A Potential Role for *Sex Hormone Receptor Antagonists* in Treatment of **Malignant Salivary Gland Tumors**, as compared to **Breast Cancer**

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Breast and salivary glands are similar **morphologically**

consequently we expect similarities in the **pathological** processes.

Since adjuvant hormonal therapy is recommended for hormone receptor positive breast tumors;

therefore the expression of sex hormones in Malignant Salivary Gland Tumors, and their potential use in treatment is being studied comparatively.

This Review discusses the following points :

1. Similarities between MSGTs and Breast Cancers
2. Role of hormones in treatment of breast cancers
3. Expression of sex steroid hormones in MSGTs
4. The potential role of hormones in treatment of MSGTs

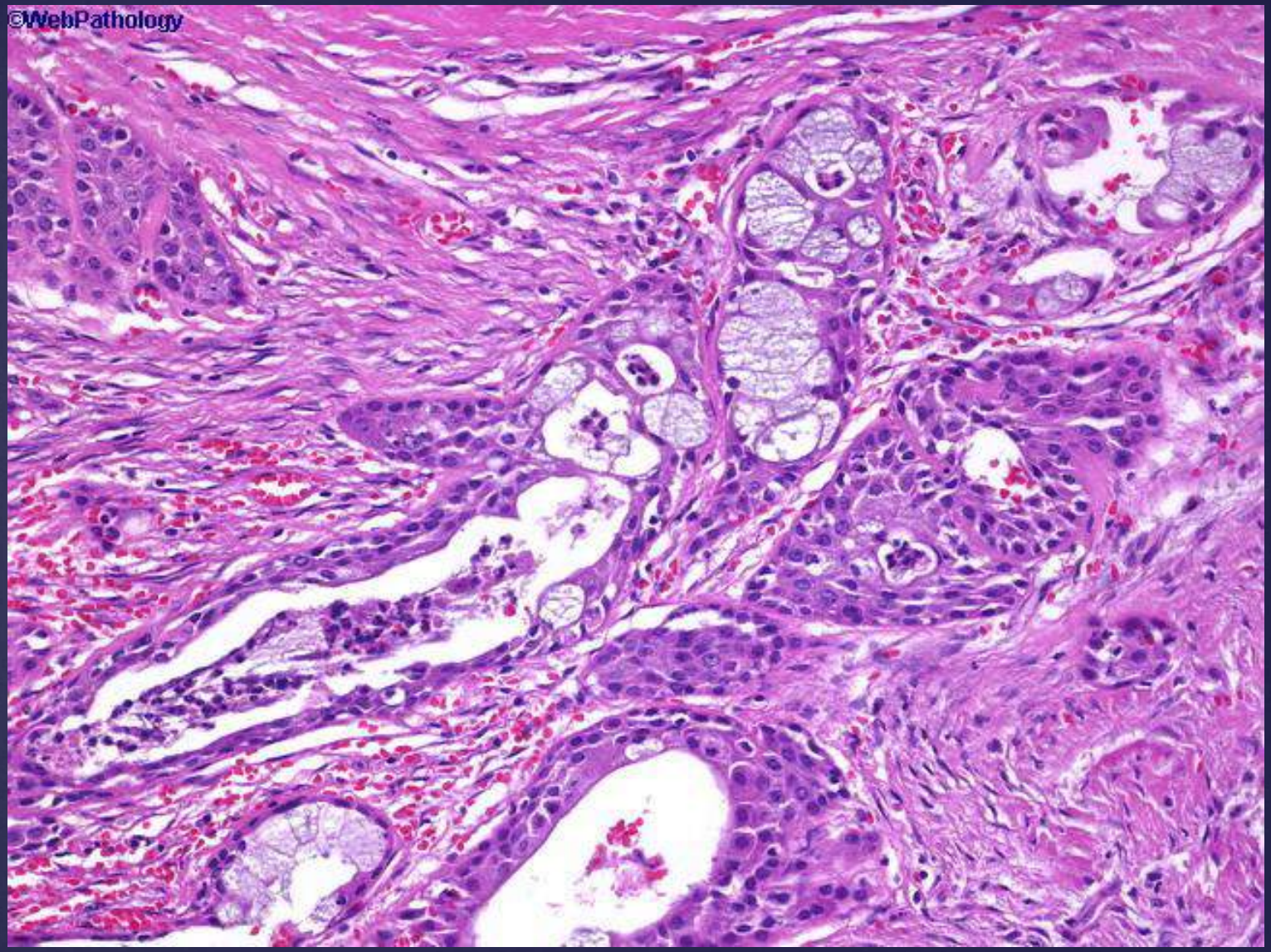
1. How are MSGTs similar to Breast Cancers?

- Breast and salivary glands are both **tubulo-acinar exocrine glands**
- The same types of neoplasms can arise in both sites; such as pleomorphic adenoma, myoepithelioma, acinic cell carcinoma, oncocytic carcinoma, AdCC, MEC and SDC.

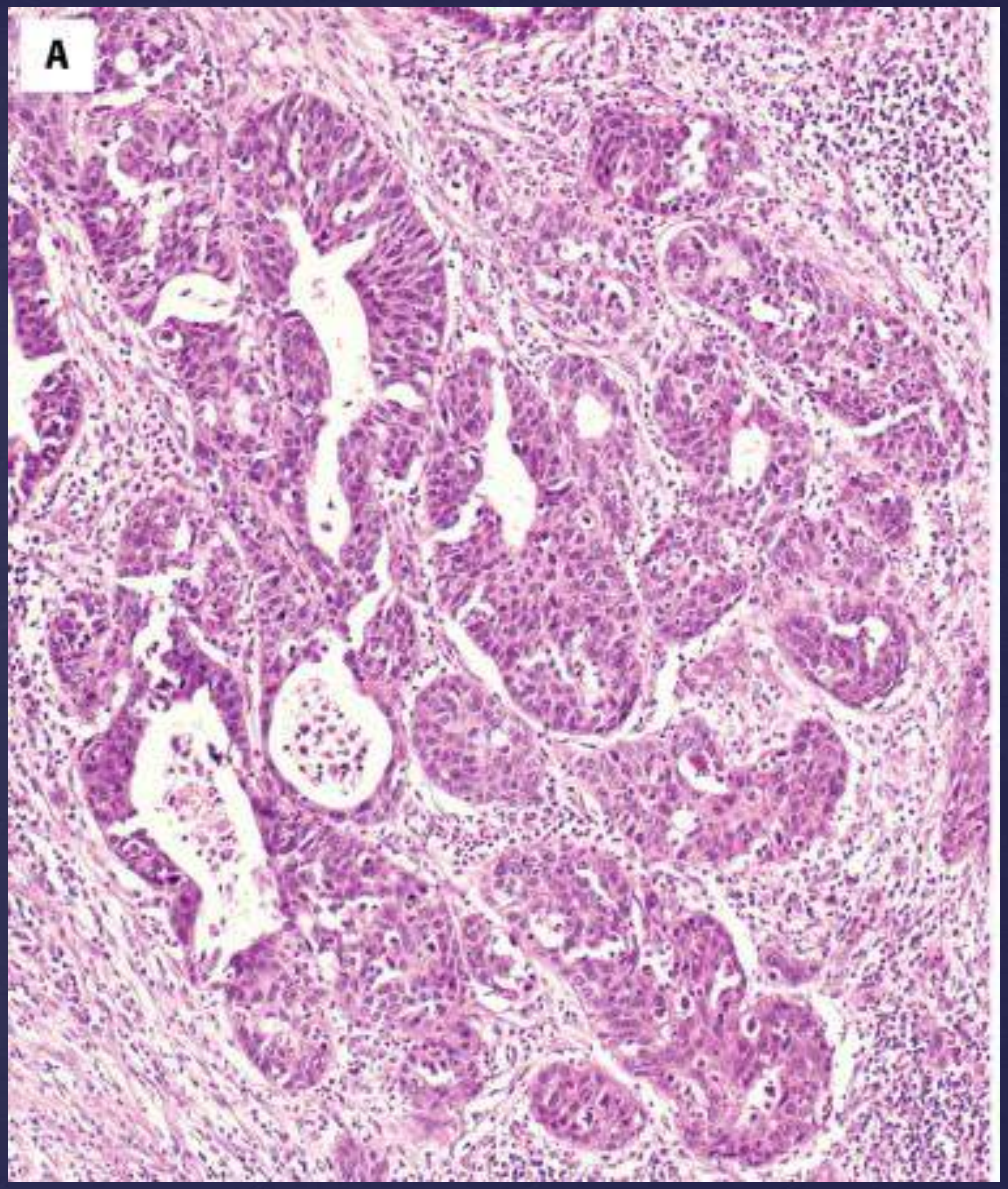
I- Mucoepidermoid Carcinoma of salivary glands

- It is composed of a mixture of mucous, epidermoid and intermediate cells.

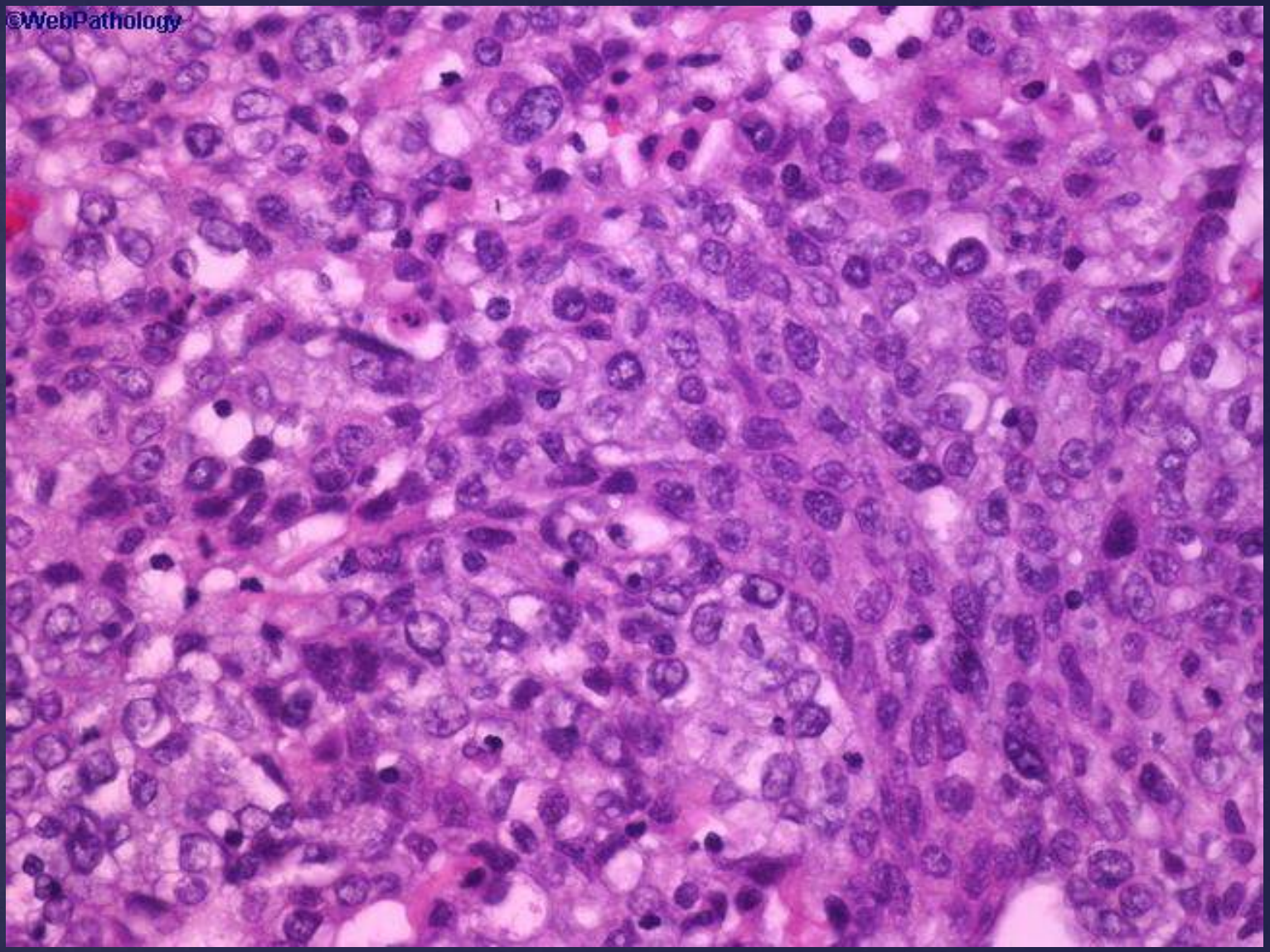
- Some tumors also show variable numbers of **clear cells**.



