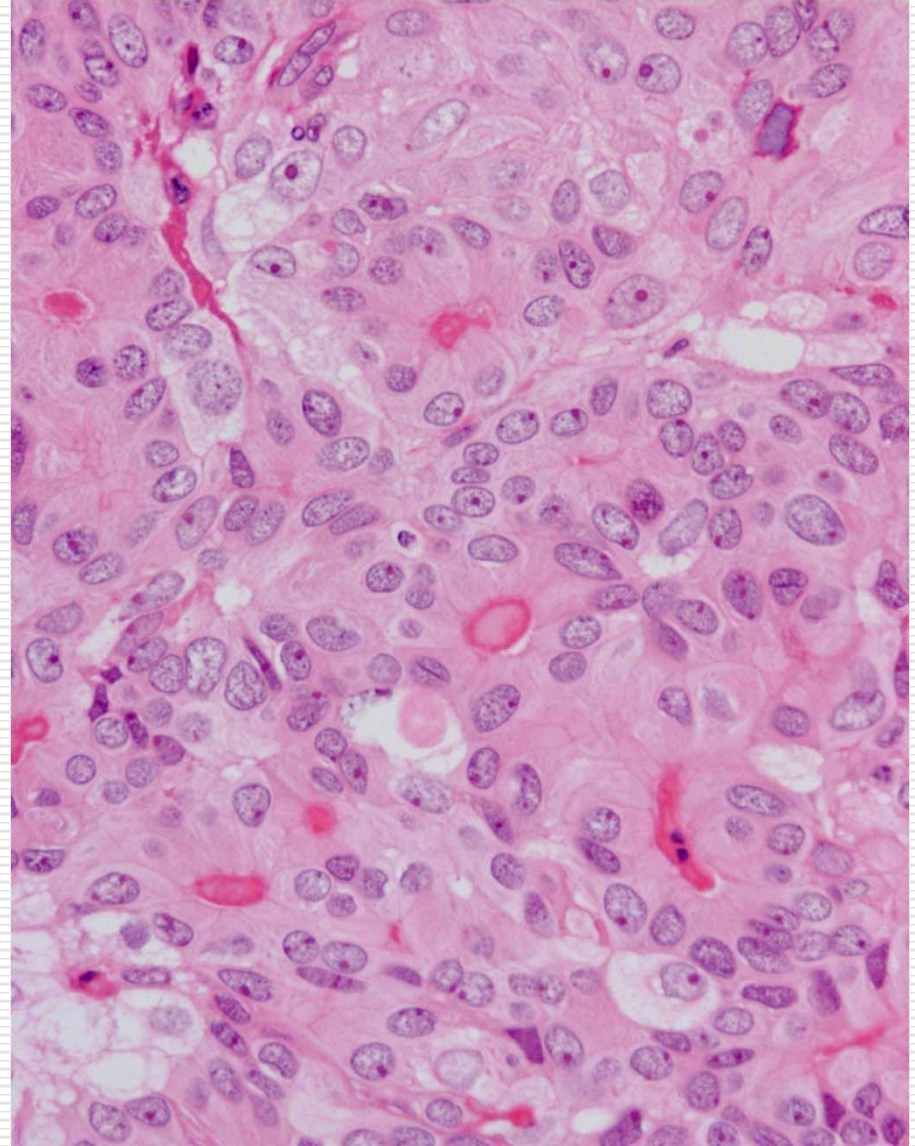
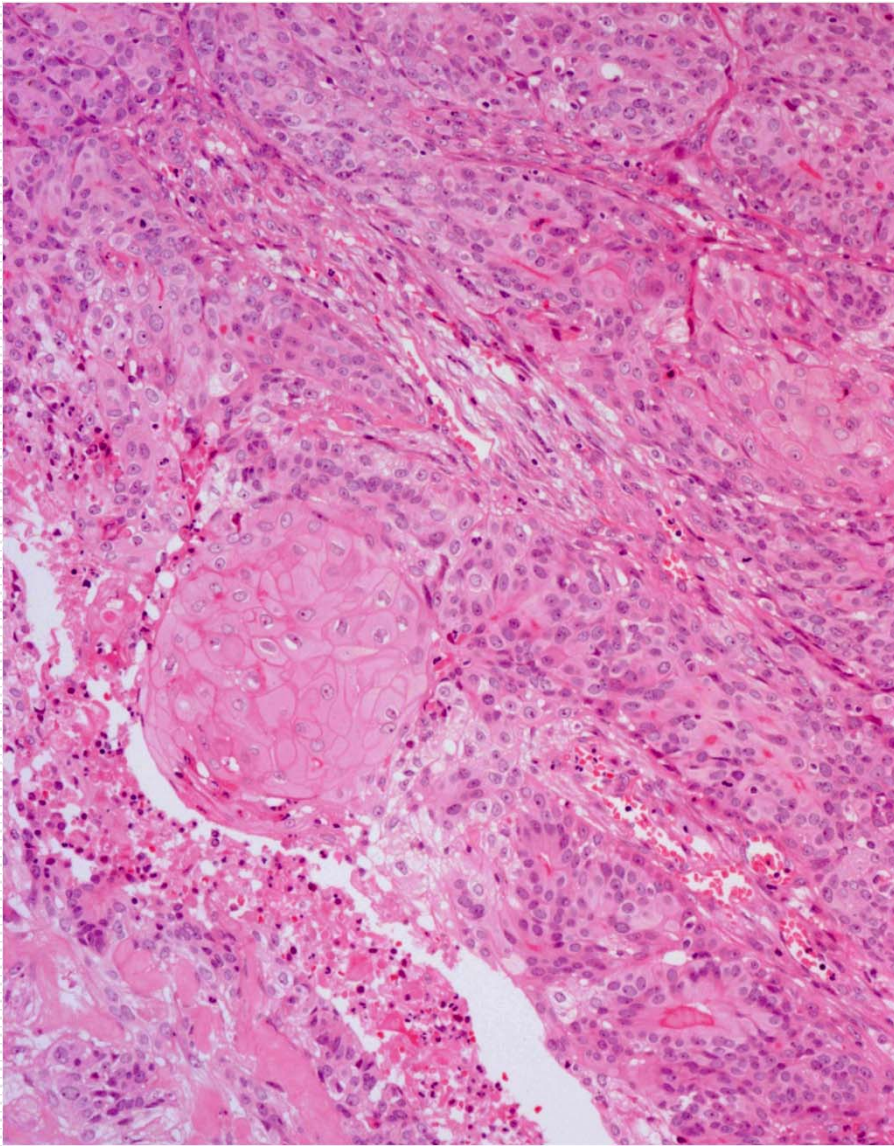
| Characteristics | MBC | IDC | Odds ratio | P value |
|----------------------|--------------------|------------------------|------------|---------|
| No | 892 | 255,164 | | |
| Mean age (y) | 61.1 | 59.7 | | < .001 |
| Proportion > 80y old | 120 (13.5%) | 24,028 (9.4%) | | < .001 |
| African American | 126 (14.1%) | 25,900 (10.2%) | 1.455 | < .001 |
| Hispanic | 49 (5.5%) | 9,947 (3.9%) | 1.817 | < .001 |
| Tumor size | | | | |
| < 2 cm | 238 (29.5%) | 149,071 (65.2%) | .7 | < .01 |
| 2-5 cm | 404 (49.6%) | 67,536 (29.5%) | | |
| > 5 cm | 165 (20.4%) | 11,894 (5.2%) | | |
| Node positive | 174 (21.9%) | 81,698 (34.3%) | 2.000 | < .001 |

Analysis of 892 cases from the National Cancer Data Base

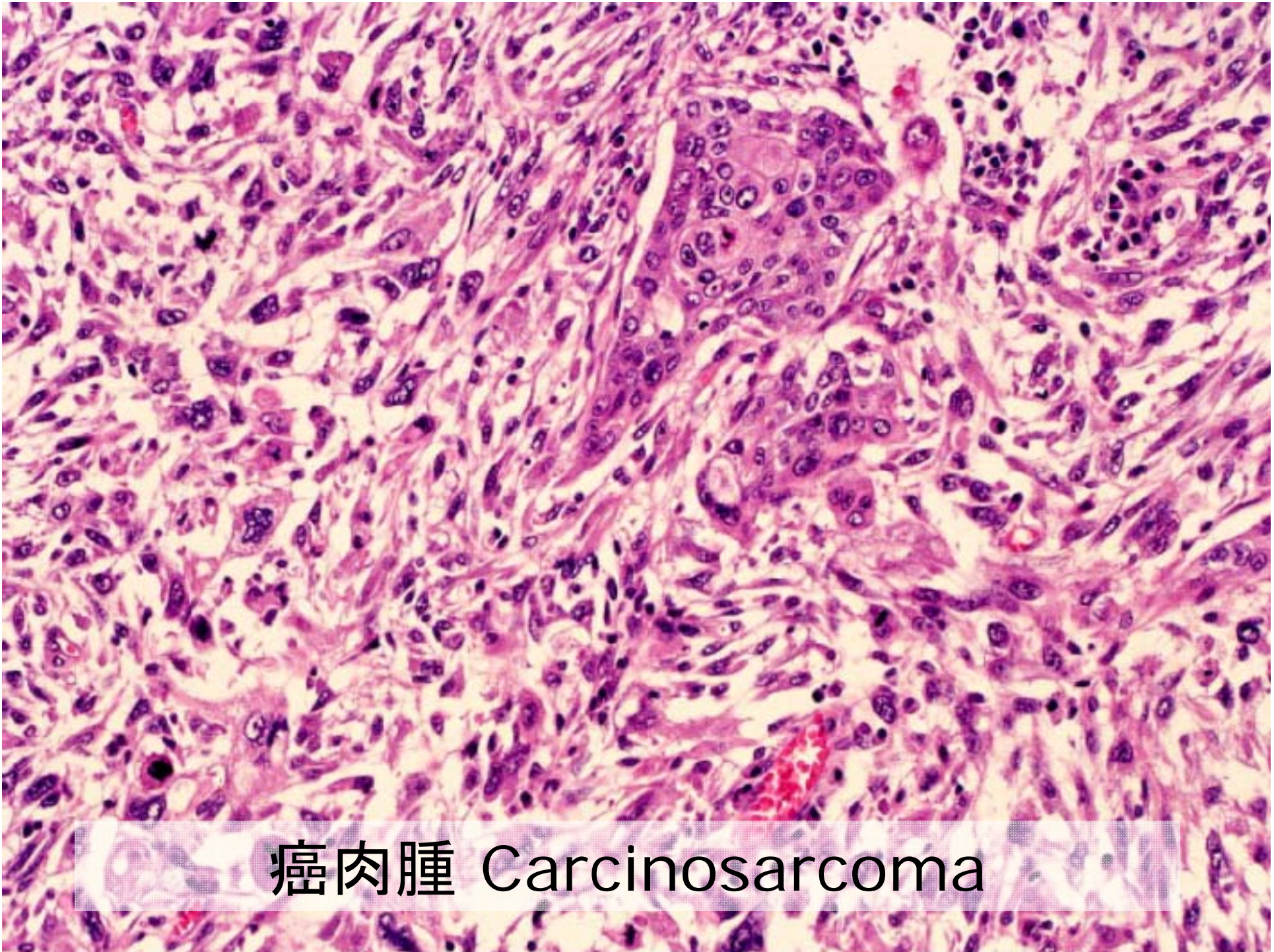
Pezzi CM et al. Ann Surg Oncol 2007; 14: 166-73.



