Salivary Gland Intraductal Carcinoma: How Do 183 Reported Cases Fit Into a Developing Classification

Lester D.R. Thompson, MD and Justin A. Bishop, MD†*

Abstract: Salivary gland intraductal carcinoma (IDC) is a very uncommon group of neoplasms. Many names, variations in diagnostic criteria, and newly observed molecular findings (including *NCOA4*::*RET*, *TRIM27*::*RET*, *HRAS* point mutations, and *PIK3CA* pathway alterations) have generated further confusion in being able to recognize and categorize this group of tumors. Different histologic appearances and patterns of growth suggest there is more than one tumor category, with intercalated duct, apocrine, oncocytic, and hybrid features seen. Frankly destructive invasion further complicates the category, as the name "intraductal" would suggest an "in situ" neoplasm. Recent evidence on fusion-positive IDC demonstrates the same molecular underpinnings in both the ductal and the myoepithelial cells, which aids in further separating these tumors. This article summarizes the historical group of 183 neoplasms classified under the umbrella of IDC and highlights the unique histologic, immunohistochemistry, and molecular features that may further guide nomenclature standardization and harmonization.

Key Words: intraductal carcinoma, salivary gland, immunohistochemistry, molecular, systematic review

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Taxonomy of human neoplasms is applied to organize and index the knowledge of them into meaningful and often hierarchical groups, so they can be recognized reproducibly to achieve harmonized management and improve patient outcome, among other goals. Still, parsing criteria to appropriately classify neoplasms is fraught with difficulty, even more so when criteria may overlap between entities and understanding of the pathogenesis is incomplete. To wit, the meronomy of salivary gland neoplasms has evolved significantly over the past decades, as more techniques have allowed us to refine neoplasms into ever more narrow categories. If ever there was a need for better classification in salivary gland tumors, it would be for the tumor family represented by the term "intraductal carcinoma"(IDC). This critique will review the 183 cases reported (Table 1)[1–50] by various terms over the years for this category of salivary gland neoplasm, and try to provide a framework for what is known, what requires further elucidation, and potential guidelines for naming conventions.

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NOMENCLATURE DEVELOPMENT

IDC is a rare salivary gland malignancy recognized as a circumscribed neoplastic glandular and myoepithelial proliferation arranged in cystic, papillary, cribriform, micropapillary, and solid proliferations within ducts. The cytology is predominantly bland, but may show severe pleomorphism, composed of cells that may have cleared, amophilic, eosinophilic, oncocytic, or apocrine appearance. Secretions, cellular debris, and secondary changes are common, with cytoplasmic vacuolization and pigmentation. Frankly destructive invasion is uncommon, but underscores the difficulties in diagnostic classification.

IDC of salivary gland was introduced by Chen et al.[1] for a minor salivary gland tumor, with cribriform salivary carcinoma of excretory ducts,[3] low-grade salivary duct carcinoma,[5] and salivary gland cystadenocarcinoma[51] used inconsistently and sometimes interchangeably over the years, along with several other names (Table 2).

Hypothetically, IDC has been interpreted to be the salivary gland equivalent of breast atypical ductal hyperplasia or ductal carcinoma in situ, with the attendant risk of progression to a frankly invasive carcinoma, such as salivary duct carcinoma (SDC) (equivalent to breast ductal carcinoma) or another salivary gland carcinoma category (epithelial-myoepithelial carcinoma, adenosquamous carcinoma, adenocarcinoma not otherwise specified).[11,12,34,39–41,44,50,52,53] The heterogeneous category that IDC represents contains potentially four usually distinct, although sometimes overlapping entities: (1) classic intercalated duct-like (representing 54% of cases); (2) purely apocrine (representing 21% of cases); (3) oncocytic (representing 7% of cases); and (4) mixed or hybrid type (representing 6% of cases; 11% of cases were not identified histologically as a specific type). It is presently not clear whether the oncocytic pattern is equivalent to other salivary gland neoplasms, where the underlying tumor category is defined, and an oncocytic histology is present: for example, oncocytic subtype of mucoepidermoid carcinoma, oncocytic myoepithelial carcinoma, and oncocytic epithelial-myoepithelial carcinoma.[32,44,54–58] Still, the oncocytic tumors show *RET* fusions, including *NCOA4*::*RET* and *TRIM33*::*RET*, but also have *BRAF* point mutations.[32,44]

It is generally accepted that the classic intercalated duct-like tumor is noninvasive and multinodular, with a proliferation of generally bland ductal cells (low grade) immunoreactive with S100 protein, SOX10, and mammaglobin, surrounded by an intact but sometimes attenuated neoplastic myoepithelial layer (whether at the periphery or within the tumor islands/nests) immunoreactive with p40, p63, CK5/6, calponin, smooth muscle actin (SMA), and/or smooth muscle myosin heavy chain (SMMHC) (Fig. 1; Table 3). This tumor characteristically shows *RET* fusions of several forms along with other rare fusions (*NCOA4*::*RET*, *RET* by FISH, *TUT1*::*ETV5*).[34,44,45,50,59] Within the IDC category, frankly destructive invasion has been reported most in the intercalated

TABLE 1. Literature Summary of Patients With Salivary Gland Intraductal Carcinoma (IDC)[1–50]

Characteristics*	All Cases (n = 183)	Intercalated Duct-Type (n = 99)	Apocrine Type (n = 39)	Hybrid Type (n = 11)	Oncocytic Type (n = 13)
Sex					
Female	82	50	12	3	8
Male	98	48	27	7	4
Unstated	3	1	—	1	1
Age (years)					
Range	17-93	17-90	38-91	44-79	38-75
Mean	61.0	58.0	65.4	61.0	58.4
Median	61.0	58.0	67.0	64.0	63.0
Symptom duration (months)					
Range	0.2-456	2-456	0.2-84	1-180	6
Mean	34.7	40.3	19.0	64.3	6.0
Site					
Major salivary gland	172	89	38	11	13
Parotid gland	150	87	38	10	9
Submandibular gland	5	2	0	1	2
Sublingual gland	1	0	0	0	0
Minor salivary gland	11	10	1	0	0
Palate	3	2	1	0	0
Buccal	3	3	0	0	0
Lip	2	2	0	0	0
Tongue	2	2	0	0	0
Lacrimal	1	1	0	0	0
Laterality					
Left	32	19	6	3	2
Right	38	20	11	0	7
Tumor size (mm)					
Range	3-86	3-60	7-46	10-43	8-35
Mean	22.0	21.1	23.4	21.5	20.5
Median	18.0	18.0	20.0	17.0	18.0
Females (mean, mm)	20.0	21.5	27.7	12.0	19.9
Males (mean, mm)	22.0	20.6	20.7	24.7	21.5
Major gland (mean, mm)	22.4	21.5	23.9	21.5	20.5
Minor gland (mean, mm)	17.2	18.0	10.0	NA	NA
Invasion histologically documented, n (%)	52 (28)	23 (23)	16 (41)	5 (45)	0
Immunohistochemistry					
Ductal proliferation					
S100 protein	118 of 138	78 of 79	9 of 25	7 of 9	13 of 13
SOX10	39 of 50	28 of 29	3 of 11	5 of 6	2 of 3
Mammaglobin	67 of 71	36 of 37	11 of 12	6 of 6	11 of 11
AR	38 of 98	3 of 44	28 of 29	6 of 9	0 of 10
GCDFP-15	16 of 31	5 of 12	9 of 9	1 of 1	0 of 8
Her2	11 of 46	2 of 15	7 of 17	2 of 3	0 of 3

TABLE 1. (*continued*)

