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RESEARCH

High Grade Differentiated Follicular Cell-Derived Thyroid Carcinoma Versus Poorly Differentiated Thyroid Carcinoma: A Clinicopathologic Analysis of 41 Cases

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Abstract

Criteria overlap for separating between malignant follicular epithelial cell-derived thyroid gland neoplasms with high grade features of increased mitoses and tumor necrosis but lacking anaplastic histology. Patterns of growth, nuclear features, tumor necrosis, and various mitotic index cutoffs are suggested, but a reproducible Ki-67-based labeling index has not been established. Forty-one cases diagnosed as poorly differentiated thyroid carcinoma (PDTC) or high grade differentiated follicular cell-derived thyroid carcinoma (HGDFCDTC) were reviewed, with histologic features, mitotic figure counts, and Ki-67 labeling index reviewed on cases within Southern California Permanente Medical Group from 2010 to 2021 to establish any potential outcome differences. There were 17 HGDFCDTC (nine papillary thyroid carcinoma; eight oncocytic follicular thyroid carcinoma), median age 64 years, affecting nine females and eight males. Tumors were large (median, 6.0 cm), usually unifocal ($n=13$), with only one tumor lacking invasion. Tumor necrosis was present in all; median mitotic count was 5/2 mm^2 (median Ki-67 labeling index 8.3%). Three patients had metastatic disease at presentation, with additional metastases in four patients (41.2% developed metastases); 11 were without evidence of disease (median 21.2 months); with the remaining six patients alive ($n=4$) or dead ($n=2$) with metastatic disease (median 25.8 months). Criteria associated with an increased risk of developing metastatic disease: widely invasive tumors; age ≥ 55 years; male; advanced tumor size and stage; extrathyroidal extension; but not increased mitotic rate or higher labeling index. There were 24 PDTC, median age 57.5 years, affecting 13 females and 11 males. Tumors were large (median, 6.9 cm), with 50% part of multifocal disease, with three tumors lacking invasion. Insular/trabecular/solid architecture was seen in all tumors; tumor necrosis was present in 23; and median mitotic count was 6/2 mm^2 (median Ki-67 labeling index 6.9%). Five patients had metastatic disease at presentation, with additional metastases in 3 patients (29.2% developed metastases); 16 were without evidence of disease (median, 48.1 months); with the remaining 8 patients alive ($n=3$) or dead ($n=5$) with metastatic disease (median, 22.4 months). Criteria associated with an increased risk of developing metastatic disease: widely invasive tumors; male; advanced tumor size and stage; extrathyroidal extension; but not increased mitotic rate or higher labeling index. HGDFCDTC shows tumor necrosis, a median Ki-67 labeling index of 8.3%, with a high percentage (41%) of patients developing metastatic disease. Extent of invasion (non-invasive, minimally invasive, angioinvasive, widely invasive) correlates strongly with developing metastatic disease. PDTC presents at a slightly younger age, with large tumors, often in a background of multifocal tumors, with tumor necrosis nearly always seen, a median Ki-67 labeling index of 6.9%, with 29% of patients developing metastatic disease. Separation between groups is meaningful as early metastatic disease is relatively common, but mitotic counts/labeling indices are not different between the groups nor able to potentially risk stratify development of metastatic disease.

Keywords Thyroid neoplasms/therapy · Thyroid neoplasms/pathology · High grade differentiated · Poorly differentiated · Follow-up studies

Introduction

Follicular cell-derived carcinomas include differentiated, poorly differentiated, and undifferentiated (anaplastic) carcinomas [1–24]. Histologic features (patterns of growth,

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presence of papillary thyroid carcinoma [PTC] nuclear features, convoluted nuclei, tumor necrosis, and an increased mitotic index) are applied in classification, although there is overlap between high grade differentiated follicular cell-derived thyroid carcinoma (HGDFCDTC) and poorly differentiated thyroid carcinoma (PDTC). Subjectivity is inherent in all classifications and attempts at using more reproducible findings to meaningfully risk stratify tumors into prognostically distinctive groups is helpful. To date, there has been no large, community practice-based evaluation of clinical and histological features, including Ki-67 immunohistochemistry labeling index, to suggest if meaningful separation between these entities can be achieved and shows distinctive management and outcome differences. This study will present clinical data, histologic findings, Ki-67 labeling index, and patient management consequences in a retrospective review of 41 cases of high grade thyroid follicular cell-derived carcinomas.

