



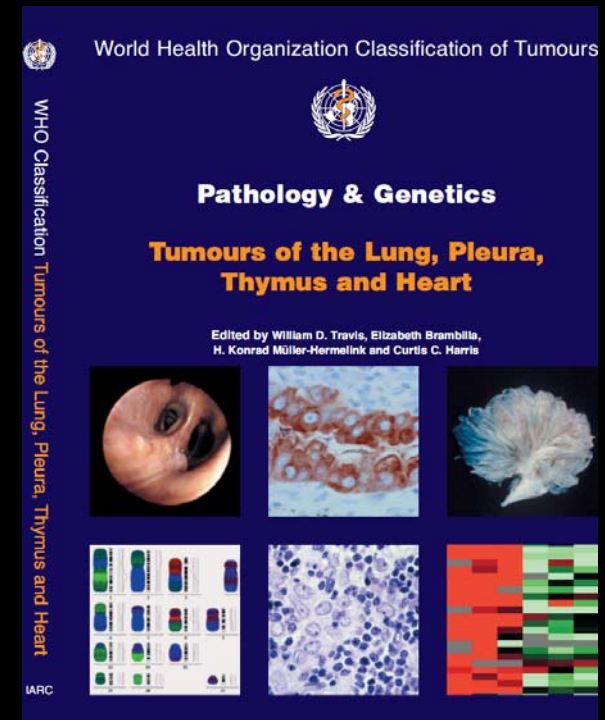
CARCINOMA ADENOIDE QUÍSTICO



WHO histological classification of tumours of the lung

Malignant epithelial tumours		Mesenchymal tumours	
Squamous cell carcinoma	8070/3	Epithelioid haemangi endothelioma	9133/1
Papillary	8052/3	Angiosarcoma	9120/3
Clear cell	8084/3	Pleuropulmonary blastoma	8973/3
Small cell	8073/3	Chondroma	9220/0
Basaloid	8083/3	Congenital peribronchial myofibroblastic tumour	8827/1
Small cell carcinoma	8041/3	Diffuse pulmonary lymphangiomatosis	8825/1
Combined small cell carcinoma	8045/3	Inflammatory myofibroblastic tumour	9174/1
Adenocarcinoma	8140/3	Lymphangioleiomyomatosis	9040/3
Adenocarcinoma, mixed subtype	8255/3	Synovial sarcoma	9041/3
Acinar adenocarcinoma	8550/3	Monophasic	9043/3
Papillary adenocarcinoma	8260/3	Biphasic	8800/3
Bronchioloalveolar carcinoma	8250/3	Pulmonary artery sarcoma	8800/3
Nonmucinous	8252/3	Pulmonary vein sarcoma	8800/3
Mucinous	8253/3		
Mixed nonmucinous and mucinous or indeterminate	8254/3	Benign epithelial tumours	
Solid adenocarcinoma with mucin production	8230/3	Papillomas	
Fetal adenocarcinoma	8333/3	Squamous cell papilloma	8052/0
Mucinous ("colloid") carcinoma	8480/3	Exophytic	8052/0
Mucinous cystadenocarcinoma	8470/3	Inverted	8053/0
Signet ring adenocarcinoma	8490/3	Glandular papilloma	8260/0
Clear cell adenocarcinoma	8310/3	Mixed squamous cell and glandular papilloma	8560/0
Large cell carcinoma	8012/3	Adenomas	
Large cell neuroendocrine carcinoma	8013/3	Alveolar adenoma	8251/0
Combined large cell neuroendocrine carcinoma	8013/3	Papillary adenoma	8260/0
Basaloid carcinoma	8123/3	Adenomas of the salivary gland type	
Lymphoepithelioma-like carcinoma	8082/3	Mucous gland adenoma	8140/0
Clear cell carcinoma	8310/3	Pleomorphic adenoma	8940/0
Large cell carcinoma with rhabdoid phenotype	8014/3	Others	
Adenosquamous carcinoma	8560/3	Mucinous cystadenoma	8470/0
Sarcomatoid carcinoma	8033/3	Lymphoproliferative tumours	
Pleomorphic carcinoma	8022/3	Marginal zone B-cell lymphoma of the MALT type	9699/3
Spindle cell carcinoma	8032/3	Diffuse large B-cell lymphoma	9680/3
Giant cell carcinoma	8031/3	Lymphomatoid granulomatosis	9766/1
Carcinosarcoma	8980/3	Langerhans cell histiocytosis	9751/1
Pulmonary blastoma	8972/3	Miscellaneous tumours	
Carcinoid tumour	8240/3	Hemangioma	8832/0
Typical carcinoid	8240/3	Sclerosing hemangioma	8005/0
Atypical carcinoid	8249/3	Clear cell tumour	
Salivary gland tumours		Germ cell tumours	
Mucoepidermoid carcinoma	8430/3	Teratoma, mature	9080/0
Adenoid cystic carcinoma	8200/3	Immature	9080/3
Epithelial-myoepithelial carcinoma	8562/3	Other germ cell tumours	
Preinvasive lesions		Intrapulmonary thymoma	8580/1
Squamous carcinoma <i>in situ</i>	8070/2	Melanoma	8720/3
Atypical adenomatous hyperplasia		Metastatic tumours	
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia			

