第１０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1回

Invasive Lobular Carcinoma
浸潤性小葉癌

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特殊型乳癌

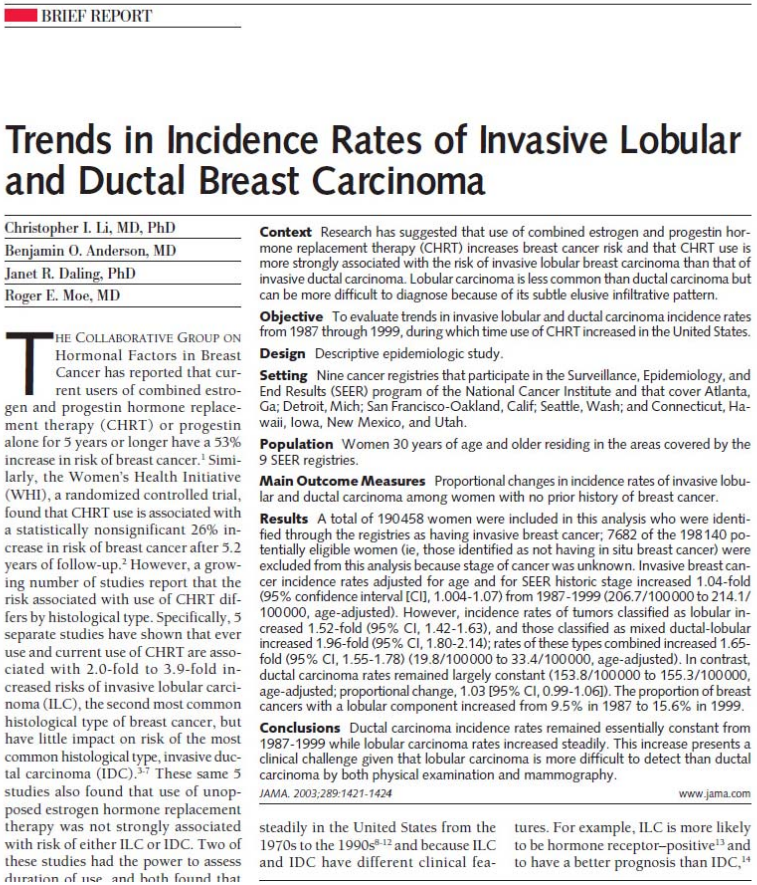
乳癌取扱い規約第16版
（2008年）

- 粘液癌
- 髄様癌
- **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%
髄様癌	2%
乳頭癌	1%
化生癌	< 1%

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



BRIEF REPORT

Trends in Incidence Rates of Invasive Lobular and Ductal Breast Carcinoma

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Janet R. Daling, PhD
Roger E. Moe, MD

Context Research has suggested that use of combined estrogen and progestin hormone replacement therapy (CHRT) increases breast cancer risk and that CHRT use is more strongly associated with the risk of invasive lobular breast carcinoma than that of invasive ductal carcinoma. Lobular carcinoma is less common than ductal carcinoma but can be more difficult to diagnose because of its subtle elusive infiltrative pattern.

Objective To evaluate trends in invasive lobular and ductal carcinoma incidence rates from 1987 through 1999, during which time use of CHRT increased in the United States.

Design Descriptive epidemiologic study.

Setting Nine cancer registries that participate in the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute and that cover Atlanta, Ga; Detroit, Mich; San Francisco-Oakland, Calif; Seattle, Wash; and Connecticut, Hawaii, Iowa, New Mexico, and Utah.

Population Women 30 years of age and older residing in the areas covered by the 9 SEER registries.

Main Outcome Measures Proportional changes in incidence rates of invasive lobular and ductal carcinoma among women with no prior history of breast cancer.

Results A total of 190 458 women were included in this analysis who were identified through the registries as having invasive breast cancer; 7682 of the 198 140 potentially eligible women (ie, those identified as not having in situ breast cancer) were excluded from this analysis because stage of cancer was unknown. Invasive breast cancer incidence rates adjusted for age and for SEER historic stage increased 1.04-fold (95% confidence interval [CI], 1.004-1.07) from 1987-1999 (206.7/100 000 to 214.1/100 000, age-adjusted). However, incidence rates of tumors classified as lobular increased 1.52-fold (95% CI, 1.42-1.63), and those classified as mixed ductal-lobular increased 1.96-fold (95% CI, 1.80-2.14); rates of these types combined increased 1.65-fold (95% CI, 1.55-1.78) (19.8/100 000 to 33.4/100 000, age-adjusted). In contrast, ductal carcinoma rates remained largely constant (153.8/100 000 to 155.3/100 000, age-adjusted; proportional change, 1.03 [95% CI, 0.99-1.06]). The proportion of breast cancers with a lobular component increased from 9.5% in 1987 to 15.6% in 1999.

Conclusions Ductal carcinoma incidence rates remained essentially constant from 1987-1999 while lobular carcinoma rates increased steadily. This increase presents a clinical challenge given that lobular carcinoma is more difficult to detect than ductal carcinoma by both physical examination and mammography.

JAMA. 2003;289:1421-1424 www.jama.com

THE COLLABORATIVE GROUP ON Hormonal Factors in Breast Cancer has reported that current users of combined estrogen and progestin hormone replacement therapy (CHRT) or progestin alone for 5 years or longer have a 53% increase in risk of breast cancer.[1] Similarly, the Women's Health Initiative (WHI), a randomized controlled trial, found that CHRT use is associated with a statistically nonsignificant 26% increase in risk of breast cancer after 5.2 years of follow-up.[2] However, a growing number of studies report that the risk associated with use of CHRT differs by histological type. Specifically, 5 separate studies have shown that ever use and current use of CHRT are associated with 2.0-fold to 3.9-fold increased risks of invasive lobular carcinoma (ILC), the second most common histological type of breast cancer, but have little impact on risk of the most common histological type, invasive ductal carcinoma (IDC).[3-7] These same 5 studies also found that use of unopposed estrogen hormone replacement therapy was not strongly associated with risk of either ILC or IDC. Two of these studies had the power to assess duration of use, and both found that steadily in the United States from the 1970s to the 1990s[8-12] and because ILC and IDC have different clinical features. For example, ILC is more likely to be hormone receptor–positive[13] and to have a better prognosis than IDC,[14]

1987~1999年の期間において乳管癌の頻度は一定であるのに対して、小葉癌は徐々に増加している

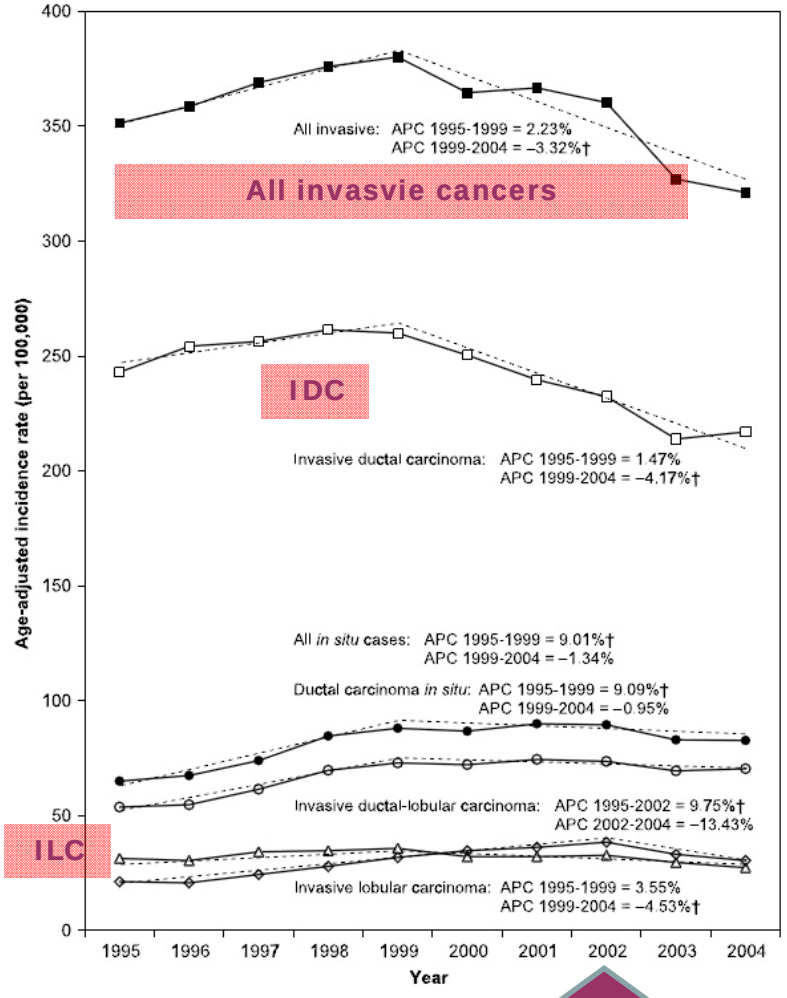
Li Cl et al. JAMA 2003; 289: 1421-4

Table 1. Age-Adjusted Incidence Rates of Invasive Breast Carcinoma by Histological Type, 1987-1999

Year	Total Population in Registries†	No. of Cases (Age-Adjusted Incidence Rate per 100 000)*				
		Overall	Ductal Carcinoma	Lobular Carcinoma	Mixed Ductal-Lobular Carcinoma	Lobular and Mixed Ductal-Lobular Carcinoma
1987	6 470 386	13 391 (206.7)	9956 (153.8)	833 (12.9)	442 (6.9)	1275 (19.8)
1988	6 600 594	13 364 (203.1)	9850 (149.5)	829 (12.5)	503 (7.8)	1332 (20.2)
1989	6 725 369	12 982 (194.6)	9606 (144.3)	812 (12.0)	454 (6.9)	1266 (18.9)
1990	6 852 588	13 650 (201.5)	9976 (147.4)	923 (13.5)	483 (7.3)	1406 (20.8)
1991	6 998 670	14 168 (205.7)	10 203 (148.1)	958 (13.8)	598 (8.9)	1556 (22.7)
1992	7 151 658	14 285 (203.1)	10 144 (144.3)	1106 (15.6)	612 (8.8)	1718 (24.4)
1993	7 283 478	14 180 (198.1)	10 150 (141.9)	1037 (14.4)	628 (8.9)	1665 (23.3)
1994	7 408 103	14 576 (200.6)	10 471 (144.4)	1170 (15.9)	640 (8.9)	1810 (24.8)
1995	7 524 437	14 982 (202.7)	10 814 (146.6)	1189 (16.0)	722 (9.9)	1911 (25.9)
1996	7 632 458	15 312 (204.3)	11 219 (150.0)	1253 (16.6)	737 (9.9)	1990 (26.5)
1997	7 732 719	16 024 (209.7)	11 795 (154.5)	1403 (18.2)	870 (11.5)	2273 (29.7)
1998	7 819 324	16 662 (214.2)	12 217 (157.3)	1459 (18.7)	1047 (13.5)	2506 (32.3)
1999	7 893 363	16 882 (214.1)	12 224 (155.3)	1514 (19.1)	1124 (14.3)	2638 (33.4)
Proportional change (95% CI)‡		1.04 (1.004-1.07)	1.03 (0.99-1.06)	1.52 (1.42-1.63)	1.96 (1.80-2.14)	1.65 (1.55-1.78)

Abbreviation: CI, confidence interval.
*Rates age-adjusted to the 2000 US standard. Because the rates are age-adjusted they do not reflect absolute numbers. The "Overall" column includes histological types in addition to those indicated above.
†Total number of women in the catchment area for the registries in the age range included in the analysis herein.
‡Proportional changes estimated using negative binomial regression and adjusted for age and for SEER historic stage of disease (because of variations in detection of stage of disease over time).

Li Cl et al. JAMA 2003; 289: 1421-4



- SEER
- 浸潤性乳管癌、浸潤性小葉癌の罹患率は1998～2004年の期間において徐々に低下
- 乳管癌
  - ≧50歳、非ヒスパニック系白人、アジア/環太平洋地域
- 小葉癌
  - 非ヒスパニック系白人

* Women's Health Initiative Trial Results → ERT 17% ⇒ 7%

Li Cl et al. Cancer Epidemiol Biomarkers Prev 2007; 16: 1773-80

1999～2004年の期間における浸潤性小葉癌の減少は乳管癌よりも顕著である

Table 6. Age-adjusted lobular and ductal invasive breast cancer incidence rates by year, females, United-States, 1999-2004

	Invasive lobular			Invasive ductal			Total invasive lobular, ductal, and mixed			All invasive breast cancers		
	Cases	Rate*	Percent change	Cases	Rate	Percent change	Cases	Rate	Percent change	Cases	Rate	Percent change
Year												
1999	16,226	11.7		128,613	94.0		155,425	113.4		183,501	133.4	
2000	16,174	11.4	−2.6	127,420	91.7	−2.4	155,581	111.8	−1.4	182,769	130.9	−1.87
2001	15,673	10.9	−4.4	123,004	87.2	−4.9	151,854	107.5	−3.9	185,044	130.5	−0.31
2002	15,431	10.6	−2.7	121,181	84.5	−3.1	150,402	104.7	−2.6	183,572	127.3	−2.45
2003	14,456	9.7	−8.5	117,522	80.7	−4.5	145,440	99.6	−4.9	175,959	120.1	−5.66
2004	13,991	9.3	−4.1	119,474	80.7	0	146,700	98.9	−0.7	175,501	117.9	−1.83
Annual percent change†	−4.6 (−5.8, −3.4)‡			−3.3 (−4.2, −2.5)			−3.0 (−3.6, −2.3)			−2.5 (−3.6, −1.5)		
Total percent change	−20.5			−14.2			−12.8			−11.6		

NOTE: Data from Maryland, Mississippi, North Dakota, South Dakota, Tennessee, and Virginia are not included.
*Rates are per 100,000 women and age adjusted to the 2000 U.S. Standard Population (19 age groups—Census P25-1130).
†Annual percent change was calculated using the weighted least squares method.
‡95% CIs were calculated using the Tiwari modification.

