Conventional Squamous Cell Carcinoma

- Squamous carcinomas are nearly always positive for cytokeratin.
- Common cytokeratin expression in squamous carcinomas includes AE1/AE3, CK5, CK5/6, CK14, and CK17.
- Nuclear p63 expression is common in squamous carcinomas but is not completely specific for squamous tumors.
- Cytokeratin stains can help detect subtle metastatic foci, particularly in the post-treatment setting in lymph nodes.

Basaloid Squamous Cell Carcinoma

- The differential diagnosis for basaloid squamous cell carcinoma (BSCC) includes adenoid cystic carcinoma and small cell neuroendocrine carcinoma.
- The best markers to differentiate these are p63 and neuroendocrine markers: BSCC will be positive for cytokeratin and p63 and negative for most neuroendocrine markers.

Verrucous Carcinoma and Papillary Squamous Cell Carcinoma

- Verrucous carcinoma (VC) and papillary squamous cell carcinoma (PSCC) have a similar gross appearance, but VC has a pushing leading edge and no atypia, whereas PSCC shows cytologic atypia and more typical invasion.
- No diagnostic immunohistochemical markers can be used to identify VC or PSCC.

Spindle Cell Carcinoma

- The diagnosis of spindle cell carcinoma (SPCC) requires the identification of a component of squamous neoplasia or epithelial differentiation of the spindle cells.
- Multiple cytokeratin and epithelial markers may be necessary to show positive staining in the spindle cells, but up to 30% of SPCCs will not stain for cytokeratin in the spindle cell component.

Olfactory Neuroblastoma

- Olfactory neuroblastoma (ONB) is composed of small round blue cells that grow in a lobular or diffuse pattern.
- The tumor cells are positive for neuroendocrine markers, and up to 30% can be positive for cytokeratin.
- Sustentacular cells surrounding the lobules of ONB stain

for S-100.

Sinonasal Undifferentiated Carcinoma

- Sinonasal undifferentiated carcinoma is composed of high-grade, small- to medium-sized cells with prominent mitoses and necrosis.
- The tumor cells are positive for cytokeratin and may be positive for EMA.
- Neuroendocrine markers are rarely positive; when they are, staining should be only focal.

Malignant Melanoma

- Mucosal melanomas stain with similar panels of markers to their cutaneous counterparts (S-100, HMB45, tyrosinase).
- Rare cases of mucosal melanomas have been reported to be positive for CAM5.2.

Small Cell Neuroendocrine Carcinoma

Neuroendocrine carcinomas are positive for cytokeratins and for typical neuroendocrine markers, such as chromogranin and synaptophysin.

Invasive-Ectopic Pituitary Adenoma

- Pituitary lesions can present in the sinonasal tract, either as invasive adenomas or as ectopic tumors.
- Functional pituitary adenomas can be found to express a variety of hormones, such as growth hormone, prolactin, thyroid-stimulating hormone, adrenocorticotropic hormone, or follicle-stimulating hormone.

Rhabdomyosarcoma

- Rhabdomyosarcoma can rarely arise in the sinonasal tract.
- This tumor stains similar to soft tissue counterparts, with desmin and myogenin positivity.

Ewing's Sarcoma and Peripheral Neuroectodermal Tumor

- Ewing's sarcoma/peripheral neuroectodermal tumor is composed of uniform round cells with a lobular configuration.
- The tumor cells are positive for vimentin and CD99.

Intestinal-Type Adenocarcinoma

- Intestinal-type adenocarcinomas resemble colorectal carcinomas at the histologic level.
- ITACs usually stain positive with CK7, CK20, and CDX2.

Glomangiopericytoma

- Glomangiopericytomas are unique lesions that occur exclusively within the sinonasal tract.
- They are strongly positive for SMA and vimentin, but less commonly for CD34.

Neuroendocrine Tumors

- The three categories of neuroendocrine tumors (carcinoid, atypical carcinoid, and small cell neuroendocrine carcinoma) are distinguished from one another mainly on the basis of histologic appearance.
- The immunophenotype of these tumors includes positivity for neuroendocrine markers and for cytokeratins.
- TTF-1 may be positive in these extrapulmonary neuroendocrine/small cell carcinomas.