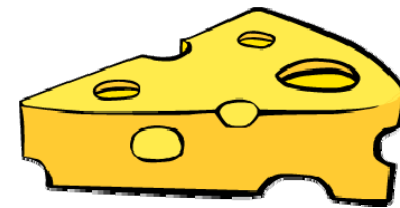
[†] Morphology code of the International Classification of Diseases for Oncology (ICD-O) (6) and the Systematized Nomenclature of Medicine (<http://snomed.org>). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.



DEFINICIÓN

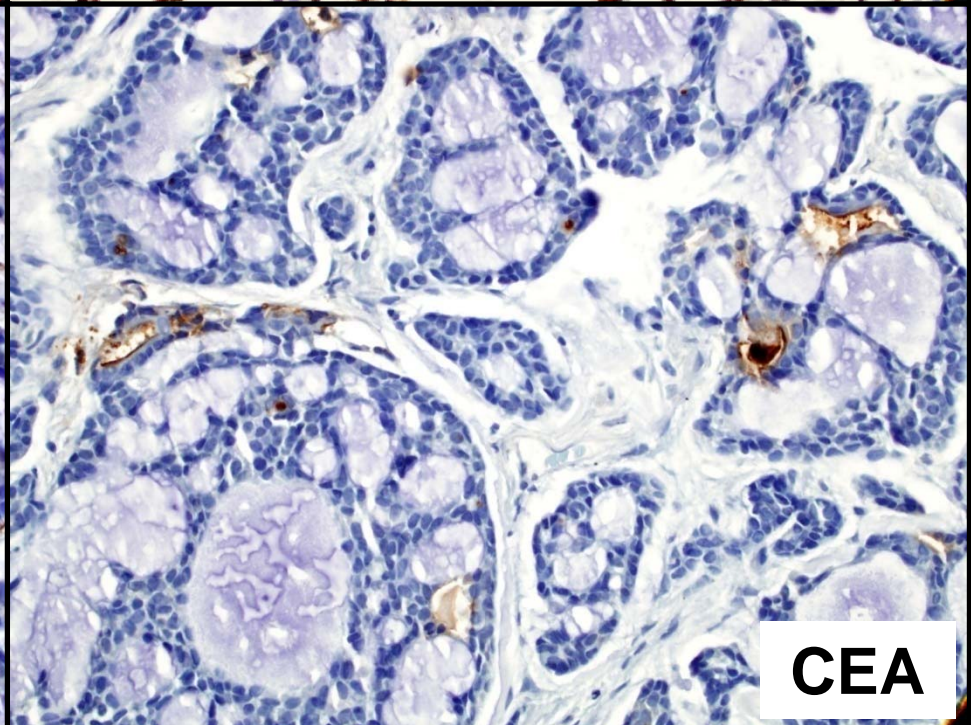