Characteristics*	All Cases (n = 183)	Intercalated Duct-Type (n = 99)	Apocrine Type (n = 39)	Hybrid Type (n = 11)	Oncocytic Type (n = 13)
Myoepithelial cells					
p63/p40	90 of 109	54 of 57	21 of 23	4 of 6	13 of 13
CK5/6	13 of 14	7 of 7	3 of 4	2 of 2	n/a
Calponin	48 of 49	22 of 22	7 of 7	1 of 1	4 of 4
SMA	48 of 50	29 of 29	11 of 12	2 of 3	6 of 6
CK14	30 of 30	19 of 19	9 of 9	1 of 1	1 of 1
Molecular findings*					
NCOA4::*RET*	32	27	0	3	1
RET by FISH	18	14	1	3	0
TRIM27::*RET*	5	0	2	3	0
TRIM33::*RET*	4	0	0	2	1
KIAA1217::*RET*	1	0	0	1	0
TUT1::*ETV5*	1	1	0	0	0
PIK3CA	13	0	13	0	0
HRAS	12	0	12	0	0
BRAF	2	0	0	0	2
TP53	2	0	2	0	0
ATM loss	1	0	1	0	0
SPEN	1	0	1	0	0
ALK	4	3	0	0	0
DFFA::*ARID1A*	1	0	1	0	0
KIF13B::*EPB414B*	1	0	1	0	0
More than one mutation identified	12	0	12	0	0
No mutations identified	12	8	2	1	1
Therapy (n = 138)					
Surgery (including neck dissection)	137	82	32	9	7
Surgery and radiation	22	9	5	3	1
Surgery, radiation, and chemotherapy	5	1	1	1	0
Patients with follow-up (n = 117) (mean months of follow-up)	117 (43.4)	—	—	—	—
Alive, no evidence of disease	109 (42.6)	57 (45.5)	21 (48.6)	7 (31.0)	9 (27.2)
Alive with disease	1 (48)	NA	NA	NA	NA
Dead, no evidence of disease	5 (70.8)	2 (44.0)	NA	1 (104)	1 (30)
Dead of disease	2 (19)	1 (7.0)	NA	NA	NA
Follow-up (mo)					
Range	1-228	1-228	1-190	4-104	1-115
Mean	43.0	44.8	48.6	40.1	27.5

*Not stated in all cases. Specific categories were not stated for 21 cases. Cases were reported multiple times in separate publications, but are only included in this table once.[12,32,34,35,38,45]
AR indicates androgen receptor; GCDFP-15, gross cystic disease fluid protein-15; SMA, smooth muscle actin.

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TABLE 2. Nomenclature History of Salivary Gland Intraductal Carcinoma

References	Name
Chen et al[1]	Intraductal carcinoma of salivary gland
Brandwein et al[3]	Cribriform salivary carcinoma of excretory ducts (2 cases described as "in situ")
Anderson et al[5]	Low-grade salivary duct carcinoma
Tatemoto et al[7]	Low malignant intraductal carcinoma
Foss et al[51]	Salivary gland cystadenocarcinoma
Ide et al[10]	Circumscribed salivary duct carcinoma
Weinreb et al[12]	Low-grade intraductal carcinoma of salivary gland
Simpson et al[13]	Salivary duct carcinoma in situ
Arai et al and Laco et al[14,16]	Low-grade cribriform cystadenocarcinoma
Palicelli et al[33]	Unicystic high-grade intraductal carcinoma

duct-type (23 cases), but destructive invasion is identified in about 23% of all IDC cases. With frankly destructive invasion (the term these authors propose and here use),[50] the layer of myoepithelial cells becomes attenuated and lost, with only the ductal component identified in the invasive tumor component thus far. Potentially, as a low-grade biphasic neoplasm, it is the ductal component that becomes higher grade, proceeding to a destructively invasive growth, conceptually similar to a carcinoma arising within a pleomorphic adenoma or sclerosing polycystic adenoma, where it is the ductal component that becomes the SDC, even though the myoepithelial component is lost and destroyed by this higher grade transformation.[45,60–63] Further support for this interpretation comes from earlier work on breast-type and salivary gland–type tumors, in which in situ triple immunofluorescence lineage/differentiation tracing and real-time polymerase chain reaction study of K5/K14-positive progenitor cells were found to differentiate into glandular- (K8/18-positive) and myoepithelial-lineage (SMA-positive)–specific cells and were also shown to generate various heterologous cell differentiations such as squamous and mesenchymal progenies.[64] This work was based on initial work showing that a CK5-only positive cell is an adult or progenitor stem cell that can give rise to glandular or myoepithelial cells, and consequently through immunofluorescence studies and Western blotting analysis, showed usual ductal hyperplasia to be myoepithelial, whereas atypical ductal hyperplasia and ductal carcinoma in situ displayed only differentiated glandular phenotypes (CK8/18/19-positive) while lacking CK5.[65] Benign myoepithelial cells may be signalized to function as a tumor suppressor at the start of malignant transformation.[66] It is also well known that basal-like breast carcinomas, specifically of salivary gland–like categories, frequently coexpress CK5/6 and S100 protein as supporting evidence of aberrant myoepithelial differentiation.[67,68] Although not specifically performed in salivary gland tumors or IDC especially, they are known to be diffusely S100 protein positive (in intercalated duct-type tumors) while also showing CK5/6-positive myoepithelial cells at the periphery in most of the neoplasm.

TABLE 3. Diagnostic Criteria

Epithelial proliferation within well-circumscribed, multilobulated, round, smooth-bordered cysts, showing a basophilic to eosinophilic appearance on low power (type dependent)
Cribriform, micropapillary, papillary, and fenestrated to solid architecture
Variable small cuboid cells with round to oval nuclei; intermediate to large cells with round nuclei, open chromatin, prominent nucleoli, and ample eosinophilic granular cytoplasm and decapitation secretions/snouts; cells with abundant granular cytoplasm; hybrid features in selected cases
Low, intermediate, or high cytologic grade
Exclude destructive invasion with thorough (complete) sampling and myoepithelial/basal cell immunohistochemistry to demonstrate presence/absence of the layer
Generally reciprocal immunohistochemistry of ductal elements with S100 protein and SOX10 versus androgen receptor and GCDFP-15; mammaglobin variable; may be patchy
NCOA4::*RET* predominant in intercalated duct-type; *HRAS* and *PIK3CA* exclusively in apocrine tumors

GCDFP-15 indicates gross cystic disease fluid protein-15.

Pure or predominantly apocrine tumors show ample eosinophilic cytoplasm, with apocrine snouts or blebs, generally show more pleomorphism, may show tumor necrosis, have increased mitoses, usually show strong androgen receptor (AR) reactivity while lacking S100 protein, SOX10, and mammaglobin (Fig. 2), with a generally more complex genetic landscape, with *RAS*, *PIK3CA*, and *TP53* alterations, similar to those reported for SDC (Table 1).[12,15,34,39–41,44,50] This tumor type shows frankly destructive invasion frequently (41%), with a similar attendant loss of the myoepithelial layer, although definitive documentation of the myoepithelial layer representing part of the neoplasm (i.e., biphasic) has not yet been documented. In fact, it may be that the myoepithelial cells in apocrine-type tumors are not neoplastic. Still, by extrapolation, destructively invasive ductal apocrine-type carcinomas also lack a myoepithelial component, and so can be interpreted similarly, just like the loss of myoepithelial cells seen in other salivary gland tumor types (i.e., adenoid cystic carcinoma). Still, it seems logical at this point to extract this category of tumor from IDC, and for pure apocrine neoplasms, align them with SDC, but specifically use salivary duct carcinoma in situ, which seems an appropriate term, as there is risk for destructive invasion, although not identified in all cases. Furthermore, there is a 2.25:1 male:female ratio of the apocrine category tumor, rather than the 1:1 ratio for intercalated duct-type, another finding similar to SDC. Similarly, nearly all (97.5%) apocrine IDC develop in major salivary gland sites, with 89% of intercalated duct-type tumors affecting major salivary glands. This separation would allow for a cleaner grouping based on the histologic features and on the molecular underpinnings of these tumors.