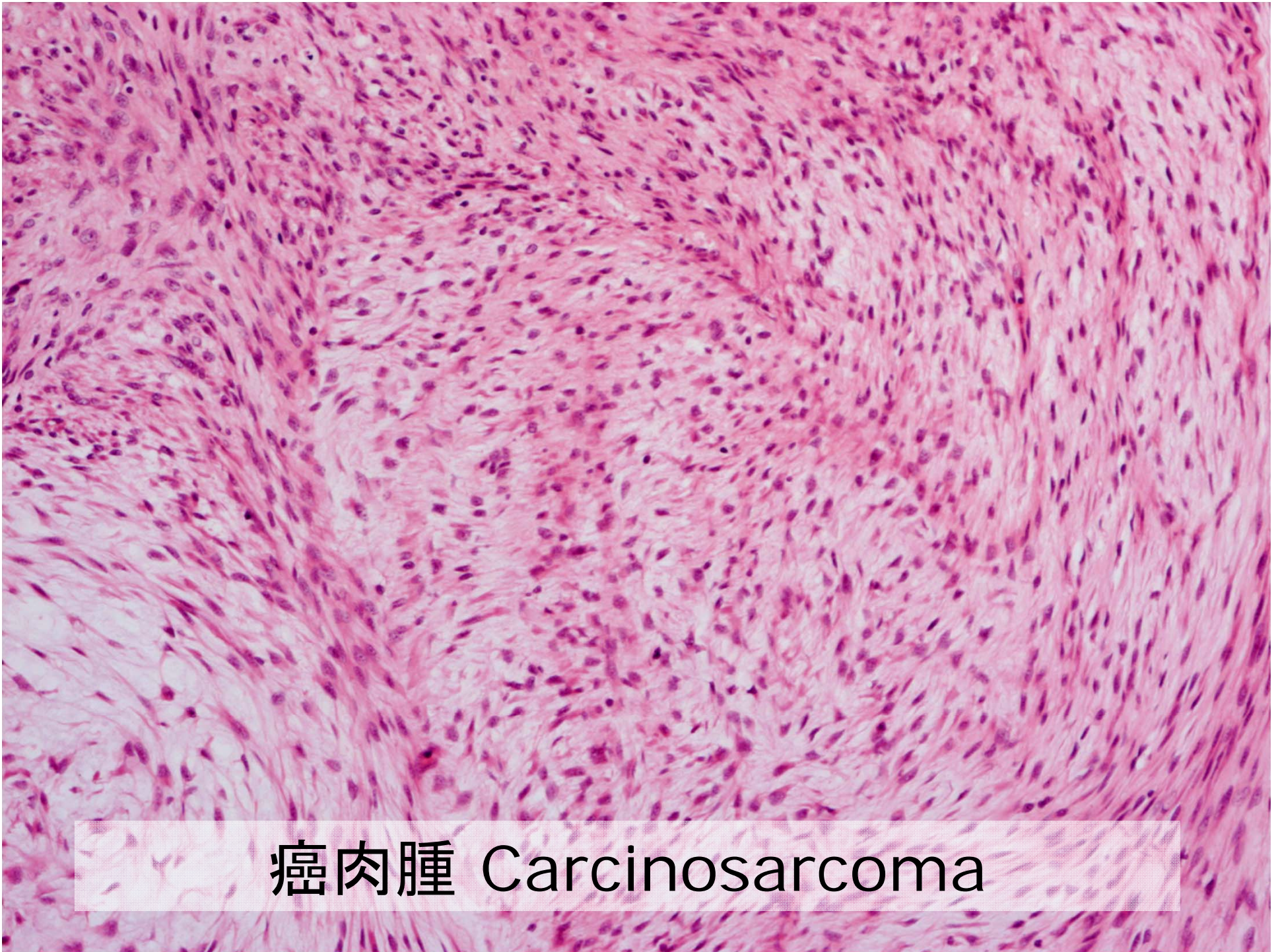
Squamous cell carcinoma



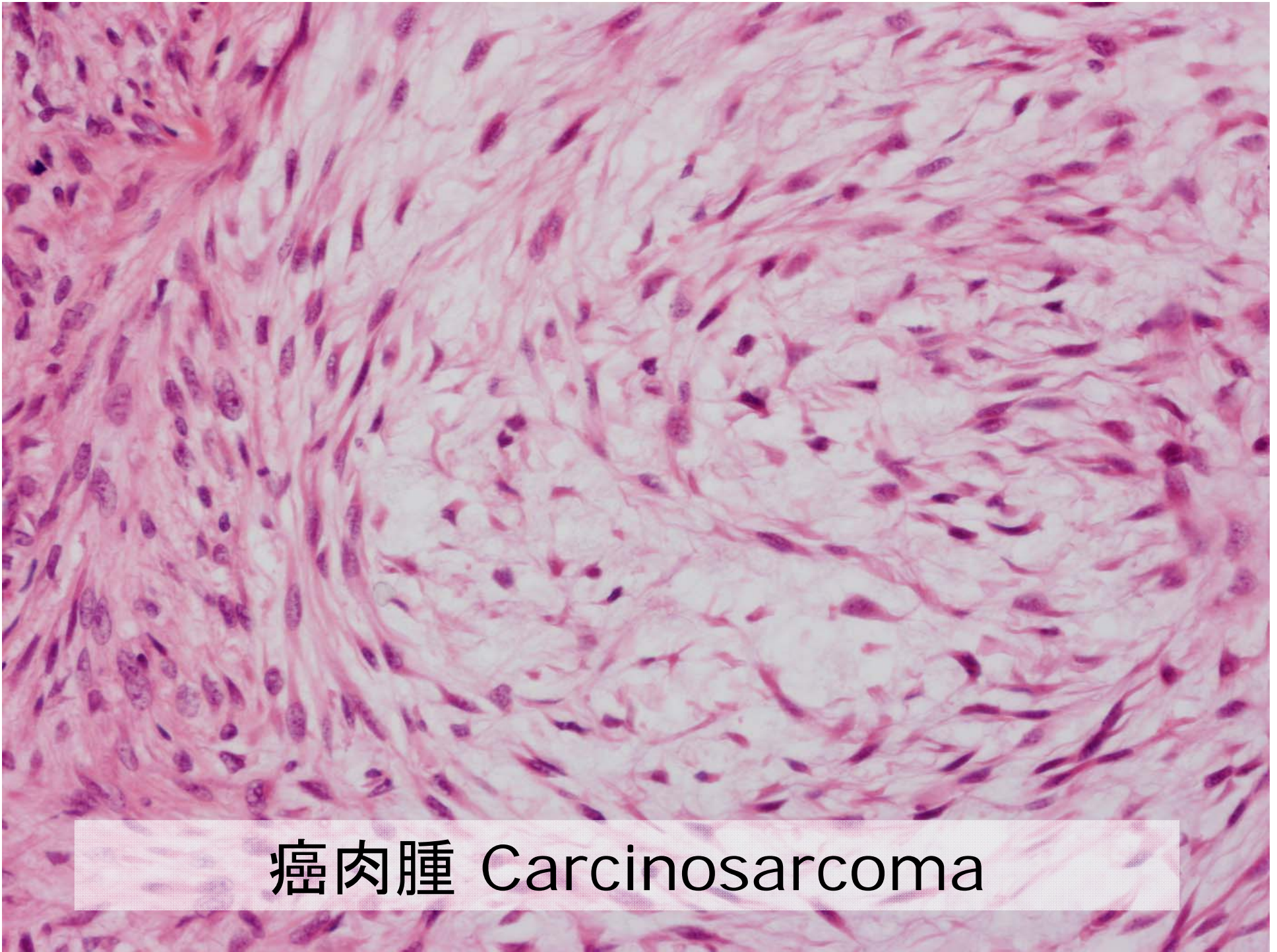
腺扁平上皮癌 Adenosquamous carcinoma



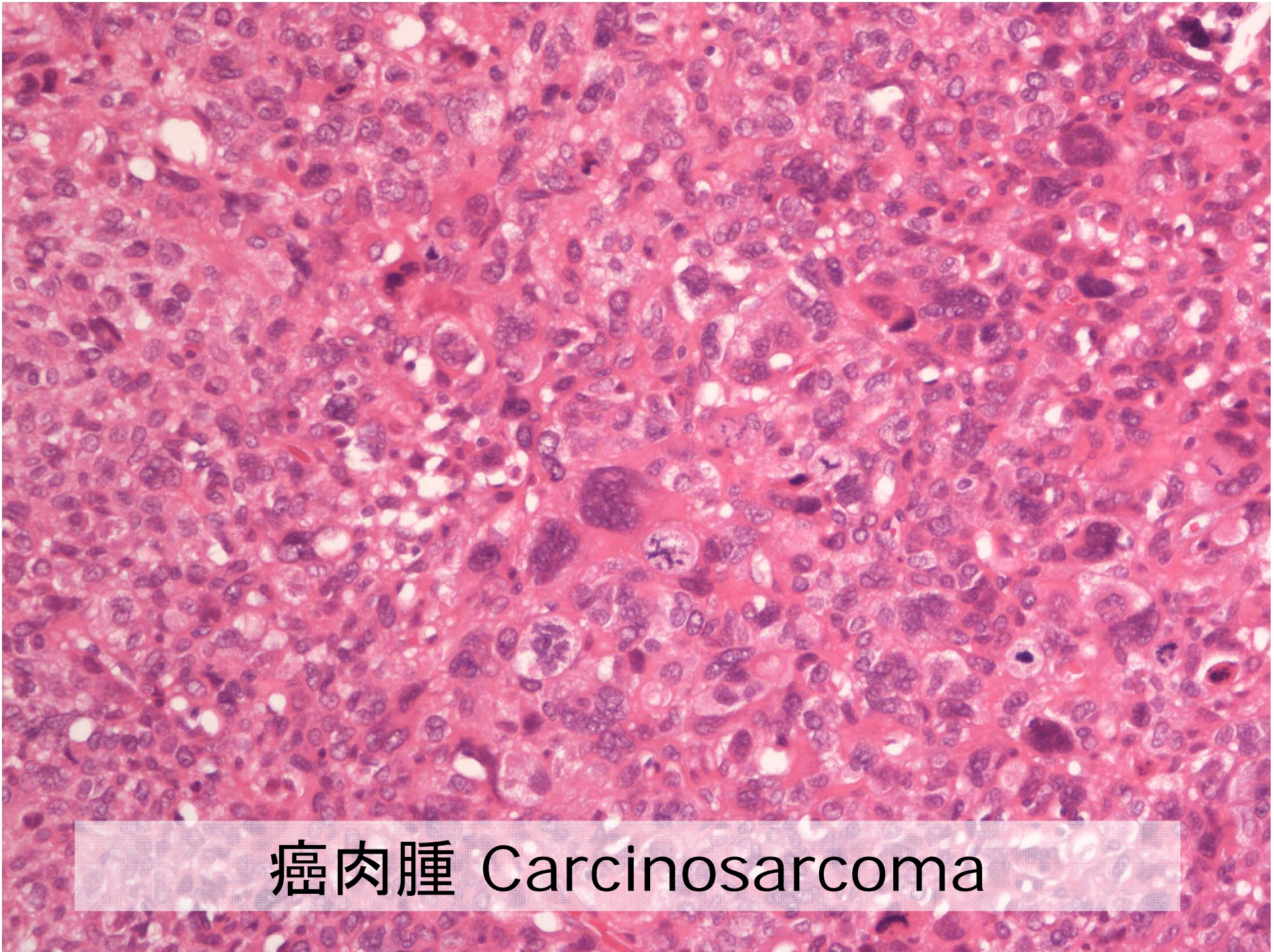
癌肉腫 Carcinosarcoma



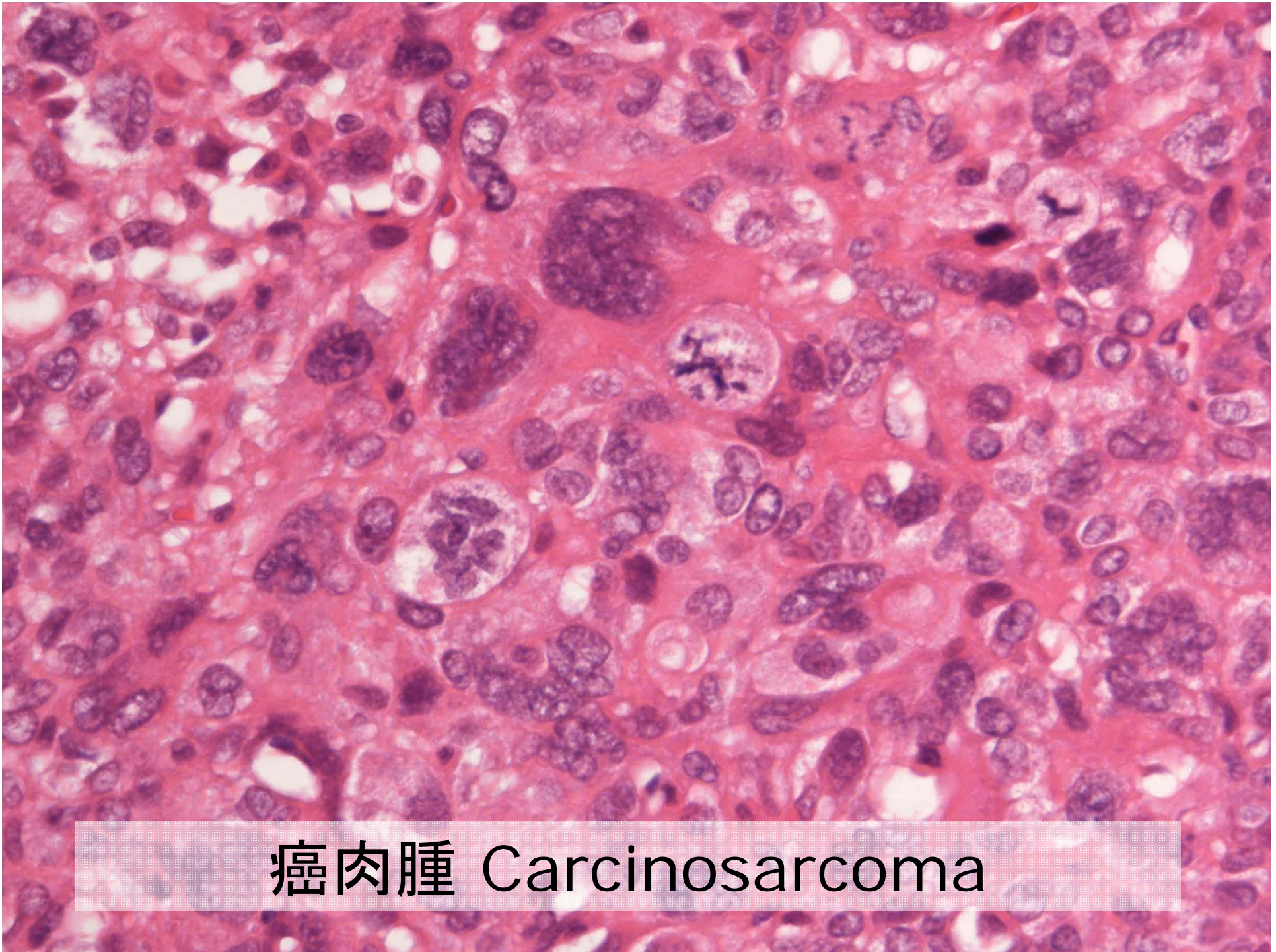
癌肉腫 Carcinosarcoma



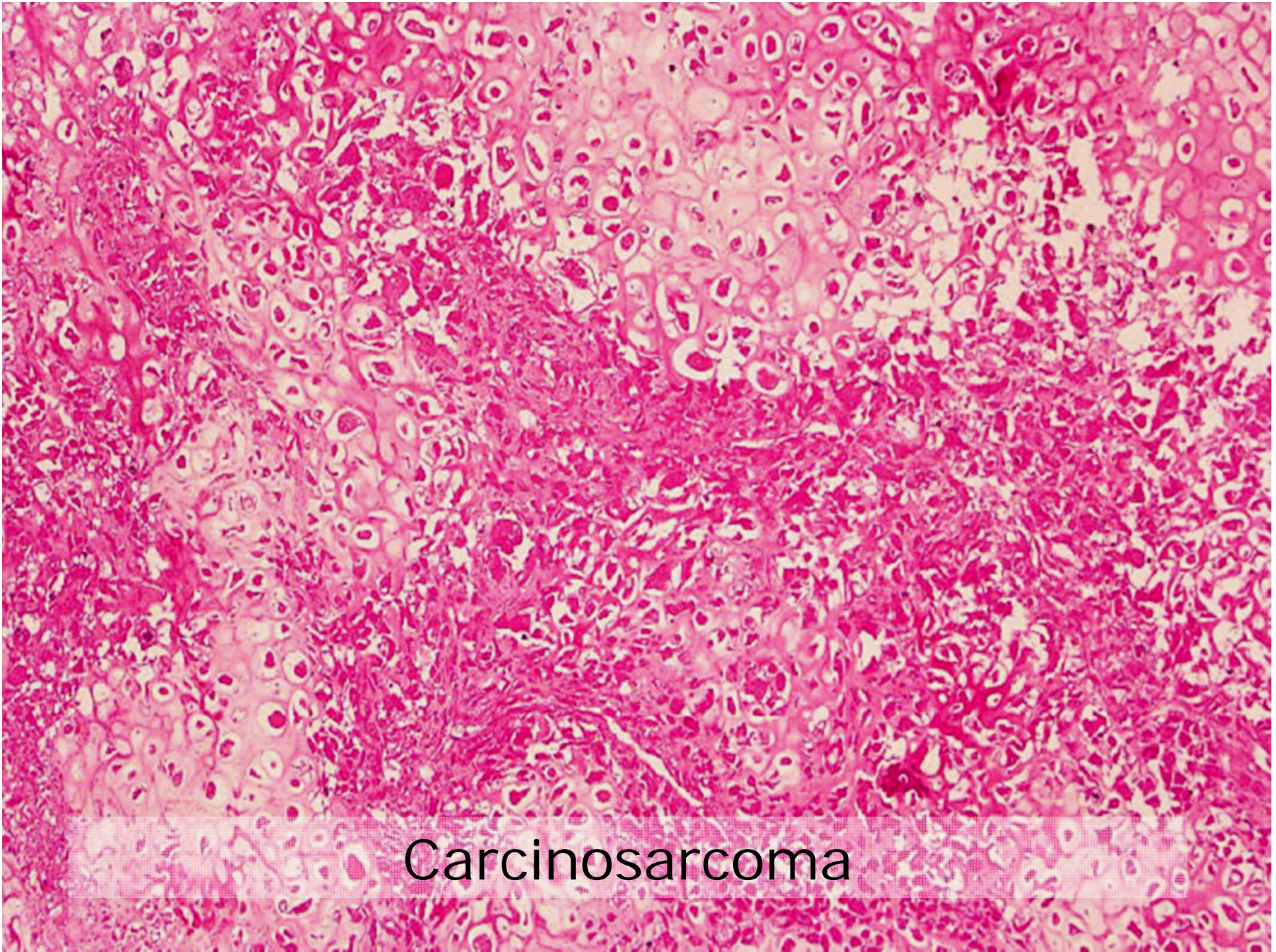
癌肉腫 Carcinosarcoma



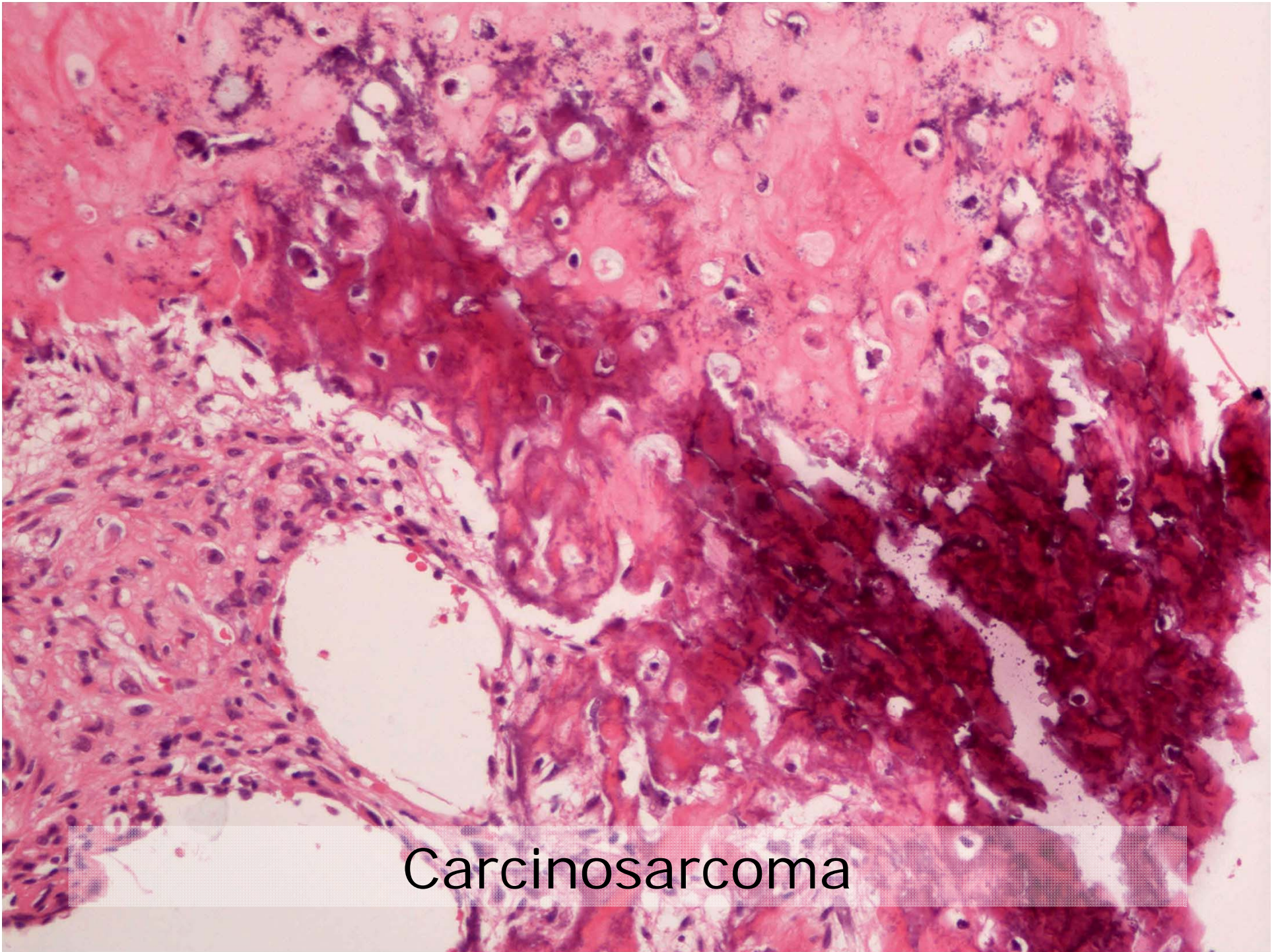
癌肉腫 Carcinosarcoma



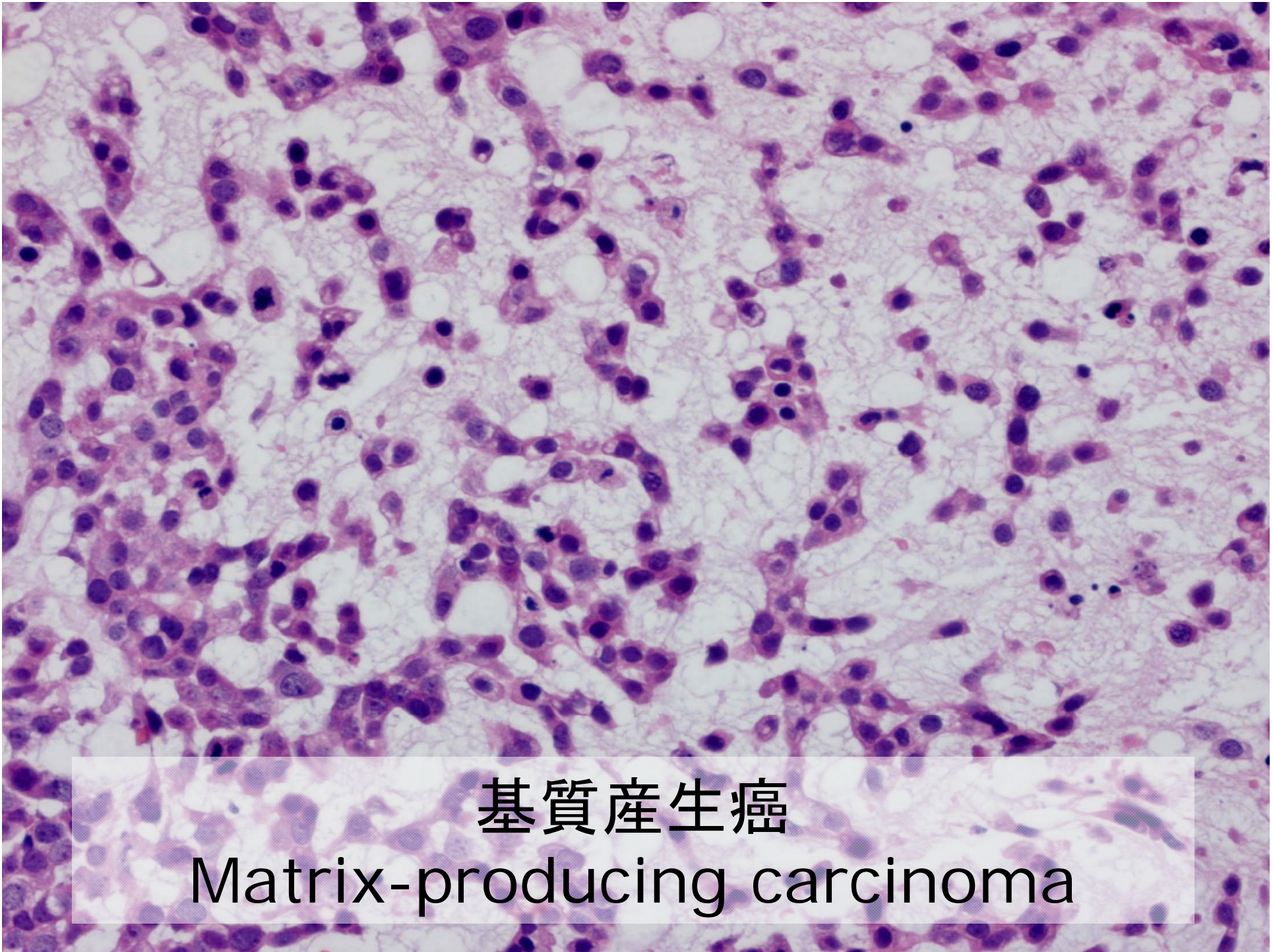
癌肉腫 Carcinosarcoma



Carcinosarcoma



Carcinosarcoma



基質產生癌

Matrix-producing carcinoma

化生癌

Metaplastic carcinoma

●免疫組織化学的表現型

- サイトケラチン
 - CAM5.2、AE1/AE3、CK7
 - 34βE12、CK5/6(基底細胞ケラチン)
- EMA(MUC1)