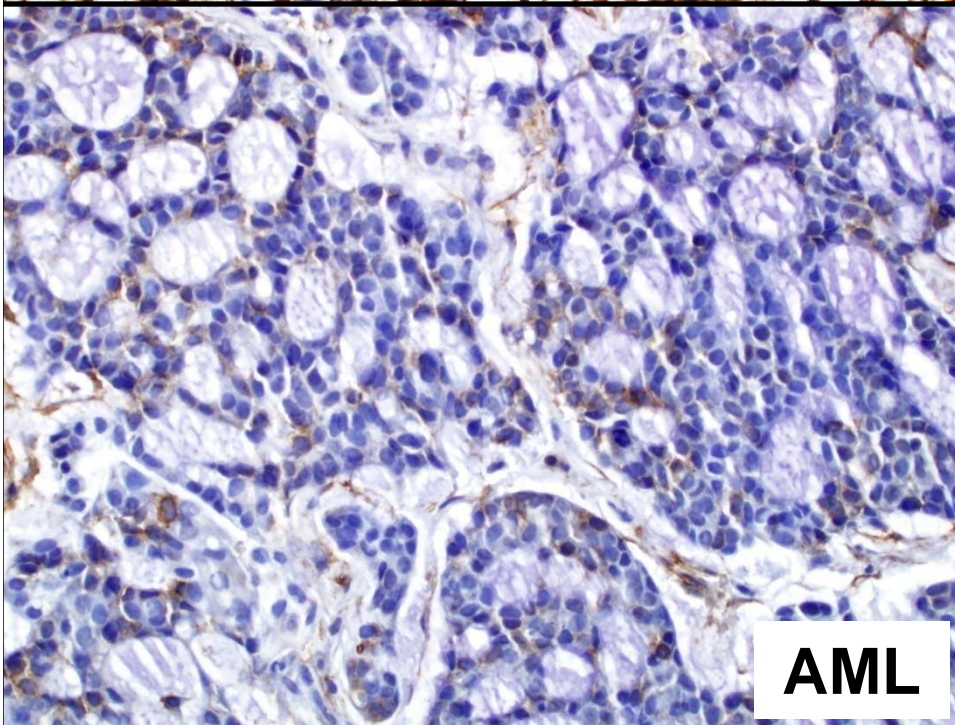
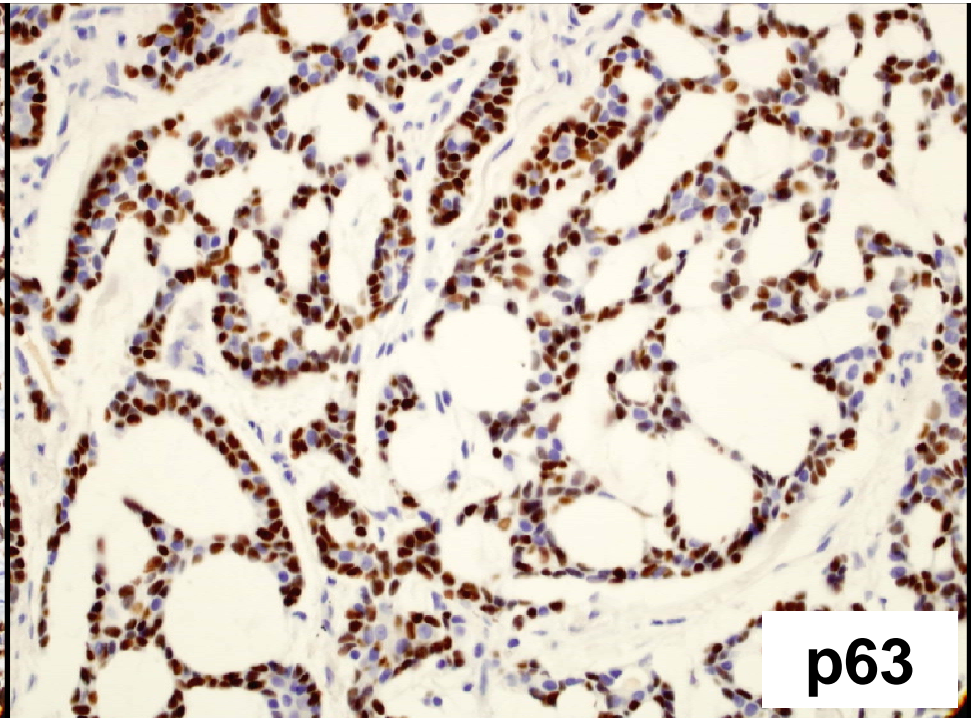
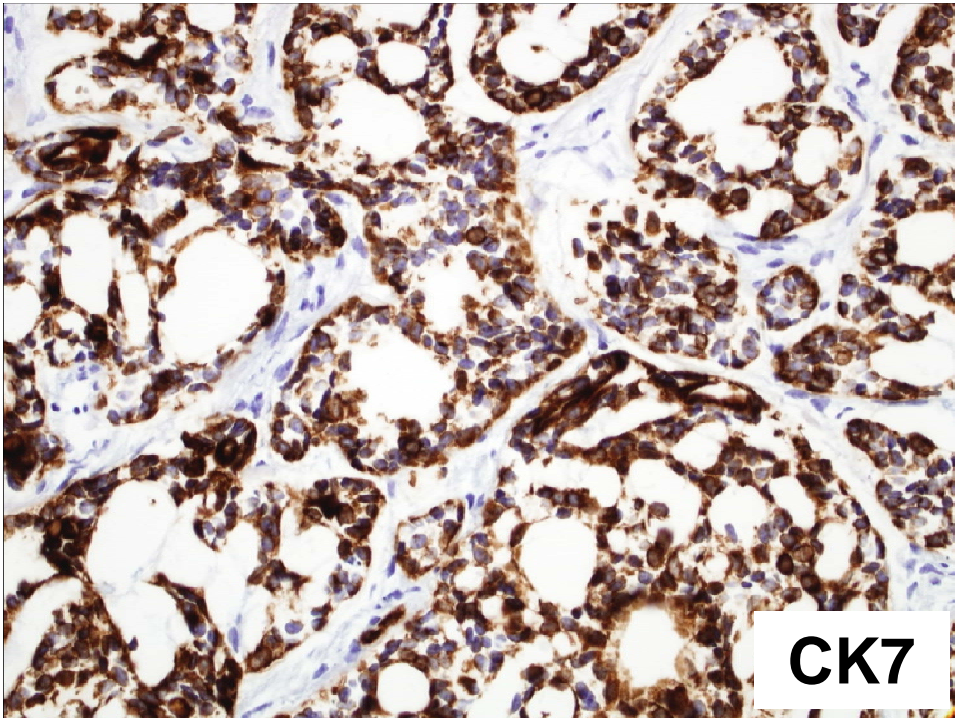
“Tumor maligno epitelial, derivado de glándulas salivares o de glándulas similares de otras localizaciones compuesto por células modificadas **mioepiteliales (adluminales)** y **ductales (luminales)**”.