As would be expected of a hybrid category, there are histologic features of any of the 3 patterns described above, although a minimum percentage or volume of a pattern is not defined for inclusion in this category (i.e., 20%, 30%, or 50% of a pattern is sufficient for inclusion in hybrid subtype). As such, hybrid tumors have overlapping immunohistochemistry (IHC) and molecular findings drawn from each histologic pattern. Therefore, there may be coexpression of S100 protein and AR (Fig. 3), gross cystic disease fluid protein-15 (GCDFP-15), SOX10, and mammaglobin, whereas the myoepithelial component is still recognized by myoepithelial markers.[12] This tumor category has the highest percentage of cases with destructive invasion (45%), but this may reflect a reporting bias, or potentially as a hybrid category, is being driven by the most biologically aggressive component (i.e., apocrine pattern). All cases thus far have developed

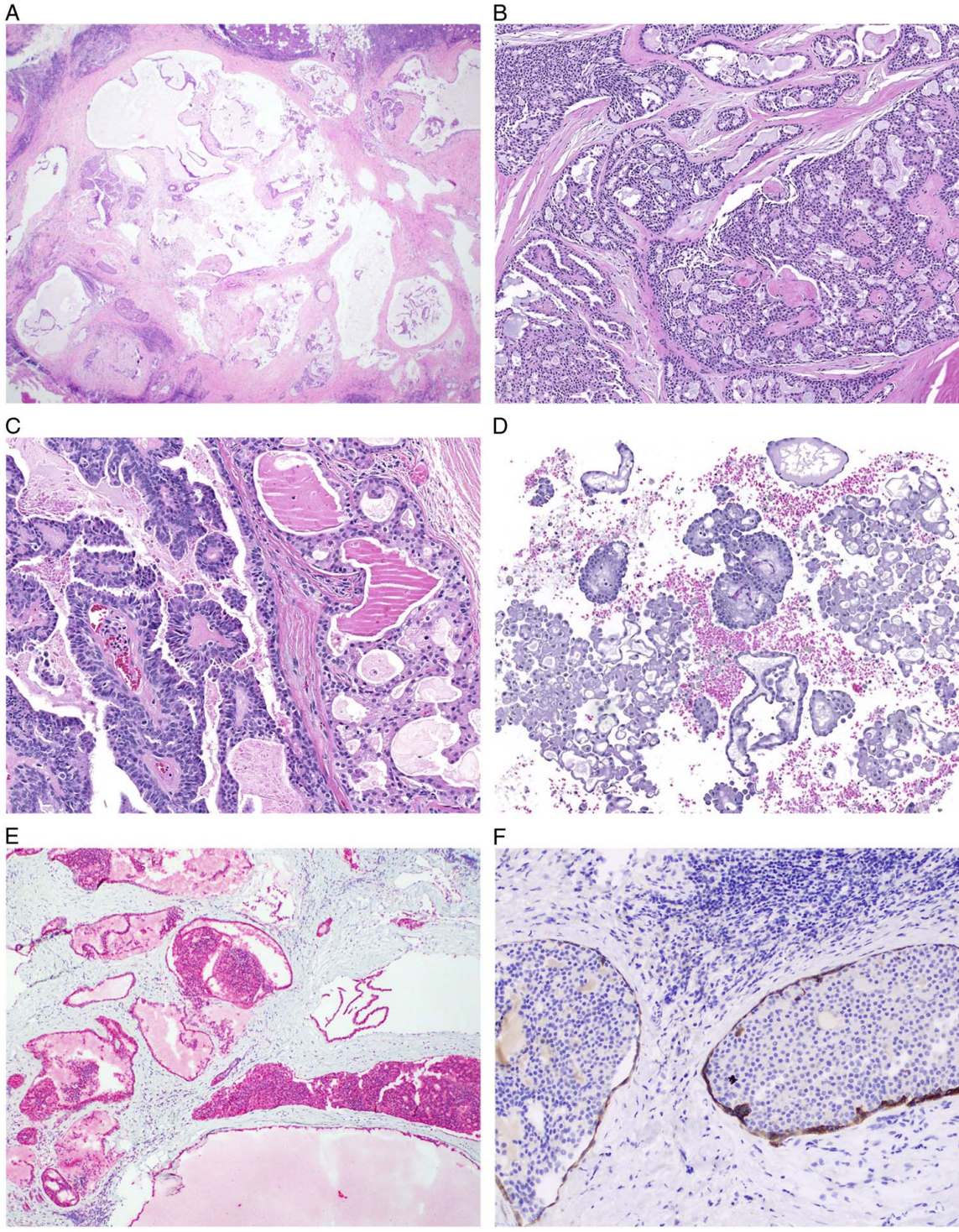

FIGURE 1. Intercalated duct-like intraductal carcinoma. A, Multinodular, cystic well-circumscribed tumor with secretions noted. B, Moderately cellular tumor with a cribriform pattern with heavy stromal fibrosis. C, Papillary projections and glandular profiles. D, Luminal papillary projections showing a secretory carcinoma-like pattern. E, Strong, diffuse, luminal, and myoepithelial S100 protein immunoreactivity. F, Myoepithelial layer highlighted by CK5/6. Please see this image in color online.

in major salivary gland sites. Just like "mixed mammary carcinoma" is a breast tumor type that shows ductal and lobular features interspersed and blended together in a single tumor mass, the intercalated duct-type, apocrine, and oncocytic types may also be blended, both intraductal and when frankly invasive. This hybrid category should be used judiciously, recognizing that until strict cutoffs have been established, it would be wise to include a