Materials and Methods

All patient records with thyroid surgical cases performed from January, 2010 to December, 2021 at the 12 Southern California Permanente Medical Group hospitals diagnosed as "poorly differentiated," "high grade differentiated," "carcinoma with atypical features," or "solid variant of papillary thyroid carcinoma" were reviewed. Histology review was performed with specific attention to the presence of tumor necrosis and mitotic counts, which eliminated eight of the 12 solid subtype of papillary thyroid carcinoma which lacked tumor necrosis and/or increased mitoses. Some of the atypical features included increased mitoses and/or tumor necrosis, and would now be called high grade differentiated follicular cell-derived thyroid carcinomas. The 41 patients included 22 females and 19 males, and included 32 Whites, two Blacks, and seven Asians. All cases except one had preoperative fine needle aspirations. Preoperative molecular pathogenic variant analysis was performed on 18 aspirations. A mass was the reason for the surgery in all patients, although 16 patients had multifocal/bilateral tumors.

Table 1 provides general clinicopathological data for the cohort of patients. Electronic medical records were reviewed. Tumor recurrence was defined as any increase in serum thyroglobulin level (biochemical recurrence) or any evidence of metastatic lesion confirmed by a pathology exam (structural recurrence). This clinical investigation was conducted in accordance with all guidelines of an Internal Review Board authorization (#5968).

A range of 3–51 slides (often with multiple sections per slide) were examined per case, with a median of 11 blocks submitted per case; with a 6 cm median tumor size, an average of 1.8 blocks/cm of tumor were submitted, with the entire periphery of each tumor embedded and histologically reviewed. The data recorded included tumor focality (unifocal, multifocal (same lobe), multicentric (bilateral)); tumor encapsulation (presence or absence); extrathyroidal extension (defined as skeletal strap muscle involvement, or adjacent organs, subcutaneous tissues, prevertebral fascia, or named nerves and/or vessels by imaging findings, intraoperatively by the surgeon, or macroscopically by the gross prosector); capsular invasion (transcapsular penetration); vascular invasion (tumor plugging a vascular channel with smooth-muscle wall within or immediately beyond the tumor capsule; tumor attached to the vessel wall; associated thrombus); lymphatic invasion; architectural pattern of growth (papillary, follicular, solid, trabecular, insular); presence of papillae; tumor necrosis; mitotic rate (mitoses were counted in 2 mm^2 on three different slides and the average recorded (see Table 1); tumor cell anaplasia; cytoplasmic quality (oncocytic/oxyphilic, cleared, amphophilic); number of lymph nodes examined, documenting metastasis and extranodal extension; concurrent/additional tumor size, location and type; nuclear features of papillary thyroid carcinoma: nuclear enlargement, crowding, overlapping, loss of polarity, elongated, ovoid, irregular contours, grooves or folds, intranuclear cytoplasmic inclusions, nuclear chromatin clearing, nuclear margination, nucleoli on nuclear membranes, and even, fine, delicate nuclear chromatin. OFTC was defined as a follicular patterned tumor with > 75% of the neoplastic cells showing abundant oncocytically altered cytoplasm.

Without a universal set of criteria defining various types of invasion for all follicular cell-derived tumors, the following criteria are generally accepted, but with expanded definitions: *non-invasive* (no evidence of capsular, lymphatic or vascular invasion in a tumor with the entire tumor-capsule-parenchymal interface submitted for histologic examination); *minimally invasive* (capsular invasion exclusively, irrespective of foci number); *encapsulated angioinvasive* (capsule may be attenuated or lost in areas; lymphatic and/or vascular invasion, irrespective of foci number; destroyed endothelium, attached tumor to vessel wall, fibrin, and/or thrombus formation); and *widely invasive* (gross extrathyroidal extension into soft tissues; multiple tumor nodules within parenchyma; > 20 foci of each/either capsular, lymphatic, and/or vascular invasion). All cases were classified by the American Joint Committee on Cancer (AJCC) staging 8th edition criteria [25], although original classification was based on earlier AJCC iterations and was updated.

Hematoxylin and eosin-stained slides from all cases were reviewed. The specific tumor type (PTC, including subtypes; oncocytic follicular thyroid carcinoma (OFTC) or follicular thyroid carcinoma (FTC)) was identified, including the particular architectural pattern (solid, follicular, papillary; Fig. 1). Anaplastic features (profound

Table 1 Clinicopathologic findings in non-anaplastic high grade follicular cell-derived carcinomas

