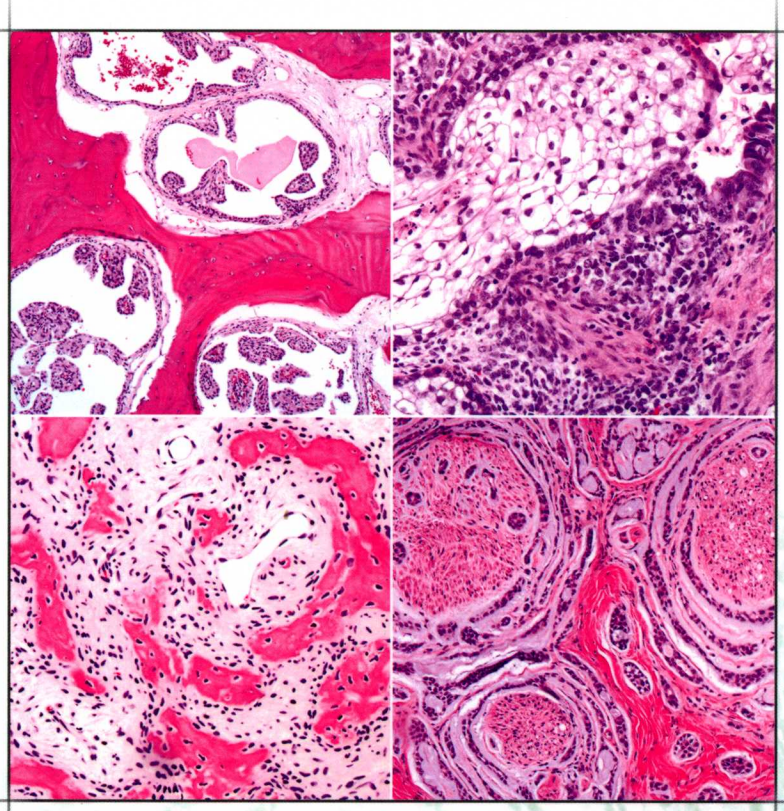
DIFFERENTIAL DIAGNOSES IN SURGICAL PATHOLOGY

Head and Neck

William H. Westra
Justin A. Bishop



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Differential Diagnoses in Surgical Pathology:
Head and Neck

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9 8 7 6 5 4 3 2 1

Printed in China

Library of Congress Cataloging-in-Publication Data
Names: Westra, William H., author. | Bishop, Justin A., author.
Title: Head and neck / William H. Westra, Justin A. Bishop.
Other titles: Differential diagnoses in surgical pathology series.
Description: Philadelphia : Wolters Kluwer, [2017] | Series: Differential diagnoses in surgical pathology | Includes index.
Identifiers: LCCN 2016028196 | ISBN 9781496309792
Subjects: | MESH: Head and Neck Neoplasms—diagnosis | Diagnosis, Differential | Pathology, Surgical—methods
Classification: LCC RC280.H4 | NLM WE 707 | DDC 616.99/491—dc23 LC record available at https://lccn.loc.gov/2016028196

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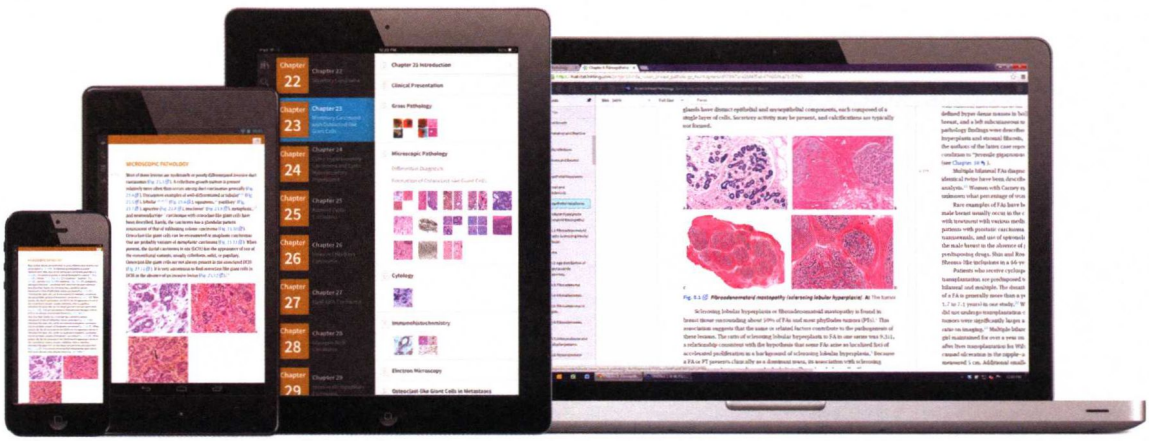

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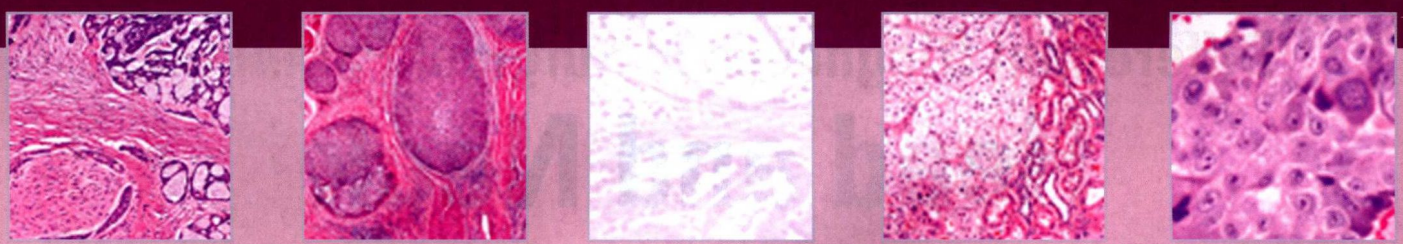