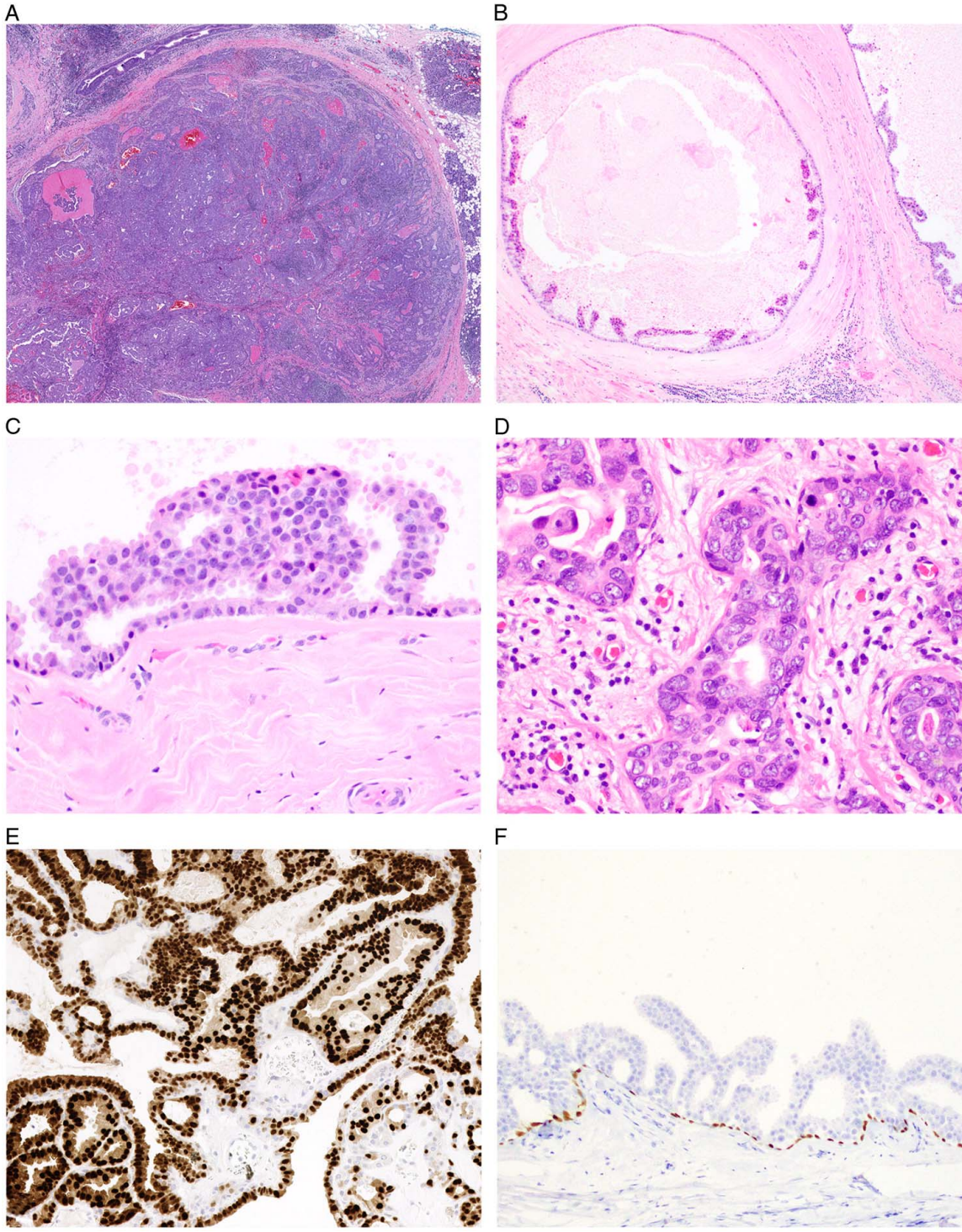

FIGURE 2. Apocrine-like intraductal carcinoma. A, A cellular, solid tumor morphology showing a large projection into the adjacent stroma. B, Micropapillary projections with cribriform appearance and centrally cystic spaces. C, Apocrine morphology with hobnail or snout appearance noted. D, Nuclear pleomorphism is noted, along with mitoses. E, Strong, diffuse, nuclear reaction with androgen receptor. F, An intact p63-positive myoepithelial layer lines the cyst. Please see this image in color online.

volume/percent estimate of each tumor type, but more importantly to definitively try to identify destructive invasion, which is the most important prognostic factor to consider.

Etiology and Pathogenesis

Given the histologic diversity, IDC shows diverse genetics. However, when separated into the 2 extremes, a more clear classification becomes apparent. Intercalated

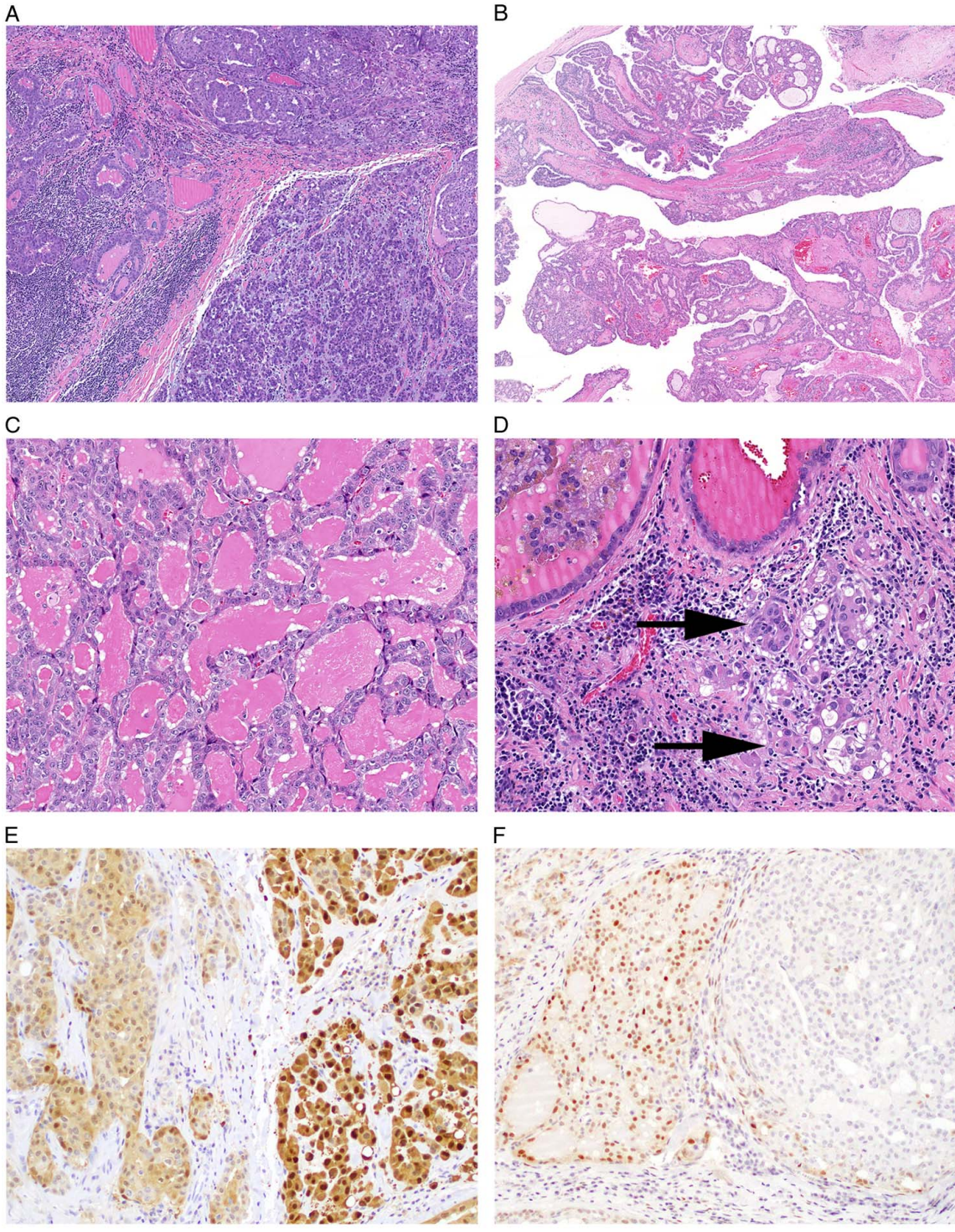

FIGURE 3. Hybrid intraductal carcinoma. A, Three different patterns of growth are seen, along with 3 different histomorphologies. B, A cystic area, but composed of oncocytically altered cells as well as more classical fenestrated glands. C, Prominent secretions are seen in this part of the tumor. D, There is infiltration into the stroma by small islands of tumor (black arrow). E, The S100 protein shows a very strong and diffuse nuclear and cytoplasmic reaction (right side) in comparison to a much weaker reaction in this hybrid tumor. F, The androgen receptor is expressed in only part of this hybrid tumor.

duct-type tumors have shown fusions and rearrangements: *NCOA4*::*RET* n = 27; *RET* FISH n = 14; *ALK* n = 3 with *STRN, EML4*, and *MYO18A* partners; and *TUT1*::*ETV5* n = 1; with many tumors tested lacking any identifiable fusions.[16,34,38,40,45,48,53] Furthermore, evidence has shown the same fusions in both the ductal and myoepithelial cells,