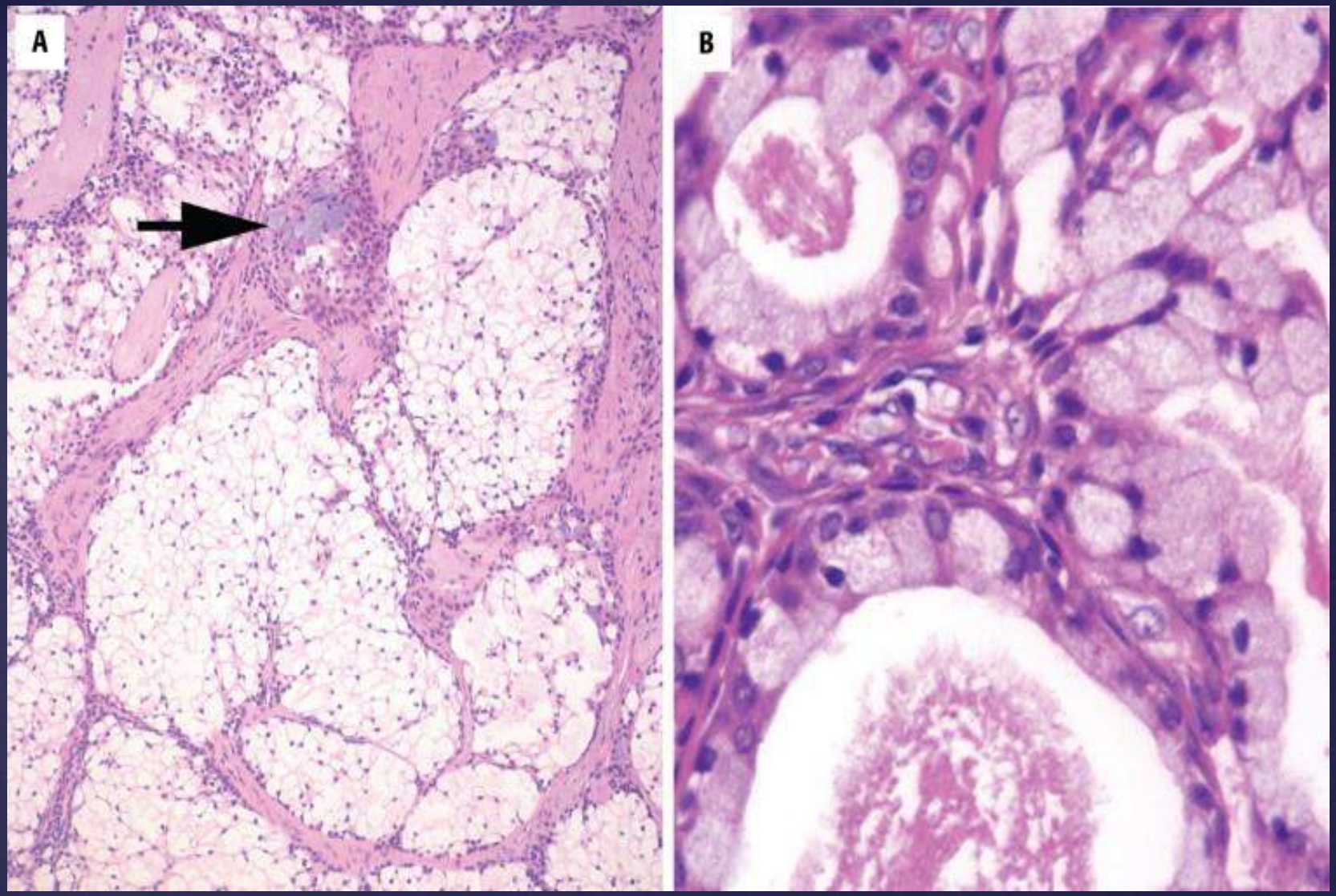
Low grade Salivary MEC



Intermediate-grade MEC showing limited cyst formation and nearly absent mucocytes.



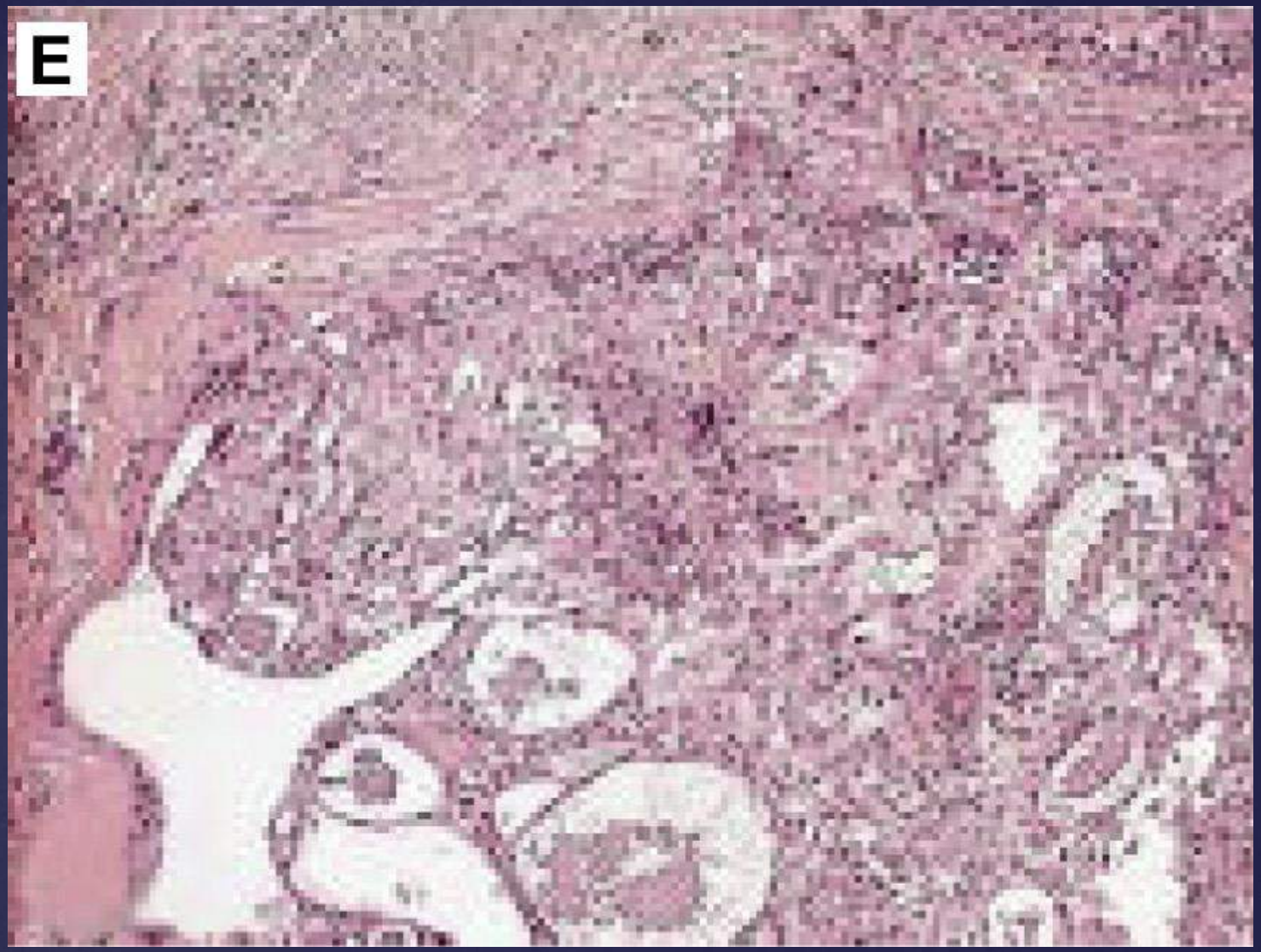
High grade Salivary MEC, A high-grade tumor with increased mitoses and profound pleomorphism.



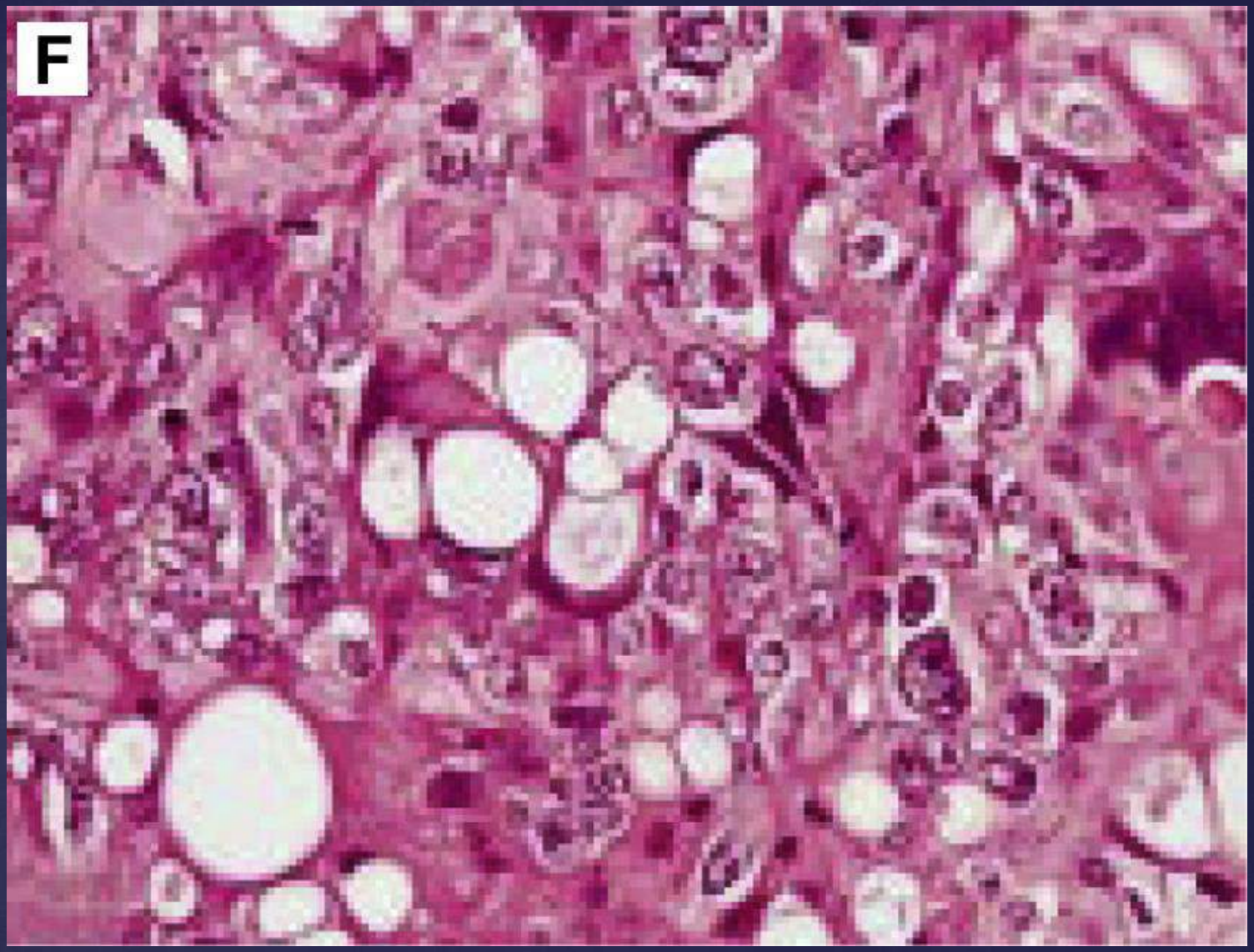
A, This mucoepidermoid carcinoma shows a predominantly clear cell pattern, although isolated mucocytes are noted (*arrow*). **B**, The mucocytes have fluffy cytoplasm and may surround secretions within the duct spaces.