- TNT(ER陰性;PR陰性;HER2陰性)
- ビメンチン、p63、EGFR
- p53

化生癌

Metaplastic carcinoma

| Characteristics | MBC | IDC | Odds ratio | P value |
|-----------------|-------------------|------------------------|------------|------------------|
| No | 892 | 255,164 | | |
| ER | | | | |
| Positive | 72 (11.3%) | 137,050 (74.1%) | 22.4 | < .001 |
| Negative | 564 (88.7%) | 47,887 (25.9%) | | |
| PR | | | | |
| Positive | 66 (10.4%) | 114,061 (62.4%) | 14.2 | < .001 |
| Negative | 566 (89.6%) | 68,875 (37.6%) | | |

Pezzi CM et al. Ann Surg Oncol 2007; 14: 166-73.

化生癌

Metaplastic carcinoma

| Characteristics | MBC | IDC | P value |
|-----------------|---------------------|----------------------|------------------|
| No | 35 | 2,839 | |
| ER | | | |
| Positive | 2 (5.7%) | 1,856 (65.4%) | < .001 |
| Negative | 33 (94.3%) | 975 (34.3%) | |
| PR | | | |
| Positive | 3 (8.6%) | 1,583 (55.8%) | < .001 |
| Negative | 32 (91.4%) | 1,250 (44.0%) | |
| HER2 | | | |
| Negative | 30 (85.7%) | 1,571 (55.3%) | 0.03 |
| Positive | 3 (8.6%) | 541 (19.1%) | |
| Unknown | 2 (5.7%) | 727 (25.6%) | |
| TNT | 28 (80.0%) | 473 (16.7%) | < .001 |
| Ki-67 | 35.5 ± 26.2% | 20.6 ± 19.8% | 0.02 |

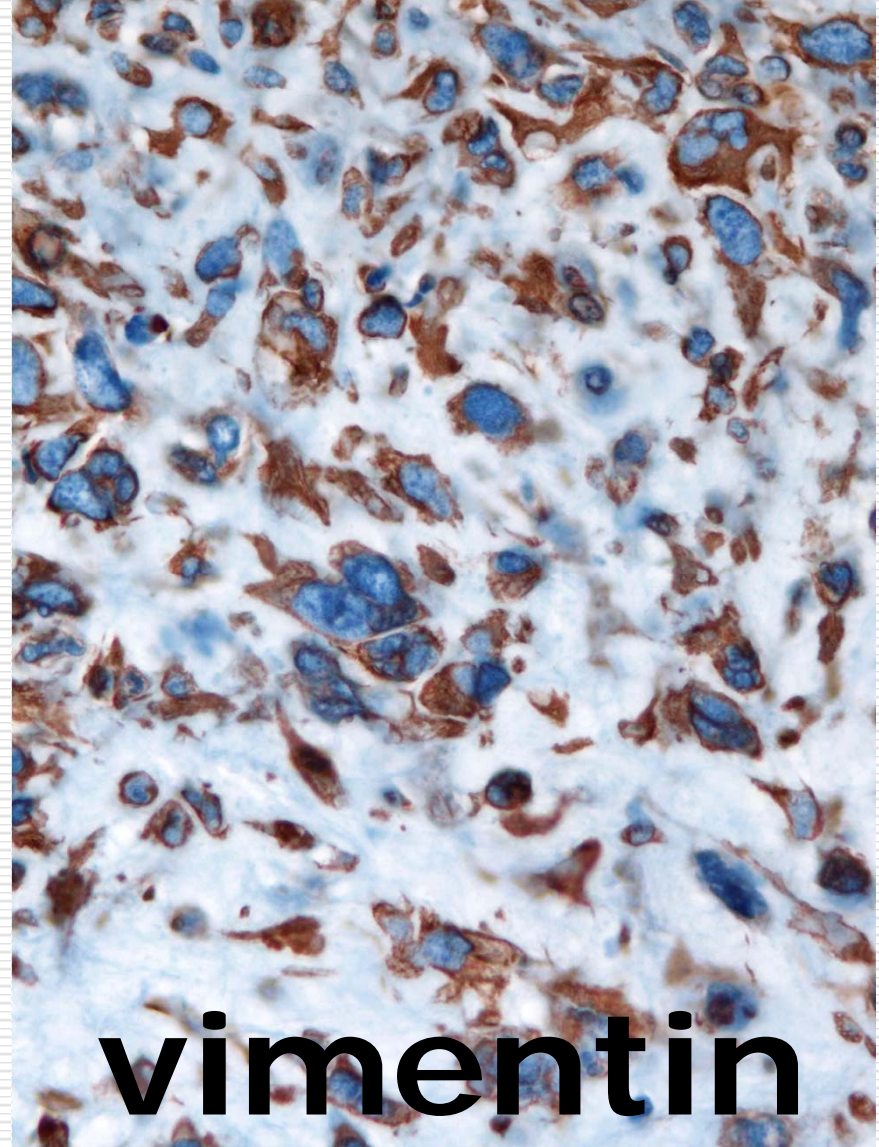
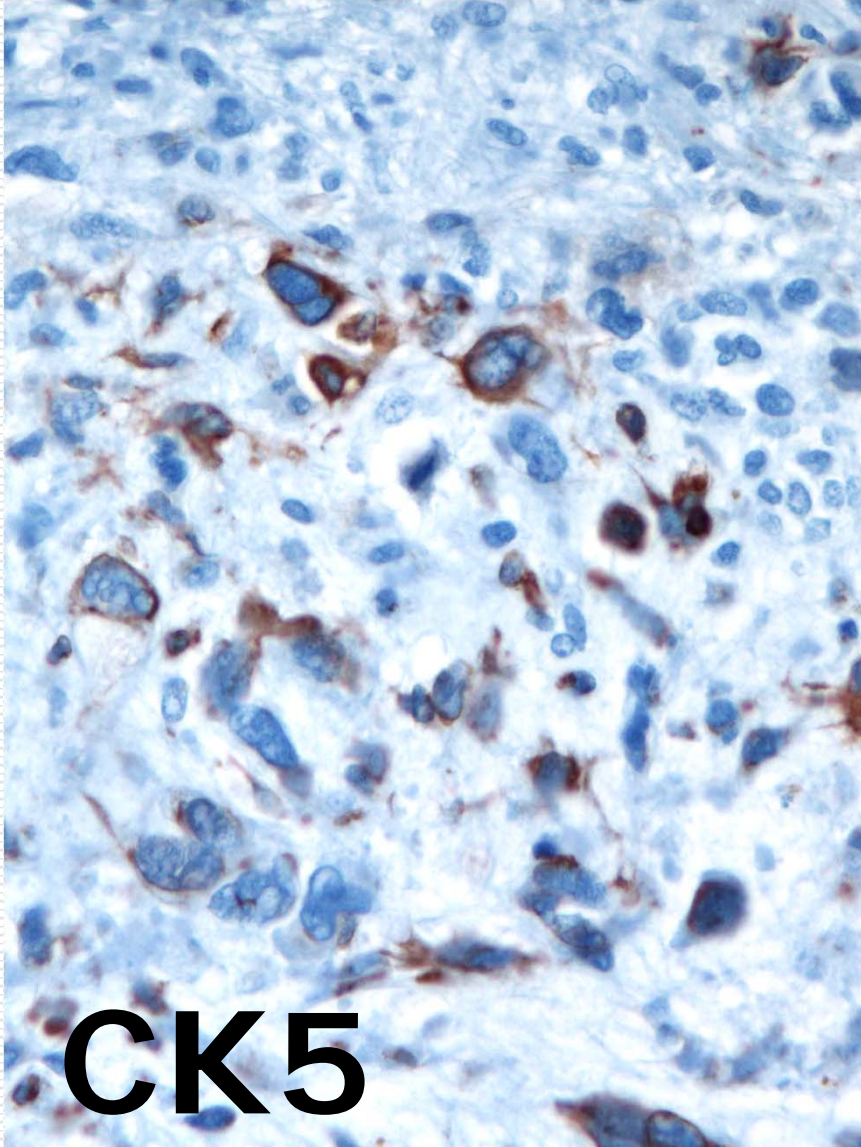
Jung SY et al. Breast Cancer Res Treat Apr;120: 627-37.