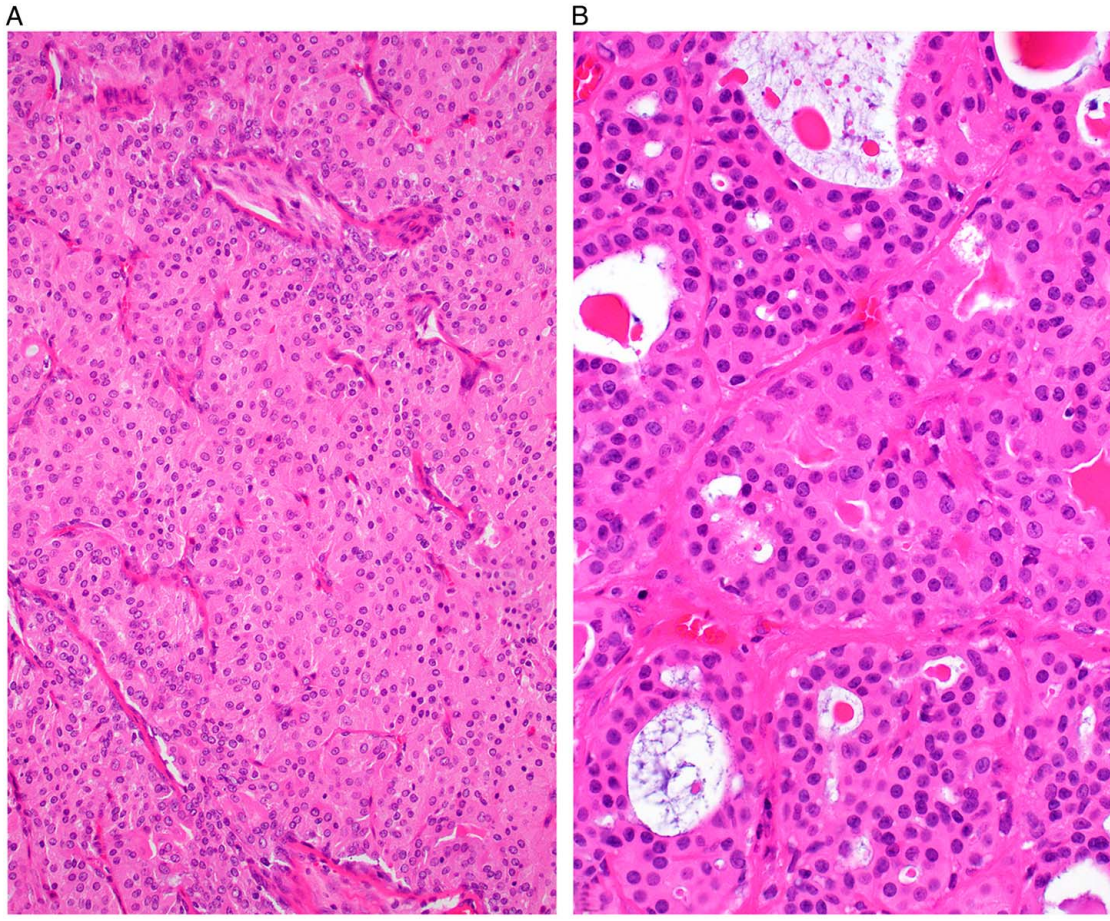

FIGURE 4. Oncocytic intraductal carcinoma. A, There are sheets and nests of oncocytically altered epithelial cells. B, Glandular profiles are noted with secretions, while all cells are oncocytically altered. Without additional immunohistochemical or molecular studies, this tumor would be difficult to definitively classify as an intraductal carcinoma, oncocytic type. Please see this image in color online.

supporting a biphasic neoplasm.[45,48] The purely apocrine tumors frequently possess multiple concurrent mutations, including *HRAS*, *PIK3CA*, *TP53*,[39,40,42,46,49] loss of *ATM*,[39] mutations in *SPEN*,[39] rarely showing fusions (*TRIM27*::*RET, DFFA*::*ARIA1A, KIF13B*::*EPB414B*),[34,35,38] whereas some tested cases lack any identifiable mutations.[34] The oncocytic type may harbor *TRIM33*::*RET*, *NCOA4*::*RET*, or *BRAF* p. V600E mutations, whereas no mutations have been detected in other tested cases.[44] As would be expected, hybrid tumors, showing mixed intercalated duct-apocrine or intercalated duct-oncocytic, or oncocytic-apocrine features, have thus far only shown fusions: *NCOA4*::*RET* n = 3; *RET* FISH n = 3; *TRIM27*::*RET* n = 3; *TRIM33*::*RET* n = 2; and *KIAA1217*::*RET* n = 1; or no identifiable mutations.[21,35,38,41,45,46,50]

Demographics

The incidence of a rare tumor is always difficult to predict. However, in a review of all salivary gland neoplasms over a 5-year period, IDC comprised 0.06% of all salivary gland neoplasms and 0.2% of malignant neoplasms (unpublished data). There is a slight male predilection of 1.2:1 male to female (Table 1). However, there is an even sex distribution for intercalated duct-type, with a male predominance for apocrine (2.25:1) and hybrid tumors (2.3:1). There is a very broad age range of 17 to 93 years, but with a median of 61 years. The apocrine tumor on average presents nearly a decade older than the intercalated duct-type tumors (67.0 vs. 58.0 median, respectively).[40,69]

Clinical Findings

Patients generally present with a painless mass of variable duration: average is 35 months, but 40.3 months for intercalated duct-type, while only 19 months for the apocrine type (Table 1). Tumors affect the major salivary glands most commonly (94%), especially the parotid gland, with oral cavity and lacrimal gland affected occasionally. All minor gland tumors, except for 1 apocrine type, were intercalated duct-type.[1,2,4,7,9,10,23,24,27,34,47] There is uncommon exclusive involvement of intraparotid gland lymph nodes (n = 10).[6,11,18,30,46,48]

Imaging Studies

Imaging findings are those of a soft tissue homogenous to heterogenous density mass, with nonspecific hypointensity to hyperintensity of complex solid to cystic masses by T1-weighted or T2-weighted magnetic resonance. Cystic changes may be seen by ultrasound or computed tomography.[14,23,30,31,33,42,45,49]

Cytology

There is a significant variation in cytomorphologic findings depending on whether the tumor is low or high grade, predominantly cystic, or whether apocrine or oncocytic.