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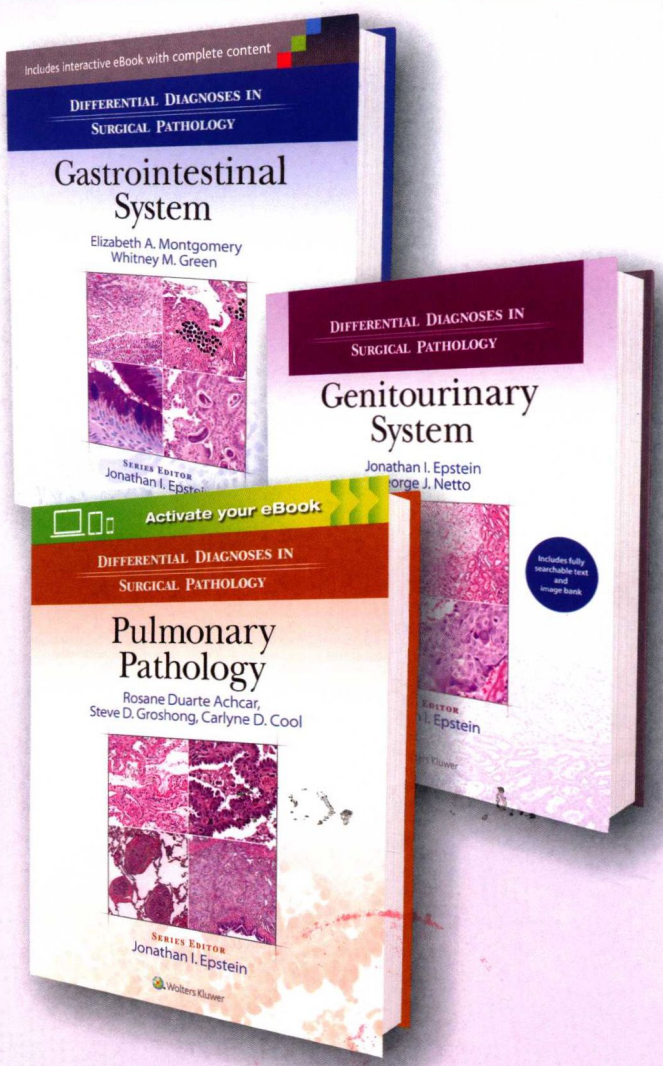

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DEDICATION

This book is for you, mom, and dad, in appreciation of your love and inspiration.
William Westra, MD

Dedicated to Ashley, Riley, and Avery.
Justin Bishop, MD

PREFACE

Most carcinomas of the head and neck are squamous cell carcinomas. Accordingly, the term "head and neck cancer" brings to the mind of the untested pathologist a uniform group of tumors that are easily recognized by an unwavering squamous morphology. But this naive approach to the practice of head and neck pathology is dissipated by any sustained exposure to the bewildering world of head and neck tumors and tumor-like conditions. Squamous cell carcinomas often deviate from their expected conventional appearance in ways that elude detection and even mimic benign processes. Conversely, benign process sometimes imitate squamous cell carcinomas. As for the nonsquamous tumors that arise from assorted tissues of the head and neck (e.g., craniofacial bones, salivary glands, soft tissues, thyroid), their sheer diversity is likely to overwhelm even the most capable pathologist. When dealing with a salivary gland epithelial neoplasm, for example, the general pathologist is expected to single out a specific diagnosis from over 30 common and esoteric salivary gland tumors that, although clinically and biologically distinct, may look very similar under the microscope. To the experienced and tested pathologist, the term "head and neck cancer" brings to the mind the most challenging and treacherous group of tumors in all of surgical pathology.

This atlas was written to help the general pathologist navigate the troubled waters of head and neck pathology. It takes on some of the most commonly encountered differential diagnoses with the aims of pointing out diagnostic pitfalls and providing pathologic clues to guide diagnostic decisions. We hope that you find it helpful.

William H. Westra, MD
Justin A. Bishop, MD

CONTENTS

1 Salivary Glands

1.1 ACINIC CELL CARCINOMA VS. MAMMARY ANALOGUE SECRETORY CARCINOMA (MASC)

	Acinic Cell Carcinoma	Mammary Analogue Secretory Carcinoma (MASC)
Age	Wide range, with slight peak in seventh decade. Slight female predominance	Usually adults, mean 47 years
Location	Parotid gland (90%), submandibular gland (5%), and minor salivary glands (5%)	Parotid (70%), oral cavity (20%), and submandibular gland (5%)
Symptoms	Painless, slow-growing mass	Painless, slow-growing mass
Signs	Generally well-circumscribed mass, sometimes with cystic features	Generally well-circumscribed mass, sometimes with cystic features
Etiology	Unknown	Unknown
Histology	1. Diagnostic feature is the serous acinar cell, a medium-to-large polygonal cell with blue–purple cytoplasmic granules (zymogen granules) *(Fig. 1.1.1)*. The number of serous acinar cells is variable 2. Numerous additional cell types may be seen, including intercalated ductlike cells, vacuolated cells, clear cells, and nonspecific glandular cells *(Fig. 1.1.2)* 3. Numerous growth patterns can be seen, including solid, microcystic, papillary–cystic, and follicular *(Figs. 1.1.3 and 1.1.4)* 4. Secretory material within microcystic spaces may be seen occasionally 5. Often well circumscribed but may be infiltrative 6. Perineural invasion, necrosis, and elevated mitotic rates are not typical but are encountered in cases showing "high-grade transformation"	1. No serous acinar cells 2. Growth patterns overlap with acinic cell carcinoma. Microcystic is most common, but follicular, papillary–cystic, and solid patterns can be seen as well *(Figs. 1.1.6, 1.1.7, and 1.1.8)* 3. Cells have apocrine features including abundant eosinophilic granular cytoplasm and a large nucleus with a prominent nucleolus *(Fig. 1.1.9)* 4. Eosinophilic secretions are seen within the glandular spaces *(Figs. 1.1.6, 1.1.7, and 1.1.9)* 5. May be infiltrative or well circumscribed 6. Perineural invasion, necrosis, and elevated mitotic rates are not seen except in rare cases of high-grade transformation
Special studies	• Positive for DOG-1 and usually negative for S100, mammaglobin, and GATA3 *(Fig. 1.1.5)* • Negative for ETV6 translocation	• Positive for S100, mammaglobin, and GATA3 *(Figs. 1.1.10 and 1.1.11)*. Staining for DOG-1 is usually negative • Positive for ETV6 translocation (usually with partner gene NTRK3) similar to secretory carcinoma of the breast *(Fig. 1.1.12)*
Treatment	Surgery only, except in those rare cases showing high-grade transformation	Therapy is not well standardized. Most have been treated with surgery, with a subset receiving radiotherapy as well. For rare aggressive cases, targeted therapies (tyrosine kinase inhibitors) may be of value
Prognosis	Good, with 10-year survival >90%	Appears to be similar to acinic cell carcinoma