Mucoepidermoid Carcinoma of breast

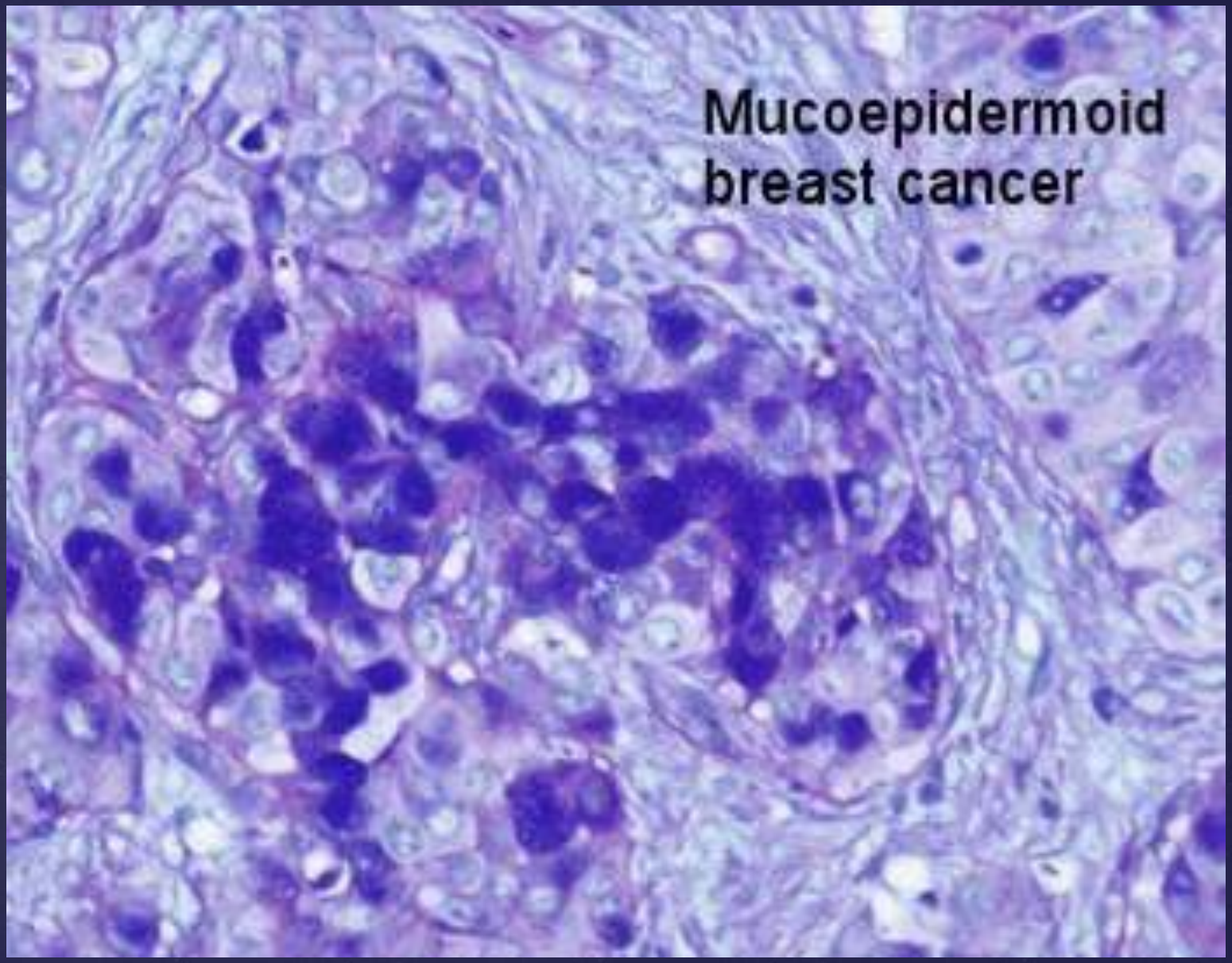
Mucoepidermoid carcinoma of the breast can also be categorized as low, intermediate and high grades.



Low grade mammary mucoepidermoid carcinoma (MEC) composed of neoplastic nests outlined by basaloid cells and centrally containing epidermoid and mucous secreting cells



high power magnification of high grade mammary MEC showing a complex admixture of basaloid and epidermoid elements and mucous secreting cells

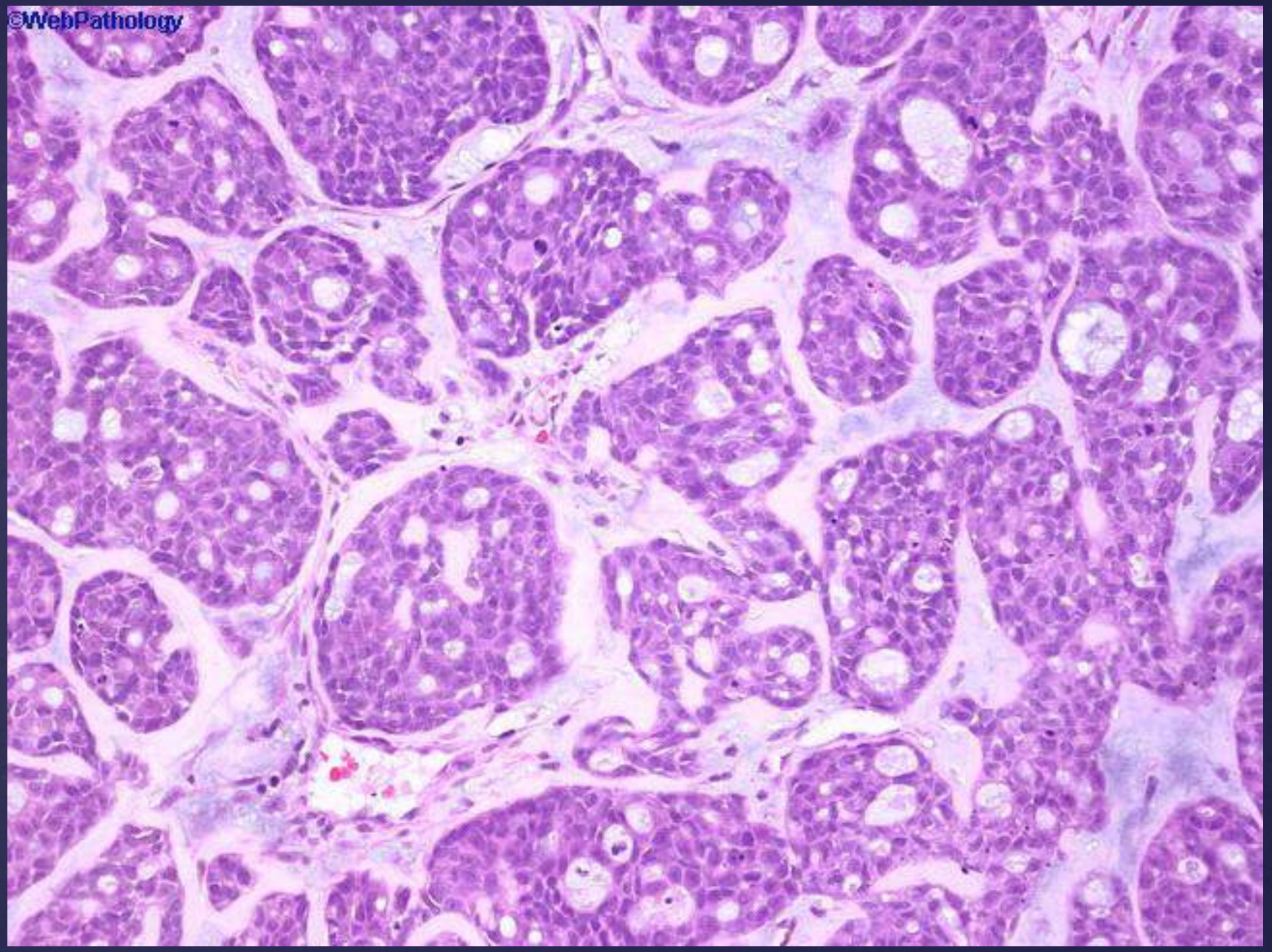


Mammary MEC, Alchian Blue

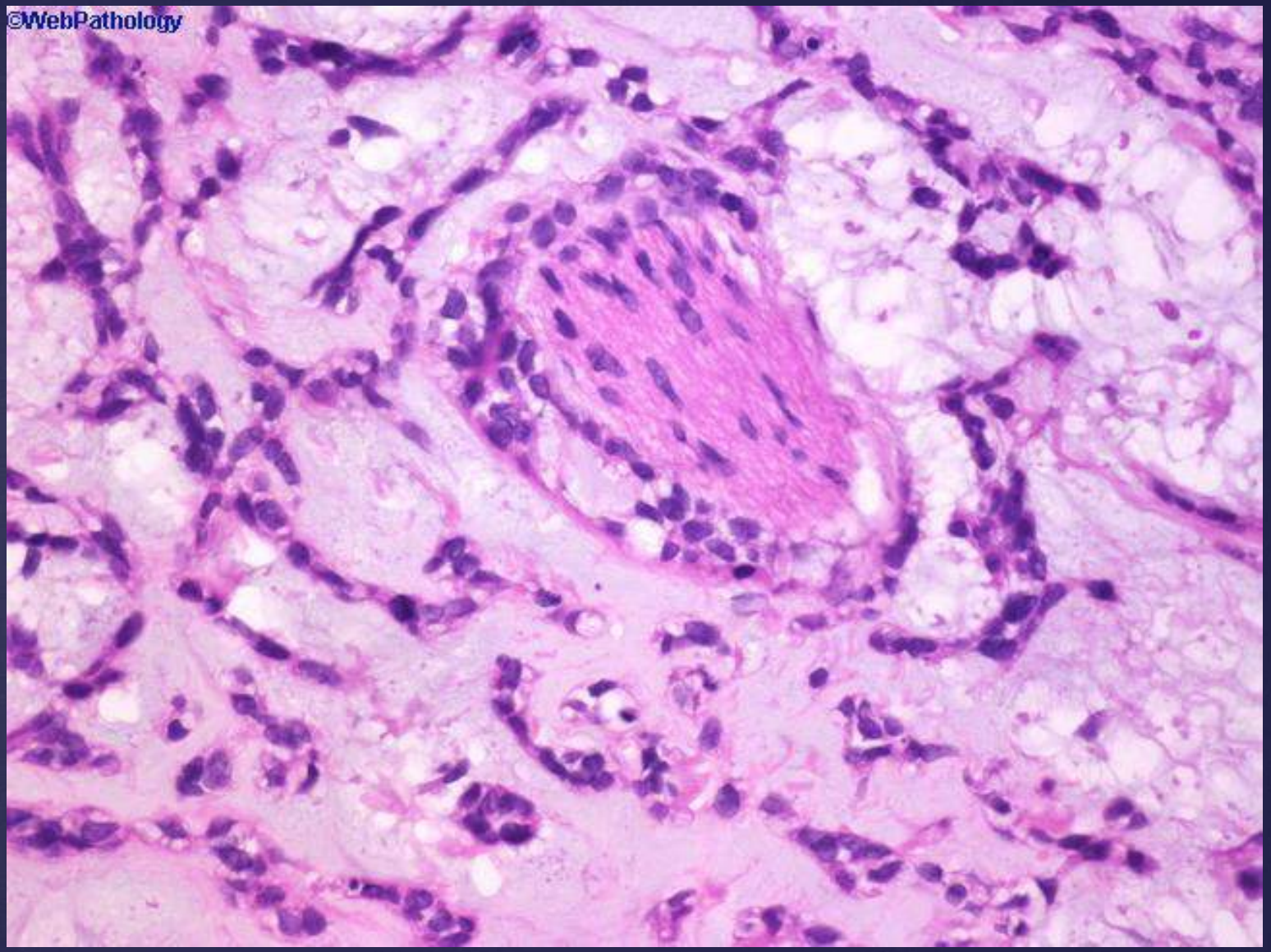
II- Adenoid Cystic Carcinoma of salivary glands

AdCC is composed of **two main types of cells**;