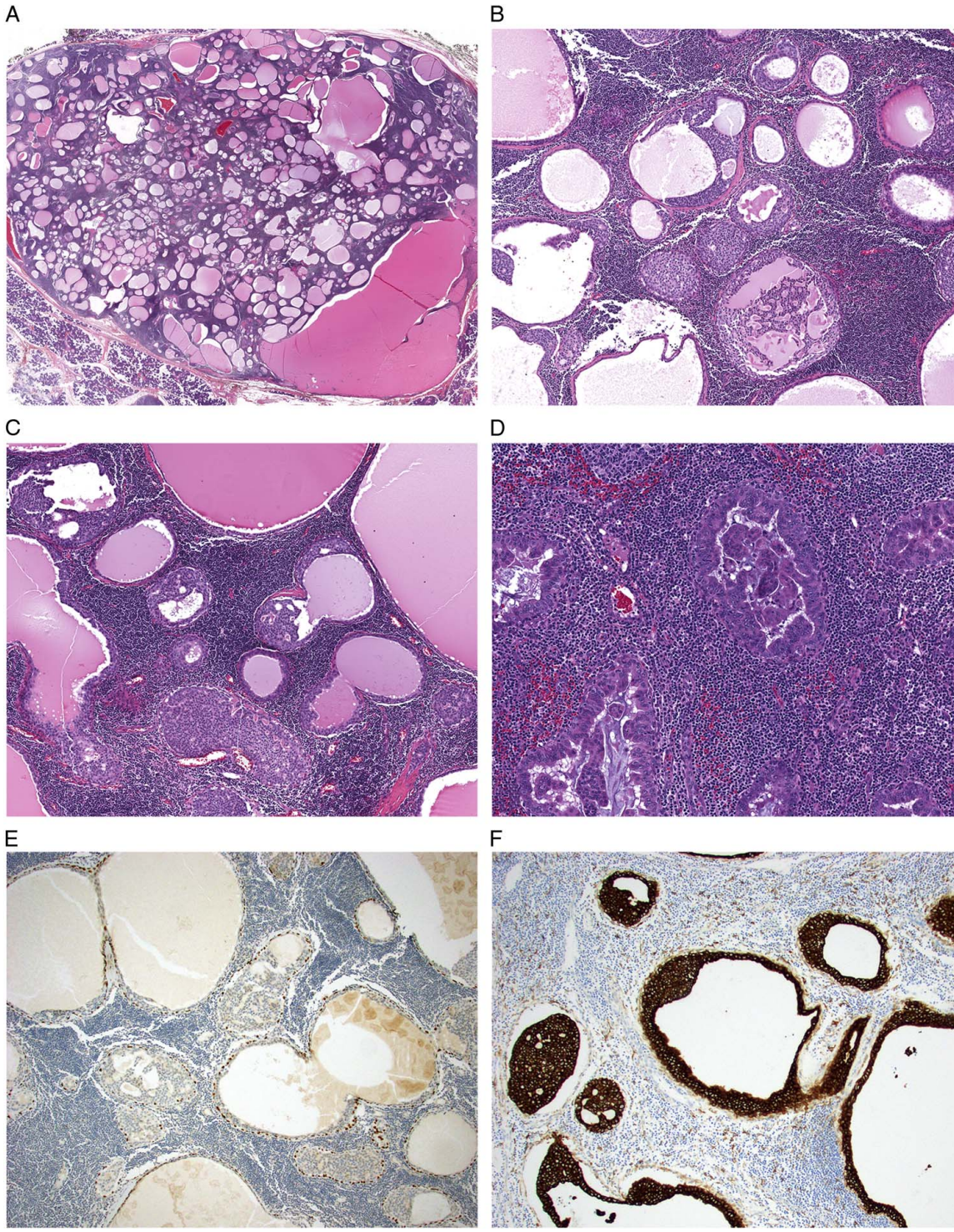

FIGURE 5. Intranodal intraductal carcinoma. A, The lymph node shows innumerable cystic structures with eosinophilic secretions. B, There is an intraepithelial proliferation of papillary and cribriform-appearing groups. C, There is an intact myoepithelial layer than creates the intact lobules of tumor set within the lymph node. D, Nuclear pleomorphism and a more complex architecture can be seen in some tumors. E, There is an intact and easily identified p63-positive myoepithelial layer surrounding the tumor islands. F, There are numerous CAM5.2-reactive extrafollicular reticulum cells that help to confirm the presence of a true lymph node. The epithelium of the tumor is strongly immunoreactive. Please see this image in color online.

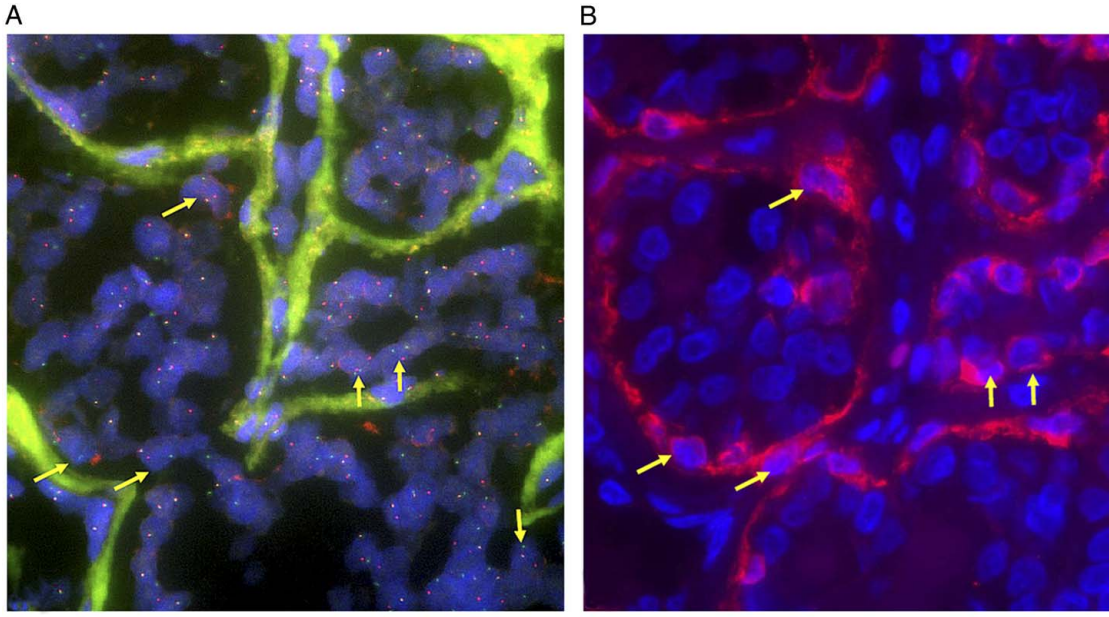

FIGURE 6. Molecular studies to confirm tumor category of this hybrid intraductal carcinoma with *TRIM27*::*RET* fusion. A, *RET* FISH demonstrating break-apart split red and green signals. B, The calponin immunofluorescence (red fluorophore) contains a rearranged *RET* gene (red and green signals apart, yellow arrow) (Hiroshi Inagaki, MD, PhD). Please see this image in color online.

Therefore, Milan categorization ranges from atypia of undetermined significance, to salivary gland neoplasm of uncertain malignant potential, to malignant. Smear cellularity is usually moderate to high, with several patterns, composed of crowded, overlapping, small tridimensional clusters, and single cells to occasionally showing sheets, papillary, pseudopapillary, or larger groups (Fig. 4). Thicker areas may show a cribriform appearance. Although not always seen, there is a biphasic appearance of the larger ductal cells (cuboidal-columnar) with less obvious myoepithelial cells. The nuclei are oval to plasmacytoid with finely distributed chromatin. There is usually an intermediate nuclear to cytoplasmic ratio, except for the apocrine or oncocytic cells, where more abundant cytoplasm is seen. Clear, single, large cytoplasmic vacuoles may be present, but only in rare ductal cells. Cytoplasmic granules (metachromatic with May-Grünwald Giemsa stain) or yellow-brown pigment is noted. Background debris, histiocytes, blood, and psammoma body-like calcifications and blood are common, with secretions in some cases.[20,21,28,29,33,41,49,70–73]

Macroscopic Features

Tumors are usually well circumscribed but not encapsulated, potentially ramifying through the ducts and appearing to be distant from the main mass. They are variably solid and cystic, often containing degenerated tissue and blood. Tumors range from 3 to 86 mm, with a median of 18 mm and a mean of 22 mm (Table 1). The apocrine tumors tend to be slightly larger. Major gland tumors are larger (mean: 22.4 mm) than minor gland tumors (mean: 17.2 mm).

Microscopic Features

All subtypes of IDC show an expansile epithelial ductal growth within rounded, large, dilated cysts and lobules with adjacent scattered smaller microcysts, showing variable proportions of solid, cribriform, micropapillary, papillary, clinging, tubular and Roman bridge-type ductal proliferations, surrounded by a continuous, usually flattened intact layer of myoepithelial cells (Fig. 1). This latter feature may be difficult to detect on standard hematoxylin and eosin–stained slides, requiring IHC to highlight these cells (Fig. 1F), but more importantly to also determine whether destructive infiltration is present when absent.[9] At least the intercalated duct-type has been proved that the myoepithelial cells are neoplastic with the same fusion as detected in the ductal epithelial cells.[45] At present, the pattern of ductal cells is used to separate the tumors into three subtypes—intercalated duct like, apocrine, and oncocytic (Fig. 4)—with the hybrid type showing features of more than one subtype, as described above. Distention of the smooth-contoured lobules results in a crowded appearance and a modest cellularity (Fig. 1). Tumors generally show a low mitotic index, although a higher proliferation index may be seen in apocrine-type tumors. Eosinophilic to amphophilic secretory material may be seen in the lumina (Fig. 1C). Secondary changes (hemorrhage, foam cells, cholesterol clefts, hemosiderin, and fibrosis) are common (Fig. 3), whereas psammoma body calcifications are also reported (n = 9).[10–13,18,19,21,38,44,49] Tumor-associated lymphoid proliferation is present (n = 26), a finding that may simulate a lymph node (Fig. 3). A subset of cases arise within the parenchyma of intraparotid gland lymph nodes (Fig. 5),[6,18,48,74] with the documentation of extrafollicular reticulum cells within the lymphoid stroma (Fig. 5F) that supports the presence of a true lymph node rather than tumor-associated lymphoid proliferation.[48] It is well known that epithelial inclusions within intraparotid gland lymph nodes can be seen, and thus a neoplasm arising from these salivary gland inclusions can certainly be seen.[75,76] The extension of the neoplastic cells beyond the contour of the lymph node into the adjacent stroma suggests destructively infiltrative growth. Central comedonecrosis is more common in the apocrine type, but is also seen in the intercalated duct-type. Importantly, a precursor lesion (such as pleomorphic adenoma, sclerosing polycystic adenoma,

and papillary cystadenoma) is absent, although an adjacent, second tumor (pleomorphic adenoma) has been reported.[46,49]