Eheman CR et al. Cancer Epidemiol Biomarkers Prev 2009; 18: 1763-9

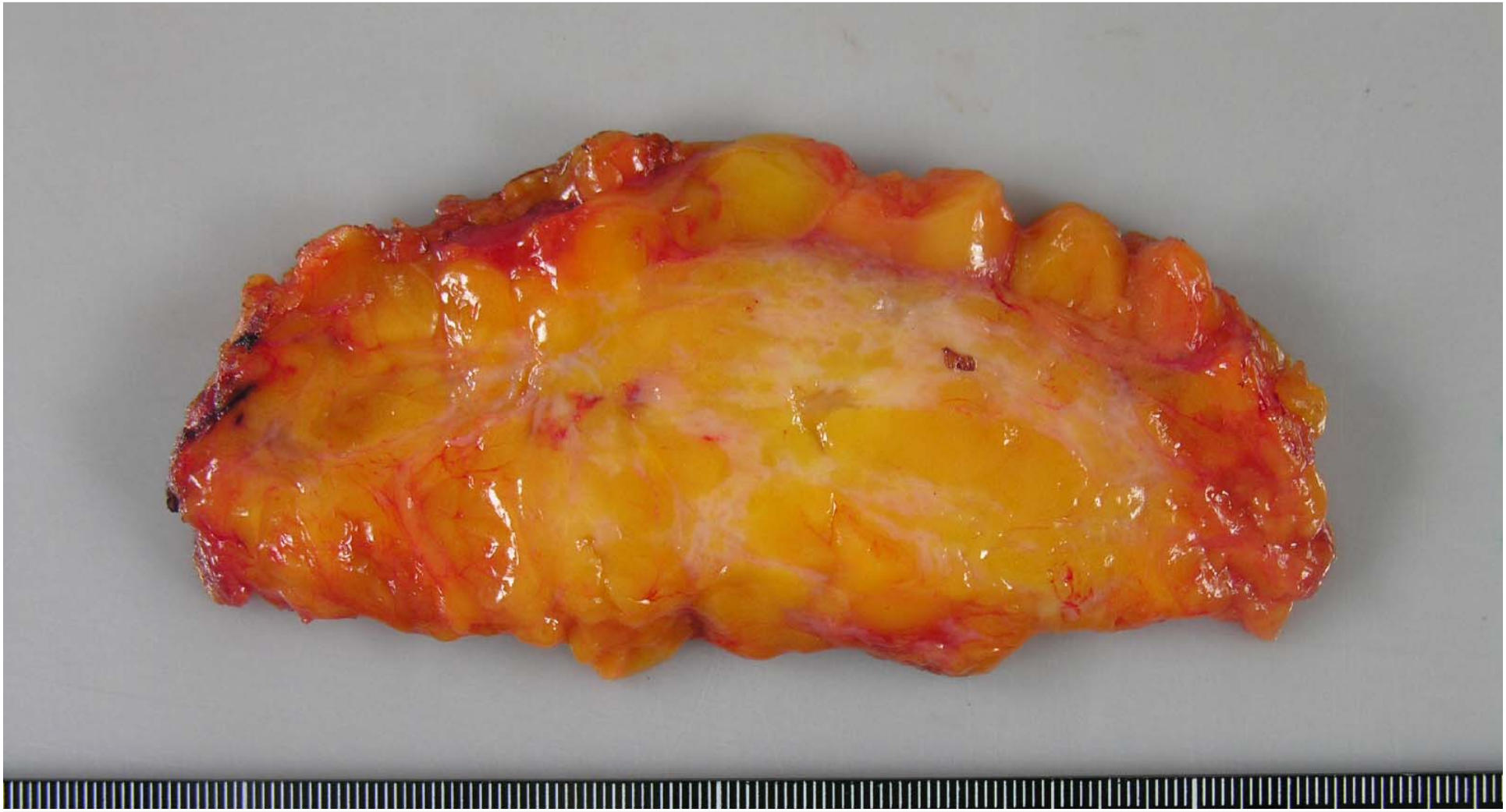
浸潤性小葉癌

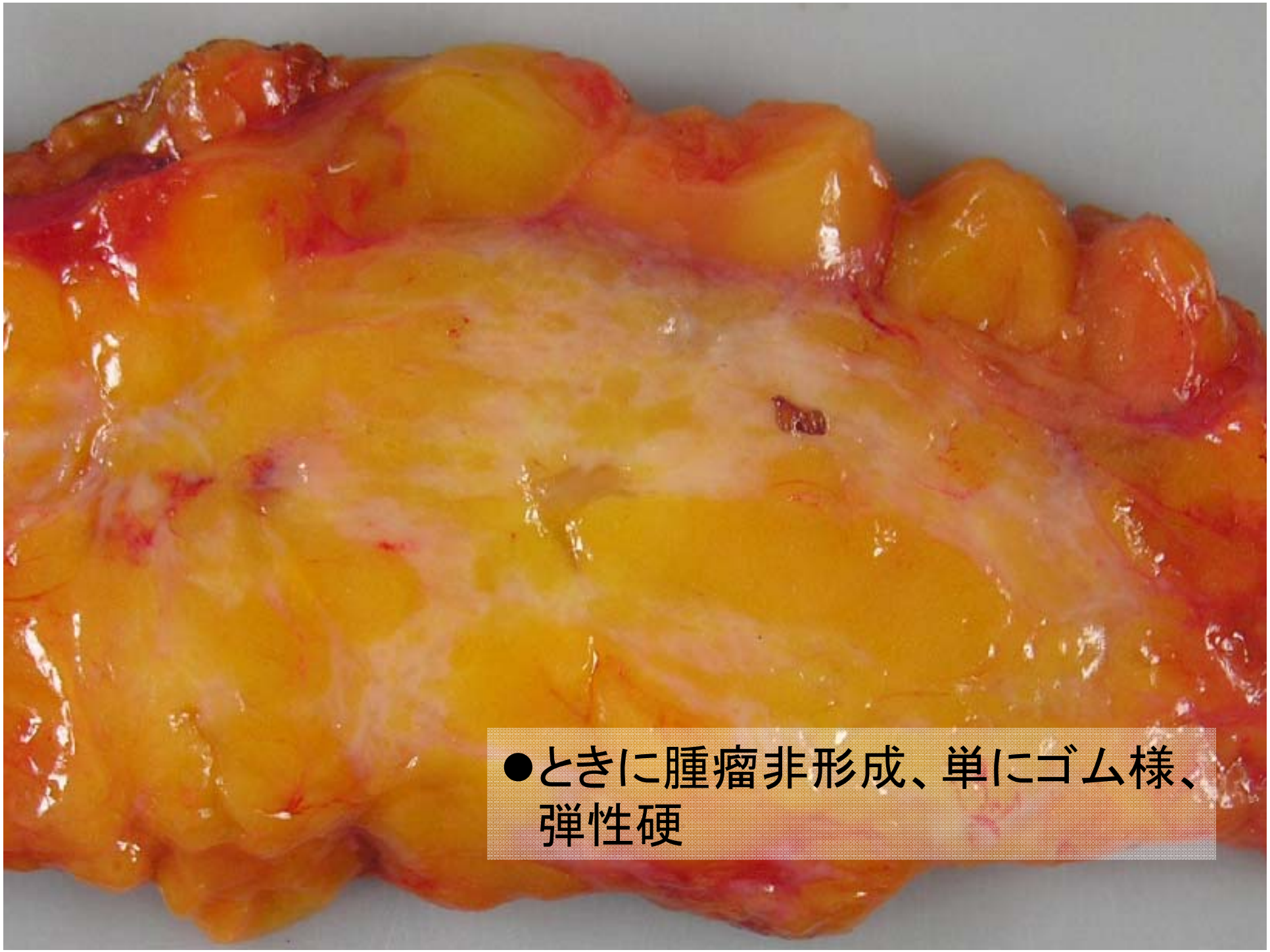
- 頻度は低い（全乳癌の5~15%）
- 閉経後のホルモン補充療法（HRT）に関連
- 50歳以降で好発
- マンモグラフィーによる検出がやや困難
- 進行例が多い（>2cm、50% vs. 39% in IDC）
- しばしば同側で多巣性（mutifocal）
- しばしば両側性（bilateral）（6~47%）

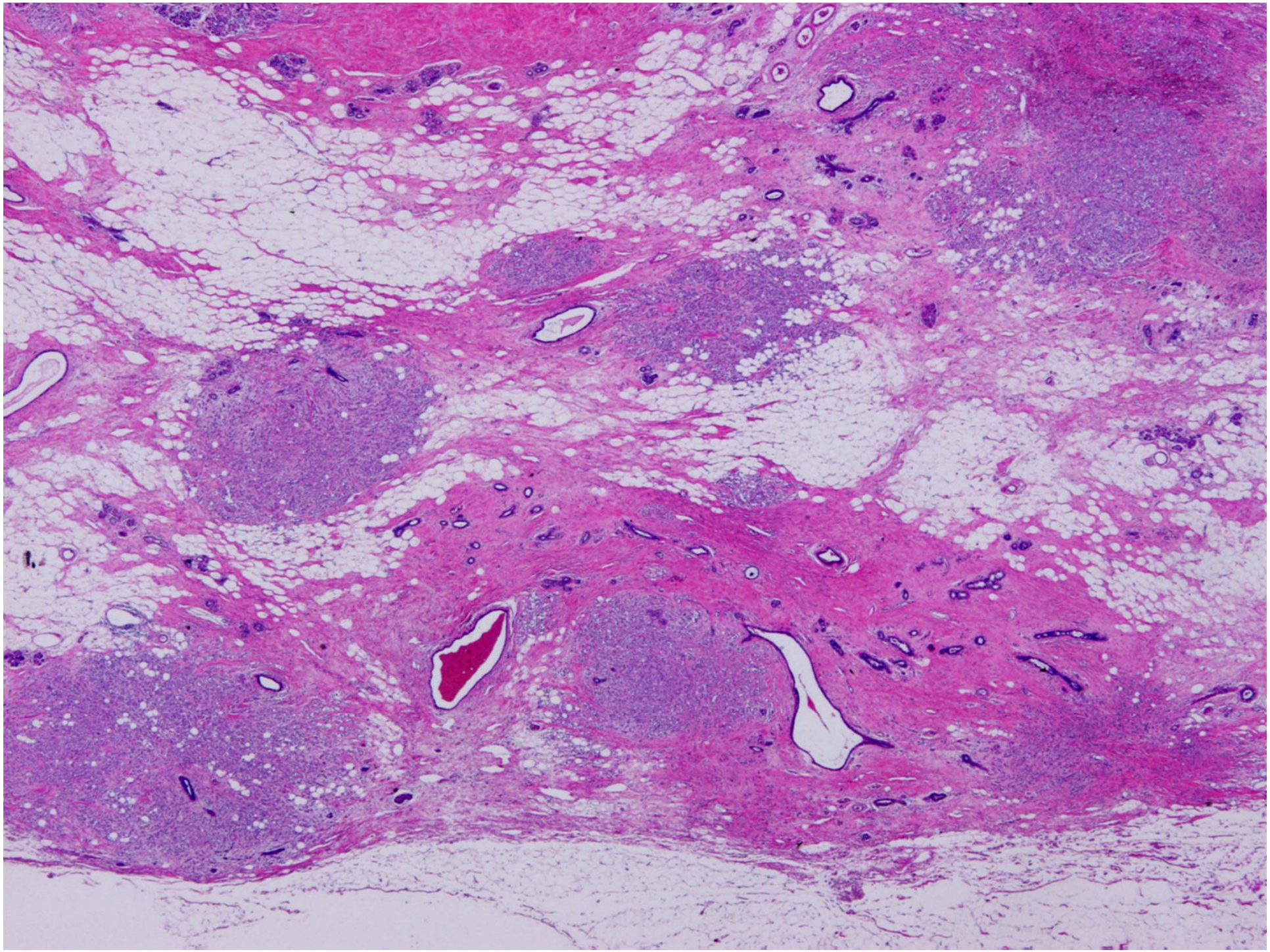
浸潤性小葉癌

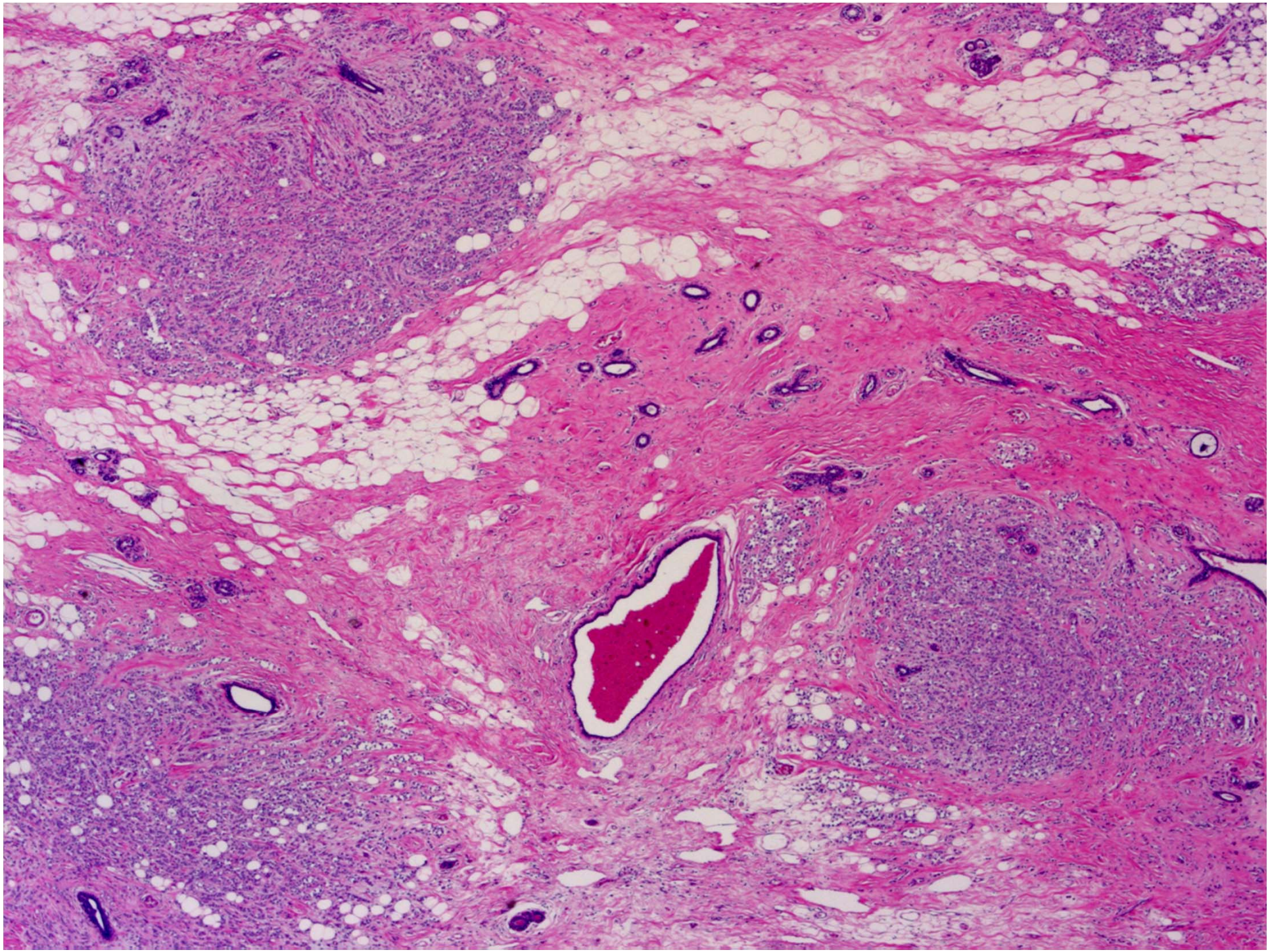
- 非浸潤性小葉癌が併存（70~80%）
- 高い断端陽性率*（43% vs. 16% in IDC）
- 多くは mSBR grade-Ⅱ（~76%）
- ER陽性（~93%）
- AR陽性（~88% vs. ~56% in IDC）
- 稀にHER2陽性（~11%）
- E-cadherin 発現の消失
- 骨、卵巣などへの転移