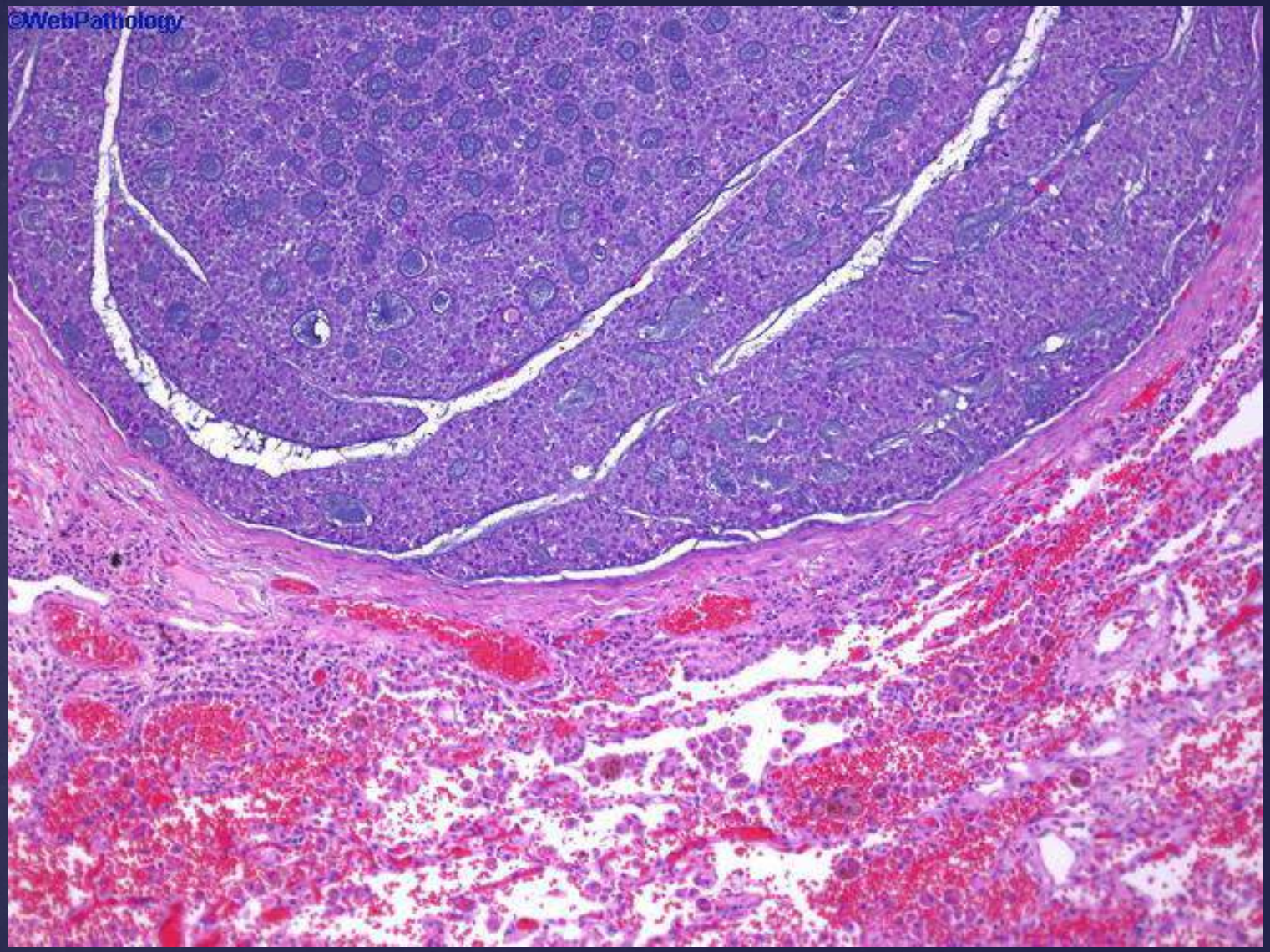
1. myoepithelial cells and
2. ductal cells.