Cystic structures are lined by a variably thick layer of proliferating, bland small-sized ductal cells creating anastomosing and filigreed intracystic micropapillae or a fenestrated appearance (Figs. 1, 2), whereas papillary projections frequently result in cribriform (Roman bridge) formations. The ductal nuclei are basally located within columnar-cuboidal cells, have evenly distributed chromatin, and are surrounded by amphophilic to vacuolated cytoplasm, frequently containing lipofuscin-like pigment (Figs. 1, 3).[6,11,12,34,35,38,39,44,48–50,53,59,69] When reported, mild atypia (48.3% and 45.5%, major and minor salivary glands, respectively) is equally represented, whereas severe atypia is reported in major salivary gland sites much more frequently than minor salivary gland sites (12.2% vs. 0%, respectively), different than previously thought.[12,18]

Apocrine tumors have large cells with snouting and decapitation secretions, usually showing deeply eosinophilic (glassy) cytoplasm, cytoplasmic vacuoles, and nuclei with central eosinophilic nucleoli (Fig. 2).[6,11,12,35,39,77] These tumors seem to represent the preinvasive phase of a SDC.[1,2,12,13,39–41,78] Still, widely invasive apocrine carcinomas have developed from a completely intraductal tumor, many months after the first surgery, suggesting recurrence as a destructively invasive carcinoma. If the previous surgery was unknown, it would have been very challenging to suggest such a development, especially as a fusion-positive SDC, with consequent therapeutic impact.[22,43,50,79]

Oncocytic tumors have large cells defined by abundant, granular, eosinophilic oncocytic cytoplasm, frequently showing prominent nucleoli within round nuclei (Fig. 4).[26,32,44,49] This subtype may show myoepithelial cells within the intraductal compartment and not just at the periphery.[32]

Overall, histologic invasion is reported in about 28%, highest in the hybrid (45%; Fig. 3D) and apocrine (41%) types, whereas lower in intercalated duct-type (23%) and not yet reported in oncocytic pattern tumors (Table 1). This finding is higher than the 10% to 12% reported rate of "carcinoma" ex pleomorphic adenoma when invasion is noted in this tumor category (i.e., not an in situ tumor).[80–82] There are no reproducible definitions of "microinvasion" or "limited" invasion,[12] but desmoplastic stromal reaction, irregular growth, single cells, hyalinization, and loss of the myoepithelial cells support destructive invasion (Fig. 3D), and are the features that must be actively confirmed.[13,33,46,50] The concept that the frankly invasive component represents a high-grade transformation of the underlying tumor category may occur in some cases, but not all destructively invasive tumors have a high-grade histology and some tumors do not fit within a specific category at all (i.e., not otherwise specified).[50] With several different frankly invasive tumor types, providing information about grade and extent of invasion seems prudent.

Immunohistochemistry and In Situ Hybridization Findings

Overlap between IHC findings can be seen, but in general, consistent findings are noted. Intercalated duct-type and oncocytic tumors are reactive in the ductal component with S100 protein, SOX10, and mammaglobin (Fig. 1), whereas generally negative for AR and gross cystic disease fluid protein-15; apocrine tumors are strongly positive with AR and mammaglobin (Fig. 2), variably with GCDFP15 and usually negative with S100 protein and SOX10 (Table 1). Obviously, focal, patchy, and weak reactivity may be present in an individual case to a variable degree no matter what the tumor category. Hybrid tumors show a mixed reactivity with all of these markers, often accentuated in an individual component (Fig. 3). Enveloping myoepithelial cells (when present) are consistently positive, although cells are attenuated and sometimes sparsely distributed, with a spectrum of myoepithelial-type markers, including p40, p63, CK5/6, SMA (more sensitive), muscle-specific actin (more specific), calponin, and CK14, although not always equivalently with each antibody (Figs. 1–3, 5).[6,9,11–13,26,30,32,33,49,50,83]

When reported, the epithelial cells are reactive with pancytokeratin (AE1/AE3), CAM5.2, 34ßE12 (K903), CK7, EMA, and CK19.[6,9,11–13,26,30,32,33,49,50,83] Variable reactivity is reported with GATA3 and DOG1 (although only rarely positive for the latter).[26,29,34,43,49,50] Neoplastic cells are nonreactive with estrogen receptor and progesterone receptor.[9,11–13,22,28,33,36,49,50] Inclusion of BRAF VE1, ALK, NRAS, and mitochondrial antibody IHC in more recent studies has shown to be of value in highlighting additional features.[32,40,42–44,47] At this time, proliferation index as tested by Ki-67 (MIB1) antibody ranges from <1 to >50%, and does not have defined cutoffs for specific tumor categories. Generally speaking, intercalated duct-type and oncocytic tumors have a low proliferation index (<5%), whereas apocrine tumors are higher (>10%).[34]

Molecular Findings

The molecular profile is usually quite uniquely matched to the histologic appearance. Most of the intercalated duct-like tumors have *NCOA4*::*RET* fusions,[34,35,38] with several hybrid and one oncocytic tumor showing similar findings, but not seen in the apocrine tumors.[44,46,50] *RET* FISH is more commonly detected in intercalated duct-type and hybrid-type tumors (Fig. 6), but rarely seen in apocrine tumors (Table 1), specifically related to a tight inversion pattern due to an intrachromosomal rearrangement not detected by routine break apart FISH (usually for *NCOA4*::*RET*).[49] *TRIM27*::*RET* and *TRIM33*::*RET* are seen in apocrine, hybrid (Fig. 6), and oncocytic tumors, but not in intercalated duct-type tumors.[41] *PIK3CA* and *HRAS* hotspot mutations are only reported in apocrine type tumors, often in those with frankly invasive growth,[35,49] whereas *TP53* alterations are also only reported in this group. *ALK* rearrangements have been identified exclusively in intercalated duct-like tumors, with the fusion partner of *EML4*, *STRN*, *CTNNA1*, and *MYO18A*.[43,47,50,84] Interestingly, other tumors with *ALK* rearrangements include SDC[43,79] and secretory carcinoma,[85] recognizing that there is histologic overlap with SDC. Several other mutations and fusions are reported in isolation (eg, *BRAF*, *ATM*, and *SPEN* loss).[32,43,47] Interestingly, multiple mutations are seen in apocrine tumors, whereas no mutations were found in each of the tumor categories.[16,34,35,38–40,44–46,49] These molecular findings, while still incomplete, suggest that the apocrine subtype may well be an in situ salivary duct carcinoma, as the IHC (androgen receptor, Her-2/neu) and molecular overlap (*HRAS* and *PIK3CA*) with SDC[86] is quite convincing.

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TABLE 4. Differential Diagnosis of Salivary Gland Intraductal Carcinoma (Placed in Most Common Tumor Category)

Differential Diagnosis	Intercalated Duct-Type	Apocrine Type	Hybrid Type	Oncocytic Type
Benign				
Cystadenoma, including oncocytic subtype	Unicystic or multicystic, well-circumscribed growths; intraluminal papillary proliferation; flat, cuboidal to columnar cells; usually amphophilic cytoplasm; no fenestrated/cribriform growth; no atypia; no mitoses; no necrosis; no invasive growth **Positive**: keratins; **Negative**: S100 protein, SOX10, GCDFP15	Rarely apocrine and mucinous pattern may be seen; epithelial tufting; columnar cells with vacuoles; isolated nuclear enlargement; and hyperchromasia may be seen; no mitoses; no tumor necrosis; lacks complex internal architecture; clear myoepithelial cells may be seen **Negative**: S100 protein, BRST-2, GCDFP-15, CK5/6		Unicystic or multicystic growths; intraluminal papillary proliferation; oncocytic cytoplasm may be present; no atypia; no mitoses; no invasive growth
Warthin tumor	True intranodal growth of a papillary and cystic tumor; tramtracked, double-layered oncocytically altered epithelium with columnar-polygonal cells; lacks myoepithelial layer			
Lymphadenoma	Intranodal proliferation of evenly spaced epithelial islands within lymphoid stroma; squamous metaplasia frequent; sebaceous islands may be seen; absent microcystic and complex architecture			
Sclerosing polycystic adenoma	Well-circumscribed unencapsulated, lobular admixture of ducts, myoepithelial cells and serous acini; fibrosis and cystic changes; vacuolated and foamy cells seen; fatty metaplasia uncommon; prominent, brightly hypereosinophilic cytoplasmic granules in acinar cells; may need immunohistochemistry to show myoepithelial cells	Frequently show apocrine metaplasia (androgen receptor positive); may rarely show intraductal carcinoma or destructively invasive carcinoma; Overlap with PI3K-Akt pathway alterations (usually *PIK3CA* point mutation); *PTEN* loss in the epithelial cells is characteristic Atypical intraductal proliferations may be indistinguishable		Oncocytic alterations may be seen, with remaining findings similar
Intercalated duct adenoma	Major salivary gland site; unencapsulated single population proliferation of intercalated ducts (cuboidal cells) blending with acinar cells; myoepithelial cells are intact; brightly hypereosinophilic cytoplasmic granules in acinar cells; focal mucinous differentiation may be seen			