Criteria	High grade differentiated follicular cell-derived thyroid carcinoma (HGDFCDTC) ($n=17$)	Poorly differentiated thyroid carcinoma (PDTC) ($n=24$)
Sex: female/male	9/8	13/11
Median age (mean), in years	64 (62)	58 (56)
Females	57 (62)	50 (50)
Males	65 (62)	66 (64)
Number ≥ 55 years of age	11 (64%)	12 (50%)
Tumor size in cm, median (mean)	5.4 (5.8)	6.9 (6.5)
Tumor focality:	13 (76%)	11 (46%)
Unifocal	4 (24%)	13 (54%)
Multifocal (i.e., other tumors present)		
Additional tumor type (when present)		
Papillary thyroid carcinoma (PTC)	4	13
Multicentric (same lobe)	0	3
Bilateral	4	10
Metastatic small cell carcinoma to thyroid gland	n/a	1
Underlying tumor type (for HGDFCDTC)		
Papillary thyroid carcinoma (PTC)	9	n/a
Solid subtype	4	n/a
Classic	3	n/a
Follicular subtype	2	n/a
Oncocytic follicular thyroid carcinoma	8	n/a
Invasion		
Non-invasive	1 (5.8%)	3 (12.5%)
Minimally invasive (capsular invasion only)	1 (5.8%)	3 (12.5%)
Encapsulated angioinvasive (lymphatic and/or vascular invasion)	7 (41.2%)	6 (25%)
Widely invasive (grossly invasive, including extrathyroidal extension; usually significant vascular invasion)	8 (47.2%)	12 (50%)
Capsular invasion present	16 (94.1%)	21 (87.5%)
Lymphatic invasion present	8 (47.1%)	15 (62.5%)
Vascular invasion present	14 (82.4%)	16 (66.7%)
Extrathyroidal extension	4 (24%)	9 (38%)
Positive margin	9 (53%)	9 (38%)
Tumor necrosis present	17 (100%)	23 (96%)
Mitoses per 2 mm^2, median (mean)	5 (6.1)	6 (11)
Ki-67 labeled tumor nuclei per 2 mm^2 (median)	684	620
Cells per 2 mm^2 (median)	8,708	10,277
Ki-67 labeling index per 2 mm^2 (median)	8.3%	6.9%
Lymph node metastases at presentation	2 (12%)	3 (13%)
Distant metastases are presentation	1 (6%)	2 (8%)
Any metastases at presentation	3 (18%)	5 (20.8%)
Additional metastases during follow-up	5 (29%)	3 (12.5%)
Lymph nodes	2 (12%)	2 (8%)
Distant metastases (lung, soft tissue, skull base)	5 (29%)	3 (12.5%)
AJCC8 stage		
Group I	7	10
Group II	7	12
Group III	2	1
Group IVA	1	1
Treatment		

Table 1 (continued)

Criteria	High grade differentiated follicular cell-derived thyroid carcinoma (HGDFCDTC) ($n=17$)	Poorly differentiated thyroid carcinoma (PDTC) ($n=24$)
Surgery only (lobectomy, thyroidectomy, and/or completion thyroidectomy)	4	4
Radioablative iodine	11	18
External beam radiation	3	5
Chemotherapy (for metastatic disease)	4	1[a]
Follow-up (median in months):	17 (35.0)	24 (35.7)
Alive, no evidence of disease	11 (35.0)	15 (49.0)
Alive, with metastatic disease	2 (40.2)	3 (23.5)
Dead, with no evidence of disease	1 (24.8)	1 (4.7)
Dead, with metastatic disease	3 (12.1)	5 (21.3)

[a]Two patients had chemotherapy for pancreatic carcinoma and small cell carcinoma but not the thyroid neoplasms

pleomorphism, marked tumor multinucleation) were absent. Unequivocal tumor necrosis, even if only focal, was defined as neoplastic cell death, with cellular swelling, plasma membrane rupture, inflammation resulting in ghost cell/nuclear outlines, and accumulated nuclear debris (Figs. 1 and 2). Apoptosis (chromatin condensation, nuclear fragmentation, membrane blebbing condensed by cell shrinkage into membrane-bounded bodies) is programmed cell death without inflammation and was for study purposes insufficient for the diagnosis of tumor necrosis. Furthermore, especially in oncocytic cell neoplasms, areas of inadequate or compromised vascularity or induced by fine needle aspiration or needle biopsies resulting in hypoxia and/or nutrient deprivation with consequent degenerative changes were not construed to be genuine tumor necrosis. The number of mitoses/2 mm^2 identified in the highest (hot spot) areas from a whole tumor-section was counted. PDTC was defined by the Turin consensus criteria [13]: malignant neoplasm based on invasion (although subset may lack invasion [11, 26]); solid-trabecular-insular growth (well-defined, elongated nests or ribbons surrounded by thin fibrovascular septa often with open spaces around tumor islands); absence of conventional nuclear features of papillary thyroid carcinoma; along with at least one of the following three criteria: convoluted nuclei, tumor necrosis, and mitoses of $\geq 3/2$ mm^2. Importantly, the nuclei are often raisinoid and hyperchromatic; cytoplasm is usually scant but can be oncocytic; intranuclear cytoplasmic inclusions are absent (Fig. 2). HGDFCDTC is defined as a thyroid follicular