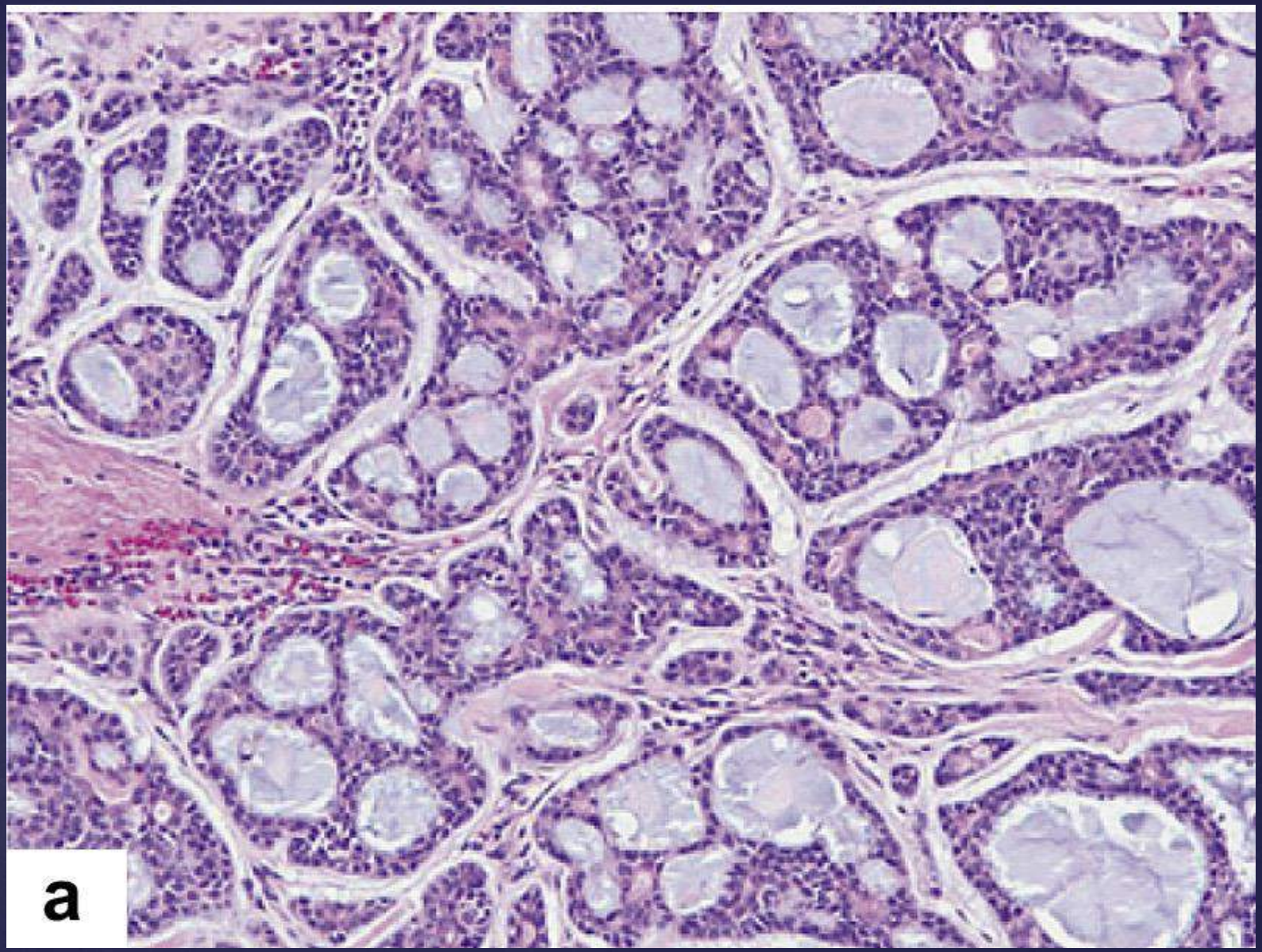
AdCC, Cribriform Pattern



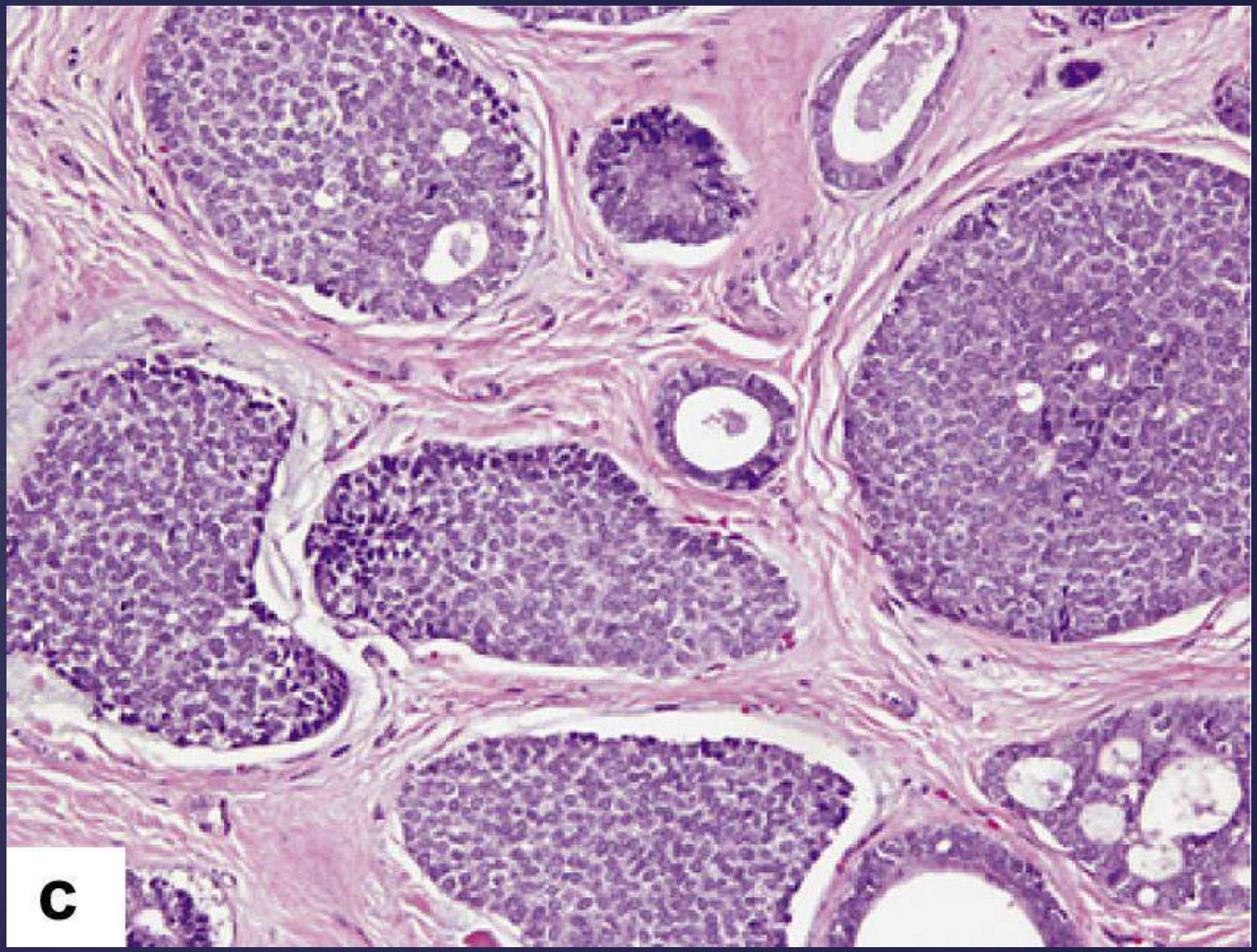
AdCC with Perineural Inavsion



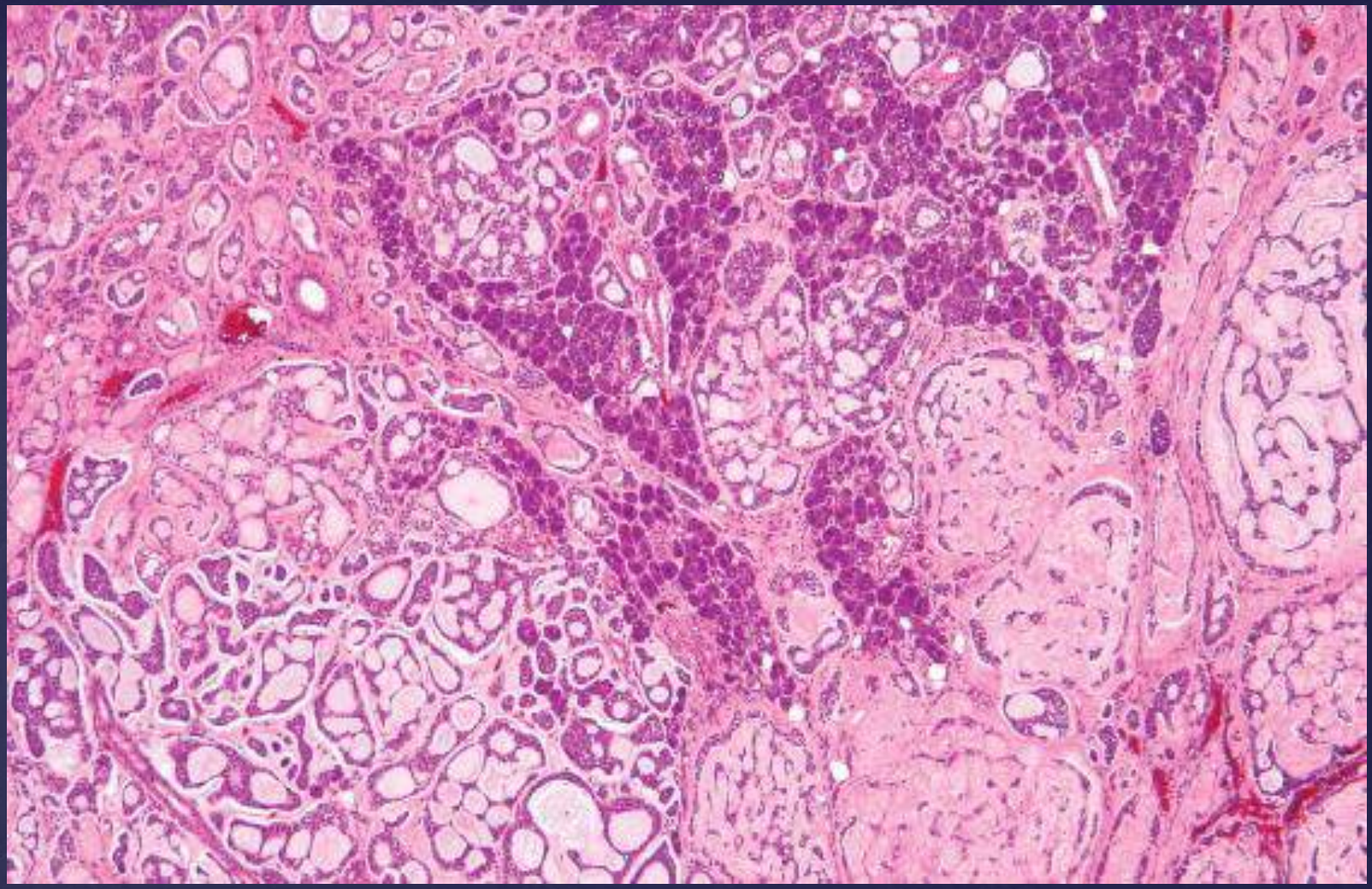
Lung metastasis of AdCC



Low-grade adenoid cystic carcinoma of the salivary gland with predominant cribriform/tubular pattern.



High-grade adenoid cystic carcinoma of the salivary gland with greater than 30% solid pattern.

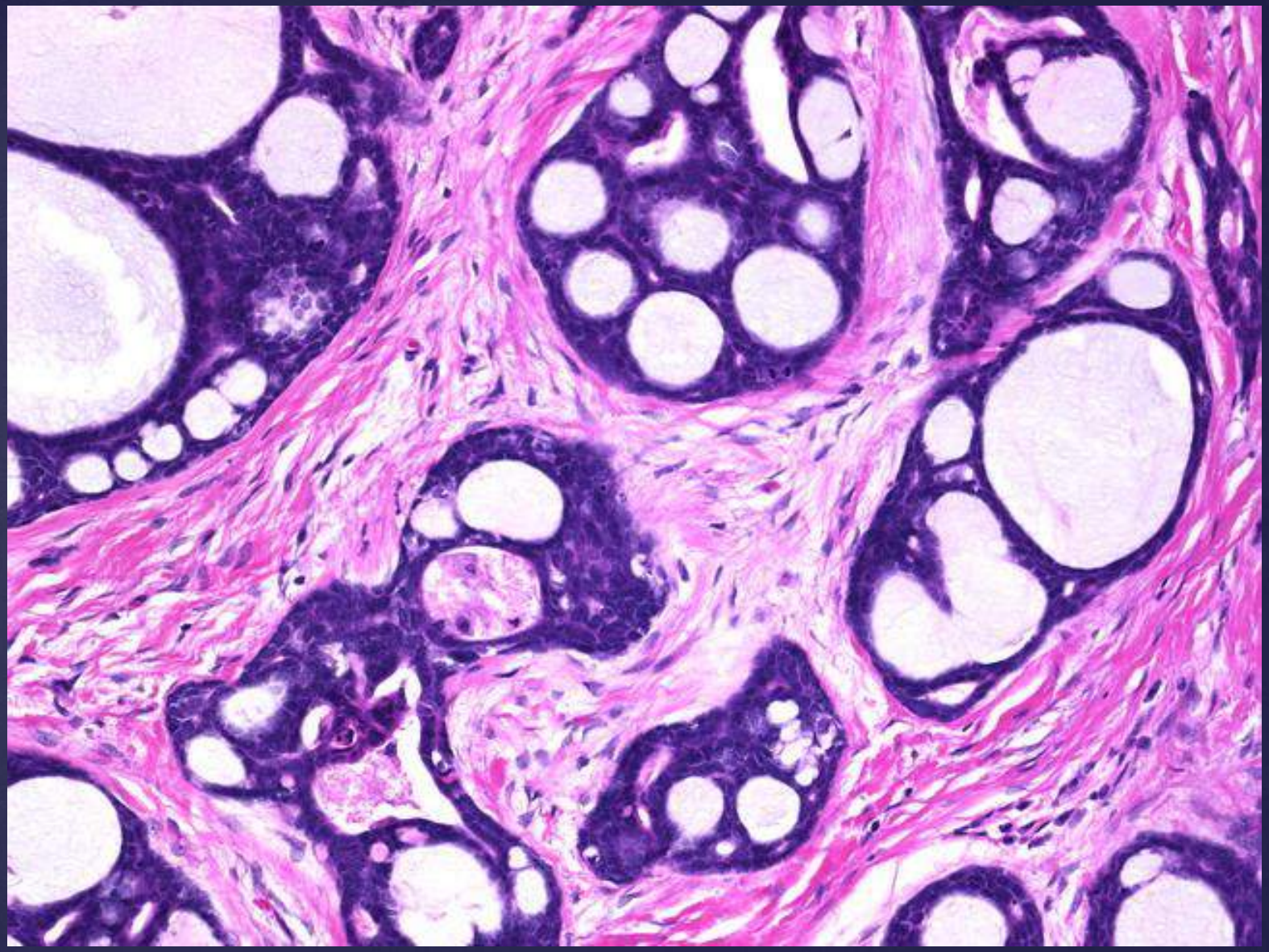


An adenoid cystic carcinoma showing multiple patterns of growth, although the cribriform and tubular areas predominate. Notice how the tumor is infiltrating between and around the parenchyma.

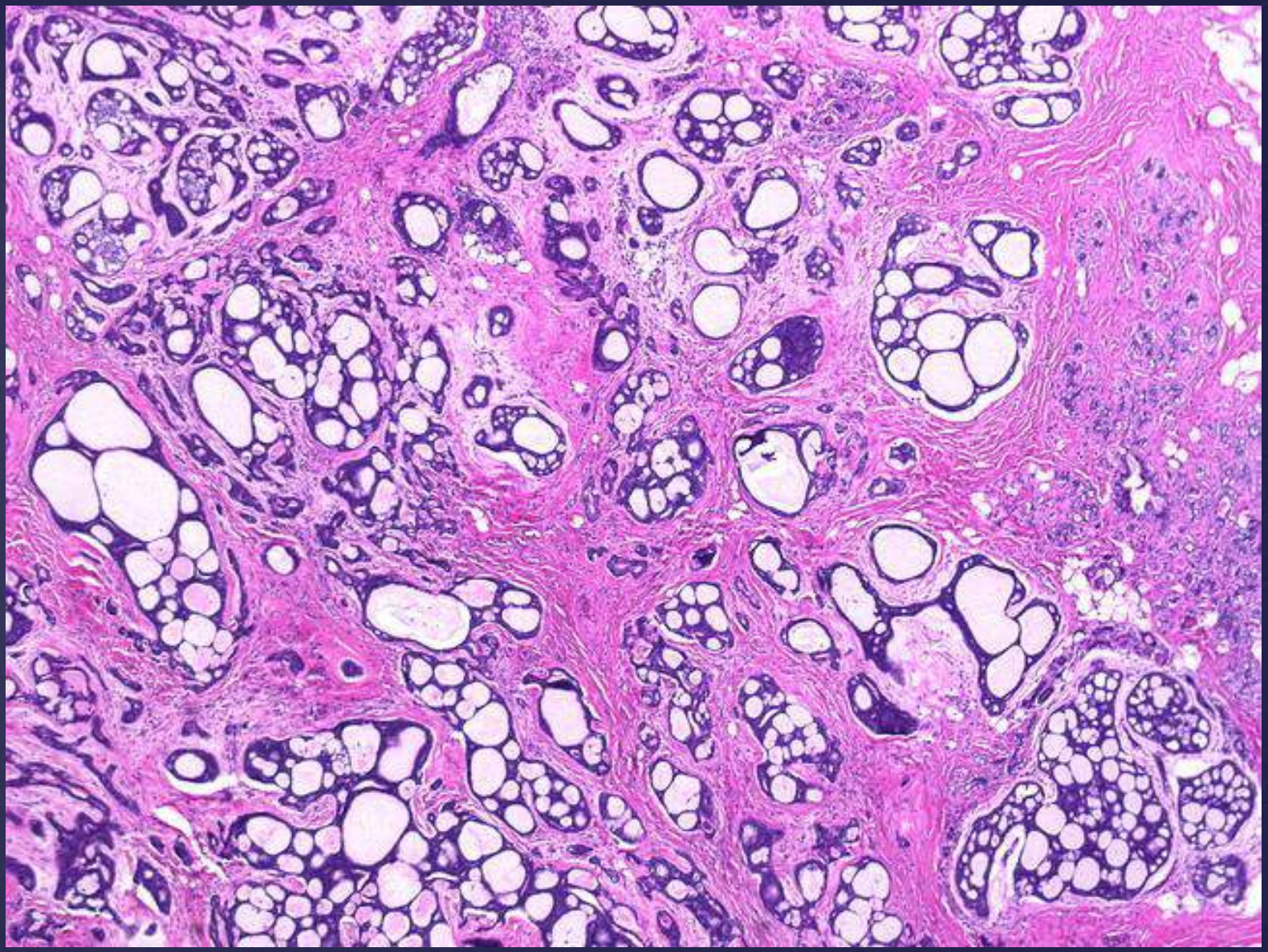
Adenoid Cystic Carcinoma of the Breast

AdCC of the breast is composed of large sheets, nests or small aggregates of round to oval cells, sometimes with hyperchromatic nuclei.