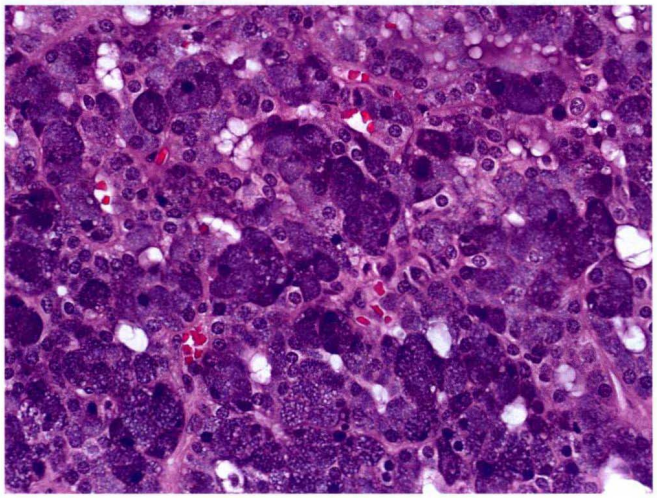


Figure 1.1.1 Acinic cell carcinoma with a solid proliferation of serous acinar cells that contain numerous blue–purple granules in their cytoplasm.

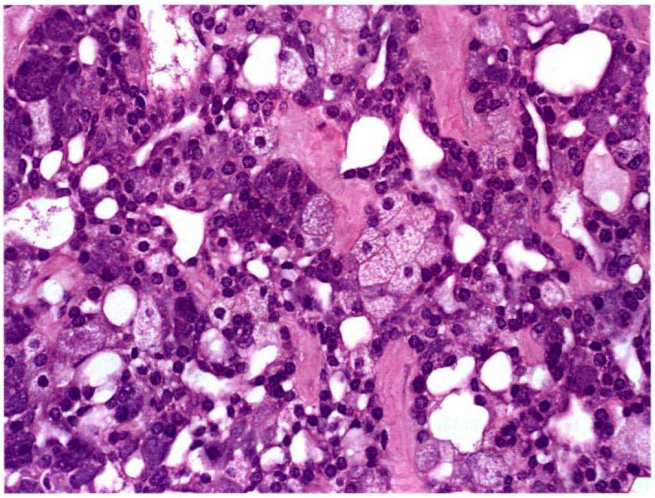


Figure 1.1.2 Acinic cell carcinomas may show a combination of cell types including serous acinar cells, vacuolated cells, clear cells, and nonspecific glandular cells.

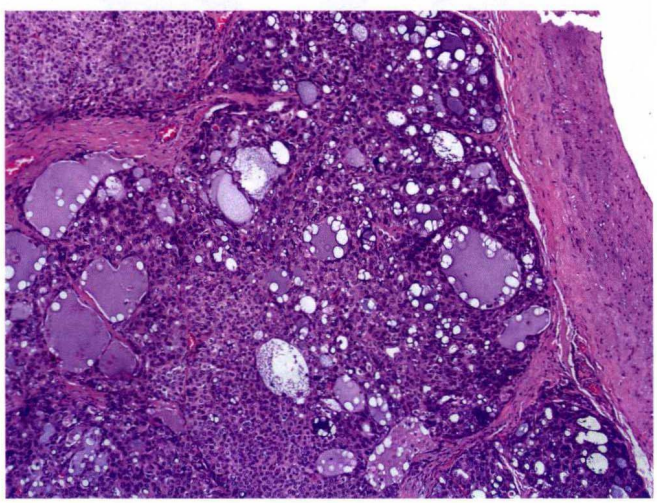
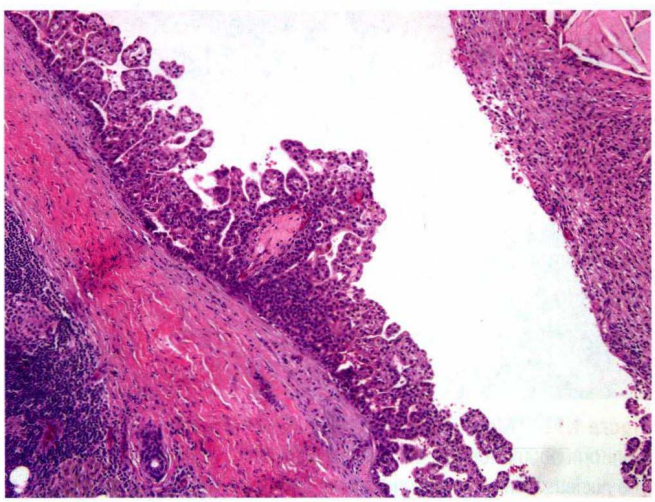


Figure 1.1.3 Acinic cell carcinoma demonstrating a mixture of solid, microcystic, and follicular growth patterns.