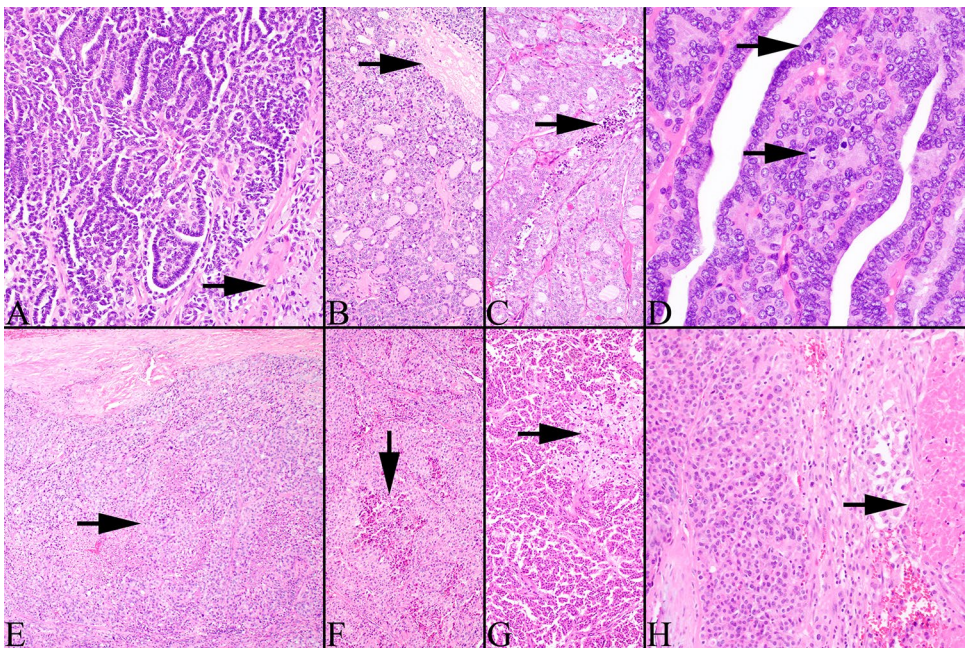

Fig. 1 Differentiated high grade follicular cell-derived carcinoma. **A**–**D** Papillary thyroid carcinoma with high grade features of **A** necrosis (black arrow), **B** focal necrosis (black arrow), **C** central necrosis, and **D** increased mitoses (3 mitoses in single high power field near black arrows). **E**–**H** Oncocytic follicular thyroid carcinoma with high grade features showing **E** central comedonecrosis (black arrow), **F** early apoptosis and necrosis (black arrow), **G** histiocytes adjacent to area of necrosis (black arrow), and **H** comedonecrosis with ghost outlines (black arrows)