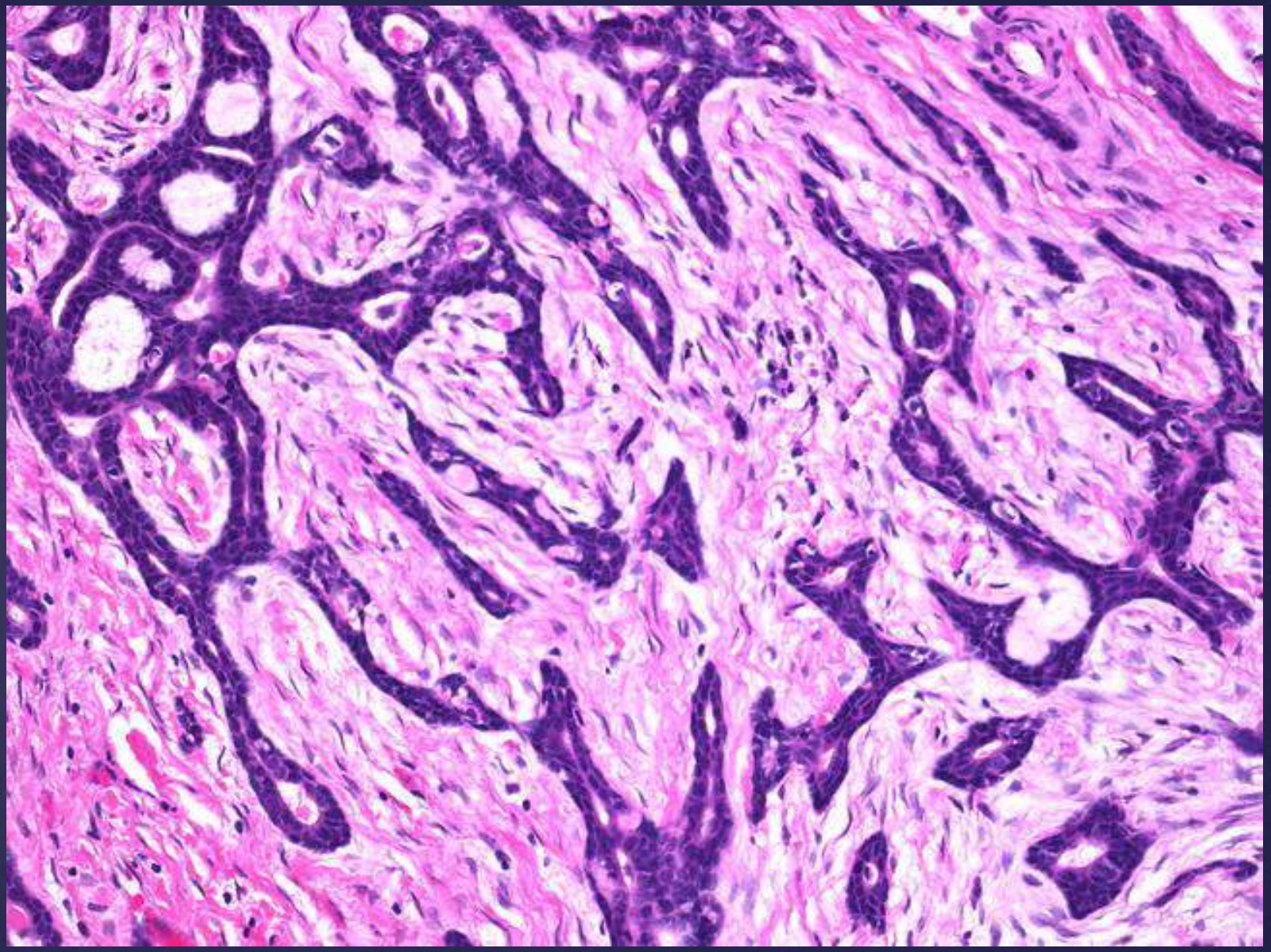
Adenoid cystic carcinoma of the breast showing cribriform architecture; composed of basaloid cells that outline spaces containing basal-like material and of eosinophilic cells lining true glandular lumina