Se diferencia de otros carcinomas de tipo glándula salival por sus características citomorfológicas y por su patrón de crecimiento formando estructuras **cribiformes**, tubulares o sólidas



INMUNOHISTOQUÍMICA

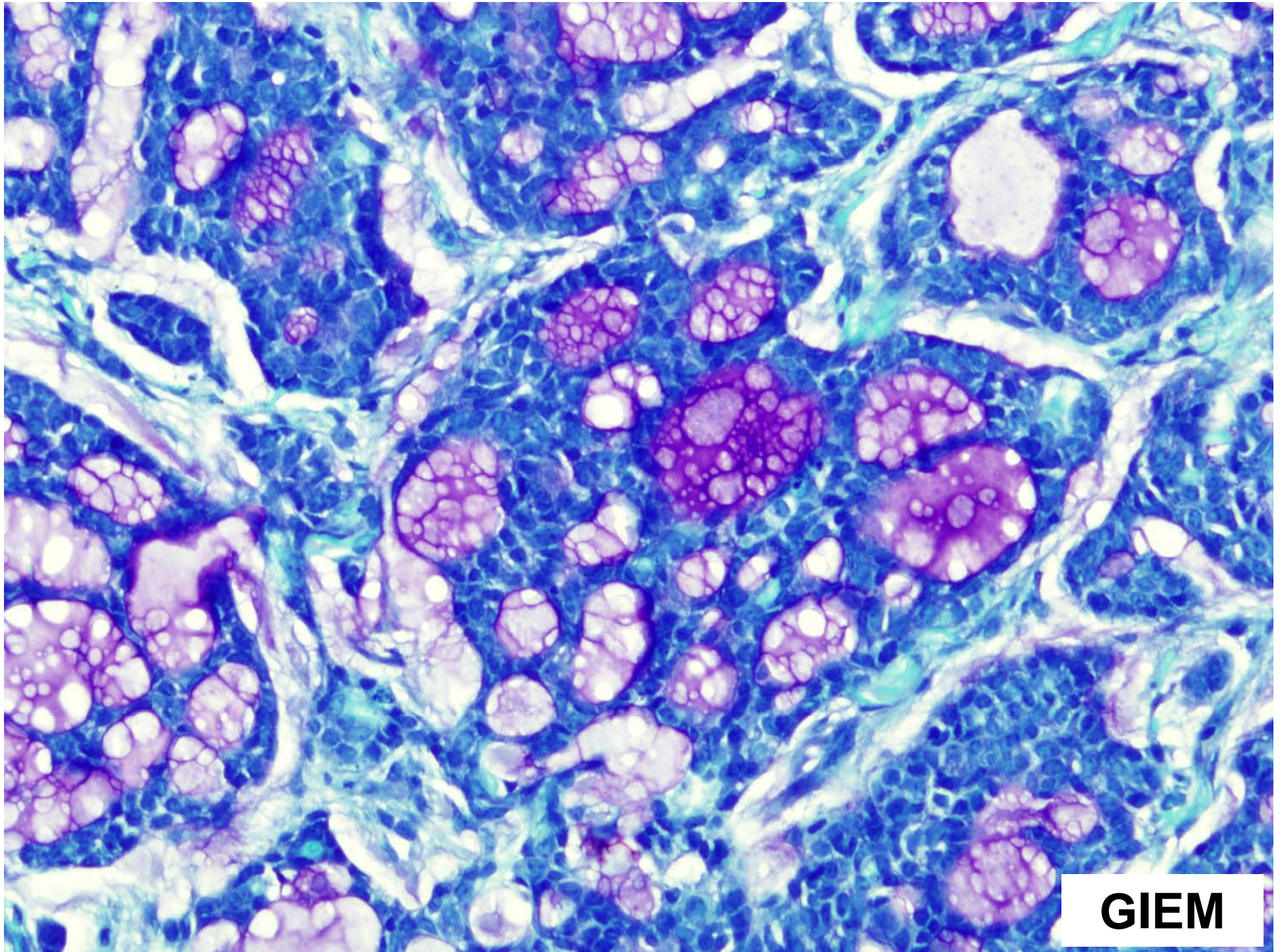
- Positividad para CK7, CK14, CK17, CK19.
- Positividad variable para vimentina, actina muscular específica y miosina.
- Expresión débil de GFAP y presencia de células S100 +.
- Sirve para poner de manifiesto la presencia de una **población celular dual:**
 - Células adluminales: p63, actina músculo liso, calponina.
 - Células lumbinales: CEA, EMA.