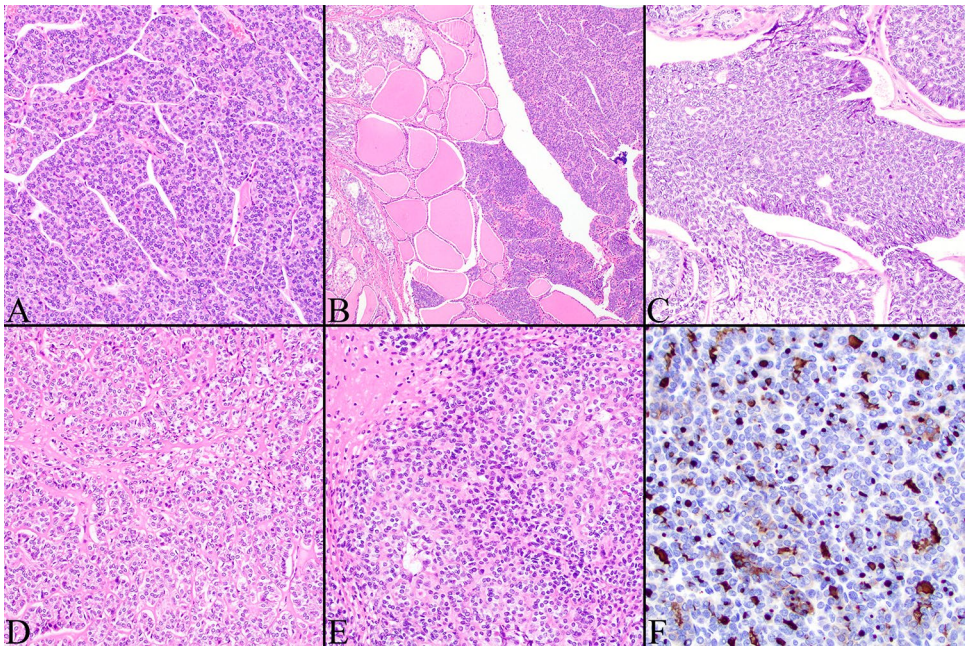

Fig. 2 Poorly differentiated thyroid carcinoma. **A** Insular architecture with cells showing a high nuclear to cytoplasmic ratio, **B** topographically separate papillary carcinoma (left) adjacent to poorly differentiated carcinoma with an insular architecture, **C** convoluted nuclei and a more solid architecture, including increased mitoses, **D** degeneration noted with fibrosis, but no true necrosis, **E** tumor necrosis and cleaved nuclei, and **F** thyroglobulin in a dot-like pattern adjacent to the nuclei

cell-derived carcinoma showing tumor necrosis and/or increased mitoses of $\geq 5/2$ mm^2, retaining the distinctive morphology of the underlying well-differentiated carcinoma category, recognizing that completely encapsulated tumors meeting these other criteria exist.

Immunophenotypic analysis was performed in cases with sufficient suitable material by a standardized method employing 4-µm-thick, formalin fixed, paraffin embedded sections. Analysis was performed on a single representative whole tumor-block section for each primary tumor using Ventana CONFIRM anti-Ki-67 (30–9) rabbit monoclonal primary antibody (Ventana Medical Systems, Inc., Tucson, AZ) using OptiView immunohistochemistry DAB detection on the BenchMark ULTRA advanced staining platform, with epitope retrieval performed using manufacturer guidelines. Standard positive and negative controls were used. As Ki-67 is a nuclear antigen expressed by proliferating cells during late G1 to M phases of the cell cycle, cytoplasmic staining was ignored. Only nuclear staining of neoplastic cells showing a homogenous, opacifying reaction was counted (intensity is considered irrelevant), selecting 2 mm^2 from hot spot areas of particularly prevalent nuclear expression. By choosing 2 mm^2, counting 2000 nuclei was not done. The total number of Ki-67 labeled tumor nuclei identified in 2 mm^2 was tabulated, divided by the total number of tumor nuclei counted to yield a Ki-67 labeling (proliferation) index to one decimal place (Fig. 3). Preanalytical factors such as tissue freezing, Bouin fixation, and overnight delay before fixation were considered exclusionary criteria for further evaluation, and thus, these tissues were not included in the evaluation. Standardized cold ischemia times and length of time fixed in neutral buffered formalin were not specifically recorded, but all cases conformed to general tissue processing standards (fixation in neutral buffered formalin for 4–72 hours before paraffin embedding).

Results

The whole 41 patient cohort contained 22 females and 19 males (Table 1), ranging from 18 to 87 years (median 63 years; average 58.6 years). Patients reported symptoms from 1 to 480 months (median 8 months; average 69 months) in the HGDFCDTC group and 1–355 months (median 6 months; average 46 months) in the PDTC group. Of note, one HGDFCDTC case presented incidentally during imaging evaluation for a different reason, while four PDTC patients had incidental tumors identified. All patients in the HGDFCDTC had preoperative fine needle aspiration (FNA), although with a range of up to five FNAs performed: five Bethesda category II; five category III; four category IV; and three category V. Only five cases had molecular investigation: one *PAX8*::*PPARγ*; one with *ARID1A*, *PIK3R1*, and *RUNX1T1*; one *TERT* and *PTEN* exon 3 mutation; one *TERT* and *NRAS* Q61R mutation; and one with multiple mutations (*CDKN2C*, *DAXX*, *NF1*, *PIK3CA*, *PPP2R1A*, *PTEN*, *RB1*, *p53*). Twenty-three patients in the PDTC group had FNAs performed, with up to five FNAs performed: three category II; six category III; 10 category IV; three category V; and one category VI. Thirteen cases had molecular investigation, including three with no mutations identified; three with *NRAS* p.Q61K; four with multiple mutations: *TERT* and *NRAS* p.Q61R; *TERT*, *NRAS* p.Q61R, and *KAT6B*; *NRAS* p.Q61R and *MUTYH* p.R245C; *NRAS* p.Q61R