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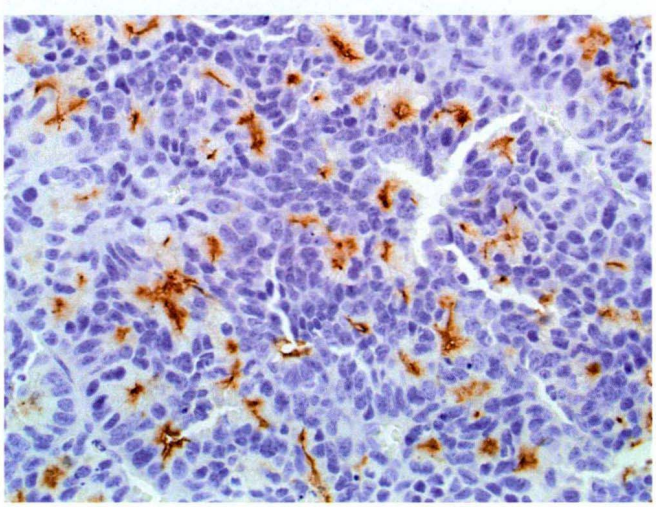

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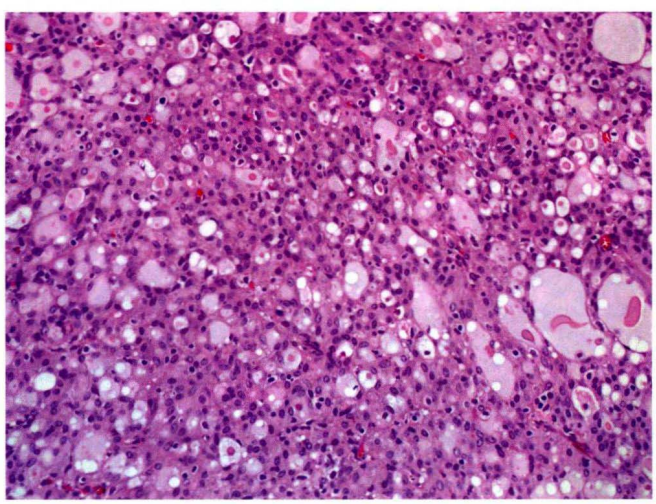
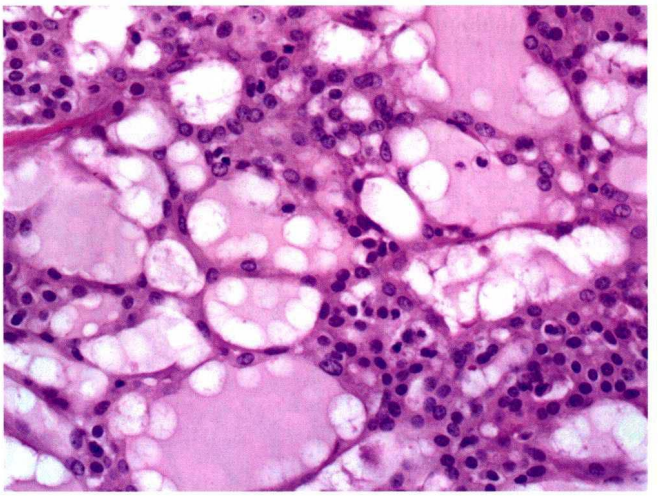


Figure 1.1.6 Mammary analogue secretory carcinoma exhibiting microcystic growth. This is the most common growth pattern of mammary analogue secretory carcinoma.



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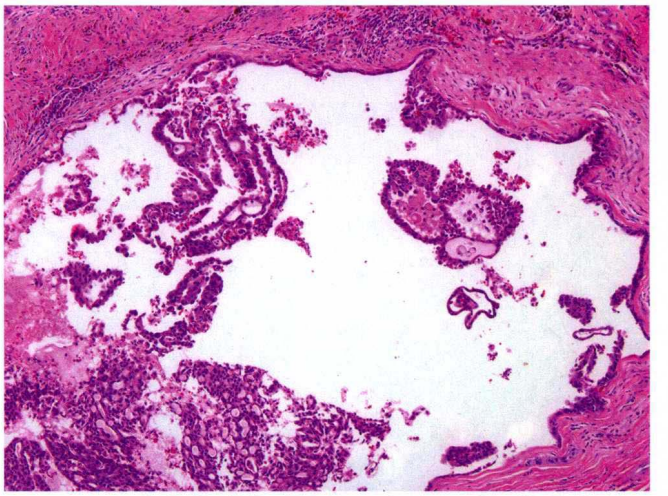

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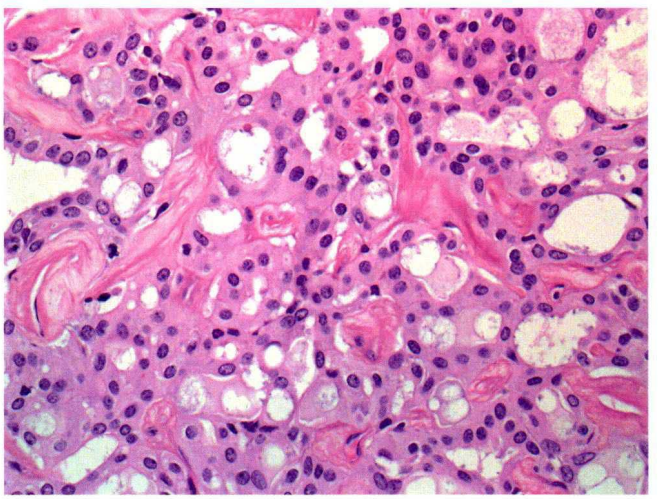


Figure 1.1.9 Mammary analogue secretory carcinoma is comprised of a uniform population of cells with an abundant, eosinophilic cytoplasm. The nucleus is large and round to oval and has a visible nucleolus.