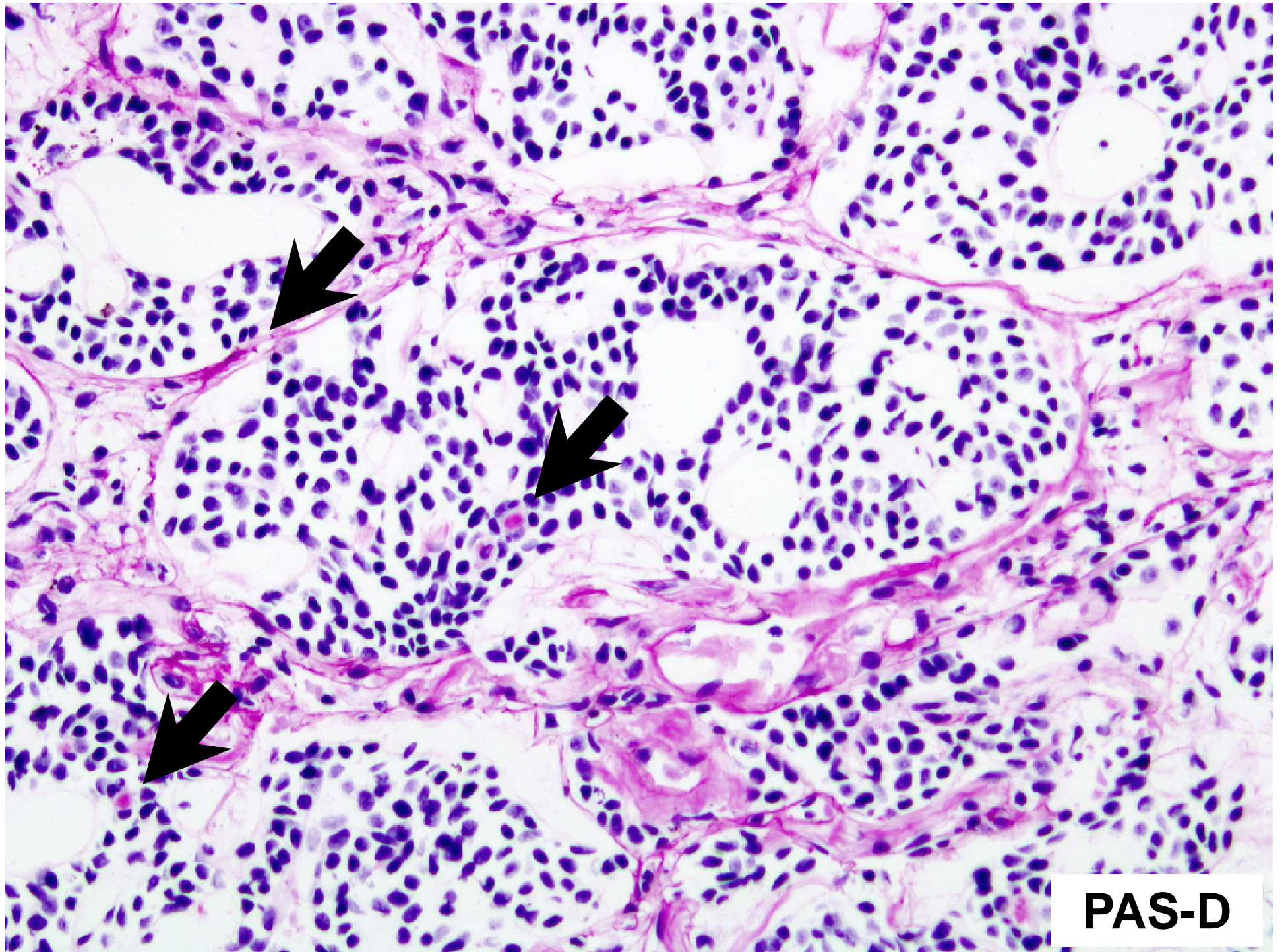
MATERIAL EXTRACELULAR

- El término adenoide-quístico se adoptó por la tendencia a la formación de espacios “pseudoglandulares” del tumor.
- Estos espacios **no representan diferenciación glandular** y contienen material acelular basófilo o hialinizado que representa membrana basal.
 - Material basófilo: Azul-Alcián + sensible a heparitinasas y condroitinasas y resistente a hialuronidasas.
 - Material hialinizado*: PAS +, Colágeno IV +, Laminina +