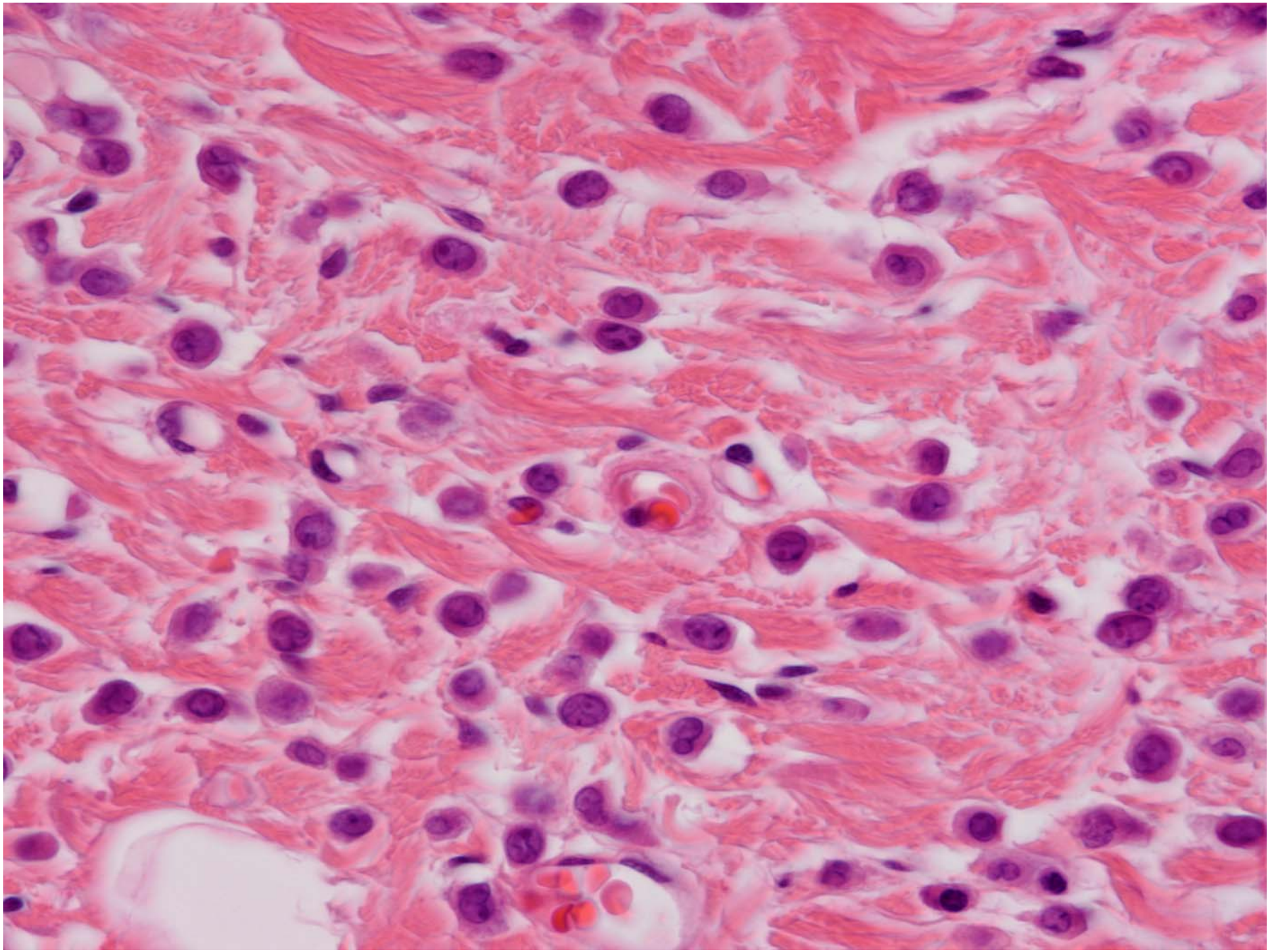
＊ 温存手術



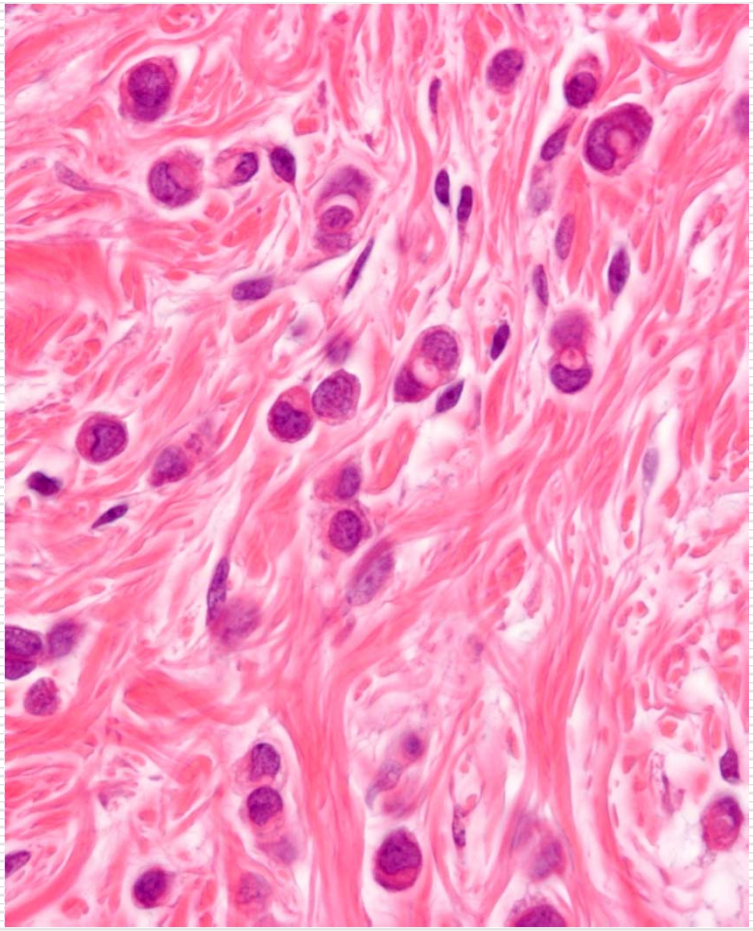

●ときに腫瘤非形成、単にゴム様、
弾性硬





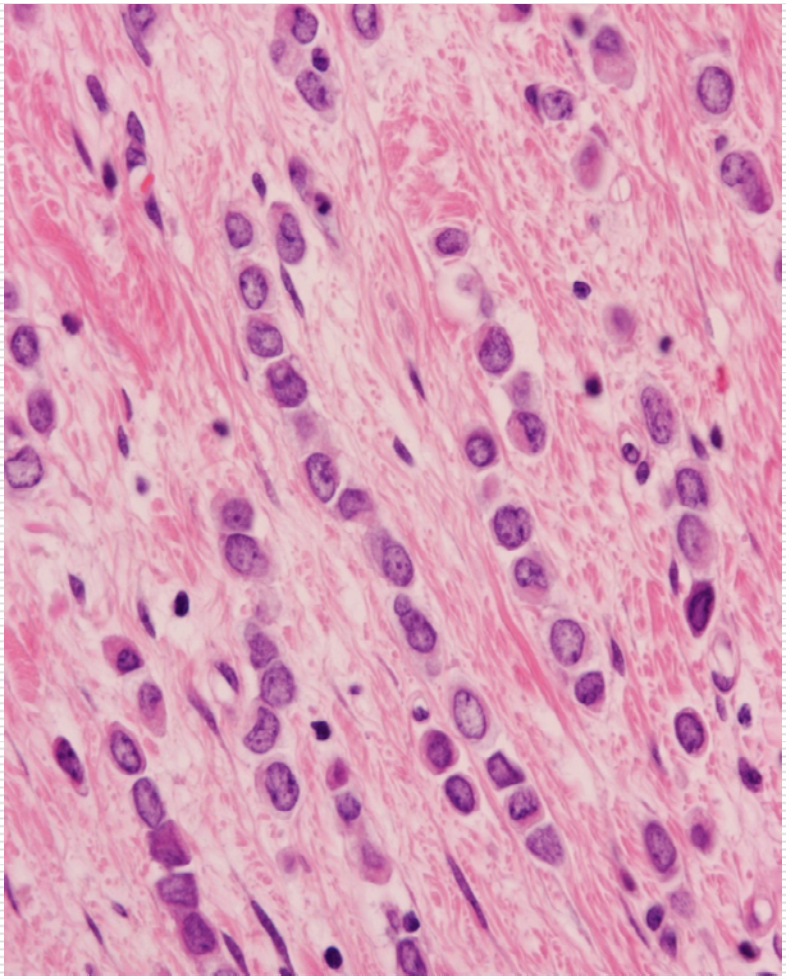


浸潤性小葉癌の病理組織像



- 細胞像
  - 小型で比較的均一
  - 円形ないし不整形
  - 核は小型かつ均一でしばしば辺縁性
  - 核分裂像は稀
  - 細胞質内小空胞（ときに印環細胞様）