Mucoepidermoid Carcinoma

- Three cell populations can generally be seen in mucoepidermoid carcinoma (MEC): epidermoid cells, mucous cells, and intermediate cells.
- No immunohistochemical stains are sensitive or specific for MEC in routine diagnostic use.
- p63 nuclear expression resides in the epidermoid component.

Polymorphous Low-Grade Adenocarcinoma

- Polymorphous low-grade adenocarcinoma (PLGA) is predominantly a tumor of minor salivary glands of the oral cavity.
- Myoepithelial cells are sparse or absent in PLGA, but S-100 protein is usually diffusely positive.

Adenoid Cystic Carcinoma

- Adenoid cystic carcinoma has three growth patterns:

cribriform, tubular, and solid.

- These tumors are composed of both an epithelial cell component and a myoepithelial component, and immunohistochemical stains can be used to identify each.

- High-grade transformation is accompanied by a change to pure epithelial cells and a complete loss of myoepithelial cells. These tumors are often p53 positive.

Epithelial-Myoepithelial Carcinoma

- Epithelial-myoepithelial carcinoma is a biphasic tumor, composed of well-organized epithelial cells growing in ducts and tubules and surrounded by myoepithelial cells; these are often encircled by dense hyalinized stroma.

- Both the epithelial and the myoepithelial cell components can be identified with immunohistochemical stains.

Salivary Duct Carcinoma

- Salivary duct carcinoma (SDC) resembles some breast carcinomas histologically.

- SDC is positive for androgen receptor and HER2/neu; HER2/neu is often amplified by FISH.

Low-Grade Cribriform Cystadenocarcinoma

- Low-grade cribriform cystadenocarcinoma is a rare tumor that grows in a variety of patterns.

- This tumor is positive for S-100 in a strong and diffuse manner.

- Because it is an *in situ* carcinoma, the nests of tumor cells are surrounded by a well-defined myoepithelial cell layer that can be detected with typical myoepithelial cell immunohistochemical markers.

Paragangliomas

- Paragangliomas of the head and neck can occur in rather specific locations.

- The tumor cells are positive for chromogranin and synaptophysin and negative for cytokeratin.

- The sustentacular, supporting cells are positive for S-100.

- Malignancy cannot be predicted by histologic features alone; only metastasis identifies a tumor as being malignant.

Metastatic Tumors

- Metastatic tumors are most commonly attributed to head and neck primary tumors, but sites below the clavicle are also possible.
- A histologically guided immunohistochemical staining panel can often help to identify the tumor type.
- Determining the source of a metastatic carcinoma in the head and neck can be difficult or impossible, even with immunohistochemical stains, and will often require clinical and radiologic correlation.

TABLE 9.11 Immunohistochemical Staining Pattern for Tumors in the Differential Diagnosis for Paragangliomas

Stain	Carcinoid Tumor	Paraganglioma	Medullary	Melanoma	Renal Cell	Metastatic (Thyroid CA, Carcinoma, or Lung Carcinoma)
Chromogranin	+	+	+	N	N	+
Synaptophysin	+	+	S	N	N	+
Cytokeratin 7	S	N	N	N	S	+
Cytokeratin 20	S	N	N	N	N	+
CEA	S	Unk	+	N	S	+
S-100	N	+ (sustentacular)	N	+	S	N
Calcitonin	N	N	+	N	N	N
TTF-1	N	N	+	N	N	+

+, almost always positive; N, negative; S, sometimes positive.

TABLE 9.9 Intestinal-type Adenocarcinoma versus Metastatic Adenocarcinoma of Colon

	CK7	CK20	CEA	CDX-2	Chromogranin	MUC2	MUC5
ITAC	S	+	S	+	S	+	R-N
Colon	R	+	+	+	R	+	R-N

+, almost always positive; N, negative; R, rare, and focally positive; S, sometimes positive.

TABLE 9.8 Differential Diagnosis of Invasive-Ectopic Pituitary Adenoma

Feature	Pituitary Adenoma	Olfactory Neuroblastoma	Paraganglioma	Carcinoid
Synaptophysin	+	+	+	+
CAM 5.2	+	S	N	S
S-100 (sustentacular cells)	N	+	+	R
Hormones	+	N	N	S
Pit-1	+	unknown	unknown	unknown

+, almost always positive; N, negative; R, rare, and focally positive; S, sometimes positive.