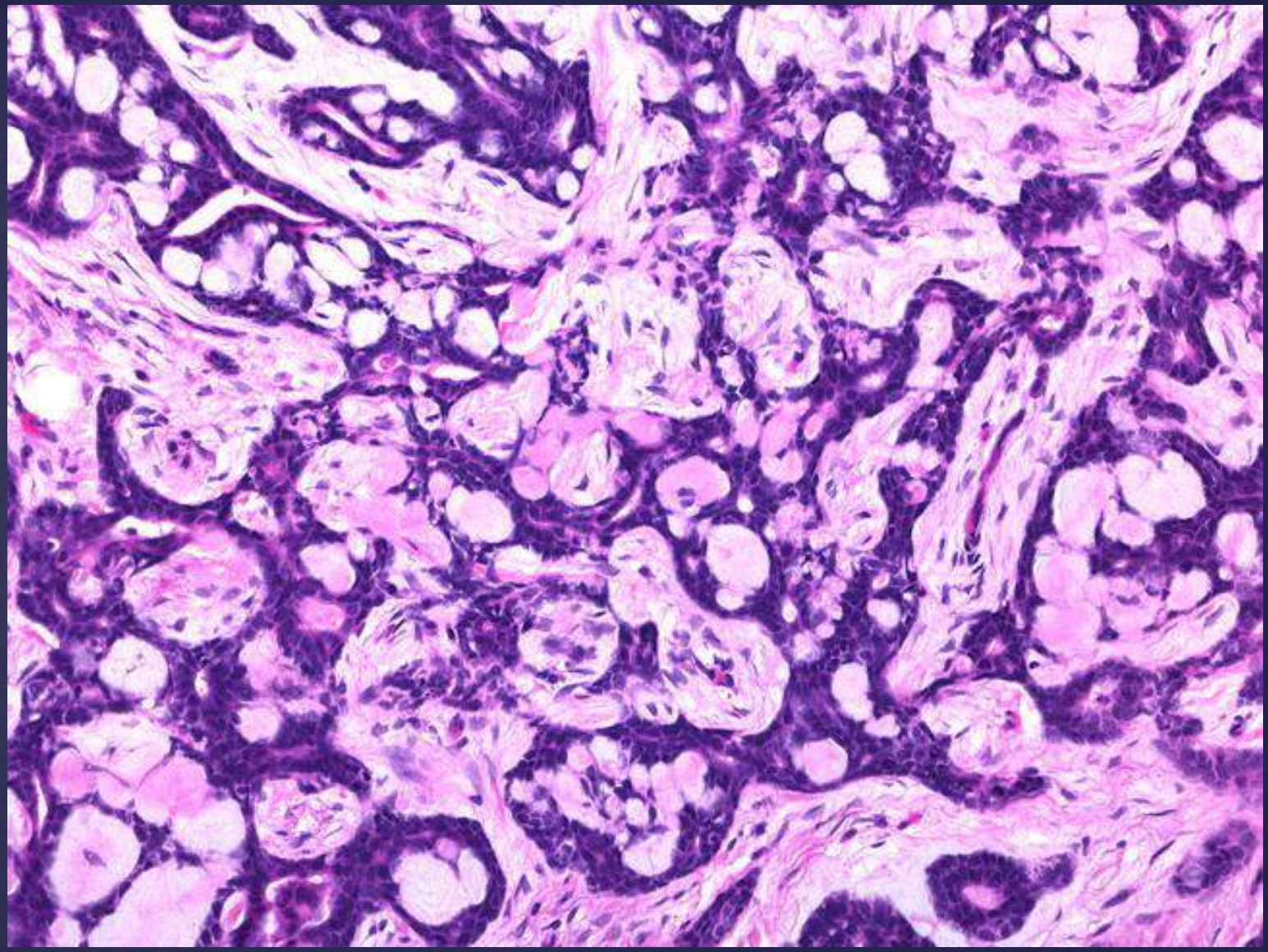
Cribriform pattern of AdCC



Cribriform pattern of AdCC



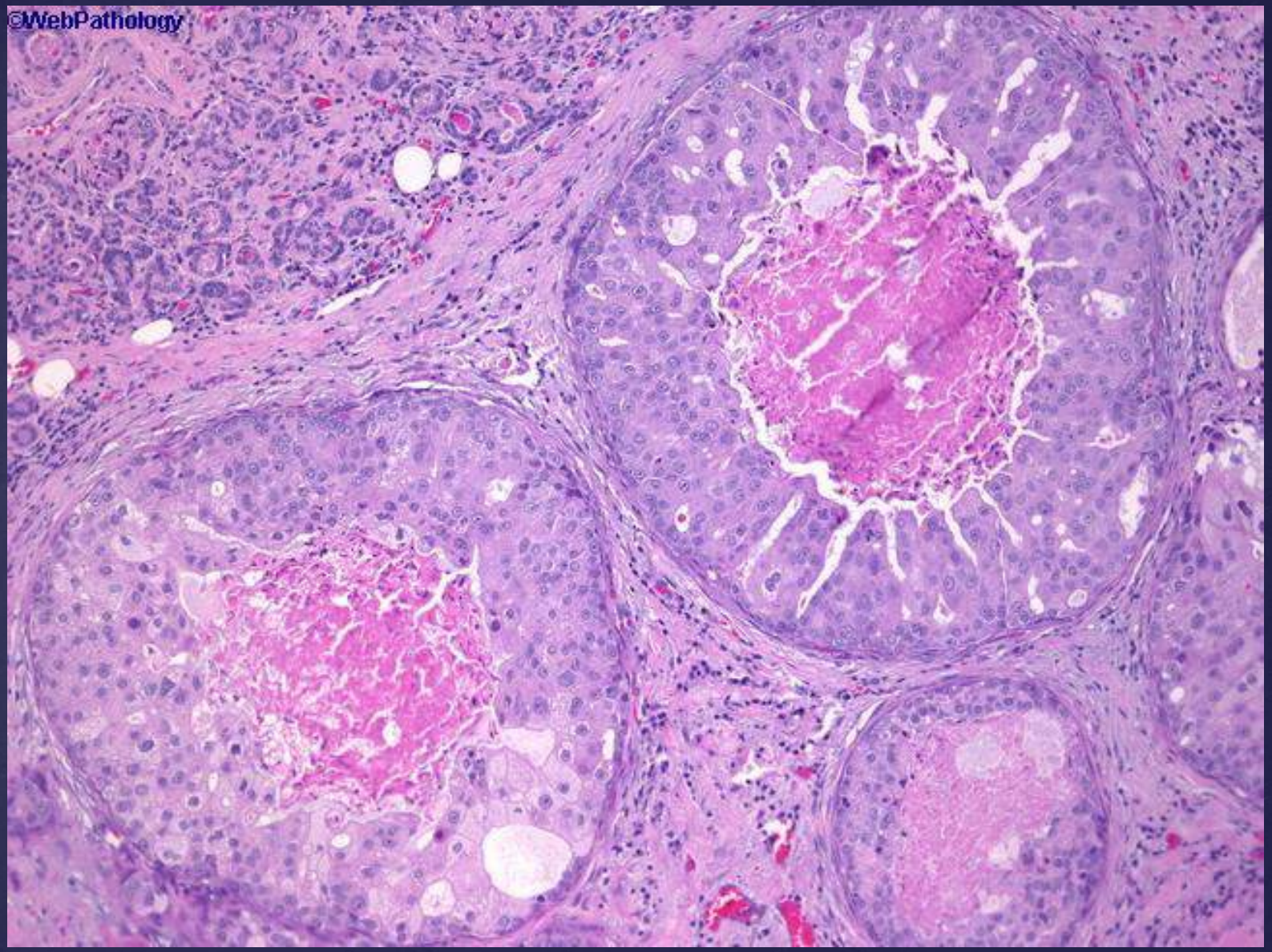
Trabecular pattern of AdCC



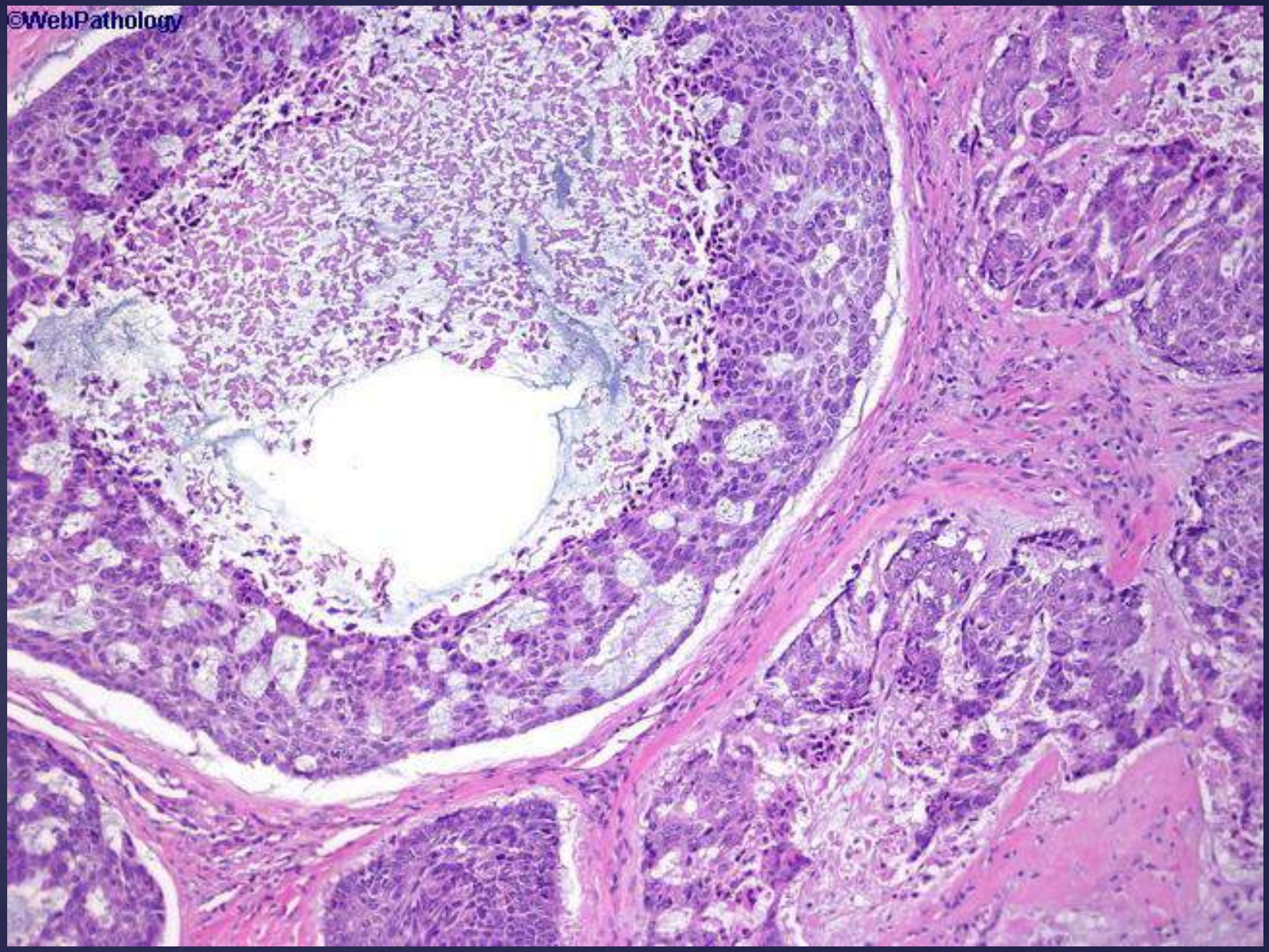
Trabecular pattern of AdCC

III- Salivary Duct Carcinoma

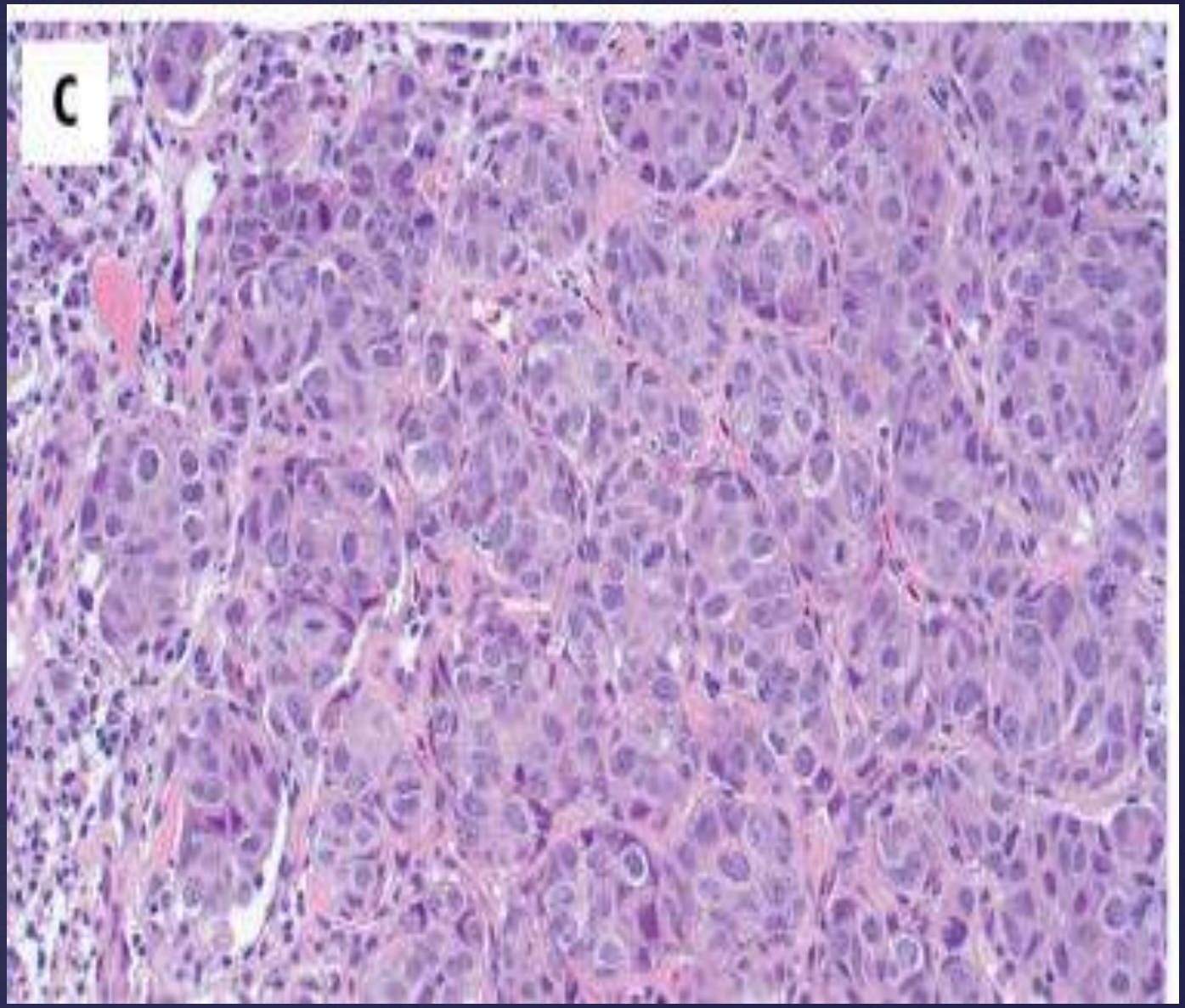
- The morphology of SDC is characterized by ***cuboidal and polygonal cells*** forming ducts and nests; often with central necrosis.



Salivary duct carcinoma



Salivary Duct Carcinoma

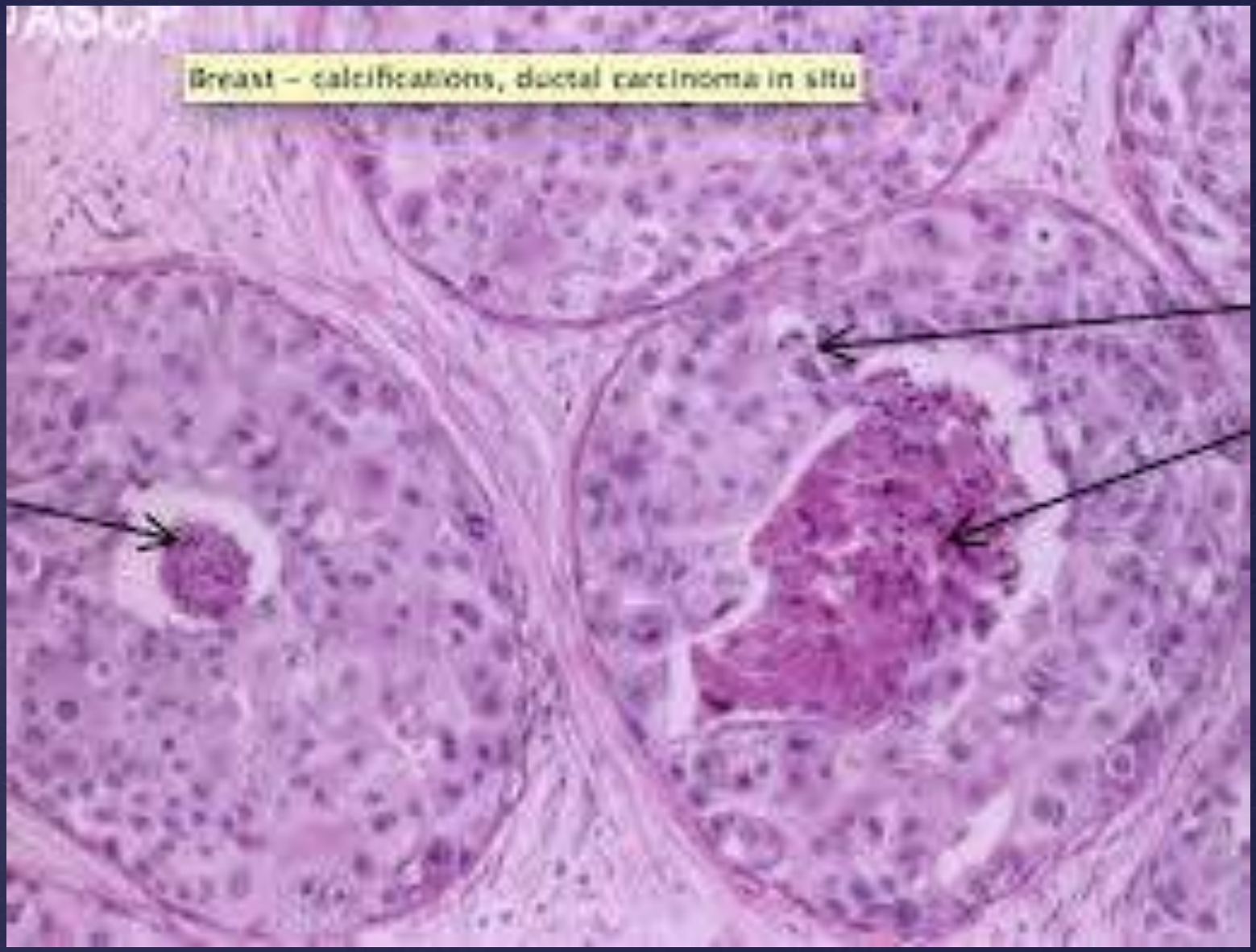


A more solid pattern of growth is noted, composed of large, polygonal tumor cells.