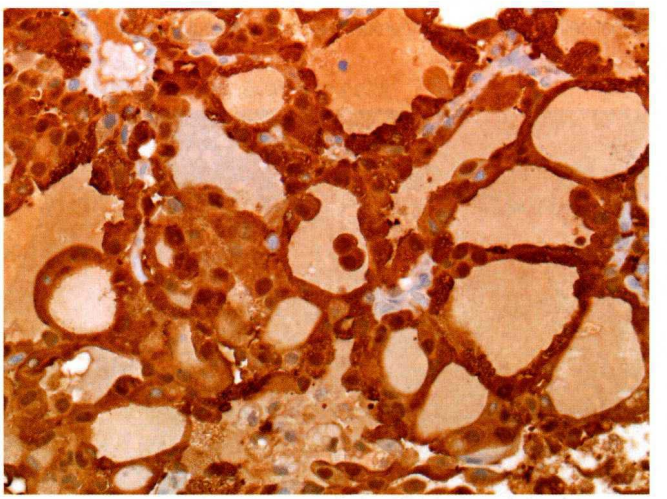
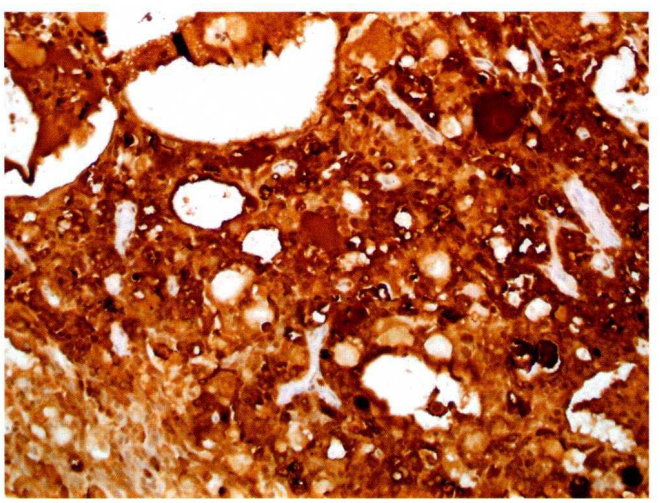


Figure 1.1.10 Mammary analogue secretory carcinoma is consistently positive for S100.



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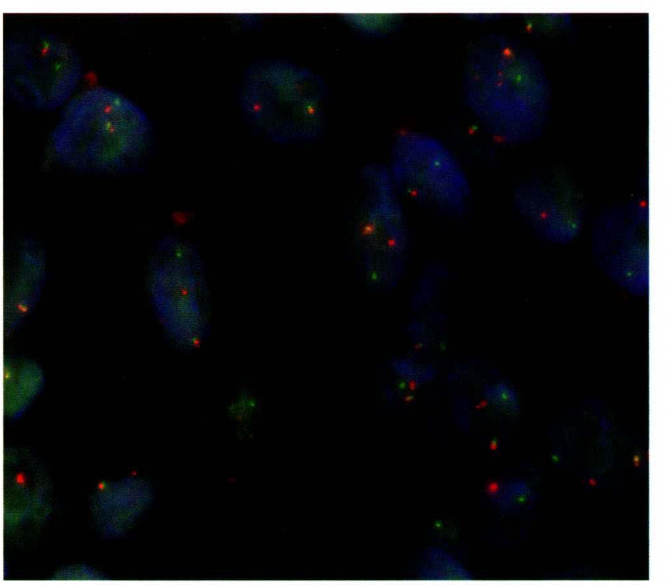

Figure 1.1.12 Mammary analogue secretory carcinoma harbors translocations for ETV6. In this break apart FISH assay, one copy of the ETV6 gene is intact (*red* and *green* signals together) and one is rearranged (*red* and *green* signals apart).

1.2 ADENOID CYSTIC CARCINOMA VS. EPITHELIAL–MYOEPITHELIAL CARCINOMA

	Adenoid Cystic Carcinoma	Epithelial–Myoepithelial Carcinoma
Age	Typically adults, peak incidence in sixth decade	Typically adults, peak incidence in sixth to seventh decades
Location	Parotid gland is most common (40%–50%) but may arise in any major or minor salivary gland	Usually parotid gland (up to 80%) and uncommonly submandibular gland or minor salivary glands
Symptoms	Slow-growing swelling sometimes pain or paralysis due to perineural invasion. Other site-specific symptoms in minor salivary locations (e.g., nasal obstruction or epistaxis for sinonasal tumors)	Slowly growing, painless mass
Signs	Palpable nodules that may become fixed to surrounding tissues	Typically circumscribed, small mass. May be grossly cystic
Etiology	Unknown	Unknown
Histology	1. Variable mixture of tubules, cribriform structures, and solid nests *(Fig. 1.2.1)* 2. Cribriform pattern is most common, with cylindromatous microcystic spaces (false ducts) filled with basophilic mucoid or hyaline basement membrane-like material *(Fig. 1.2.2)* 3. Two cell types: ductal and myoepithelial. The myoepithelial cells predominate. They are monotonous and basaloid and have hyperchromatic, angulated nuclei with indistinct nucleoli and small amounts of clear to eosinophilic cytoplasm. The ducts are often subtle and are comprised of cuboidal cells with eosinophilic cytoplasm *(Fig. 1.2.2)* 4. Sometimes, the proportion of ducts to myoepithelial cells may be higher. These areas may closely resemble epithelial–myoepithelial carcinoma *(Fig. 1.2.3)* 5. Highly infiltrative, with perineural invasion very commonly identified 6. Tumor necrosis and elevated mitotic rates are uncommon but are more common in tumors with a predominant solid pattern	1. Tightly coupled biphasic tumor cell population with ducts surrounded by a row of myoepithelial cells, typically with clear cytoplasm *(Fig. 1.2.4)* 2. Cribriform growth is absent or, at most, very focal 3. Compared to adenoid cystic carcinoma, tumor cells exhibit nuclei with more open chromatin and more prominent nucleoli *(Fig. 1.2.5)* 4. Ductal cells are usually evident, but in some cases, the myoepithelial cell component can overgrow the ducts in a sheetlike manner *(Fig. 1.2.6)* 5. Often relatively circumscribed, though infiltrative growth is present at least focally in the form of nodular growth or invasion of benign tissues *(Fig. 1.2.7)*. Perineural invasion may be seen but less frequently than in adenoid cystic carcinoma 6. Tumor necrosis and elevated mitotic rates are not seen, except in rare cases of high-grade transformation