TABLE 9.7 Sinonasal Undifferentiated Carcinoma versus Undifferentiated Nasopharyngeal Carcinoma (UNPC)

Feature	SNUC	UNPC
Location	Sinonasal tract	Nasopharynx
Clinical	Large primary, ± cervical lymph nodes	Small primary, positive cervical lymph nodes
X-ray	Marked destruction and spread beyond site of origin	Little destruction or spread beyond site of origin
Growth	Trabeculae, nests, sheets	Syncytial
Cells	Hyperchromatic to vesicular nuclei with or without nucleoli	Large, vesicular nuclei with prominent nucleoli
Mitoses	Very prominent	Not prominent
Necrosis	Very prominent	Not prominent
Vascular invasion	Very prominent	Not prominent
Lymphocytes	Absent to mild	Heavy infiltrate
Epstein-Barr virus (USA)	Negative	Positive
CK5/6 & 13	Negative	Positive
CK7	±	Negative

TABLE 9.4 Olfactory Neuroblastoma (ONB) versus Sinonasal Undifferentiated Carcinoma (SNUC)

Feature	ONB	SNUC
Age (average)	40-45	58
Site	Roof of nasal cavity	Multiple sites
Prognosis/survival	60%-80% 5 yr	18-mo median
Ocular-cranial nerve	Occasional	Common
Anaplasia	Occasional	Common
Mitoses	Variable	Numerous
Necrosis	Occasional	Prominent
Vascular invasion	Occasional	Prominent
Neurofibrillary stroma	Common	Absent
Homer Wright rosettes	Common	Absent
Keratin	25%-35%	90%
EMA	0%	65%
NSE	80%-100%	50%
S-100	60%	0%-15%
Synaptophysin	100%	0%
Neurosecretory granules	Numerous	Rare

ONB is typically negative but may infrequently focally express low-molecular-weight cytokeratin.

TABLE 9.3 Immunohistochemical Staining of Round Cell Tumors of the Sinonasal Tract

Tumor	CK	EMA	LCA	Synaptophysin	HMB-45	Desmin	Vimentin	CD99
SNUC	+	+	N	N	N	N	N	N
ONB	S	N	N	+	N	N	N	N
NPC	+	+	N	N	N	N	N	N
Lymphoma	N	N	+	N	N	N	+	S
Melanoma	N	N	N	N	+	N	+	N
Rhabdomyosarcoma	N	N	N	N	N	+	+	N
Small cell carcinoma	+	+	N	+	N	N	N	N
ES/PNET	N	N	N	+	N	N	+	+

CK, cytokeratin; EMA, epithelial membrane antigen; LCA, leukocyte common antigen; NPC, nasopharyngeal carcinoma; ONB, olfactory neuroblastoma; ES/PNET, Ewing's sarcoma/peripheral neuroectodermal tumor; SNUC, sinonasal undifferentiated carcinoma.
+, almost always positive; S, sometimes positive; N, negative.

TABLE 9.2 Differentiating Basaloid Squamous Cell Carcinoma from Adenoid Cystic and Small Cell Neuroendocrine Carcinoma

	Tumor Type		
Antibody Marker	Basaloid Squamous Cell Carcinoma	Adenoid Cystic Carcinoma	Small Cell Neuroendocrine Carcinoma
Cytokeratin	+	+	+
Chromogranin	N	N	+
S-100	S	+ (peripheral, myoepithelial)	N
p53	+	S	+
Ki-67	High	Low	High
C-*kit*	S	+	+
p63	+ (diffuse and strong)	+ (peripheral, myoepithelial)	S

+, almost always positive; N, negative; S, sometimes positive.