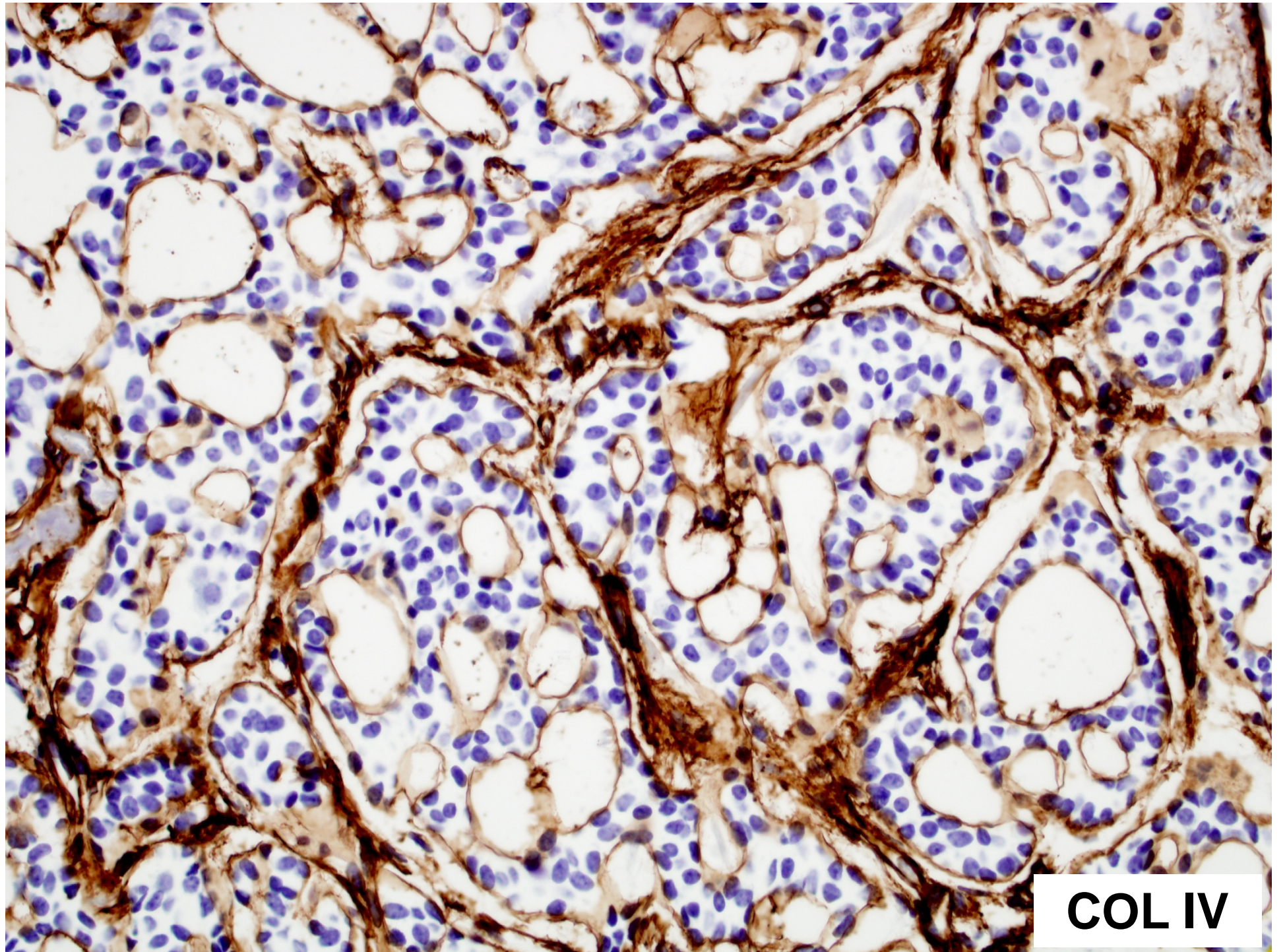
* Cheng J, Saku T et al. **Basement membranes in Adenoid Cystic Carcinoma.** Cancer 1992;69:2631-40.