浸潤性小葉癌の病理組織像



- 浸潤･進展様式
  - 個別性に浸潤
  - びまん性、多巣性（不連続）
  - 膠原線維間で一列に配列（“indian file”）

浸潤性小葉癌の病理組織像

- 浸潤･進展様式
  - 個別性に浸潤
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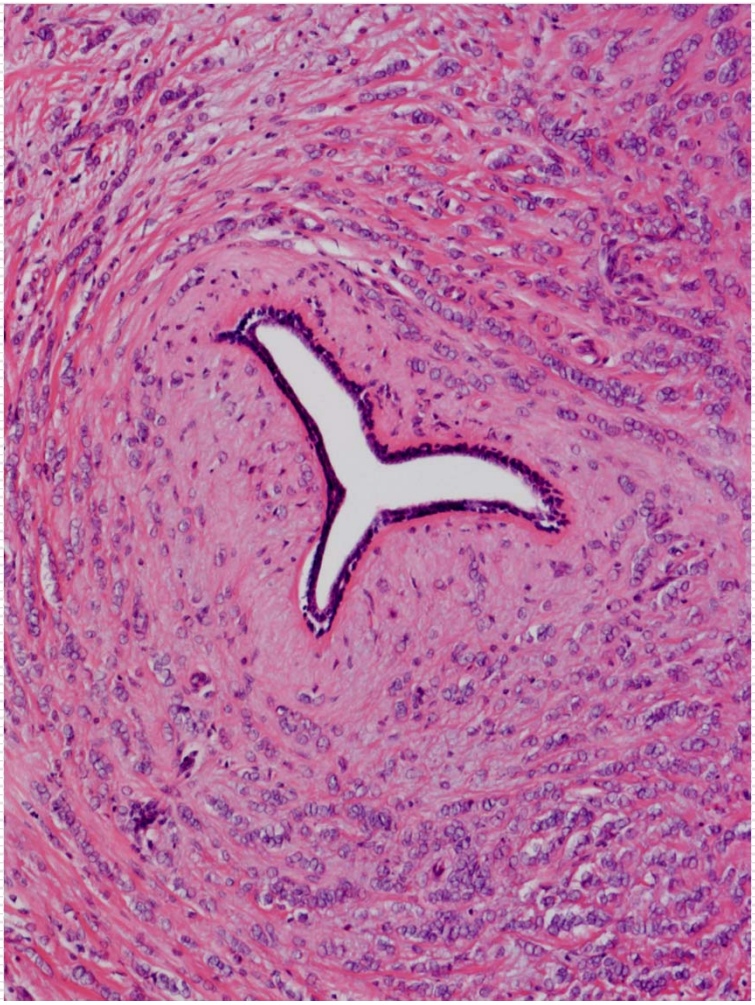
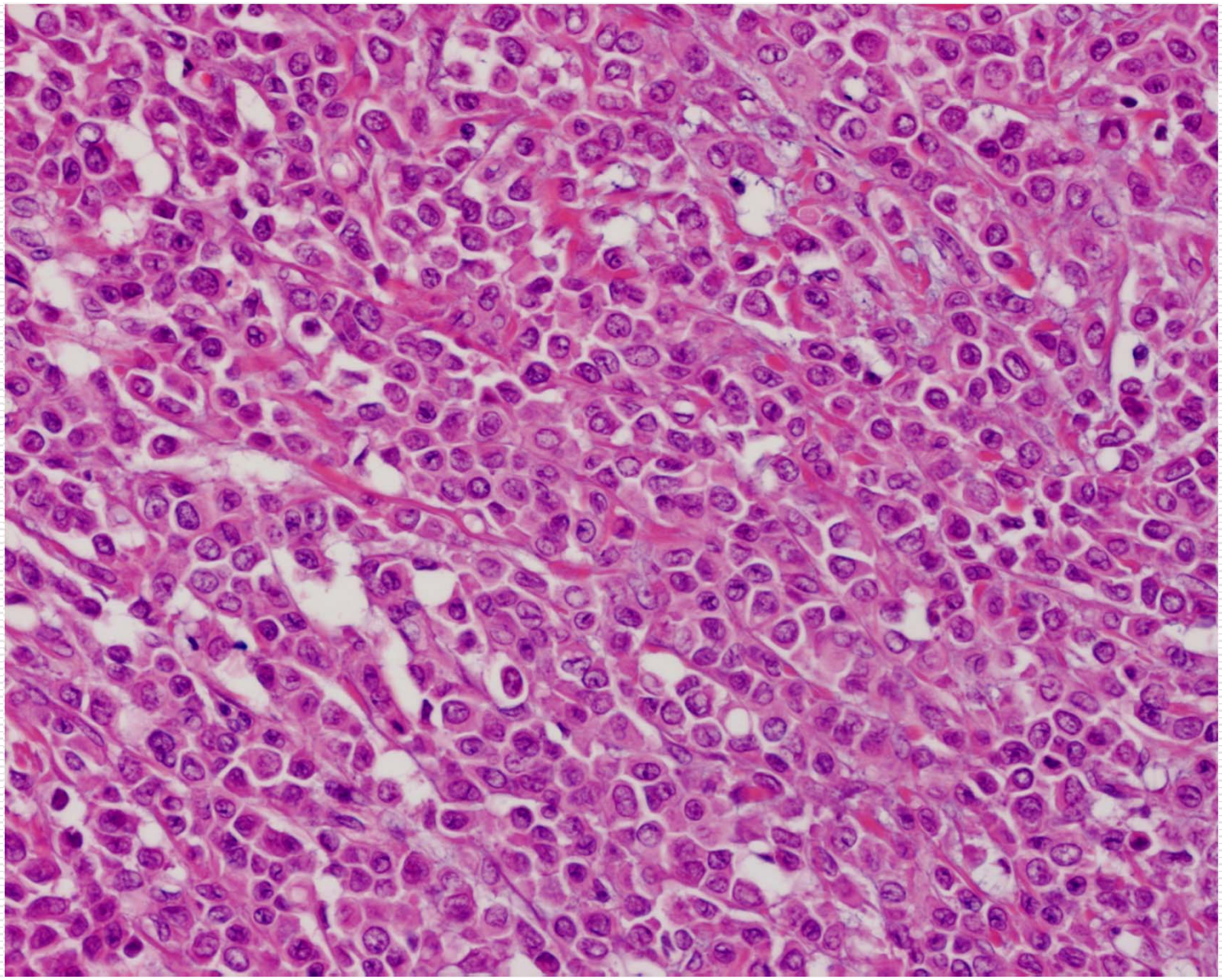
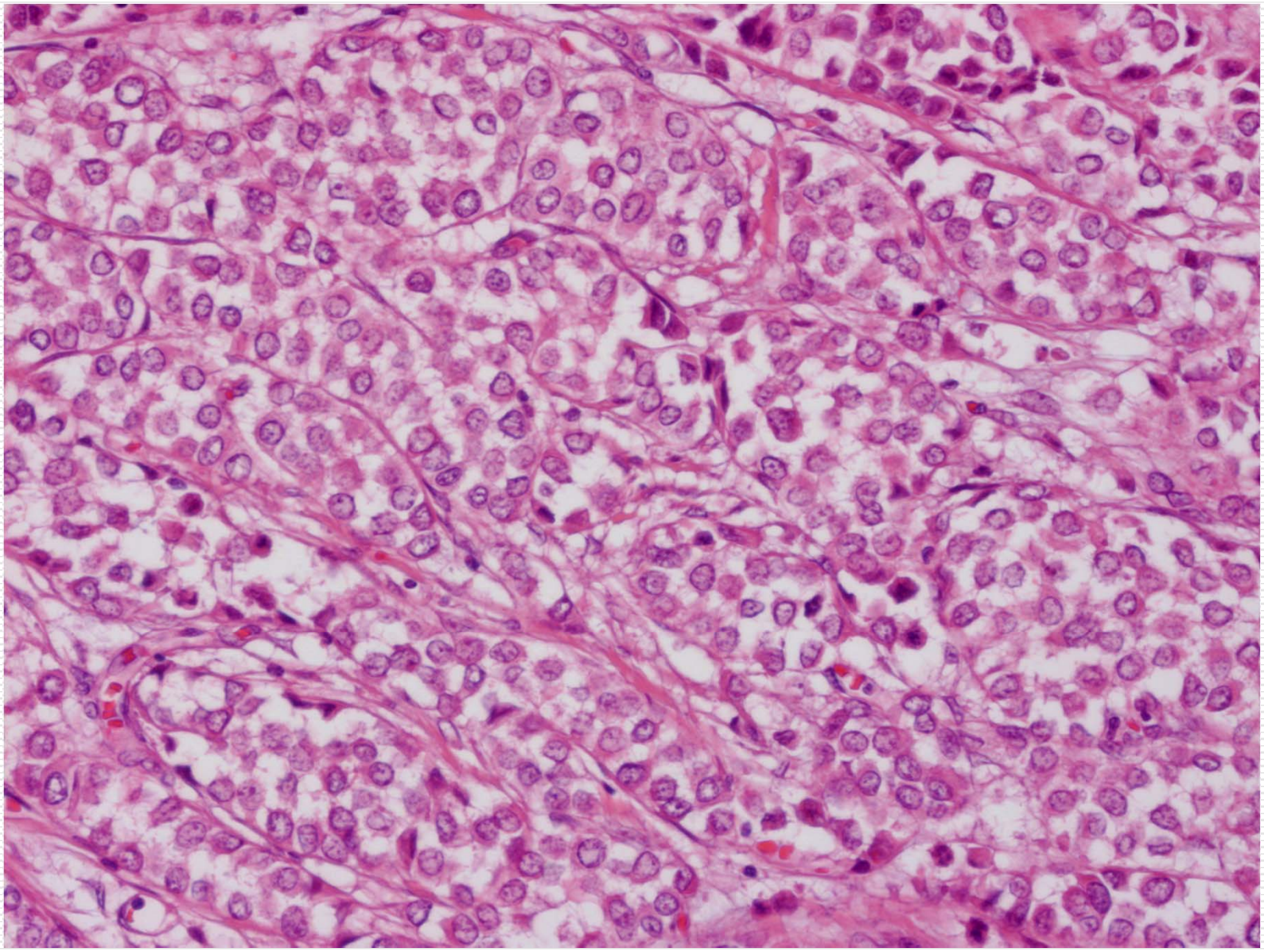
浸潤性小葉癌の病理組織像



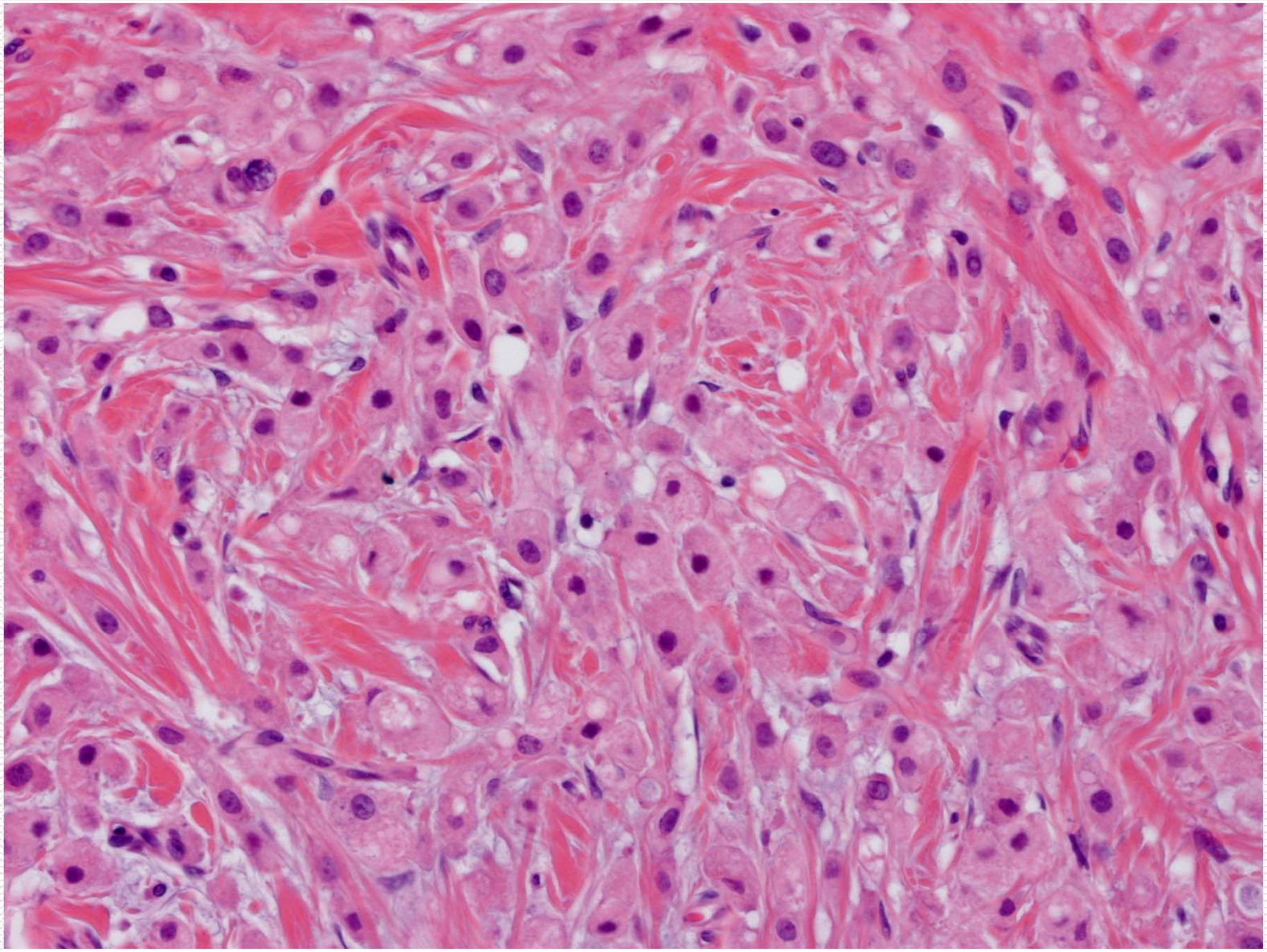
- 浸潤･進展様式
  - 個別性に浸潤
  - びまん性、多巣性（不連続）
  - 膠原線維間で一列に配列（“indian file”）
  - 乳管を取り巻く（“ targetoid / onion skin”）
  - ときに小管形成 (tubulolobular variant)
  - 線維形成性間質反応なし