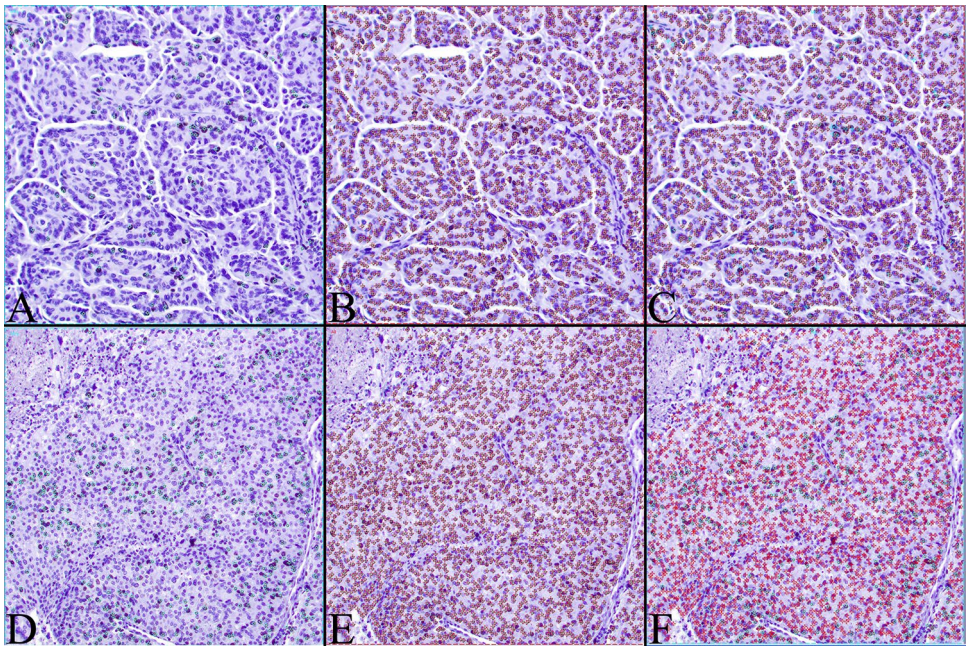

Fig. 3 Manual Ki-67 labeling index determination. Each square represents 8% of a mm^2. Each Ki-67 labeled tumor nucleus was counted (CellSense counting tool), then all tumor nuclei were counted, with a final percentage determined based on the total Ki-67 labeled tumor nuclei over all tumor nuclei counted. **A**–**C** Differentiated high grade thyroid follicular epithelial carcinoma. **A** Blue marks over each Ki-67 labeled tumor nucleus; **B** red marks over all tumor nuclei; and **C** combination of blue and red marks. **D**–**F** Poorly differentiated thyroid carcinoma. **D** Blue marks over each Ki-67 labeled tumor nucleus; **E** red marks over all tumor nuclei; and **F** combination of blue and red marks. Note, tumor necrosis is in the upper left corner of each of the lower panel cases

and *PALB2* p.R170tfs*14; and one each *PTEN* deletion, *WHSC1L1*::*NUTM1*, and *PAX8*::*PPARγ*. No specific comment can be made on the relatively low sensitivity of some of the FNA category classifications, other than many different pathologists interpreted the cases over a broad time range. Of note, one tumor in the HGDFCDTC category and three in the PDTC category lacked capsular, lymphatic, or vascular invasion, but met all other histologic criteria for inclusion, and were thus included as a subset of cases that may lack invasion and still qualify for inclusion in the category [11, 26]. All cases presented with a nodule/mass, although multinodular goiter was noted in six HGDFCDTC and nine PDTC cases. Overall, eight of 41 patients (19.5%) had metastatic disease at presentation (lymph node = 5; lung = 3; bone and mediastinum = 1 each). Using the criteria established above, tumors were separated into the two categories for further evaluation.

Pathologic Features

Macroscopic Findings

The HGDFCDTC group included nine PTCs (four solid; three classic; two follicular subtype) and eight oncocytic FTCs. The PTCs ranged from 3.8 to 13.5 cm (median 6 cm; average 6.6 cm), with well-defined capsules. Five presented as a single tumor and four were part of multifocal/bilateral tumors. The OFTCs ranged from 2.5 to 7 cm (median 4.8 cm; average 4.8 cm), with well-defined capsules. All were identified as single tumors without other neoplasms identified.

The PDTC cases ranged from 1.9 to 11 cm (median 6.9 cm; average 6.5 cm), with well-formed capsules identified. Eleven presented as single tumors, with the remaining 13 identified as part of multifocal/bilateral disease. All of the additional tumors were PTCs, although an additional patient had a metastatic neuroendocrine carcinoma, small cell type to the thyroid gland. Based on these findings, there was no statistically significant difference in size between the tumors, although there was trend to the PDTC being larger. Multifocality was more common with the PDTC category (54 versus 24%).

Microscopic Findings

HGDFCDTC All tumors demonstrated a well-developed fibrous connective tissue capsule with smooth muscle-walled vessels in the fibrosis, supporting interpretation of a true capsule. One tumor was *non-invasive* (a 3.8 cm unifocal solid PTC; alive, no evidence of disease (NED) at 17.4 months), but all of the other tumors showed capsular invasion ($n = 16$), lymphatic invasion ($n = 8$), and/or vascular invasion ($n = 14$).