GIEM



PAS-D



COL IV

**La lesión extirpada al paciente en
la fosa nasal era también un
CARCINOMA ADENOIDE QUÍSTICO**



METÁSTASIS (1)

- El carcinoma adenoide quístico de glándula salivar y de senos nasales produce metástasis a distancia (25-50%).
- Las metástasis en ganglios linfáticos loco-regionales son infrecuentes.
- El pulmón es órgano más frecuentemente afectado*, seguido por el hueso.
- Las metástasis pulmonares se descubren más tardíamente que en otros órganos.

* Spiro RH. **Distant metastasis in adenoid cystic carcinoma of salivatory origin.** Am J Surg 1992;164:623-628.

DISTANT METASTASES OF ADENOID CYSTIC CARCINOMA OF THE SALIVARY GLANDS AND THE VALUE OF DIAGNOSTIC EXAMINATIONS DURING FOLLOW-UP

Jacqueline E. van der Wal, DDS, MD, PhD,¹ Alfred G. Becking, DDS, MD, PhD,¹ Gordon B. Snow, MD, PhD,² Isaac van der Waal, DDS, PhD¹

Head & Neck 2002

Table 2. Distribution of distant metastases of 51 patients with an adenoid cystic carcinoma of the salivary glands according to localization and treatment.

	S			S + R			S + R + C			Total
	L	E	L + E	L	E	L + E	L	E	L + E	
Parotid gland (n = 8)				1					1	2
Submandibular gland (n = 2)					2					2
Intraoral glands (n = 30)	4			5	1	5				15
Maxillary sinus (n = 6)					1	4				5
Nasal cavity (n = 5)		1		2		1				4
Total	4	1		8	4	10			1	28

Abbreviations: C = chemotherapy; E = metastases elsewhere in the body; L = metastases in the lungs; R = radiotherapy; S = surgery.

Table 4. Distribution of distant metastases of adenoid cystic carcinoma of the salivary gland according to localization of the primary tumor.*

Localization	Lung	Cerebrum	Bone	Liver	Thyroid	Spleen
Parotid gland (n = 8)	2	—	1	1	1	—
Submandibular gland (n = 2)	—	1	1	—	—	—
Intraoral glands (n = 30)	14	5	1	—	—	—
Maxillary sinus (n = 6)	4	2	5	1	—	—
Nasal cavity (n = 5)	3	1	—	—	—	1

*In some patients distant metastases occurred at different sites, which increases the total number of metastases.

METÁSTASIS (2)

- Las metástasis pulmonares típicamente son de **crecimiento lento e indolente**.
- Se han descrito **metástasis tardías** por este tumor hasta 24 años después de la exéresis de la lesión primaria*
- Las metástasis extrapulmonares confieren peor pronóstico.
- No existe un tratamiento que haya demostrado efectividad para la enfermedad diseminada.

* Aguiar-Quevedo K, Cerón-Navarro J, et al. **Delayed lung metastasis secondary to salivary gland cancer. Clinical observations and clinicopathological considerations.** J Cir Esp 2010.

CITOGENÉTICA Y BIOLOGÍA MOLECULAR

- 30% de los casos translocaciones de 9p13-23.
- t(6;9)(q21-24;p13-23) la más frecuente.
- Deleciones e hipermetilaciones en p16INK4a.
- Pérdidas alélicas en 1p, 2p, 6q, 12q, 17p, 19q, 20p.
- LOH 6q23-25.
- Sobreexpresión de Sox4, AP-2 α , AP-2 γ , NGFI-a bp 1.
- Sobreexpresión de p53 infrecuente (factor de riesgo de recurrencia y progresión).
- Mutaciones mitocondriales (complejo NADH, D- loop)*

*Mithani SK, et al. **Mitochondrial mutations in adenoid cystic carcinoma of the salivary glands.** Plos

MOLECULAR BIOLOGY OF ADENOID CYSTIC CARCINOMA

Jia Liu, MHS,¹ Chunbo Shao, PhD,² Marietta L. Tan, MD,² David Mu, MS,³
Robert L. Ferris, MD, PhD,⁴ Patrick K. Ha, MD^{2,5}

¹ University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

² Johns Hopkins Department of Otolaryngology, Baltimore, Maryland. E-mail: phal@jhmi.edu

³ Johns Hopkins School of Medicine, Baltimore, Maryland

⁴ University of Pittsburgh Medical Center, Department of Otolaryngology, Pittsburgh, Pennsylvania

⁵ Milton J Dance Jr. Head and Neck Center at the Greater Baltimore Medical Center, Baltimore, Maryland