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TABLE 4. (*continued*)

Differential Diagnosis	Intercalated Duct-Type	Apocrine Type	Hybrid Type	Oncocytic Type
Striated duct adenoma				Encapsulated, usually solid pure striated duct proliferation; closed opposed ducts lined by a single layer of columnar cells with eosinophilic cytoplasm separated by fibrovascular stroma; lacks myoepithelial layer; no cribriform, papillary or micropapillary architecture; no pleomorphism, no necrosis, no increased proliferation index **Positive**: keratins, S100 protein; SOX10 **Negative**: androgen receptor, GCDFP15, mammaglobin
Malignant				
Secretory carcinoma	Circumscribed, not encapsulated; solid, cystic, microcystic, oligocystic, and tubular patterns; eosinophilic to vacuolated secretions; papillary fronds with hobnailed cells; medium cells with vacuolated cytoplasm, vesicular nuclear chromatin and distinct nucleoli **Positive**: S100 protein, mammaglobin, SOX10, MUC4, GCDFP-15 **Negative**: p63, androgen receptor Usually *ETV6*::*NTRK3* fusion			
Cystadenocarcinoma		Rare tumors may show apocrine morphology with hobnailing and decapitation-like secretions	Heterogeneous, predominantly cystic tumor with simple to complex arborizing papillary architecture; infiltrative growth with desmoplasia; tumor-associated lymphoid proliferation frequently seen; usually a low-grade morphology, but larger cuboidal cells may be seen; lacks cytoplasmic golden brown pigment; low proliferation index; absence of myoepithelial cells; secondary changes related to cyst rupture common; extracellular mucin is common Mucinous tumors considered a separate category	Rare tumors may show oncocytically altered cytoplasm
Acinic cell carcinoma	Infiltrative tumor; serous acinar differentiation required with fine to coarse cytoplasmic granules, but multiple cell types can be seen;			

	secretions often prominent; lacks myoepithelial cells **Positive**: DOG1, NR4A3, GATA3 **Negative**: SOX10, S100 protein, mammaglobin			
Salivary duct carcinoma		Intraductal and widely infiltrative, high-grade neoplasm; perineural and lymphovascular invasion common; cribriform, solid and papillary architecture; central comedonecrosis; high proliferation index; often associated with pleomorphic adenoma (chondromyxoid matrix present) **Positive**: androgen receptor, GCDFP-15, often Her-2/neu expressed; rarely mammaglobin **Negative**: SOX10, S100 protein		
Polymorphous adenocarcinoma, cribriform type			Infiltrative neoplasm, comprised of a single-cell population of cells lacking a myoepithelial layer; cribriform, papillary, and glomeruloid patterns; tumor necrosis; increased proliferation index; perineural invasion; lacks large cystic spaces; clear to eosinophilic cytoplasm surrounding pale, vesicular nuclei **Positive**: S100 protein, SOX10, CK-pan, p63 **Negative**: p40, androgen receptor	Rarely, an oncocytic pattern predominates, but generally other cytologic features are present
Oncocytic subtypes of: mucoepidermoid carcinoma, salivary duct carcinoma, myoepithelial carcinoma, epithelial-myoepithelial carcinoma				Predominance of oncocytic appearance; underlying pattern of growth and cytology usually allows for separation; tumors lack circumferential layer of myoepithelial cells; selected and pertinent immunohistochemistry and occasionally, molecular testing, allows for classification (e.g., *CRTC1*::*MAML2* seen in mucoepidermoid carcinoma)

TABLE 4. (*continued*)

Differential Diagnosis	Intercalated Duct-Type	Apocrine Type	Hybrid Type	Oncocytic Type
Metastatic neoplasms: melanoma, squamous cell carcinoma, prostate adenocarcinoma, breast ductal carcinoma		Epithelioid pattern in melanoma may mimic solid-apocrine patterns of IDC; prominent nucleoli and intranuclear cytoplasmic inclusions **Positive**: S100 protein, SOX10, Melan-A, HMB45, PRAME **Negative**: CK-pan, mammaglobin, androgen receptors	Squamous cell carcinoma, breast ductal carcinoma, and prostate adenocarcinoma may show morphologic overlap; keratinization, intercellular bridges, intracytoplasmic mucin vacuoles are not seen in IDC; clinical and imaging history and pertinent immunohistochemistry will aid in separation (e.g., estrogen/progesterone receptors present in breast tumors; NKX3.1 in prostate carcinoma)	

GCDFP-15 indicates gross cystic disease fluid protein-15.

Differential Diagnosis

Several tumors need to be considered in the differential diagnosis (Table 4). There are several patterns of growth, which bring to mind-specific tumors, whereas the cytomorphologic features also bring to mind a broader and sometimes different set of differential considerations. The specific features and tumor category in which they may be seen are highlighted in Table 4 and will not be repeated here. Suffice it to say, cystadenoma (including oncocytic subtype), sclerosing polycystic adenoma, intercalated duct adenoma, and striated duct adenoma are the benign tumors, whereas secretory carcinoma and SDC, along with cystadenocarcinoma, acinic cell carcinoma, and oncocytic patterns seen in other neoplasms, are the most important malignant neoplasms to be considered. No matter what the differential considerations raised, the most significant evaluation must include documentation of myoepithelial cells by IHC, and further to document their presence or absence as part of the evaluation of frankly invasive carcinoma.[6,12,24,31,70,78,87–89] Furthermore, it is significant that there is remarkable overlap between apocrine-type IDC arising in a sclerosing polycystic adenoma and apocrine type IDC; some secretory carcinomas may show significant overlap that requires molecular studies for a more definitive diagnosis; and invasive SDC may be indistinguishable from destructively invasive apocrine type IDC.[37,41,90] Finally, when there is exclusively intralymph node involvement of an IDC, it should not be misdiagnosed as metastatic carcinoma or melanoma.

Treatment and Prognosis

The optimal management of any tumors in this category is surgery, with complete excision with negative margins desirable. In general, a selected neck dissection is not necessary, as lymph node disease is uncommon: 5.5% (n = 10), but enriched by reporting of a series of 10 frankly invasive tumors exclusively.[50] Still, even in patients with metastatic disease, three had evidence of disease: one alive with disease (48 mo) and two dead of disease (median: 19 mo). Overall, in those with follow-up, 93.2% (n = 109) are alive with no evidence of disease (Table 1), <1% (n = 1) are alive with disease, 4.3% (n = 5) are dead without disease, and 1.7% (n = 2) died with disease. Thus, the overwhelming majority behave in an indolent manner, even though 28% of cases demonstrate invasion. There is no specific type that is more likely to result in patient death. Furthermore, patients with incomplete resection initially are more likely to have recurrence. In this setting, especially if *RET* or *ALK* rearrangements are present, *RET* or *ALK* inhibitor therapies may show benefit.[12,35,49,50,91,92]

SUMMARY CONCLUSIONS

With additional research and evaluation of cases, it seems that the category of IDC will become better understood, ultimately leading to a classification that reflects the histologic, immunohistochemical, and molecular findings of the various neoplasms that presently comprise this category. With strict morphologic and immunohistochemical criteria as outline here, better classification will lead to better patient management and outcome.

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