

## The Inbred Upheaval-Intraductal Carcinoma-Salivary Gland

**Anubha Bajaj\***

*Department of Histopathology, Panjab University/A.B. Diagnostics, India*

**\*Corresponding Author:** Anubha Bajaj, Department of Histopathology, Panjab University/A.B. Diagnostics, India.

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Intraductal carcinoma of salivary gland is an exceptionally discerned neoplasm exhibiting distinct histological variants with unique molecular characteristics and specific reactions upon immunohistochemistry. Commonly, parotid gland is incriminated. Characteristically, tumefaction is composed of intra-cystic or intra-ductal proliferation of neoplastic epithelial cells.

Tumefaction is additionally designated as low grade cribriform cystadenocarcinoma, low grade intraductal carcinoma, low grade salivary duct carcinoma or salivary duct carcinoma in situ.

Intraductal carcinoma of salivary gland simulates ductal carcinoma in situ of mammary gland and represents with distinctive architectural configurations as cribriform, micro-papillary, solid, comedo or clinging subtype.

Intraductal carcinoma of salivary gland manifests variants as the frequently encountered intercalated duct-like variant, apocrine variant and a mixed or hybrid variant. An oncocyctic variant may be described which appears indicative of intercalated duct-like subcategory of intraductal carcinoma.

Morphologically, apocrine variant appears reminiscent of salivary duct carcinoma whereas intercalated duct-like or oncocyctic variants appear disparate.

Extensive tissue sampling is mandated in order to exclude tumour invasion or a distinct myoepithelial cell layer discernible with precise immunohistochemistry.

The infrequent intraductal carcinoma incriminates individuals within comprehensive age groups. A mild female preponderance is observed with female to male proportion of ~1.5:1 [1, 2].

Intercalated duct-like tumour cells frequently depict RET genetic fusions. Besides, NCOA4-RET genomic fusion is commonly encountered.

Chromosomal rearrangement of RET is encountered within constituent epithelial cells and myoepithelial cells, thereby indicating the neoplastic nature of cellular populations.

Apocrine tumour cells configure complex genetic modifications as hotspot mutations within HRAS and PIK3CA genes.

Mixed or hybrid neoplasms display RET genetic fusions, especially within TRIM27 genes.

Oncocyctic tumour cells delineate RET genetic fusion and genomic mutations within TRIM33 and BRAF V600E [2, 3].

Intraductal carcinoma of salivary gland commonly incriminates parotid gland (~84%) in addition to intraparotid lymph nodes, accessory parotid gland, submandibular gland or minor salivary glands.

Generally asymptomatic, intraductal carcinoma may represent as a gradually progressive tumefaction [2, 3].

Cytological examination displays sheets and cellular groups with overlapping cells demonstrating dense intercellular connections. Neoplastic cells may depict cribriform, micro-cystic, solid or pseudo-papillary cellular configurations. Tumour cells are imbued with abundant, well defined, eosinophilic or apocrine cytoplasm and spherical to elliptical, mildly irregular nuclei with prominent nucleoli [3, 4].

Grossly, a well circumscribed neoplasm is observed with focal to predominant cystic areas [3, 4].

Upon microscopy, tumour recapitulates morphological features of mammary intraductal carcinoma demonstrating diverse configurations as cribriform, micro-papillary, solid, comedo or clinging patterns.

Low power examination depicts a well circumscribed and non encapsulated tumefaction configuring cysts and ducts of variable magnitude. Tumour associated lymphoid proliferation (TALP) may be discerned.

~Intercalated duct-like subtype is composed of miniature cuboidal cells permeated with eosinophilic to amphophilic cytoplasm and miniature, ovoid nuclei with dispersed nuclear chromatin and inconspicuous nucleoli. Nuclear features simulate features of low grade neoplasms.

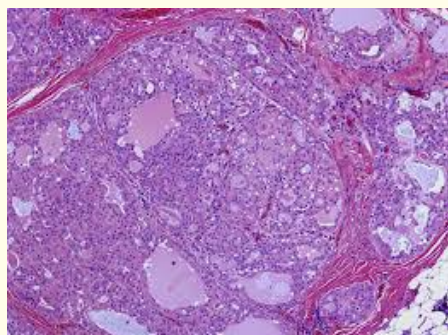
~Apocrine subtype delineates tumour cells pervaded with abundant, granular, eosinophilic cytoplasm and enlarged, spherical, vesicular nuclei with macro-nucleoli. Cells may depict apocrine snouts and intracytoplasmic secretions. Tumour cell nuclei are reminiscent of high grade neoplasms.

~Oncocytic subtype may appear as a distinct variant or display oncocytic metaplasia within adjoining intraductal carcinoma. Tumour cells are permeated with abundant, granular, eosinophilic cytoplasm and spherical nuclei of intermediate magnitude.