One tumor was *minimally invasive*, eight were *encapsulated angioinvasive*, and seven were *widely invasive*. Extrathyroidal extension was identified in four tumors (two classic PTC and two OFTCs). Tumor was on the inked margins in nine tumors. Lymph node metastases were identified in two patients at the time of initial presentation. There were seven group I, seven group II, two group III, and one group IVA AJCC8 stage tumors.

Histologically, the classical morphologic features of the underlying tumor type were present for PTC (classic; invasive follicular, and solid subtypes) and OFTC (Fig. 1). One PTC was non-invasive; one was minimally invasive; four were encapsulated angioinvasive; and three were widely invasive. Within the OFTCs, areas of infarction or degeneration due to outgrowing its blood supply or after needle biopsies (FNA or core needle) were carefully examined, with only genuine, tumor comedonecrosis (as previously defined) considered acceptable. Four tumors were encapsulated angioinvasive and four were widely invasive.

While mitoses were counted in 2 mm^2 on three different slides, there were no widely disparate results, and for practical purposes, a single 2 mm^2 region is sufficient, using tumor cellularity as a guide. Mitotic counts ranged from 1 to 14/2 mm^2, with a median of 5 (SD 3.4) and average of 6. The number of cells in 2 mm^2 ranged from 4024 to 11,846, with a median of 8708 (average 8119), with the number of Ki-67 positive nuclei ranging from 278 to 1874, with a median of 684 (average 775), yielding a Ki-67 labeling index from 2.3 to 19.6% with a median of 8.3% (SD 4; average 9.4%).

In the background, four cases had another tumor identified in the same lobe; or contralateral lobe in 3 completion thyroidectomies. They were classic (including microscopic) and follicular subtype. Other thyroid gland disease was noted: multinodular hyperplasia (follicular nodular disease/adenomatoid nodules; $n=9$, 53%), chronic lymphocytic thyroiditis ($n=3$, 18%), and included benign perithyroidal lymph nodes ($n=5$, 29%).

PDTC The tumors demonstrated a well-developed fibrous connective tissue capsule with smooth muscle-walled vessels in the fibrosis, although the capsule was discontinuous and attenuated in areas. Three tumors were *non-invasive* (one with multifocal disease; two with unifocal tumors; all alive with no evidence of disease, median 19.0 months). Twenty-one tumors showed capsular invasion, with lymphatic invasion ($n=15$), and/or vascular invasion ($n=16$). There were three *minimally invasive* tumors; six *encapsulated angioinvasive* tumors; and 12 widely invasive tumors. There was extrathyroidal extension in nine tumors, while tumor was identified on the inked margins in nine tumors (six of these cases showed both features). Lymph node metastases were identified in three patients at the time of initial presentation. Based on these findings, there were 10 group I, 12 group II, one group III, and one group IVA AJCC8 staged tumors.

Histologically, tumor cells were arranged in insular, solid, and trabecular architecture, with follicular structures noted in many areas to confirm follicle-cell derivation (Fig. 2). Drop-like colloid was noted in the center of follicles, as an opacified eosinophilic substance, highlighted by thyroglobulin (Fig. 2), although not a required immunohistochemistry evaluation for the tumor classification. The insular growth had nests surrounded by thin fibrovascular septa, with cleft artifacts between the stroma and neoplastic cells, creating a patulous, open or fenestrated appearance (Fig. 2). Trabeculae were wider ribbons of neoplastic cells. The tumors tended to be quite monotonous, with the neoplastic cells relatively small with a very high nuclear to cytoplasmic ratio (Fig. 2). There was usually scant to almost absent cytoplasm in most of the tumors, without any showing oncocytic cytoplasm. The nuclei appeared raisinoid, with dense, heavy nuclear chromatin, and occasional small nucleoli. Nuclear convolutions, folds, or grooves could be seen (Fig. 2), but the composite nuclear features of PTC were absent. Intranuclear cytoplasmic inclusions were absent. Mucinous, signet-ring, and rhabdoid cells were not identified. These features composed more than 30% of the tumor volume, and in many cases, the only pattern present. Tumor necrosis was identified in 23 tumors. Mitotic counts ranged from 2 to 39/2 mm^2, with a median of 6 (SD 10.6) and average of 11. The number of cells in 2 mm^2 ranged from 4962 to 14,200, with a median of 10,277 (SD 3182; average 9911), with the number of Ki-67 positive nuclei ranging from 26 to 1924, with a median of 620 (SD 734, average 833), yielding a Ki-67 labeling index from 0.3 to 27.2% with a median of 6.9% (SD 7; average 8.4%; Fig. 3).