化生癌

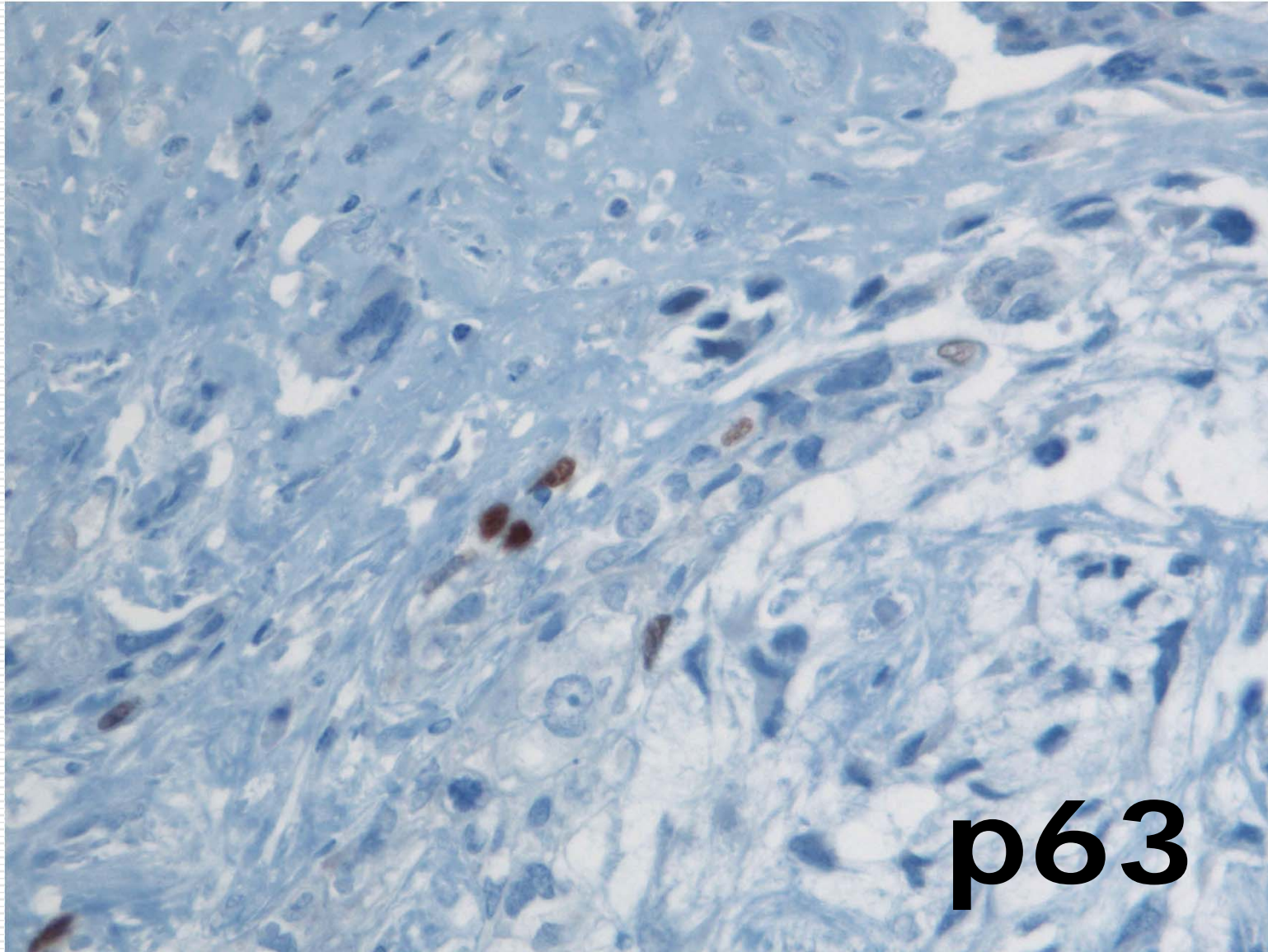
Metaplastic carcinoma

| Case | Diagnosis | ER | PR | HER2 | CK5/6 | CK14 | p63 | EGFR |
|------|--|------|------|------|-------|------|------|-------|
| 1 | Carcinoma with chondroid metaplasia | — | — | — | ++ | + | + | +++ |
| 2 | Carcinoma with spindle cell metaplasia | — | — | — | +++ | ++ | — | +++ |
| 3 | Adenosquamous carcinoma | — | — | — | ++ | — | — | ++ |
| 4 | Squamous carcinoma | — | — | — | +++ | ++ | + | +++ |
| 5 | Carcinoma with chondroid metaplasia | — | — | — | ++ | ++ | ++ | ++ |
| 6 | Carcinoma with osseous metaplasia | — | — | — | ++ | — | — | ++ |
| 7 | Carcinoma with chondroid metaplasia | — | — | — | ++ | — | + | — |
| 8 | Carcinoma with spindle cell metaplasia | — | — | — | +++ | +++ | + | +++ |
| 9 | Squamous carcinoma | — | — | — | +++ | + | ++ | ++ |
| 10 | Squamous carcinoma | — | — | — | +++ | +++ | + | +++ |
| 11 | Adenosquamous carcinoma | — | — | — | +++ | + | — | +++ |
| 12 | Squamous carcinoma | — | — | — | +++ | ++ | ++ | — |
| | | 0/12 | 0/12 | 0/12 | 12/12 | 9/12 | 8/12 | 10/12 |

Wang H et al. Med Oncol Mar; 28: 42-50.