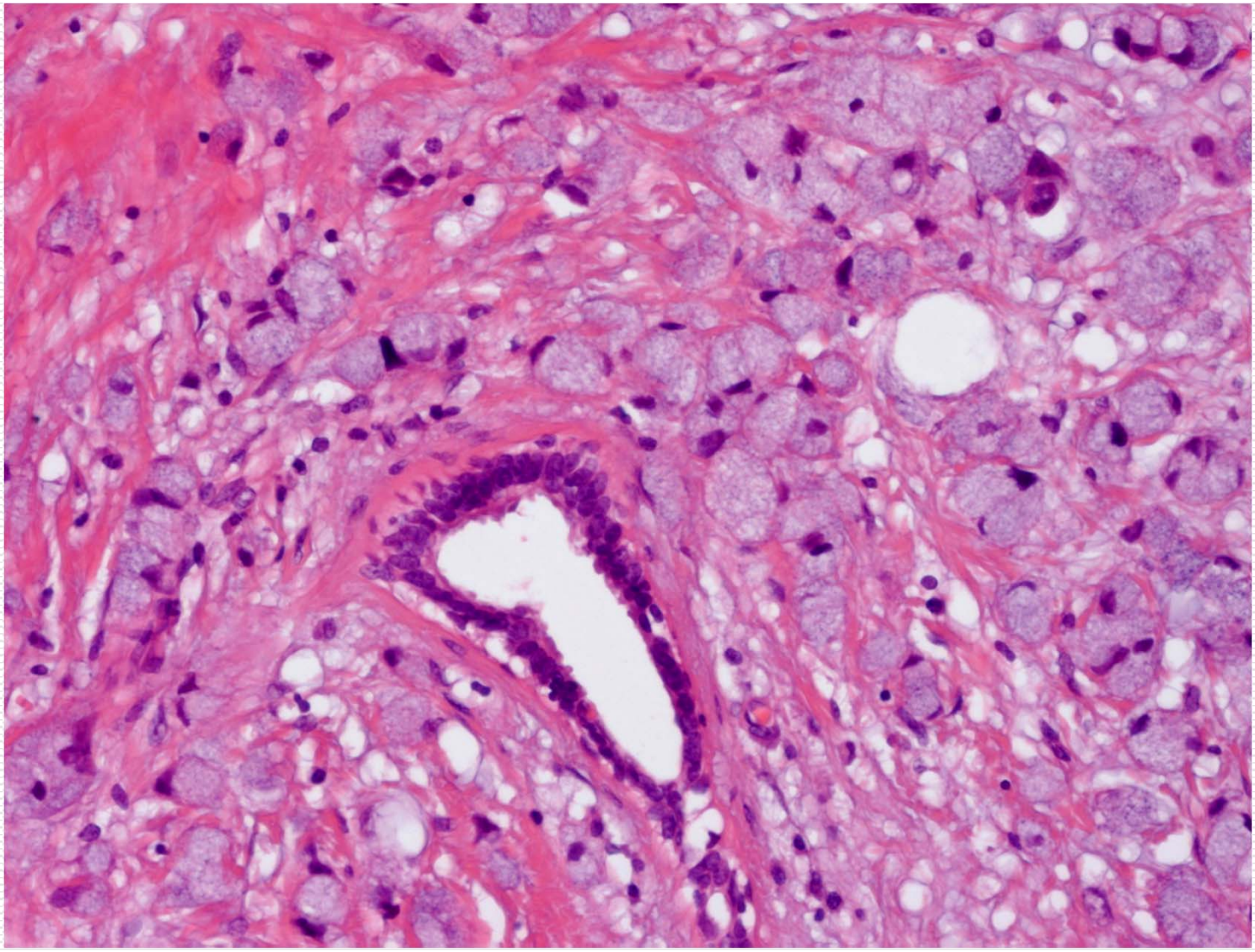
充実型　Solid ILC



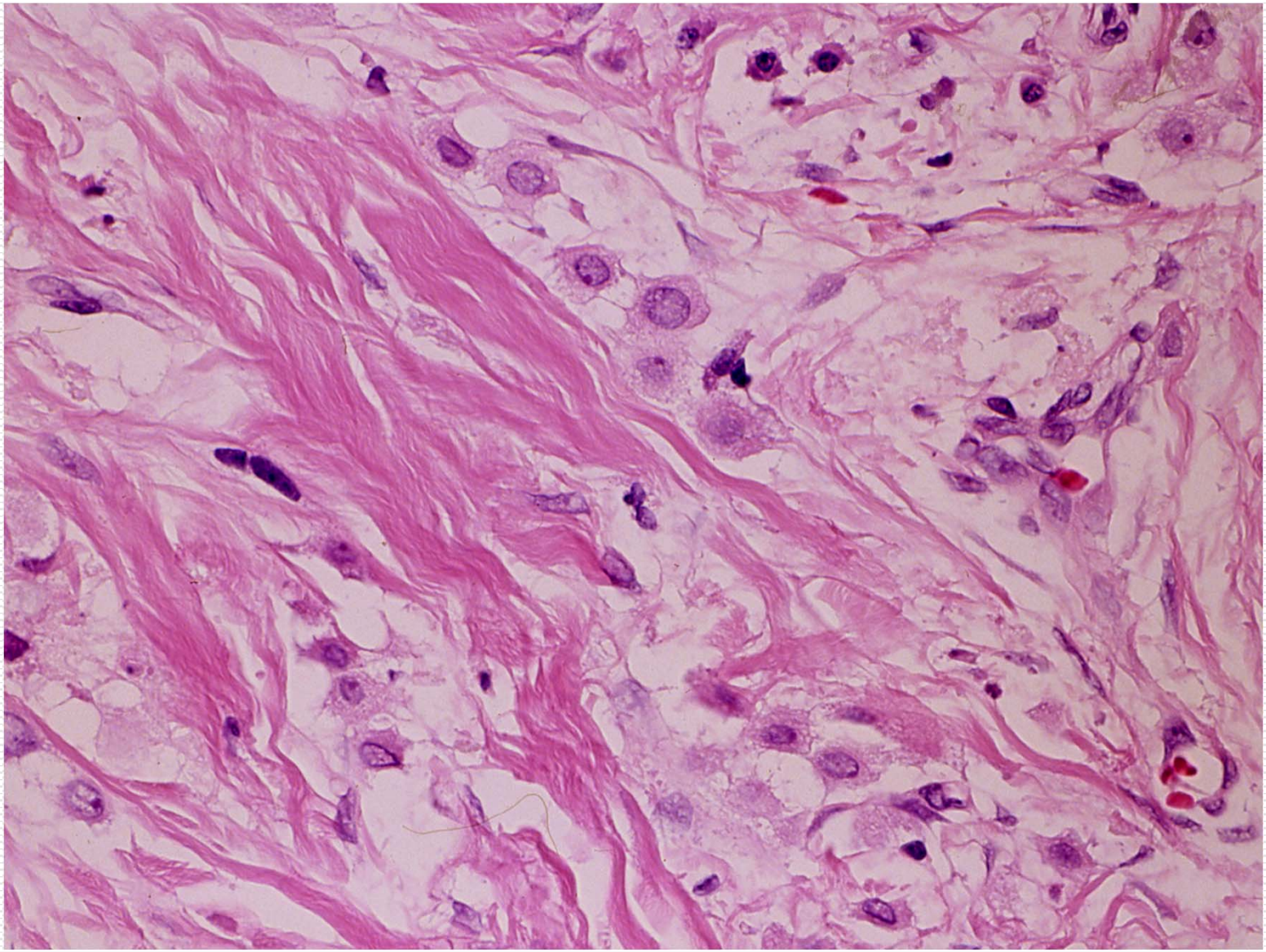
胞巢型 Alveolar ILC



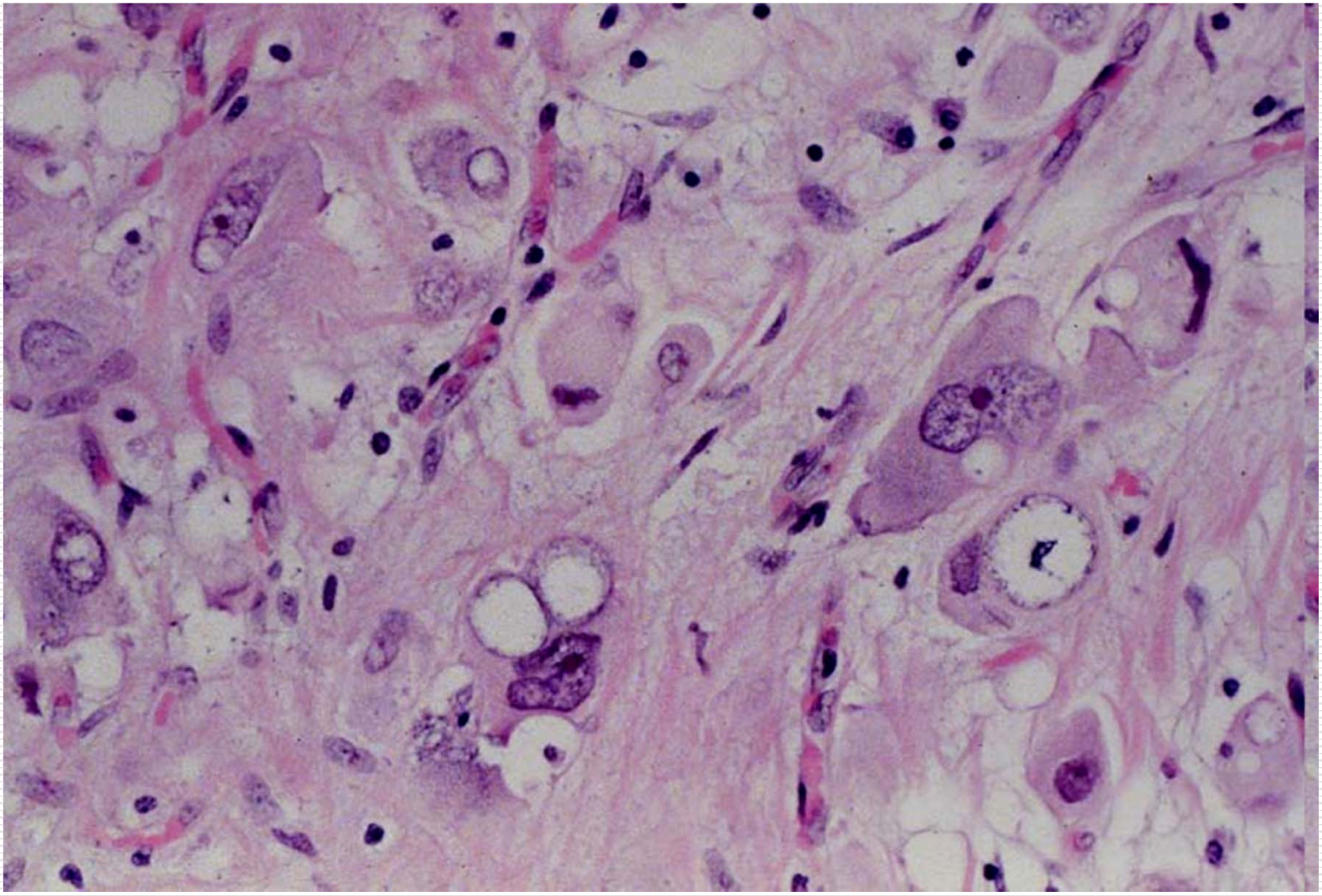
アポクリン型　Apocrine ILC



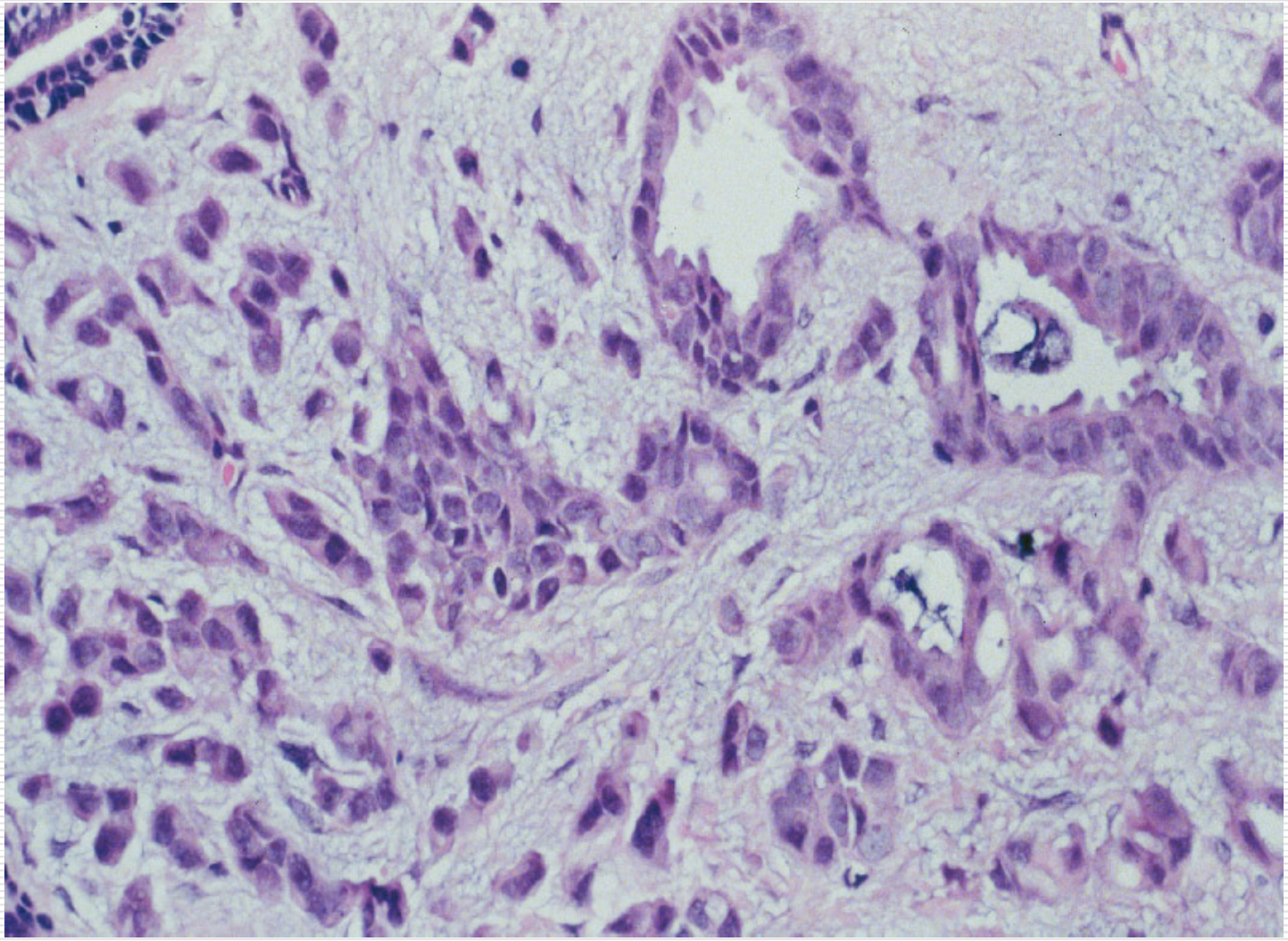
印環細胞型　Signet-ring cell ILC



組織球様　Histiocytoid ILC



多形型 Pleomorphic ILC



管状小葉癌

Tubulolobular carcinoma

浸潤性小葉癌の遺伝子プロファイル

Weigelt B et al. J Pathol 2009;220:45-57

- 浸潤性乳管癌（grade、molecular subtype をマッチ）との間で 5.8% の遺伝子発現に違い

Down-regulation	Up-regulation
● E-cadherin 遺伝子 ● アクチン細胞骨格リモデリング関連遺伝子 ● ユビキチン遺伝子 ● DNA修復関連遺伝子 ● 細胞接着関連遺伝子 ● TGF-βシグナル伝達関連遺伝子	● 転写因子/最初期遺伝子 ● 脂質/プロスタグランジン生合成遺伝子 ● 細胞遊走関連遺伝子

古典型 vs 多形型

- 古典型 Classical
  - Lumina 型
  - ER/PR 陽性
  - HER2 陰性
  - 低悪性度（mSBR grade Ⅰ,Ⅱ）
- 多形型 Pleomorphic
  - Luminal, HER2, あるいはアポクリン型
  - 高悪性度（mSBR grade Ⅲ）
  - 予後不良（Aggressive！！）