	Adenoid Cystic Carcinoma	Epithelial–Myoepithelial Carcinoma
Special studies	• Actin, calponin, S100, p63, and p40 highlight myoepithelial cells, while c-kit and EMA typically stain ductal component • Approximately 50% of adenoid cystic carcinomas harbor a (6;9) translocation resulting in MYB–NFIB gene fusion	• Actin, calponin, S100, p63, and p40 highlight myoepithelial cells, while c-kit and EMA typically stain ductal component • Negative for MYB rearrangements. Some cases harbor RAS mutations
Treatment	Wide local resection with adjuvant radiotherapy. Neck dissection not usually performed because lymph node metastases are uncommon. Chemotherapeutic agents are generally ineffective	Surgical excision. Adjuvant radiation considered if there are aggressive histologic features (e.g., perineural invasion, large tumor size)
Prognosis	Patients have a good 5-year survival (75%–80%) but poor 15-year survival (25%–30%) due to slow but relentless growth. Tumors metastasize to lung, bone, liver, and brain. Tumors with a predominantly solid pattern are more aggressive	Good. Recurrences and metastases are uncommon

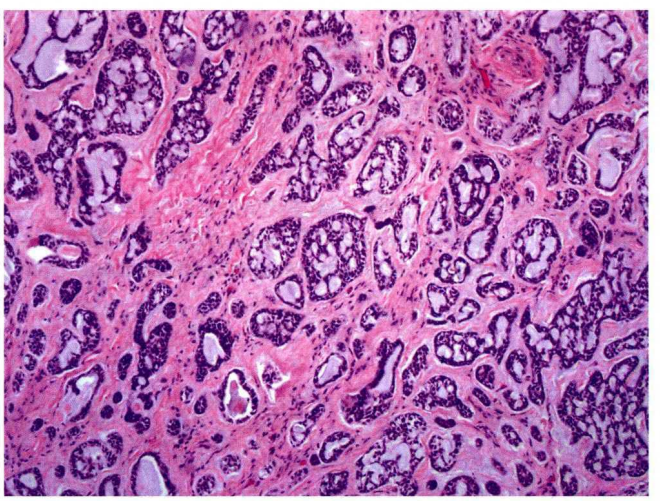

Figure 1.2.1 Adenoid cystic carcinoma with an infiltrative collection of tubules and cribriform structures.

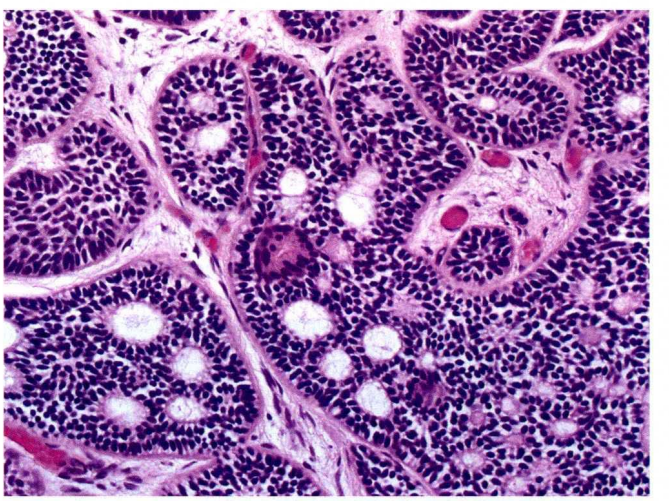

Figure 1.2.2 Adenoid cystic carcinoma with cribriform growth. There is a true duct (**center**) with eosinophilic cytoplasm, numerous pseudoducts, and a predominance of myoepithelial cells with dark, angulated nuclei.

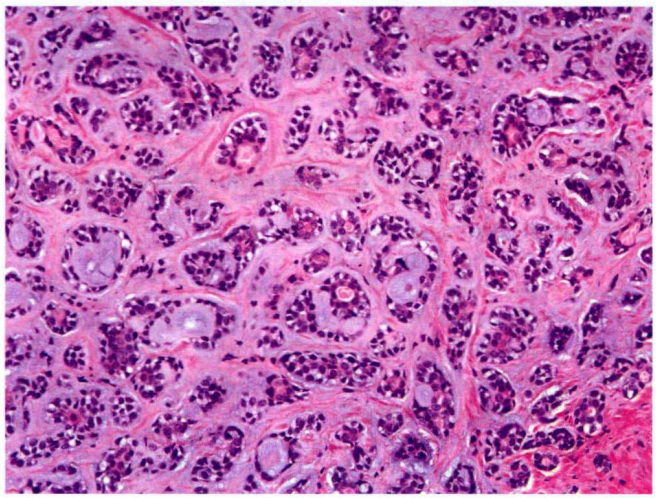

Figure 1.2.3 Adenoid cystic carcinomas are comprised of true ductal cells and myoepithelial cells. In this tumor, the eosinophilic ductal cells are surrounded by a zone of clear myoepithelial cells in a way that resembles epithelial–myoepithelial carcinoma. The basophilic stromal matrix is characteristic of adenoid cystic carcinoma.