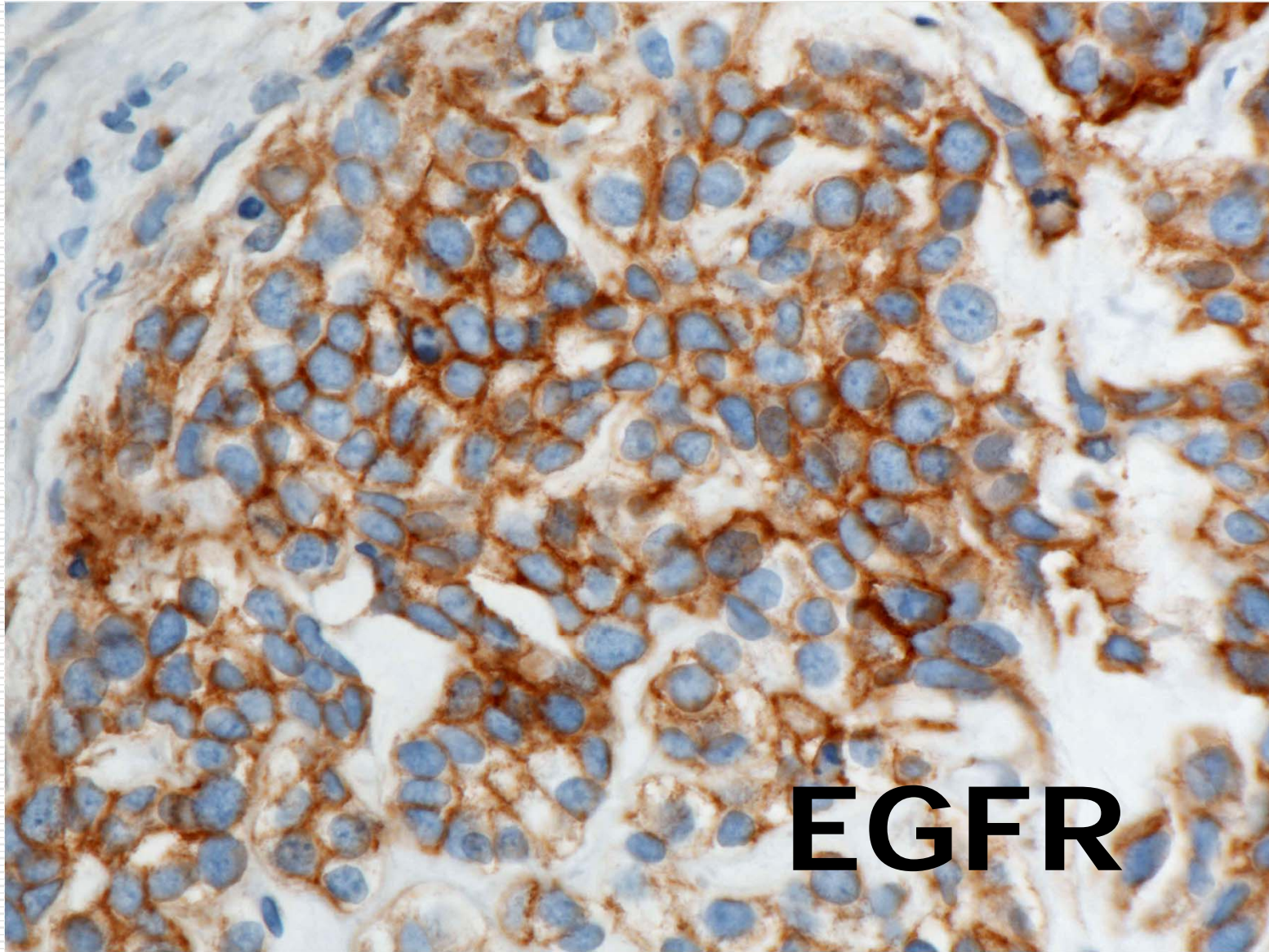


Carcinosarcoma



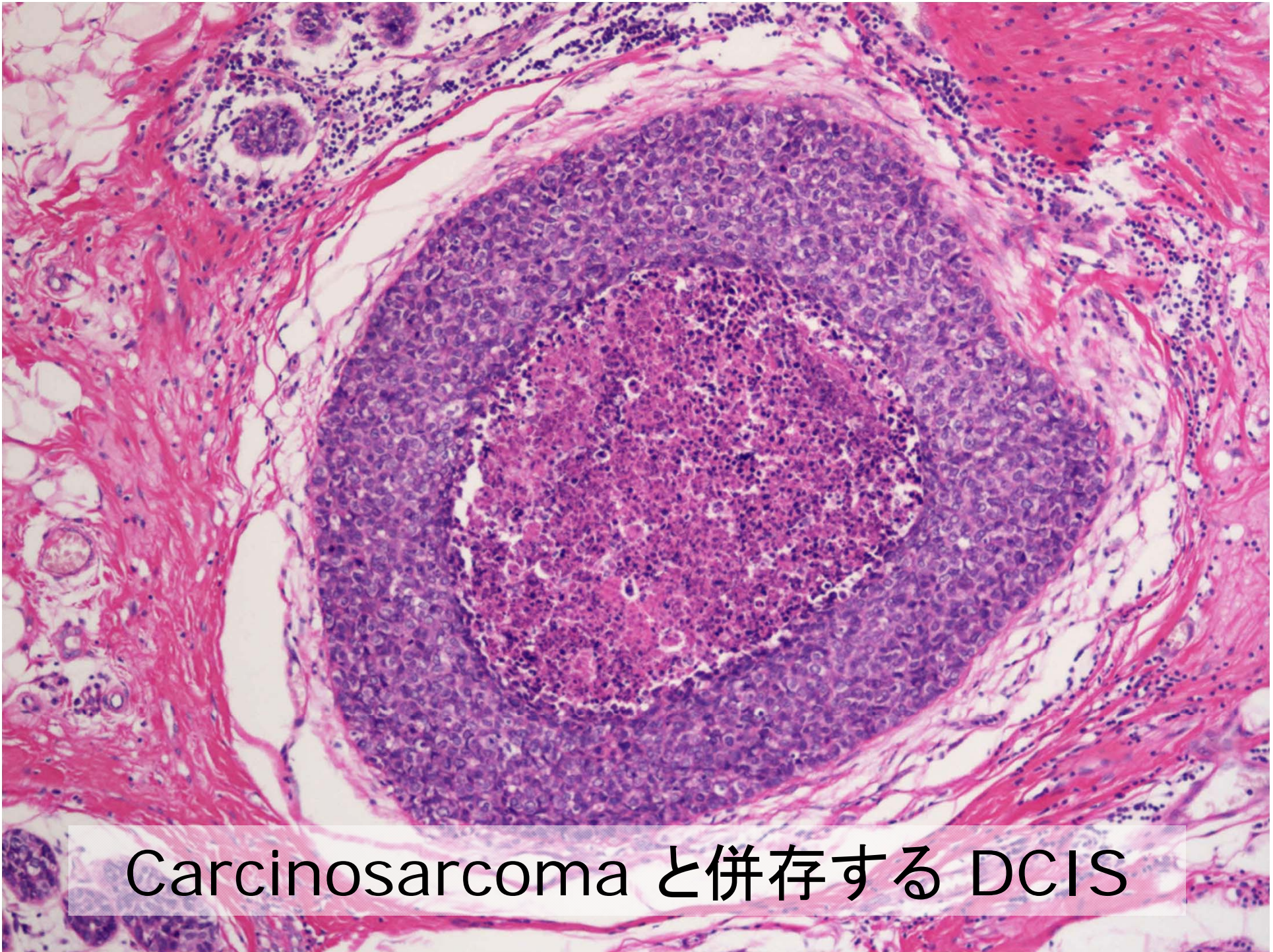
p63

Carcinosarcoma

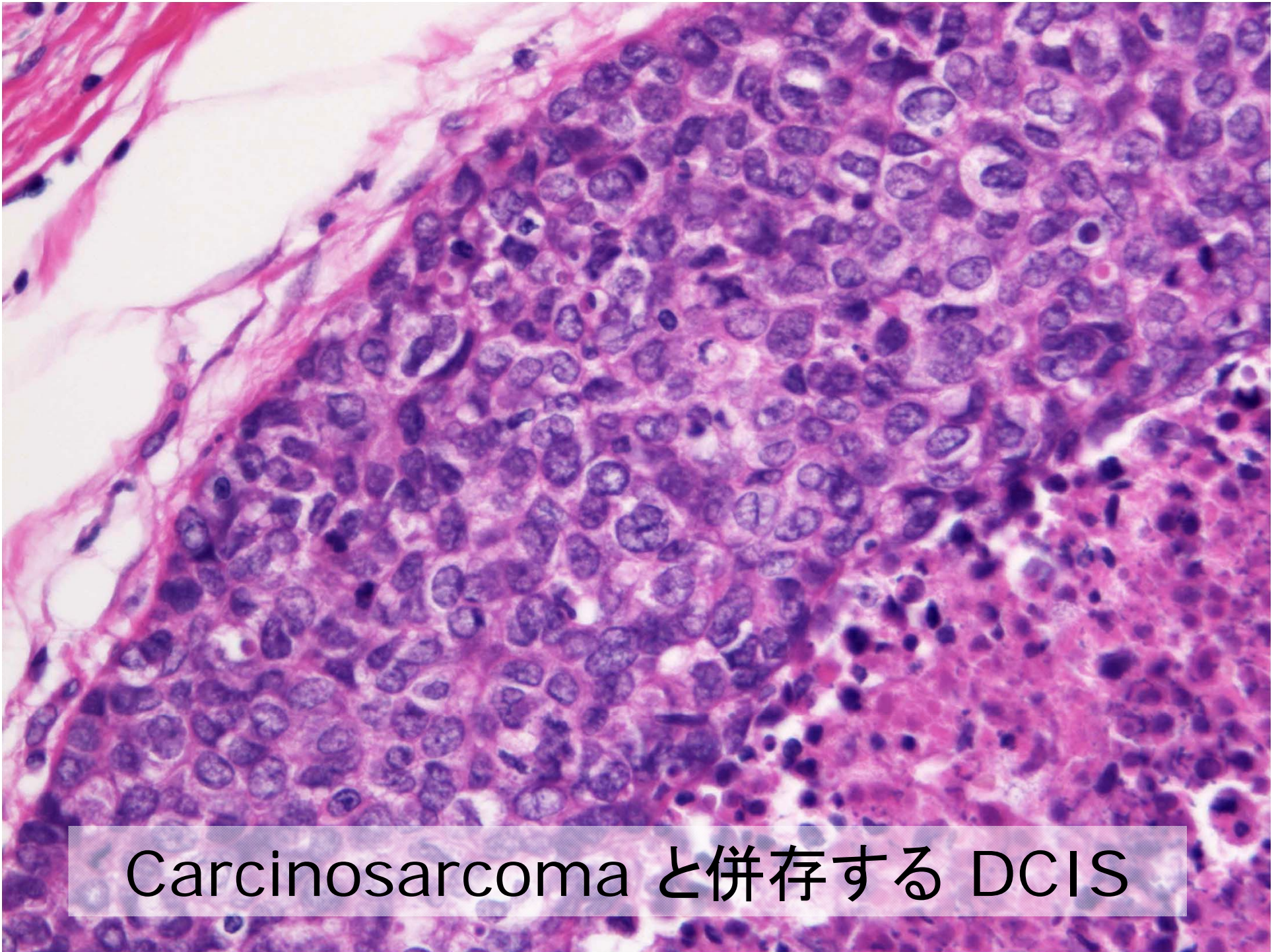


EGFR

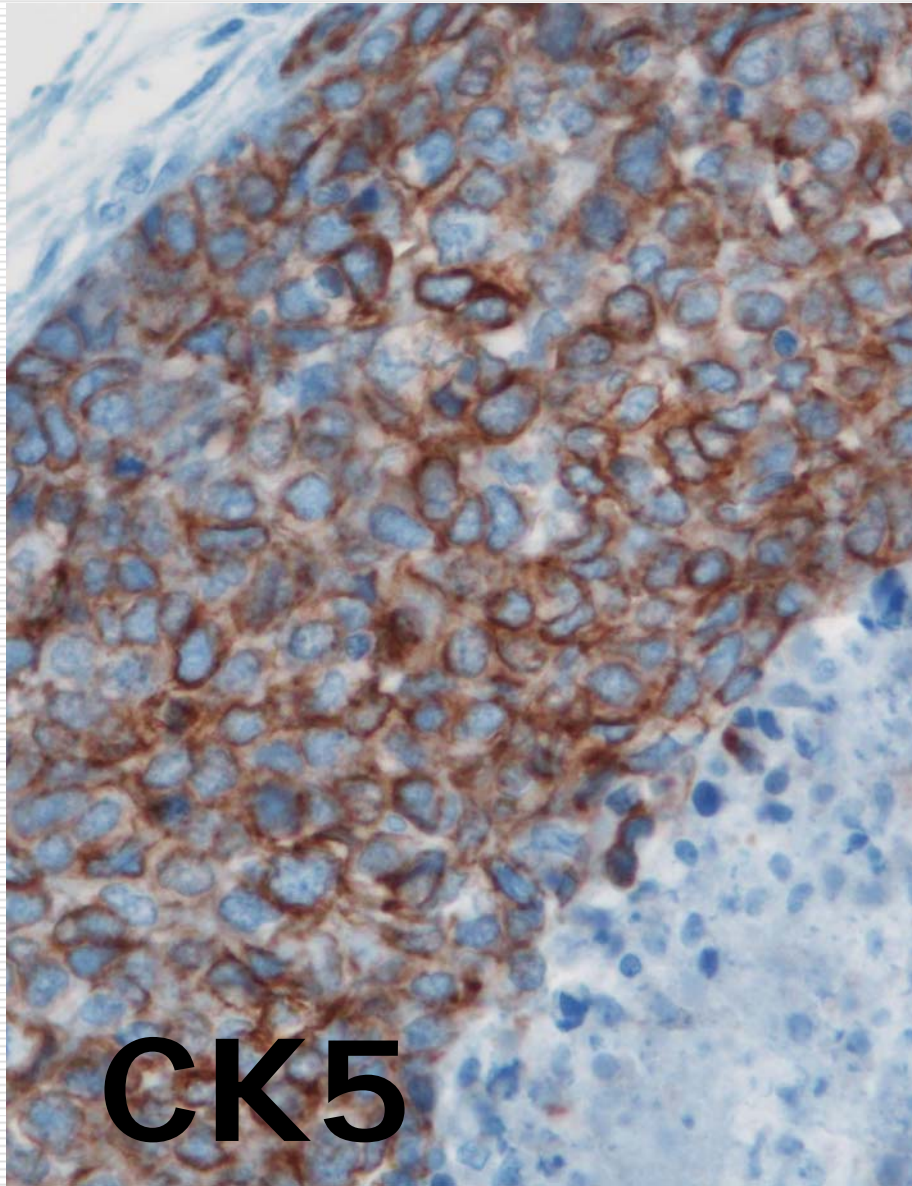
Carcinosarcoma (matrix-producing)