Invasive lobular carcinoma

Weigelt B et al. J Pathol 2009;220:45-57

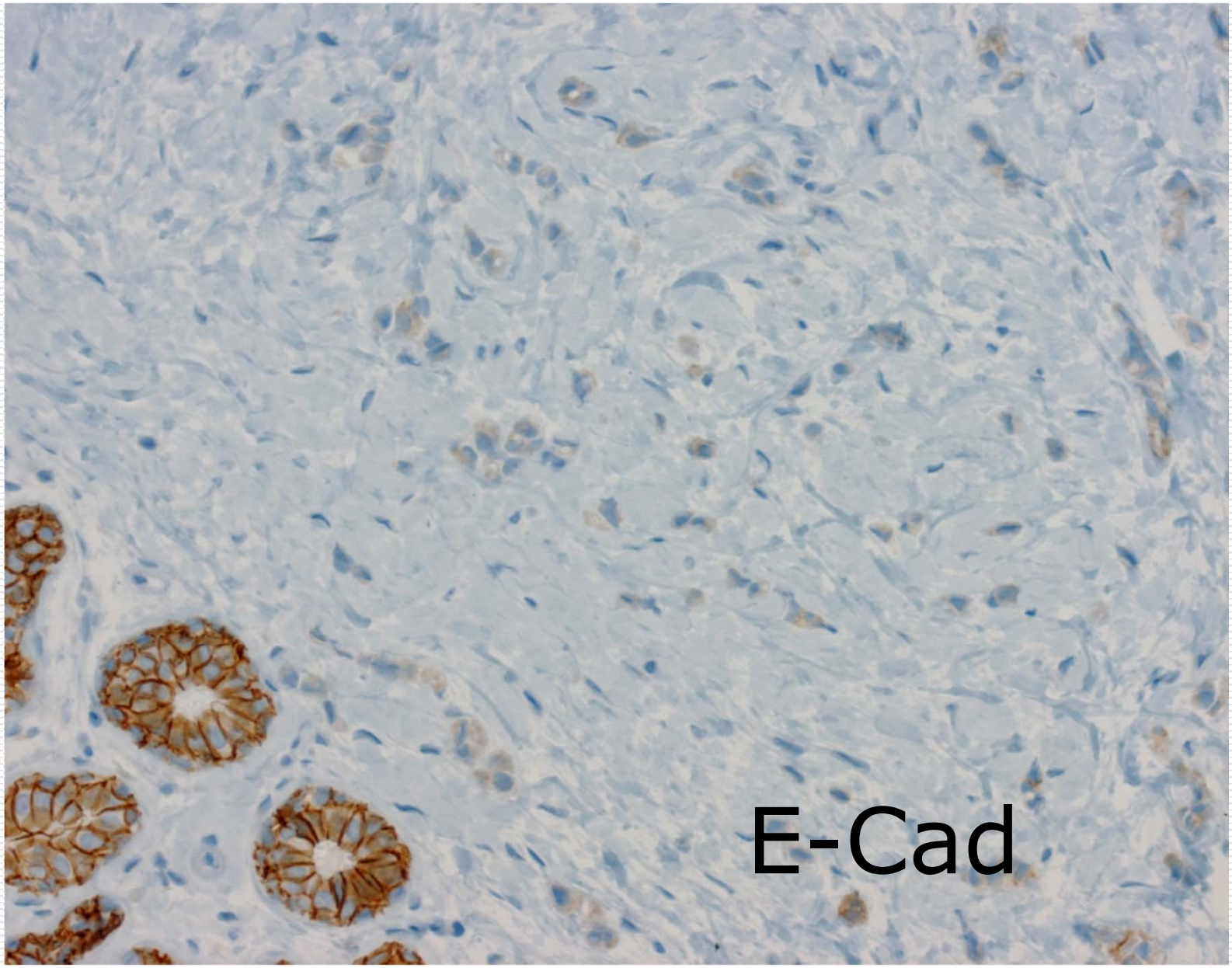
- 古典型と多形型の遺伝子発現プロファイルの違いは 0.1% 未満

  ⇒ 両者は一連のスペクトラム

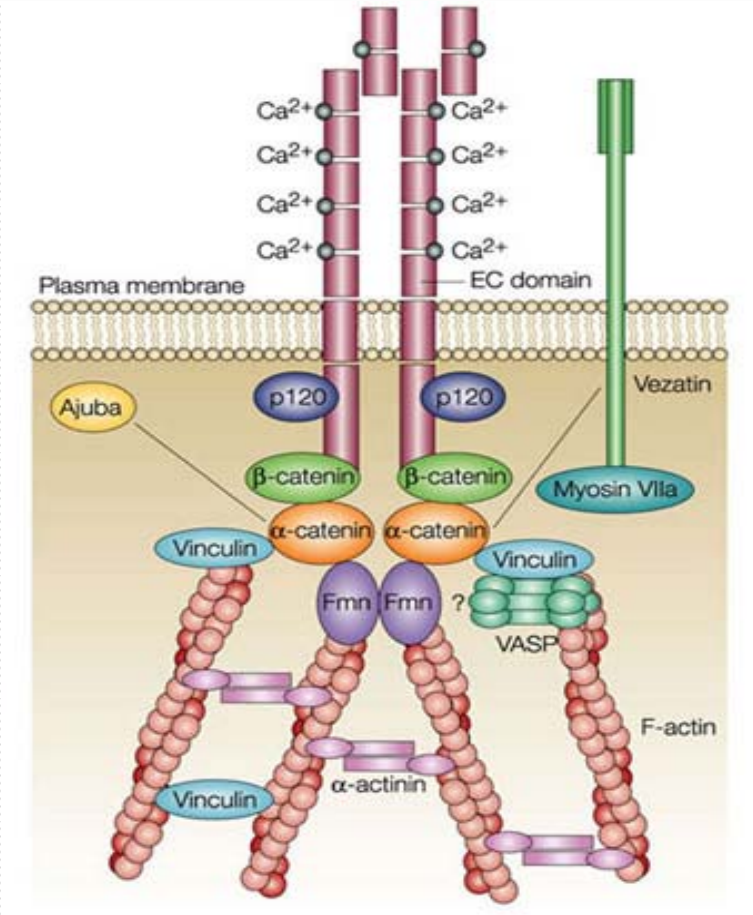
浸潤性小葉癌と浸潤性乳管癌（N0症例）におけるバイオマーカー発現の違い

Gonzalez-Angulo AM at al. Clin Breast Cancer 2006; 7: 396-400

- HER2 陰性（92% vs. 68%）
- CD44 過剰発現（31% vs. 16%）
- 間質での VEGFR2 発現低下（36% vs. 47%）
- ラミニン5発現低下（15% vs. 25%）
- E-cadherin 発現低下（0% vs. 90%）

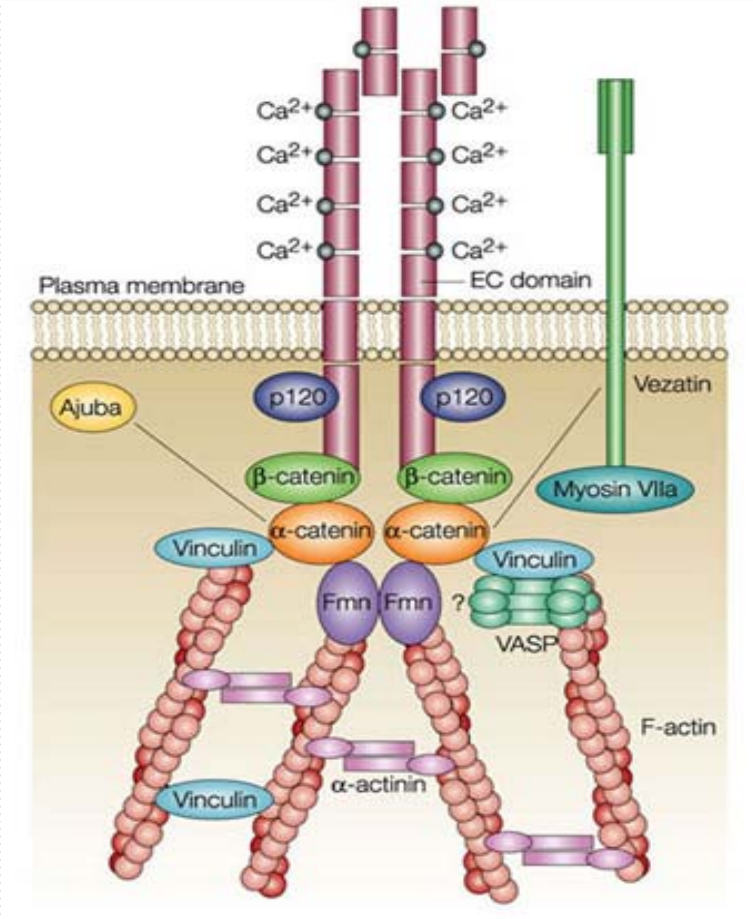

E-Cad

E-cadherin



- 上皮特異的な細胞接着に関与するカルシウム依存性接着分子（糖蛋白質）
- 5つの細胞外ドメイン
- 細胞内ドメインにカテニンが結合し、アクチンフィラメントに連結

E-cadherin



- 浸潤性小葉癌で発現消失
  - 第16染色体(Ch 16q22.1)のLOH (E-cadherin 遺伝子)
  - E-cadherin 遺伝子変異
  - プロモーターのメチル化
- 非浸潤性小葉癌でも消失~弱陽性
  - 併存する浸潤性小葉癌と同様の遺伝子変異、LOH

浸潤性小葉癌におけるE-Cadherin 発現

Rakha EA et al. Am J Surg Pathol 2001;34:1472-79

- 16% (38/239)で E-Cadherin 陽性
- 組織亜型（tubulolobular, mixedなど）、血管侵襲（陽性例は血管侵襲↑、43% vs 19%）と相関
  - その他の臨床病理学的因子、腫瘍の進展、免疫組織化学的表現型と相関なし
- カテニン複合体を構成する α, β, γ-カテニン、p120の異常発現
  （p120のびまん性細胞質陽性所見など）
- E-カドヘリン-カテニン複合体の結合性の低下を反映


Macy's

浸潤性小葉癌の悪性度評価

- mSBR system は有効か？
  - Grade は腫瘍径（中央値）とリンパ節転移（AJCC stage）と相関する
  - ER, PR, E-cadherin、HER2の発現状況とは相関しない（Bane AL et al. 2005）

浸潤性小葉癌の悪性度評価

- mSBR system は有効か？

mSBR grade と10年生存率

	Overall	Grade-Ⅰ	Grade-Ⅱ	Grade-Ⅲ
乳管癌（非特殊型）	46	76	55	39
小葉癌（Classical）	53	71	55	38

Periera et al. Histopathol 1995; 27219-226

浸潤性小葉癌における mSBR grade の分布（N=517）

Grade		
1	62	12
2	394	76
3	61	12
Tubule formation		
1	0	0
2	41	10
3	374	90
Pleomorphism		
1	16	4
2	344	83
3	56	13
Mitotic count		
1	333	81
2	50	12
3	30	7

Rakha EA et al. Breast Cancer Res Treat 2008; 111: 121-7

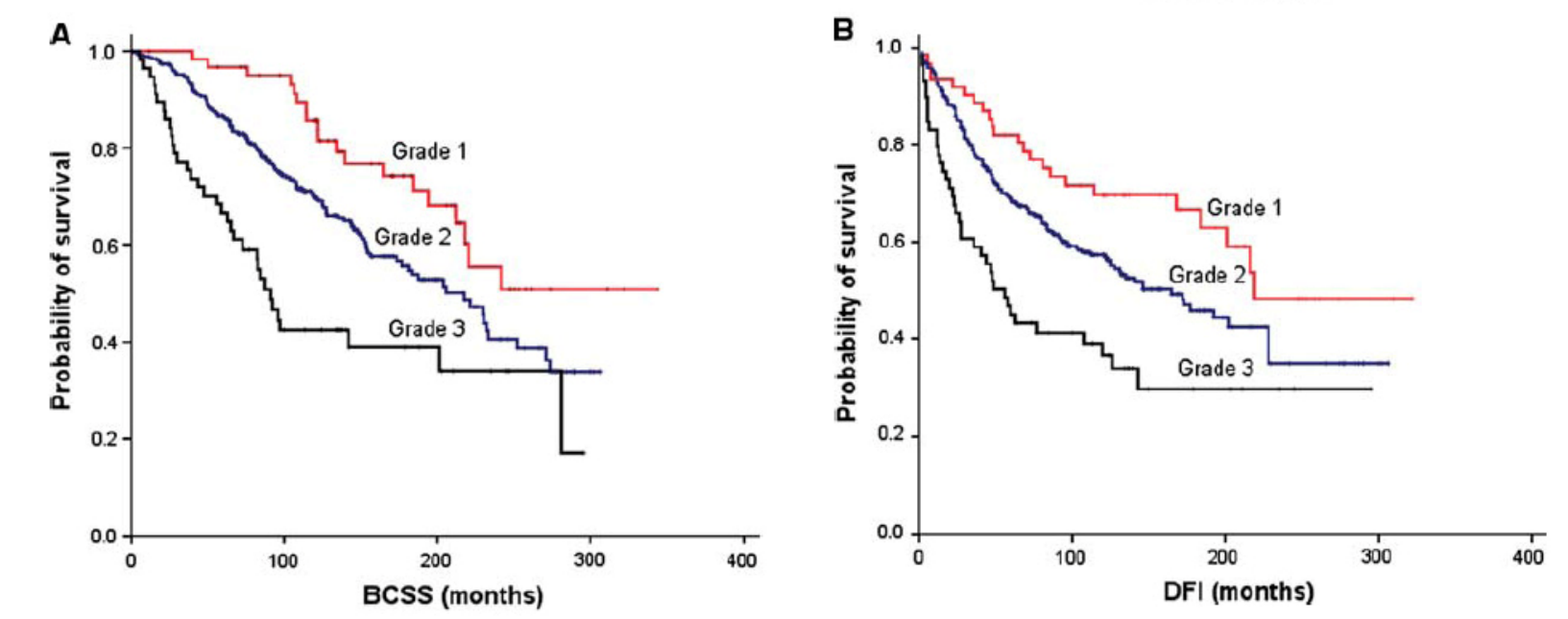


Fig. 1 Relation between histologic grade of ILC and (**A**) breast cancer specific survival (BCSS) (Log Rank (LR) = 23.1, $P < 0.001$) and (**B**) disease free interval (DFI) (LR = 17.9, $P < 0.001$)

Rakha EA et al. Breast Cancer Res Treat 2008; 111: 121-7

乳管癌、小葉癌の別は予後に影響を与えない

Fritz P et al. Anticancer Res 2010;30;5137-44

- 浸潤性小葉癌は：
  - 高頻度でER/PR陽性、HER2陰性
  - 平均年齢が高い
  - 再発率が低い (3.5% vs. 6.2%; p=0.031)
- 多変量解析では、① ER/PR 発現状況、②リンパ節転移の有無、③ 悪性度（grade）、④ 腫瘍径が、予後予測に有用

病期別では浸潤性小葉癌は浸潤性乳管癌よりも予後良好である

Wasif N et al. Ann Surg Oncol 2010;17;1862-9

- SEER データベース（1993-2003）に基づいた263,408 例の浸潤性乳癌の解析
  - 浸潤性乳管癌：235,769例（89.5%）
  - 浸潤性小葉癌：27,639例（10.5%）
- 浸潤性小葉癌は高頻度に：
  - 径2 cm をこえる（43.1 vs. 32.6%; P < 0.001）
  - リンパ節転移（36.8 vs. 34.4%; P < 0.001）
  - ER 陽性（93.1 vs. 75.6%; P < 0.001）

病期別では浸潤性小葉癌は浸潤性乳管癌よりも予後良好である

Wasif N et al. Ann Surg Oncol 2010;17;1862-9

- 5年疾患特異的生存率
  - **Overall（90 vs. 88%; P < 0.001）**
    - stage T1N0 (98 vs. 96%; P < 0.001)
    - stage T2N0 (94 vs. 88%; P < 0.001)
    - stage T3N0 (92 vs. 83%, P < 0.001)
    - stage T1N1 (89% vs. 88%; P = NS)
    - stage T2N1 (81 vs. 73%; P < 0.001)
    - stage T3N1 (72 vs. 56%; P < 0.001)
- Survival benefit）⇒14%

  （ハザード比 0.86, 95% CI 0.80-0.92）

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COMMENTS AND CONTROVERSIES

Neoadjuvant Chemotherapy: Not the Best Option in Estrogen Receptor–Positive, HER2-Negative, Invasive Classical Lobular Carcinoma of the Breast?