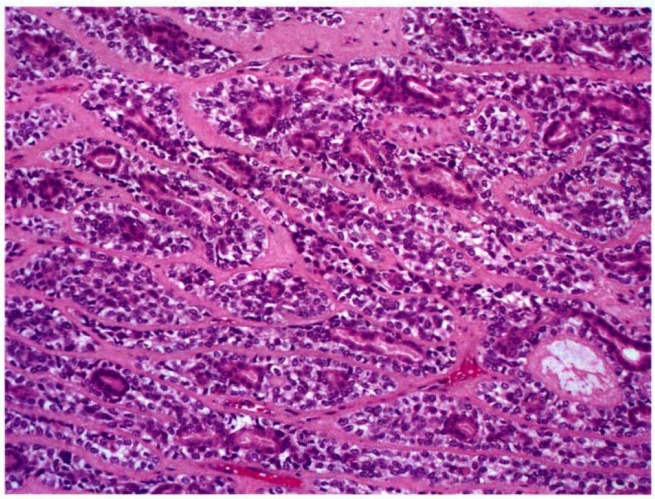

Figure 1.2.4 Epithelial–myoepithelial carcinoma with numerous eosinophilic ducts that are tightly coupled with a surrounding layer of myoepithelial cells with abundant clear cytoplasm.

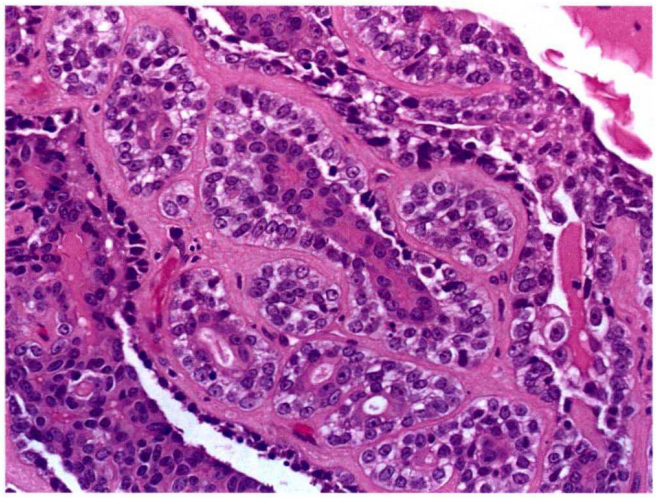

Figure 1.2.5 Epithelial–myoepithelial carcinoma with myoepithelial cells demonstrating large nuclei with open chromatin and prominent nucleoli.

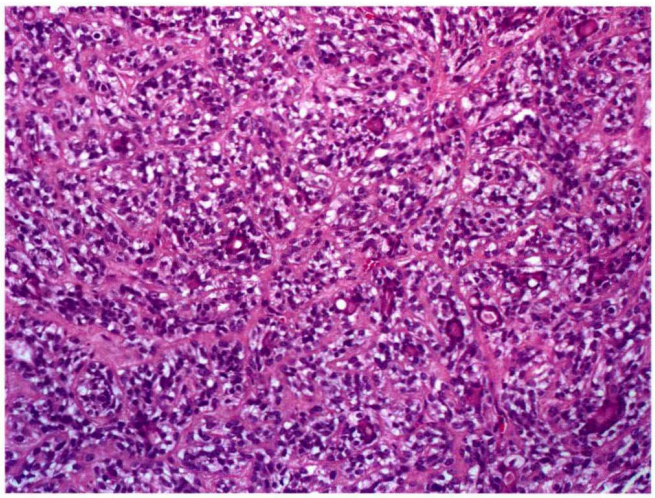

Figure 1.2.6 Epithelial–myoepithelial carcinoma with a predominance of myoepithelial cells.

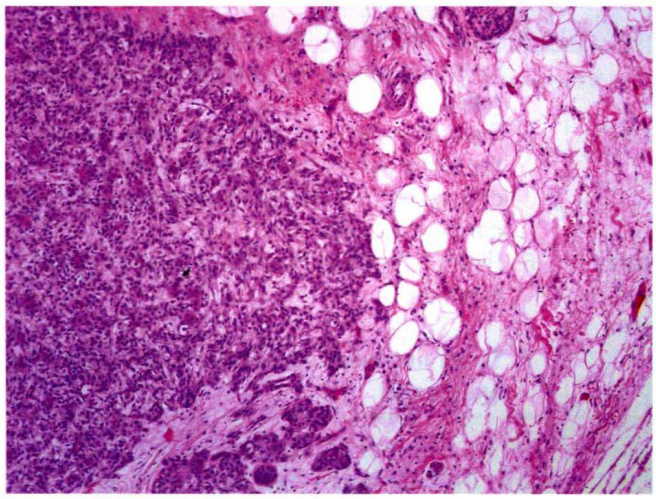

Figure 1.2.7 Epithelial–myoepithelial carcinoma demonstrating irregular infiltration intro surrounding fat.