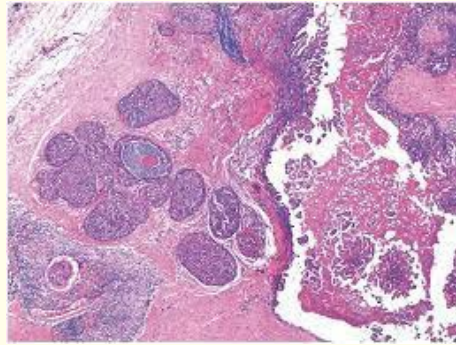
~Hybrid or mixed subtype demonstrates features of intercalated duct-like and apocrine cells [4, 5].

Tumefaction may be graded as low grade, intermediate grade or high grade. However, standardized criterion applicable to cogent tumour grading remain absent [4, 5].

Extensive tissue sampling with cogent immunohistochemistry is necessitated in order to discern a distinct myoepithelial cell layer circumscribing epithelial cell nests or exclusion of an invasive component [4, 5].



**Figure 1:** Intraductal carcinoma depicting intercalated duct-like appearance composed of nests of miniature cuboidal cells imbued with eosinophilic cytoplasm and ovoid nuclei demarcated by fibrous tissue septa [7].



**Figure 2:** Intraductal carcinoma exhibiting clusters and aggregates of neoplastic cuboidal epithelial cells incorporated with eosinophilic cytoplasm and ovoid nuclei encompassed by abundant, fibrotic stroma [8].

<i>Low grade</i>	<i>Intermediate grade</i>	<i>High grade</i>	<i>Variable grade</i>
Acinic cell carcinoma	Myoepithelial carcinoma	Salivary duct carcinoma	Mucoepidermoid carcinoma
Basal cell adenocarcinoma	Sebaceous adenocarcinoma	Squamous cell carcinoma	Adenoid cystic carcinoma
Epithelial-myoepithelial carcinoma	Lymphoepithelial carcinoma	Small cell carcinoma	Salivary carcinoma NOS
Secretory carcinoma		Large cell neuroendocrine carcinoma	Intraductal carcinoma
Polymorphous adenocarcinoma		Large cell undifferentiated carcinoma	Carcinoma ex pleomorphic adenoma
Hyalinising clear cell carcinoma		Carcinosarcoma	
Mucinous adenocarcinoma		Salivary gland carcinomas with high grade transformation	
Micro-secretory adenocarcinoma			
Sclerosing microcystic adenocarcinoma			
Sialoblastoma			
Metastasizing pleomorphic adenoma			

NOS: Not otherwise specified.

**Table 1:** Histopathological stratification of salivary gland malignancies [3].

Epithelial cells configuring intraductal carcinoma of salivary gland appear immune reactive to AE1 / AE3, CAM 5.2, cytokeratin 7 and epithelial membrane antigen (EMA).

Myoepithelial cells appear immune reactive to p63, p40, calponin or smooth muscle actin (SMA). Intercalated duct-like tumour cells appear immune reactive to S100 protein or SOX10.

Apocrine tumour cells appear immune reactive to androgen receptors (AR) or gross cystic disease fluid protein15 (GCDFP-15). Oncocytic cells appear immune reactive to S100 protein.

Mixed or hybrid tumours delineate an immune reactive profile concurrent to discernible or predominant neoplastic component [5, 6].

Intercalated duct-like and oncocytic tumour cells are immune non reactive to androgen receptors (AR), gross cystic disease fluid protein 15 (GCDFP-15). Apocrine tumour cells appear immune non reactive to S100 protein and SOX10.

Mixed or hybrid neoplasms demonstrate immune non reactive profile pertaining to preponderant cellular component [5, 6].

Intraductal carcinoma of salivary gland requires segregation from neoplasms such as cystadenoma, cystadenocarcinoma, sclerosing polycystic adenosis, salivary duct carcinoma, papillary cystic variant of acinic cell carcinoma or secretory carcinoma [5, 6].

Neoplastic infiltration requires exclusion which may be ascertained by extensive surgical tissue sampling or occurrence of a distinct myoepithelial cell layer as observed with cogent immunohistochemistry.

Intraductal carcinoma can be appropriately treated with comprehensive surgical extermination of the neoplasm. Currently, adoption of radiation therapy following surgical excision remains superfluous and non recommended [5, 6].

'Pure' intraductal carcinoma of salivary gland is devoid of tumour reoccurrence or distant metastasis. Few neoplasms display localized tumour invasion whereas innumerable lesions demonstrate widespread neoplastic dissemination and invasion [5, 6].

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7. Image 1 Courtesy: Surgical Pathology Clinics.
8. Image 2 Courtesy: Cambridge University Press.

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