Arnie Purushotham and Sarah Pinder, *King's College London and Guy's and St Thomas's NHS Foundation Trust, London, United Kingdom*
Massi Cariati, *King's College London, London, United Kingdom*
Mark Harries, *Guy's and St Thomas's NHS Foundation Trust, London, United Kingdom*
Aron Goldhirsch, *Istituto Europea di Oncologica, Milan, Italy*

In 1973, the European Institute of Oncology performed the first prospective neoadjuvant chemotherapy study in locally advanced, inoperable breast cancer. The original purpose was to downstage the primary tumor in order to achieve surgical resection.[1] This approach has subsequently increased in popularity, and in the last 10 years, randomized controlled trials of neoadjuvant chemotherapy have been performed with a view to further downstage the primary tumor and lymph nodes in order to achieve greater rates of breast-conserving surgery and to test whether systemic therapy given earlier would confer a survival benefit. Although the net result of these trials did demonstrate a higher rate of breast conservation, no overall survival benefit was seen.[2,3] However, in subgroup analysis, there was a significant survival benefit in patients in whom a complete pathologic response (pCR) was achieved. In the National Surgical Adjuvant Breast and Bowel Project B-18 trial of neoadjuvant chemotherapy, at 9 years median follow-up, the overall survival rate for patients

carcinoma have been shown to be 2% or less.[5-7] Katz et al[8] reviewed randomized trials of neoadjuvant chemotherapy and noted that the pCR rate was 1.7% in invasive lobular carcinoma and 11.6% in invasive ductal breast carcinoma (no special type). Regarding invasive lobular carcinoma, they concluded: "the benefit from systemic chemotherapy for individuals with this form of breast disease is unclear."[8p55]

Similarly, two retrospective studies have demonstrated low rates of successful breast conservation for patients with lobular carcinoma who underwent neoadjuvant chemotherapy.[9,10] In patients who received breast-conserving surgery after neoadjuvant therapy, Soucy et al[9] found surgical margin involvement in 43% of patients with lobular carcinoma compared with 16% of patients with invasive ductal carcinoma (no special type). Another study, from the M. D. Anderson Cancer Center, of 284 consecutive patients diagnosed with pure invasive lobular carcinoma between 1998 and 2006

浸潤性小葉癌では
術前化学療法後の完全寛解率が低い

- 病理学的完全寛解率（pCR）
  - 浸潤性乳管癌（非特殊型）

    ⇒ 15% 以下
  - 浸潤性小葉癌(古典型)

    ⇒ 2% 以下

温存手術における切除断端にNACは影響を与えるか

Soucy G et al. J Am Coll Surg 2009; 206: 1116-1121

Table 3. Logistic Regression Model for Variables Associated with Margin Status

Characteristic	p Value
Age	0.192
Histologic grade	0.151
pN staging	0.284
Pathologic tumor size	0.172
Hormonal receptors	0.014
Guidewire	0.139
Histologic type	0.002
Neoadjuvant systemic therapy	0.331

pN, pathologic nodal.

温存手術における切除断端にNACは影響を与えるか

Soucy G et al. J Am Coll Surg 2009; 206: 1116-1121

- 断単陽性率

NAC群	非NAC群	
21%	18%	p=0.51

浸潤性小葉癌	浸潤性乳管癌（NST）	
43%	16%	p=0.002

ER/PR+	ER/PR-	
20%	10%	p=0.014

浸潤性小葉癌の転移様式

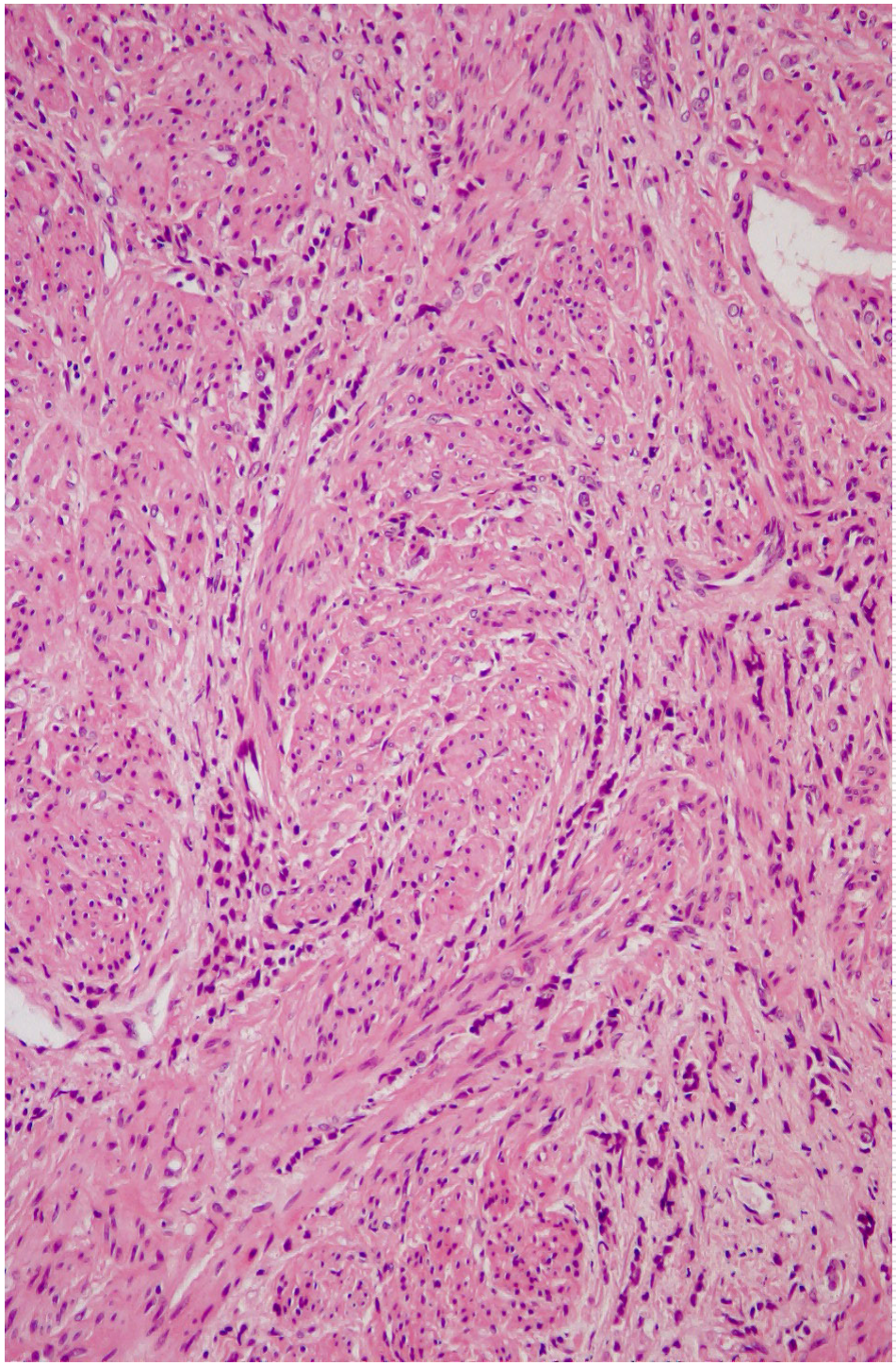
- 肺、肝臓、脳実質は比較的稀
- 髄膜 leptomeninges
- 漿膜面 peritoneal surface
- 後腹膜 retroperitoneum
- 消化管（胃など）
- 生殖器（卵巣、子宮など）
- 骨

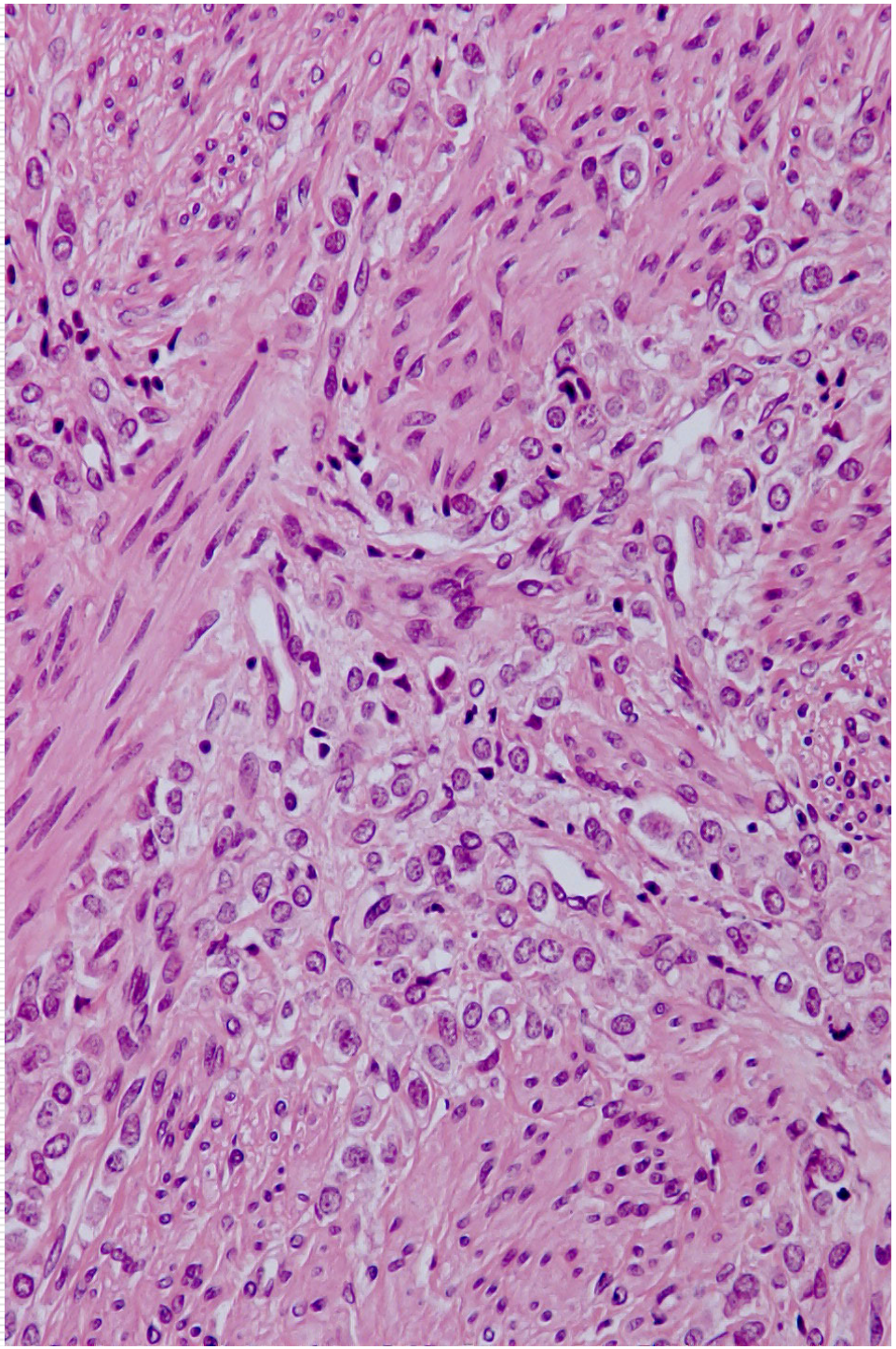
稀な転移様式

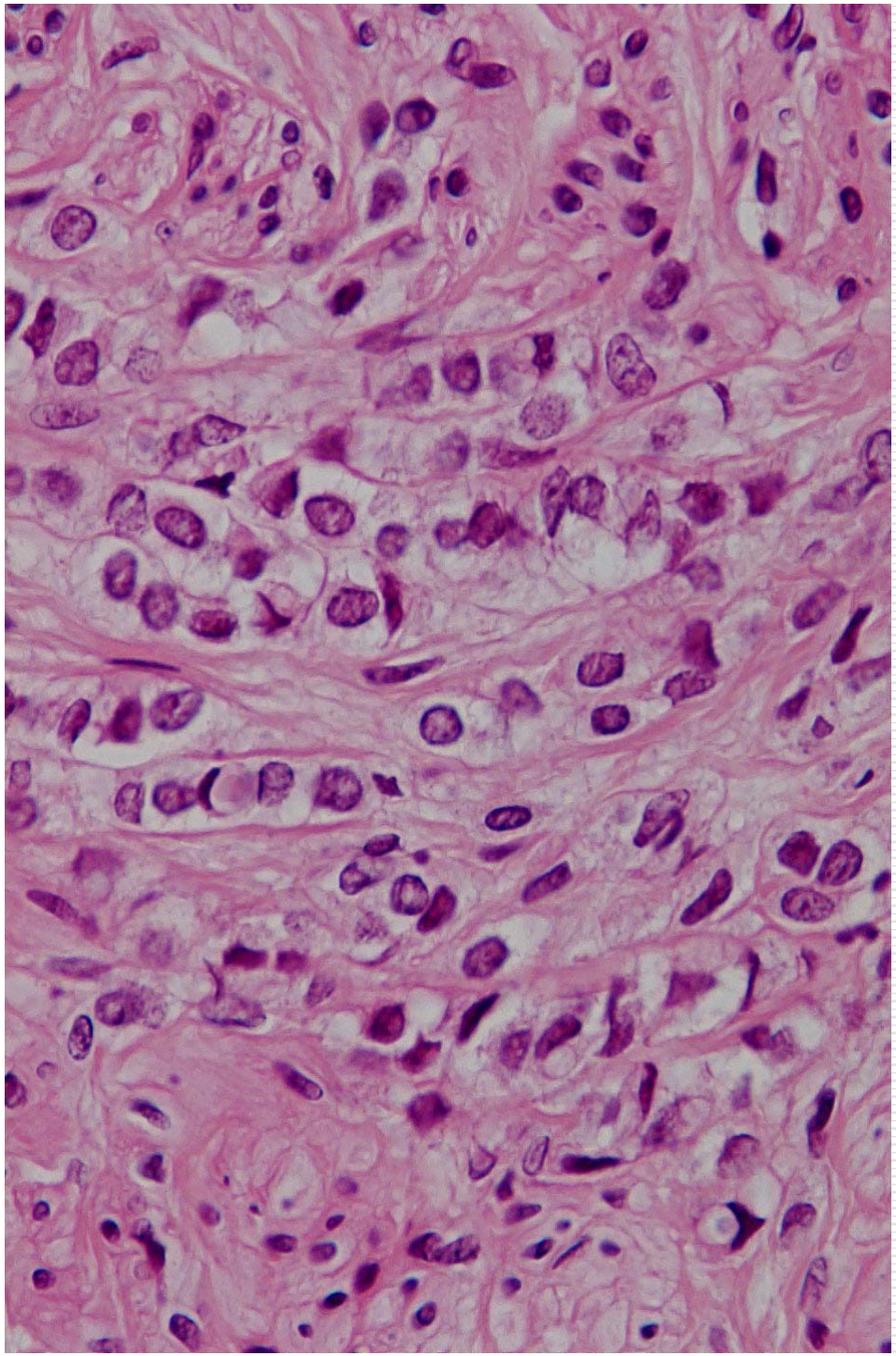
- 後腹膜線維症
- 頻尿（膀胱転移）
- 粘液塞栓による脳梗塞
- “子宮肉腫”（自験例）