TABLE 9.1 Antibodies Used in the Evaluation of Head and Neck Specimens

Antibody	Source	Dilution
Androgen receptor	Biogenex	1:2000
Bcl-2	Dako	1:200
β-Catenin	BD Transduction Laboratories	
Calponin	Dako	1:200
Calretinin	Zymed	1:750
CD31	Dako	1:40
CD34	Dako	1:800
CD99	Dako	1:20
CD x 2	Bio Genex	1:50
CEA	Boehringer-Mannheim	1:4000
Chromogranin	Boehringer-Mannheim	1:4000
Desmin	Biogenex	1:2000
EMA	Dako	1:400
FLI-1	Santa Cruz	1:40
GFAP	Dako	1:300
HER2/neu	Dako	1:100
HMB-45	Biogenex	1:60
AE1/3	Boehringer-Mannheim	1:100
CAM5.2	Becton-Dickinson	1:200
CK4	Novocastra	1:100
CK5/6	Roche	1:20
CK7	Biogenex	1:800
CK8	Novocastro	1:60
CK10	Novocastro	1:50
CK13	Dako	1:100
CK14	Novocastro	1:40
CK19	Novocastro	1:50
CK20	Dako	1:40
CK903	Sigma	1:20
Ki-67	AMAC	1:200
Laminin	Sigma	1:20
LCA	Dako	1:20
Melan-A	Novocastro	1:40
Microphthalmic transcription factor	Neomarkers	1:40
Muscle-specific actin (HHF-35)	Enzo	1:8000
MUC2	Novocastro	1:100
MUC5	Novocastro	1:150
Myogenin	Novocastro	1:30
Neuron-specific enolase	Bio Genes	1:450
Pit-1	Santa Cruz	
p53	Oncogene	1:160
p63	Neomarkers	1:200
S-100 protein	Dako	1:1000
Smooth muscle actin	Dako	1:80
Synaptophysin	Boehringer-Mannheim	1:40
Thyroid transcription factor	Neomarkers	1:50
Tyrosinase	Novocastro	1:20
Vimentin	Biogenex	1:20

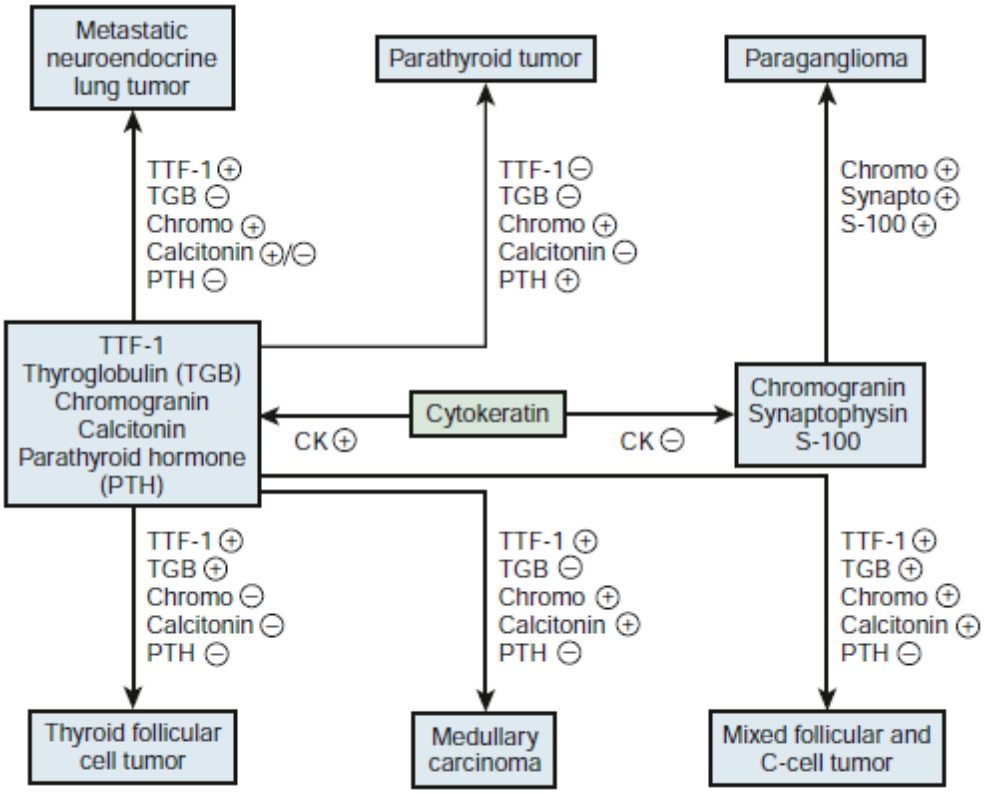

FIGURE 10.24 Algorithm of head and neck endocrine tumors.