1.3 ADENOID CYSTIC CARCINOMA VS. BASALOID VARIANT OF SQUAMOUS CELL CARCINOMA

	Adenoid Cystic Carcinoma	Basaloid Variant of Squamous Cell Carcinoma
Age	Typically adults, peak incidence in sixth decade	Adults, peak in seventh decade
Location	Parotid gland is most common (40%–50%) but may arise in any major or minor salivary gland	Mucosal head and neck sites, most commonly larynx. Does not arise the major salivary glands, though rarely may involve them by metastatic spread
Symptoms	Slowly growing swelling, sometimes pain or paralysis due to perineural invasion. Other site-specific symptoms in minor salivary locations (e.g., nasal obstruction or epistaxis for sinonasal tumors)	Depends on site. In larynx, patients present with hoarseness and dysphagia
Signs	Palpable nodules that may become fixed to surrounding tissues	Ulcer and ill-defined mucosal-based mass
Etiology	Unknown	Strongly related to tobacco and alcohol consumption
Histology	1. Variable mixture of tubules, cribriform structures, and solid nests *(Fig. 1.3.1)* 2. Cribriform nests have cylindromatous microcystic spaces (false ducts) *(Fig. 1.3.2)* 3. Two cell types: ductal and myoepithelial. The myoepithelial cells predominate; they are monotonous, basaloid, and have hyperchromatic, angulated nuclei with indistinct nucleoli and small amounts of clear to eosinophilic cytoplasm. The ducts are often subtle and are comprised of cuboidal cells with eosinophilic cytoplasm *(Fig. 1.3.2)* 4. Squamous differentiation is absent 5. Highly infiltrative. Perineural invasion is very common 6. Tumor necrosis and elevated mitotic rates are uncommon but are more common in tumors with a predominant solid pattern	1. Rounded nests of cells separated by thin lines of hyalinized stroma, creating a jigsaw puzzle–like pattern *(Fig. 1.3.5)* 2. Frequent deposition of hyaline basement membrane-like material, creating pseudoglandular spaces and a cribriform-like appearance *(Fig. 1.3.6)* 3. No true ducts 4. Nests exhibit peripheral palisading, and tumor cells have high nuclear to cytoplasmic ratios 5. Squamous differentiation is present within the tumor itself where it is often abrupt or in the form of overlying squamous cell carcinoma in situ *(Fig. 1.3.7)* 6. Highly infiltrative. Perineural invasion is very common 7. Tumor necrosis and elevated mitotic rates are present

	Adenoid Cystic Carcinoma	Basaloid Variant of Squamous Cell Carcinoma
Special studies	• Actin, calponin, p63, S100, and p40 highlight myoepithelial cells, while c-kit and EMA typically highlight the ductal component *(Figs. 1.3.3 and 1.3.4)* • Approximately 50% of adenoid cystic carcinomas harbor a (6;9) translocation resulting in MYB–NFIB gene fusion	• The tumor is diffusely positive for p63, CK5/6, and CK903 *(Fig. 1.3.8)*. S100 and actin are negative. C-kit may be positive • Negative for (6;9) translocation
Treatment	Wide local resection with adjuvant radiotherapy. Neck dissection not usually performed because lymph node metastases are uncommon. Chemotherapeutic agents are generally ineffective	Surgery, radiotherapy, and chemotherapy. Neck dissection often performed, as nodal metastases are common
Prognosis	Patients have a good 5-year survival (75%–80%) but poor 15-year survival (25%–30%) due to slow but relentless growth. Tumors metastasize to lung, bone, liver, and brain. Tumors with a predominantly solid pattern are more aggressive	Poor. Basaloid variant appears to be more aggressive than conventional squamous cell carcinoma

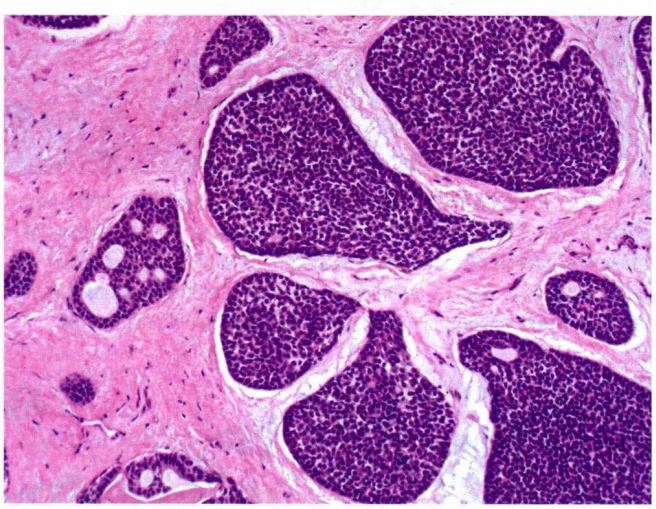

Figure 1.3.1 Adenoid cystic carcinoma growing as cribriform and solid nests of basaloid cells.

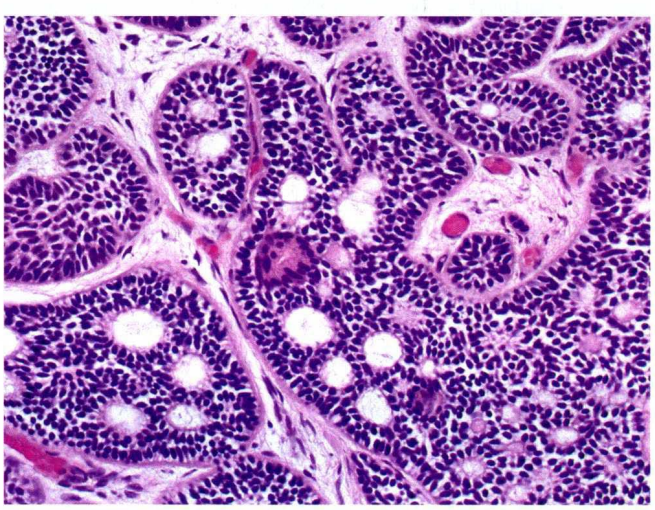

Figure 1.3.2 Adenoid cystic carcinoma consisting predominantly of myoepithelial cells characterized by hyperchromatic and angulated nuclei. They form rounded cylindromatous (pseudoglandular) spaces. A few true ducts lined by cells with eosinophilic cytoplasm are also present.