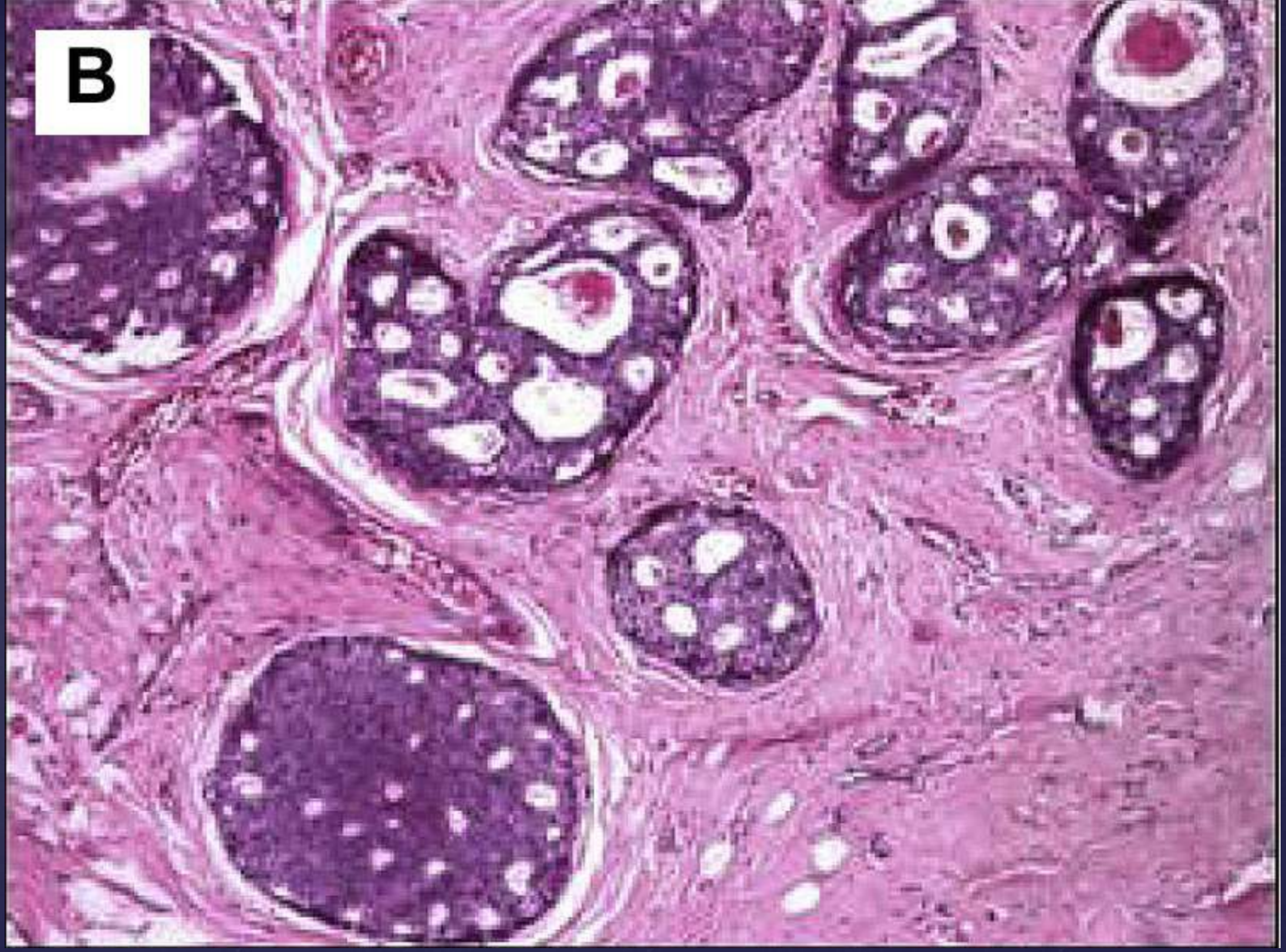
Mammary Duct Carcinoma

Several forms of histological architecture are recognised, the most common of which are:

1. cribriform,
2. solid,
3. Papillary, etc.



Ductal Carcinoma in-situ



Cribriform-type ductal carcinoma in situ

1. Similarities between MSGTs and Malignant Breast Tumors
2. Role of hormones in treatment of breast cancers
3. Expression of sex steroid hormones in MSGTs
4. The potential role of hormones in treatment of MSGTs

2. Role of sex hormones in treatment of Breast Cancer

Estrogen promotes the growth of about **2 out of 3** of breast cancers; ER -positive cancers.

Because of this, several approaches to **blocking the effect of estrogen** or **lowering estrogen levels** are used to treat hormone receptor-positive breast cancers.

Tamoxifen, an ER antagonist

- In **ER-positive** Breast Cancer patients, tamoxifen reduces recurrence and death rates significantly.

- However Tamoxifen has no significant benefit in **ER-negative** women.

Strategies for treatment of ER-positive breast cancer:

1. **Blocking ovarian function**
    1. Ovarian ablation: by surgery or radiation. This has a *permanant effect*.
    2. Ovarian suppression: using drugs as GnRH. This has a *temporary effect*.

2. Blocking estrogen production

Using Aromatase Inhibitors- in postmenopausal women.

3. **Blocking estrogen's effects**

SERMs such as tamoxifen, bind to estrogen receptors; preventing estrogen from binding.

Hormone therapy can be used as:

1. *Adjuvant therapy for early-stage breast cancer* to increase the likelihood of a cure.

2. *Treatment of metastatic breast cancer* several types are approved to treat metastatic hormone-sensitive breast cancer.

3. ***Neoadjuvant treatment of breast cancer*** The use of hormone therapy to treat breast cancer before surgery to reduce the size of a breast tumor to allow breast conserving surgery.

4. ***Prevention*** of the development of breast cancer ***in high risk women;*** since most early breast cancers are ER-positive.

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3. Expression of sex steroid hormones in MSGTs:

Steroid receptors to estrogen and progesterone are present in:

1. Human breast cancer
2. Cancer of the prostate
3. Human colorectal cancer
4. Lymphoblastic leukaemia
5. Endometrial cancer

- Expression of hormone receptors in salivary glands has been studied since White and Garcelon first described therapy with estrogen in salivary gland tumors in **1955**.

Tables 1-3 summarize the reports of Estrogen, Progesterone and Androgen Receptors in AdCC, MEC and SDC respectively.

Table 1: Summary of the reports of ER, PR and AR in **Adenoid Cystic Carcinoma**

Author	Year	No. of Cases	ER+	PR+	AR+
Shick et al.	1995	12	0	6	0
Jeannon et al.	1999	6	3	0	Np
Dori et al.	2000	27	0	2	Np
Moriki et al.	2001	6	Np	Np	0
Nasser et al.	2003	10	0	0	2
Pires et al.	2004	72	0	Np	Np
Miller et al.	2004	5	0	Np	Np
Ito et al.	2009	30	0	0	2
Riad S.	**2009**	**11**	**0**	**1**	**8**
TOTAL			3/173	9/96	12/69
			1.73%	**9.4%**	**17.4%**

Table 2: Summary of the reports of ER, PR and AR in **Mucoepidermoid Carcinoma**

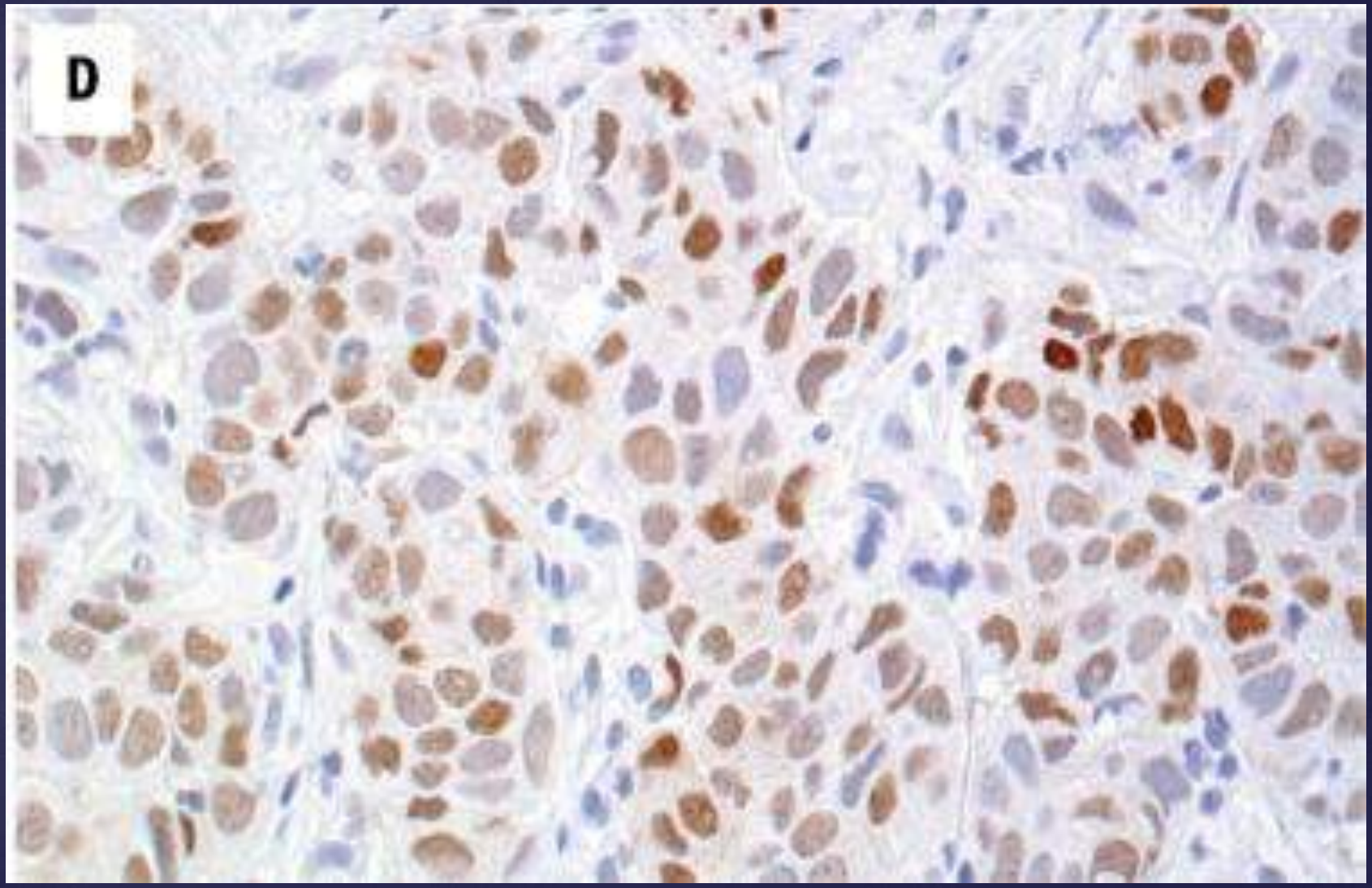
Author	Year	No. of Cases	ER+	PR+	AR+
Lamey et al.	1987	1	0	0	Np
Jeannon et al.	1999	10	3	0	Np
Moriki et al.	2001	8	Np	Np	0
Nasser et al.	2003	10	1	1	2
Pires et al.	2004	136	0	Np	Np
Ito et al.	2009	30	0	0	2
TOTAL			4/187	1/51	4/48
			2.1%	**2%**	**8.3%**

Table 3: Summary of the reports of ER, PR and AR in **Salivary Duct Carcinoma**

Author	Year	No. of Cases	ER+	PR+	AR+
Fan CY	2000	13	Np	Np	9
Fan CY	2001	12	Np	Np	11
Nasser	2003	10	0	0	6
Williams	2007	84	Np	Np	56
TOTAL			0/10	0/10	82/119
			0 %	0 %	**68.9%**

- Most of these studies do not support a role for ER and PR in AdCC, MEC and SDC.

- However, SDC expresses androgen receptor (AR) in the majority of patients (68.9%).



Androgen receptor gives a strong diffuse reaction in most of the tumor cell nuclei in salivary duct carcinoma

Therefore..

1. Immunostaining for AR on cytologic smears is useful for the **diagnosis** of these patients.
2. It was also suggested that the high expression of AR in SDC may play a role in **tumor progression**.
3. This may assist in triaging patients with SDCs for **novel therapies**.

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4. What is the potential role of Hormones in treatment of MSGTs?

- To date, no phase II trials have been performed, so it is difficult to define the role of hormone therapy in MSGTs.

Case # 1: Partial Remission of a case of AdCC by Tamoxifen

In 1997, Shadaba et al., UK reported a patient with an inoperable local recurrence of previously irradiated adenoid cystic carcinoma.

He was treated with tamoxifen, an estrogen receptor antagonist.

After 18 months of treatment, MRI showed a partial response, and further clinical progression of the disease was halted.

Case # 2: Partial Remission of 2 Patients with AdCC by Tamoxifen

Elkin and Jacobs in 2008 reported partial remission of two cases of AdCC in which tamoxifen, an ER anatagonist, was used.

Both patients obtained long-term stability of disease with no associated toxicity.

This treatment was recommended because:

1. There are no successful treatment modalities available for AdCC.
2. The low toxicity of ER antagonists.
3. This treatment (tamoxifen) has a potential disease-stabilizing effect.

Case # 3: A recurrent case of adenocarcinoma in the parotid gland

- In 2003, Locati et al reported complete remission of a recurrent case of AR-expressing adenocarcinoma in the parotid gland.

- The patient was administered complete anti-androgen blockade.

- Skin lesions reduced rapidly, until disappearance 2 months later.

- Complete remission was confirmed by a CT scan.

Complete Remission of the Case of Adeno-carcinoma with Anti-androgens, 2 months later

Conclusion

In conclusion, MSGTs refractory to conventional therapy would possibly benefit from hormonal therapy.

However, there is no clear evidence that such treatment can bring clinical benefits.

Recommendations

1. Further studies concerning the expression of sex hormone receptors need to be evaluated with greater number of samples.
2. Standard protocols for such studies should be clarified by an approved organization to allow meta-analysis.

3. Clinical trials may be conducted in advanced cases, when the disease is refractory to conventional treatment (after taking the patients' consents).

Thank You

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