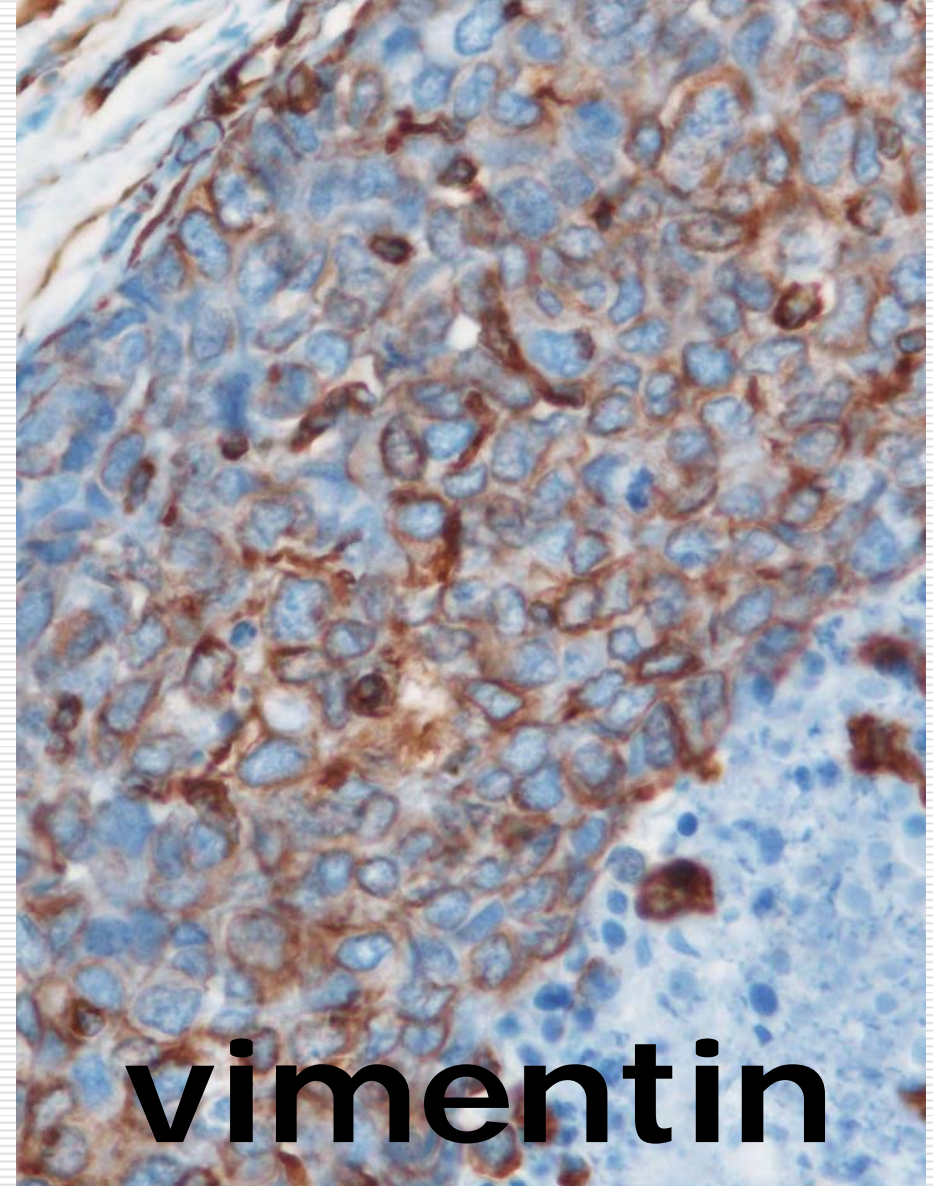
Carcinosarcoma と併存する DCIS



Carcinosarcoma と併存する DCIS



CK5



vimentin

Carcinosarcoma と併存する DCIS

化生癌の95%は基底様分子亜型に属する

Table 1 Characteristics of 20 metaplastic breast cancers

| MBCs | Molecular subtype ^a | Histological grade | ER | PgR | HER2 | CK5/6 |
|------------------|--------------------------------|--------------------|-----|-----|------|-------|
| Metaplastic_3651 | Basal-like | 2 | -ve | -ve | -ve | -ve |
| Metaplastic_3653 | Basal-like | 3 | -ve | -ve | -ve | +ve |
| Metaplastic_3654 | Basal-like | 3 | -ve | -ve | -ve | -ve |
| Metaplastic_3659 | Basal-like | 3 | -ve | -ve | -ve | +ve |
| Metaplastic_3660 | Basal-like | 3 | -ve | -ve | -ve | -ve |
| Metaplastic_3661 | Basal-like | NA | -ve | -ve | 1+ | +ve |
| Metaplastic_3664 | Basal-like | 3 | -ve | -ve | -ve | +ve |
| Metaplastic_3666 | Basal-like | 3 | -ve | -ve | -ve | +ve |
| Metaplastic_3667 | Basal-like | 3 | -ve | -ve | 1+ | +ve |
| Metaplastic_3701 | Basal-like | 3 | -ve | -ve | -ve | -ve |
| Metaplastic_3702 | Basal-like | 3 | -ve | -ve | -ve | +ve |
| Metaplastic_3703 | Basal-like | 3 | -ve | -ve | -ve | -ve |
| Metaplastic_3704 | Basal-like | 3 | -ve | -ve | -ve | +ve |
| Metaplastic_3705 | Basal-like | 3 | -ve | -ve | -ve | -ve |
| Metaplastic_3706 | Basal-like | 3 | -ve | -ve | -ve | -ve |
| Metaplastic_3707 | Basal-like | 3 | -ve | -ve | -ve | -ve |
| Metaplastic_3708 | Basal-like | 2 | -ve | -ve | -ve | +ve |
| Metaplastic_3709 | Basal-like | 3 | -ve | -ve | -ve | -ve |
| Metaplastic_3710 | Normal | 3 | -ve | -ve | -ve | -ve |
| Metaplastic_3711 | Basal-like | 2 | -ve | -ve | -ve | -ve |

Histological grade according to Bloom and Richardson [50]; hormone receptors considered positive if $\geq 10\%$ of tumour cells showed nuclear staining; HER2 staining according to the revised ASCO guidelines [51]; CK5/6 considered positive if any cytoplasmic staining was present. Detailed information on the antibodies, immunohistochemical staining and scoring methods is described elsewhere [22]. MBC, metaplastic breast carcinoma; ER, oestrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor-2; CK, cytokeratin

-ve: Negative; +ve: Positive

^a As defined by Hu et al. centroids [33]

化生癌

Metaplastic carcinoma

● 鑑別診断

- 血管肉腫を含む原発性肉腫
- 筋線維芽細胞腫 (myofibroblastoma)
- 線維腫症 (fibromatosis)
- PASH (pseudoangiomatous stromal hyperplasia)
- 炎症性筋線維芽細胞腫瘍
(inflammatory myofibroblastic tumor)
- 葉状腫瘍 (phyllodes tumor)
- 悪性黒色腫 (malignant melanoma)

化生癌

Metaplastic carcinoma

- 予後と治療

- 通常の浸潤性乳管癌より高悪性度
- 進行例が多い
- 診断時に15%は転移
- リンパ節転移の頻度が比較的低い
- 転移経路は通常の乳癌と同様
(純粋な紡錘細胞癌は肉腫に類似)

化生癌

Metaplastic carcinoma

- 予後と治療

- 局所再発の頻度が高い
- 全身化学療法への反応性は一般に不良
- タキサン系薬剤がある程度有効

化生癌

Metaplastic carcinoma

- 予後不良因子

- 腫瘍径 (>3cm、>4cm)

- 年齢(50歳以上)

- 皮膚浸潤

- リンパ節転移

- リンパ節転移巣における扁平上皮癌成分

(化生癌の亜型分類は予後と相関しない)

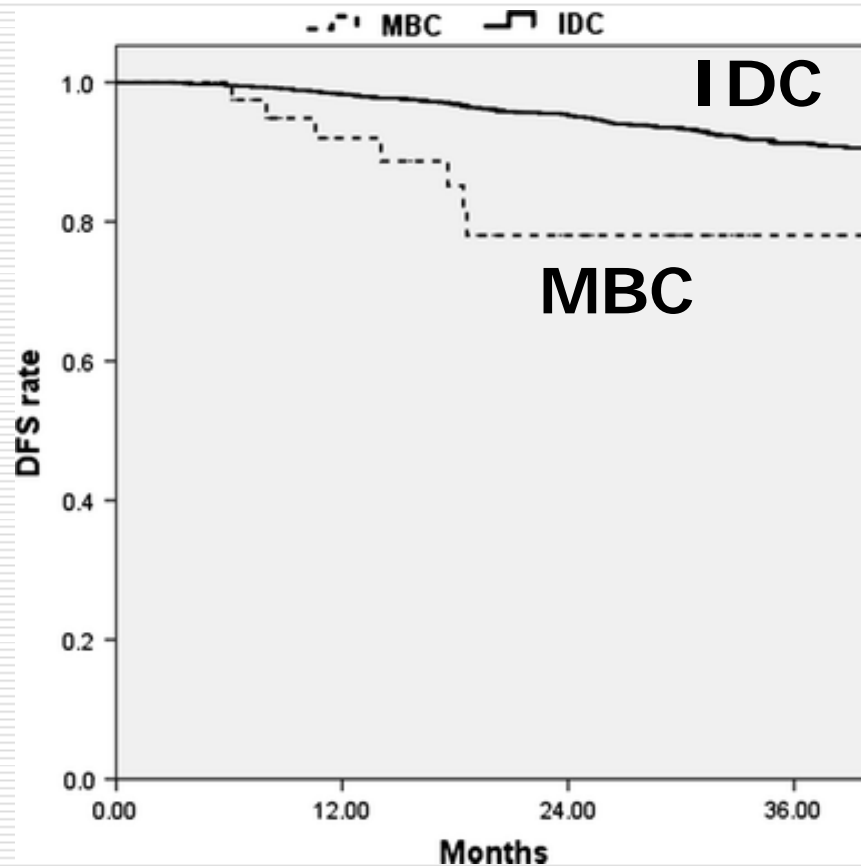
化生癌

Metaplastic carcinoma

- 紡錘細胞(肉腫様)癌(F/U、24例)
 - 1-120ヶ月(median、20ヶ月)
 - リンパ節転移:5%(1/20)
 - 局所再発:12.5%(3/24)
 - 転移(リンパ節以外):46%(11/24)、肺が最多
 - DOD:42%(10/24、1-46ヶ月、med 11.5ヶ月)
 - AWD:12.5%(3/24、med 29.5ヶ月)

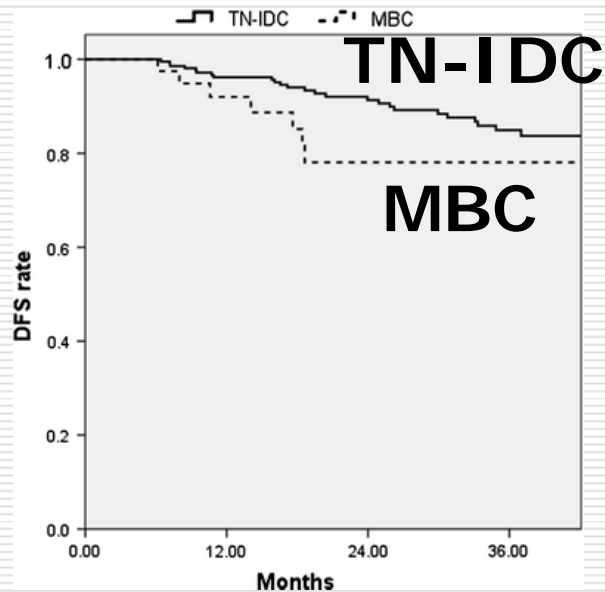
Carter MR et al. AJSP 2006; 30:300-309.

SUMSUNG MED CENTER, KOREA STUDY (47 MBC vs 1,346 IDC)



- 3年無病生存率
 - 化生癌 : 78.1%
 - IDC : 91.1%
- ($P < 0.001$)

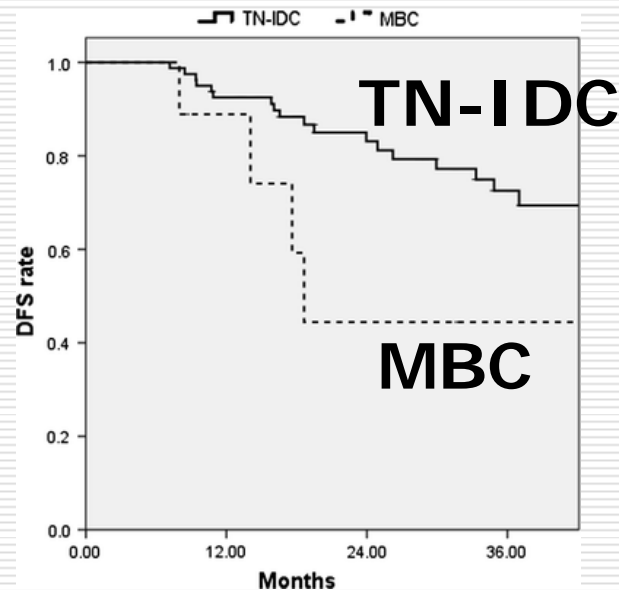
Bae SY et al. Breast Cancer Res Treat Apr;126(2):471-8.



● 3年無病生存率

- 化生癌 : 78.1%
 - TN-IDC : 84.9%
- } NS

(P = 0.114)



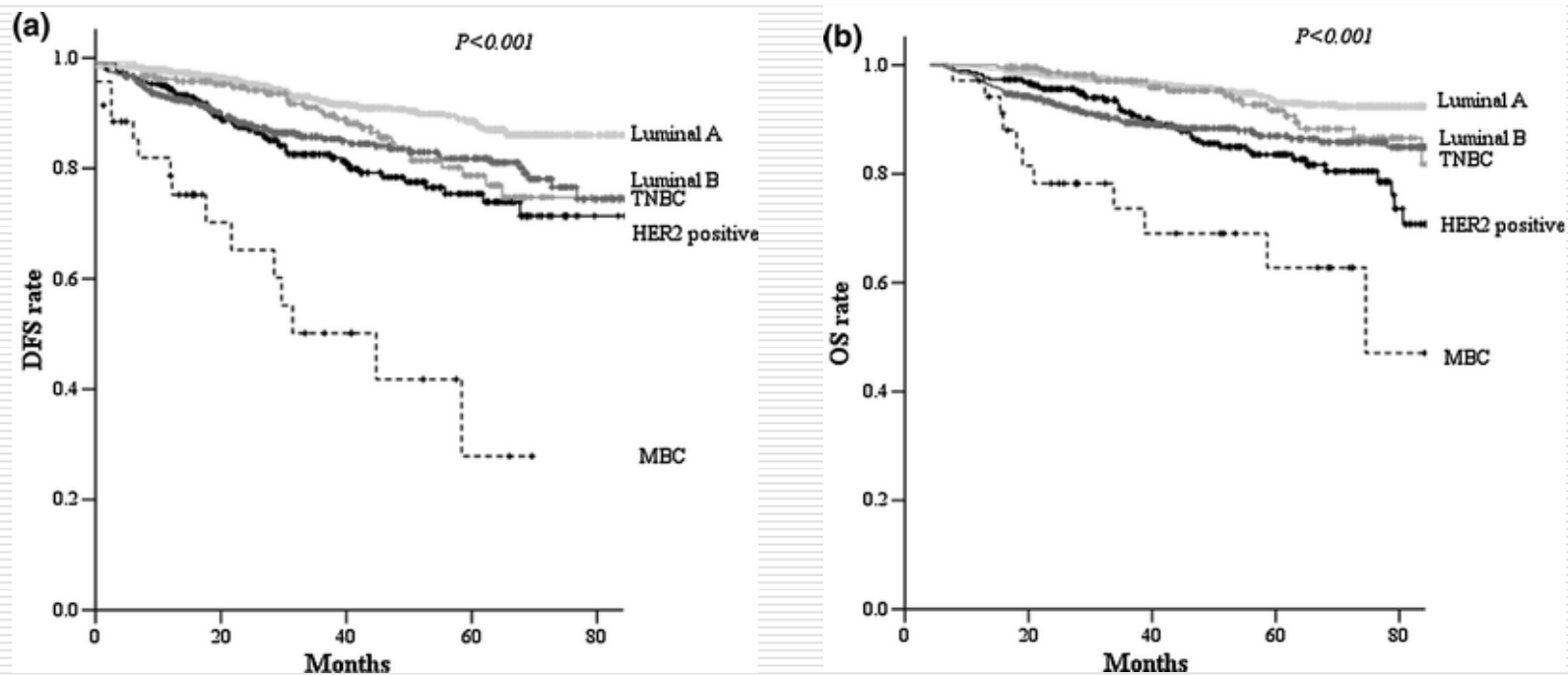
● 補助化学療法を受けた
N(+)患者の3年無病生存率

- 化生癌 : 44.4%
- TN-IDC : 72.5%

(P = 0.025)