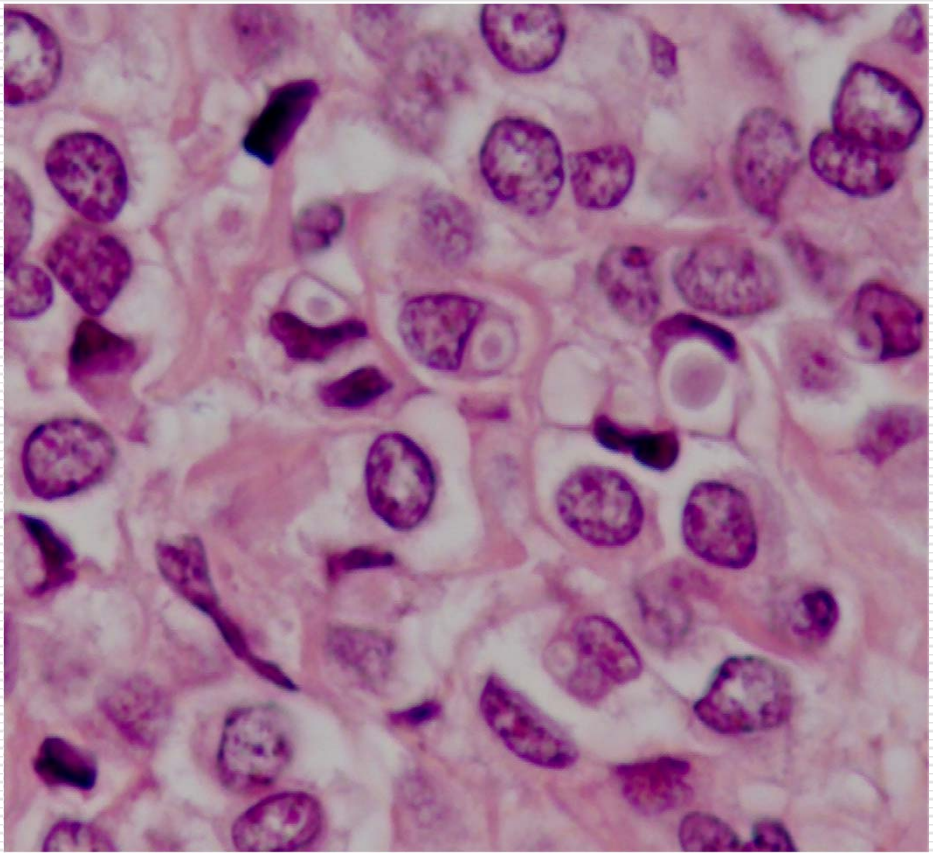
Case

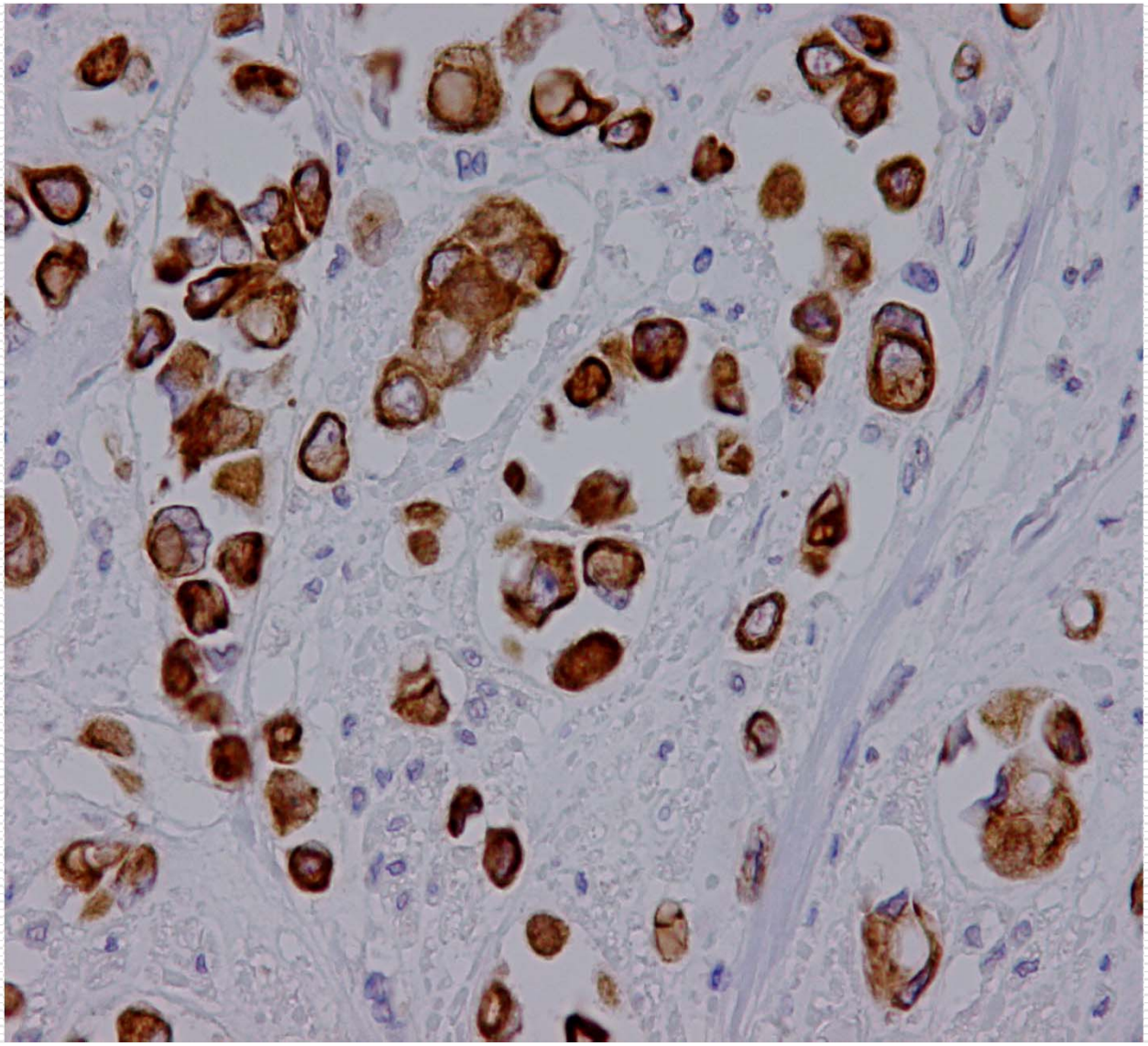
- 56歳、女性
- 子宮体部腫瘍の診断で子宮筋層生検
- 特記すべき既往歴なし











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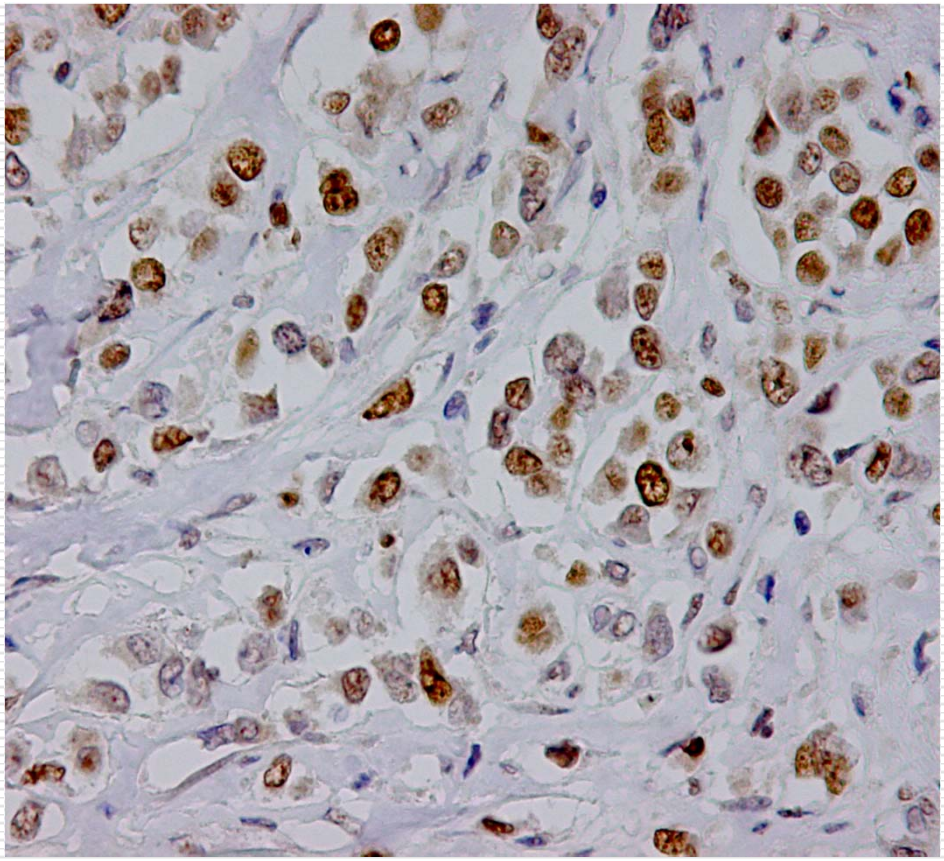

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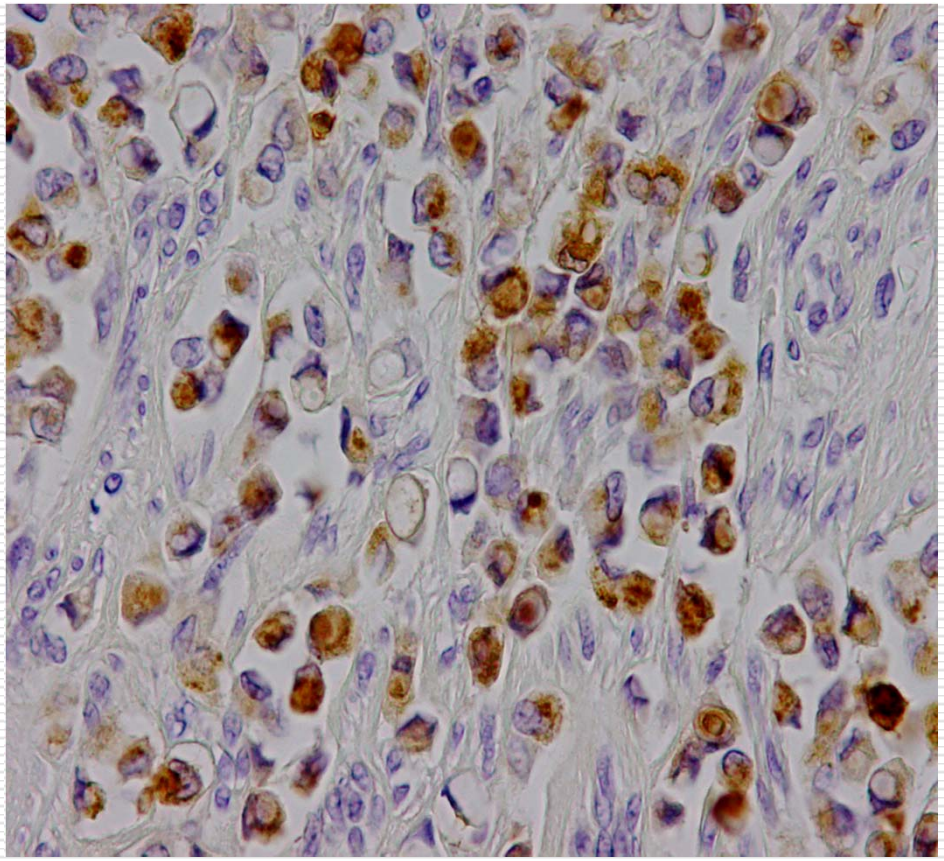


GCDFP-15

TAKE HOME

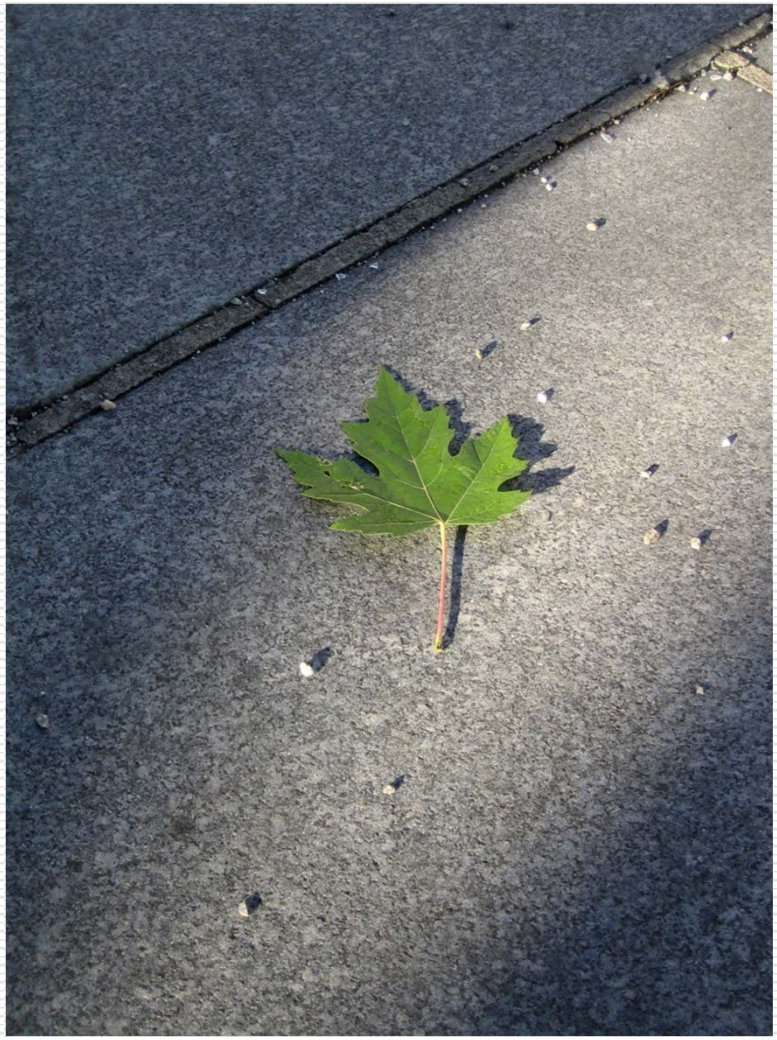
- 頻度は低い（全乳癌の5~15%）
- 閉経後のホルモン補充療法（HRT）に関連
- 50歳以降で好発
- マンモグラフィーによる検出がやや困難
- 進行例が多い（>2cm、50% vs. 39% in IDC）
- しばしば同側で多巣性（mutifocal）
- しばしば両側性（bilateral）（6~47%）

TAKE HOME

- 非浸潤性小葉癌が併存（70~80%）
- 高い断端陽性率*（43% vs. 16% in IDC）
- 多くは mSBR grade-Ⅱ（~76%）
- ER陽性（~93%）
- AR陽性（~88% vs. ~56% in IDC）
- 稀にHER2陽性（~11%）
- E-cadherin 発現の消失
- 骨、卵巣などへの転移

＊ 温存手術

ご清聴ありがとうございました



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