Head & Neck 2011

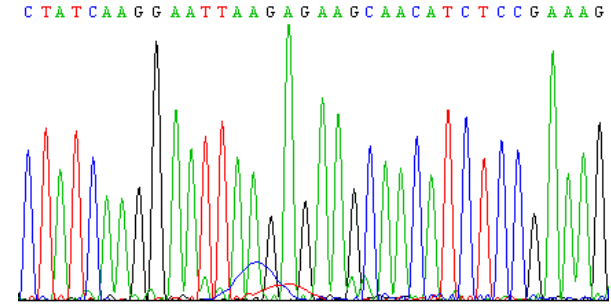
Table 2. Oncogenes involved in ACC pathogenesis.

Type	Protein	Normal function	Role in ACC
Developmental proteins	<i>Sox4</i>	Proper development of the cardiac outflow tract, pro-B-lymphocyte differentiation, and CNS development ^{22,23}	Cell survival, proliferation, and apoptosis ²⁴ Possibly plays role in metastasis ²⁵
	<i>c-kit</i>	Binds stem cell factor and promotes cell growth and differentiation ²⁶ Hematopoiesis, spermatogenesis, and growth and migration of melanocytes ^{27,28}	Expression correlates with tumor grade ²⁹ Acts with <i>Slug</i> to control cell migration ³⁰ Associated with advanced stage, perineural invasion, local regional recurrence and metastases ³¹
	<i>MYB</i>	Various; cell cycle regulation	Fusion <i>MYB-NFIB</i> transcripts causes <i>MYB</i> overexpression ^{5,6,10}
Growth factors	<i>EGF/EGFR</i>	Various; cell proliferation and survival	Cell survival, proliferation, oncogenesis, metastasis ³²⁻³⁴ <i>EGFR</i> expression correlates with tumor grade but not patient prognosis ³⁵
	<i>VEGF/VEGFR</i>	Angiogenesis ^{36,37}	Increases microvessel density ^{38,39} Prognosticator of survival ^{38,40}
	<i>BDNF</i> and <i>NGF</i>	Neurotrophins; promote survival, differentiation, and function of neurons ⁴¹	Facilitating perineural invasion ^{41,42}
Signaling molecules	<i>Wnt/β-catenin</i>	Activates genes important for growth and proliferation ^{43,44}	Reduced membranous expression of <i>β-catenin</i> associated with metastasis ⁴⁵ Expression of <i>Galectin-3</i> , a regulator of <i>Wnt/β-catenin</i> , ⁴⁶ is associated with metastases and a more aggressive tumor phenotype ^{46,47}

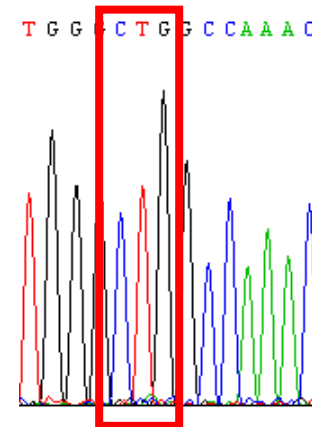
Abbreviations: ACC, adenoid cystic carcinoma; CNS, central nervous system; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor.

MUTACIONES EN EGFR

- Existe terapia biológica para carcinomas pulmonares con mutaciones de EGFR (Erlotinib®).
- No existen datos sólidos sobre la eficacia de estos tratamientos en M1 de carcinomas adenoides quísticos de origen extrapulmonar*
- Ante la duda de un tumor primario vs metastásico se solicitó estudio de mutaciones en EGFR.
- **No se detectaron mutaciones en este caso.**



Wild type Ex19



Wild type L858

* Dahse R, Driemel O, Schwarz S, et al. **KRAS status and epidermal growth factor receptor expression as determinants for anti-EGFR therapies in salivary gland carcinomas.** Oral Oncology 2009;45:826-826

CONCLUSIONES

- ✓ **La citología permite el diagnóstico de variantes infrecuentes de carcinomas pulmonares**

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- ✓ **La citología permite el diagnóstico de variantes infrecuentes de carcinomas pulmonares**
- ✓ **El estroma es también importante para clasificar tumores**
- ✓ **El carcinoma adenoide quístico puede producir metástasis tardías**
- ✓ **La correlación clínico-patológica y la historia clínica es esencial para obtener un buen diagnóstico**

A nighttime photograph of a city skyline reflected in water. The sky is a mix of dark blue and orange from the setting or rising sun. Several tall buildings are lit up, and their lights are reflected in the calm water. In the foreground, the dark silhouette of a boat is visible. Overlaid on the center of the image is the word "GRACIAS" in large, blue, outlined letters.

GRACIAS