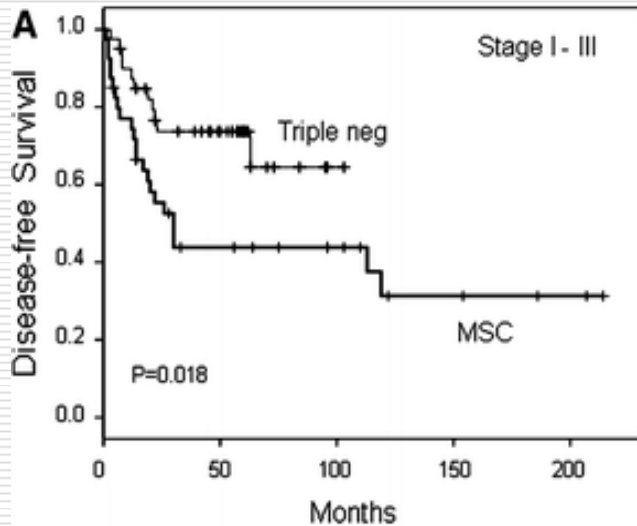
NCC, KOREA STUDY (35 MBC vs 2,839 IDC)

- 化生癌は通常の浸潤性乳管癌あるいはトリプルネガティブ乳癌よりも悪性度が高い



Jung SY et al. Breast Cancer Res Treat Apr;120:627-37.

MDACC STUDY (47 Cases)



- 化生癌はその他のトリプルネガティブ乳癌よりも予後不良

- 5年無病生存率 (I - III期)

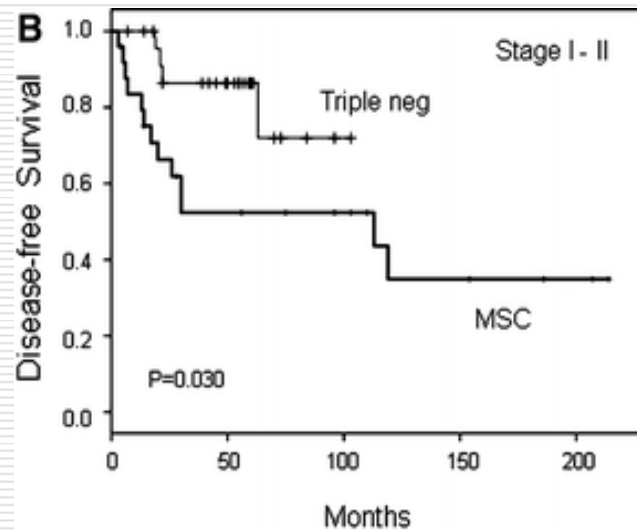
- 化生癌: $44 \pm 8\%$

- TNT: $74 \pm 7\%$

- 5年無病生存率 (I - II期)

- 化生癌: $53 \pm 10\%$

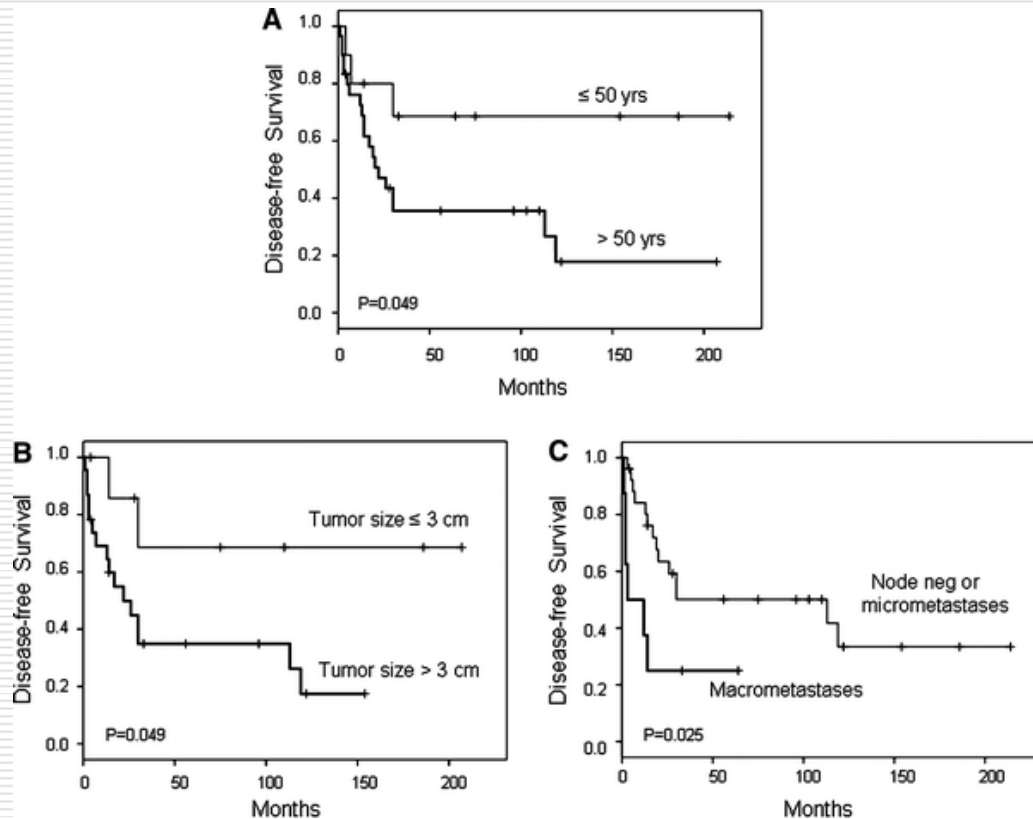
- TNT: $87 \pm 7\%$



Disease-free survival for stage I-III MSC patients versus triple-negative breast cancer patients (a) and for early-stage (stage I-II) MSC patients versus triple-negative breast cancer patients (b).

Lester TR et al.. Breast Cancer Res Treat Jan;131(1):41-8.

MDACC STUDY (47 Cases)

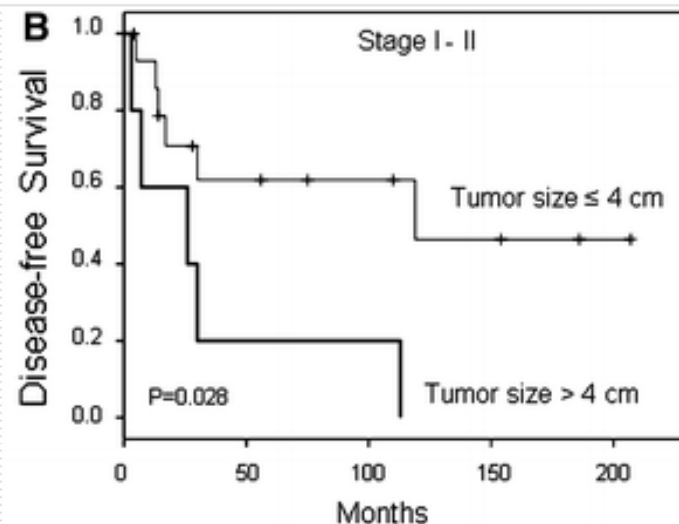
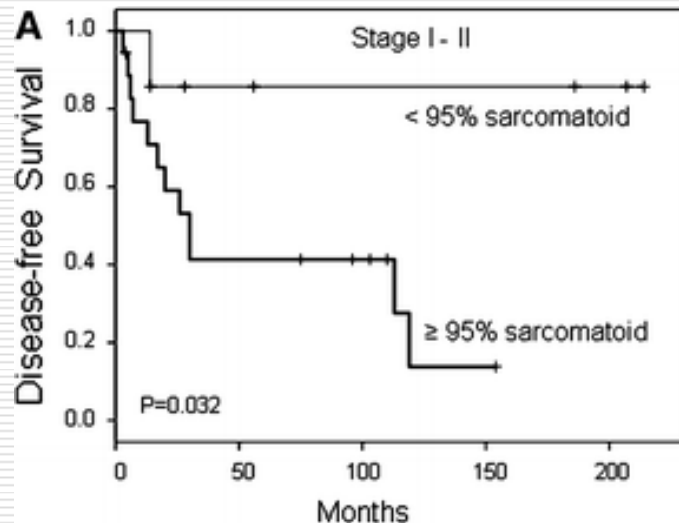


- 予後不良因子 (I - III期)
 - 年齢 (> 50 歳) ($P=0.049$)
 - 腫瘍径 (> 3 cm) ($P=0.049$)
 - リンパ節転移 ($P=0.025$)

Disease-free survival for stage I–III MSC patients according to patient age (a), tumor size (b), and lymph node status (c)

Lester TR et al.. Breast Cancer Res Treat Jan;131(1):41-8.

MDACC STUDY (47 Cases)



● 予後不良因子 (I - II 期)

- 肉腫成分の量 (>95%)
($P=0.032$)
- 腫瘍径 (>4cm)
($P=0.028$)

Disease-free survival for early-stage (stage I-II) MSC patients according to proportion of sarcomatoid component (a) and tumor size (b)

Lester TR et al.. Breast Cancer Res Treat Jan;131(1):41-8.

化生癌

Metaplastic carcinoma

● 組織発生

- 少なくとも化生癌の一部は通常の乳癌（非浸潤性、浸潤性）の表現型が変化することによって生じる
- 基底細胞由来ではなく、脱分化による

an Deurzen CH et al. Pathol Aug;224(4):434-7.

化生癌 Metaplastic carcinoma versus Basal-like IDC

| 発現低下 | 発現亢進 |
|---|--|
| <ul style="list-style-type: none">➤ BRCA1➤ <u>PTEN</u>➤ <u>TOP2A</u>➤ 上皮性分化関連遺伝子群 E-cadherin<ul style="list-style-type: none">• zona occludens: ZO1• desmoplakin: DSP• keratin 7: KRT7• keratin 18: KRT18• keratin 19: KRT19 | <ul style="list-style-type: none">➤ 筋上皮分化関連遺伝子群<ul style="list-style-type: none">• p-cadherin• prion protein• calponin• vimentin• p63)➤ EMT関連遺伝子群<ul style="list-style-type: none">• vimentin• snail homolog 2: SLUG |

Weigelt B et al Breast Cancer Res Treat 2009; 117: 273-80

ご清聴ありがとうございました



三上芳喜(みかみよしき)
京都大学医学部附属病院病理診断部(4月より病理診断科)
mika@kuhp.kyoto-u.ac.jp