In the background, three cases had multifocal (same lobe) PTC, while 10 cases had bilateral (contralateral lobe) tumors: eight PTC, one additional PDTC, and one metastatic small cell carcinoma to the thyroid gland. The PTCs were classic ($n=2$), microscopic classic ($n=7$), and follicular subtype with invasion ($n=1$) (more than eight total, as several microscopic PTCs may have been present). Other thyroid gland disease was noted: multinodular hyperplasia (follicular nodular disease/adenomatoid nodules; $n=15$, 63%), chronic lymphocytic thyroiditis ($n=7$, 29%), diffuse hyperplasia ($n=1$, 4%), and included benign perithyroidal lymph nodes ($n=5$, 21%).

Clinical Treatment and Patient Outcome

Patients were managed by surgery only ($n=6$); radioablative iodine in 28; external beam radiation in eight; and chemotherapy in five, with various combinations of the latter therapies in several patients.

Of those with surgery only, all six are without disease, five alive and one dead (median 4.0 months, average 3.7 months), but only followed for a short period. Surgery and radioablative iodine was used in 29 patients, but 6 of these also had other therapies; thus, only 24 patients were managed by just surgery and radioablative iodine: 20 of 24 were with NED (alive = 19; dead = 1; median 34.3 months; average 37.1 months); and four were dead with disease (median 28.0 months; average 26.5 months). Those managed with follow-up radioactive iodine ablation treatment were treated by a range 29–212 μCi ^{131}I (median 153; average 154). External beam radiation was used in eight patients. Chemotherapy was employed in five patients, although chemotherapy was also used to treat a separate pancreatic adenocarcinoma and widely metastatic small cell carcinoma, but not a specific regimen for thyroid cancer.

HGDFCDTC

In the HGDFCDTC group, overall follow-up was a median of 23.9 months (average 27.0 months), with 10 alive with NED (median 19.7 months; average 22.5 months), one dead with NED (24.8 months), four alive with metastatic disease (median 25.8 months; average 37.8 months), and two dead with metastatic disease (median and average 29.4 months). Thus, overall, there were six patients with metastatic disease at last follow-up (median 25.8 months, average 35.0 months) and 11 patients without metastatic disease (median 21.2 months, average 22.7 months); overall 41.2% (7/17) had developed metastatic disease (one patient has no evidence of disease after treatment for lymph node metastases at presentation). Three patients (17.6%) had metastatic disease at presentation, two to lymph nodes and one to lymph nodes and lung: two patients were dead with disease (median and average, 29.4 months) and one was alive with NED (21.2 months).

The overall survival of patients based on invasion is as follows:

a) The one patient with a *non-invasive* tumor was alive with NED at 3.2 months;
b) The one patient with a *minimally invasive* tumor was alive with NED (5.6 months);
c) The seven patients with *encapsulated angioinvasive* tumors: one with lymphatic and capsular invasion was alive with NED (35.6 months); with the remaining six had vascular and capsular invasion: one was dead with metastatic disease (6.8 months); one alive with metastatic disease (27.6 months); and four alive with NED (median 26.6 months; average 31.5 months): 28.6% of patients with *encapsulated angioinvasive* tumors developed metastatic disease;
d) The eight patients with *widely invasive* tumors: four are alive/dead with NED (median 23.0 months; average 20.1 months); the remaining four with metastatic disease: three alive (median 23.9 months; average 41.1 months), and one dead (52.0 months): 50% of patients with *widely invasive* tumors developed metastatic disease.

Four patients were managed by surgery alone: one developed lung metastatic disease 28 months after surgery treated with radioablative iodine at that time, and he is alive with metastatic disease at 27.6 months (he also has metastatic prostate adenocarcinoma being separately managed); the other three are alive with NED (median 3.2 months). One patient had surgery and external beam radiation and is alive with NED at 33.0 months. One patient had surgery without radioablative iodine, but had metastatic lung disease at the time of presentation, treated with chemotherapy, and died with disease 6.8 months after surgery. Eleven patients had surgery followed by immediate radioablative iodine: one patient had metastatic disease at presentation, with subsequent metastatic disease to lymph nodes and lung, with various chemotherapy regimens employed, he died with disease at 52 months; one developed metastatic disease to lymph nodes 79 months after surgery, and is alive with disease at 87.8 months after external bean radiation and additional radioablative iodine; one developed lung metastatic disease 4 months after surgery and received chemotherapy and radioablative iodine and is alive with disease at 11.6 months; one developed metastatic disease to the lungs 16 months after surgery, managed with external bean radiation and chemotherapy and is alive with disease at 23.9 months; the remaining seven patients remain with NED (one died of renal failure; six are alive), median 24.8 months (average 29.6 months).

Overall, six patients were < *55 years* at presentation: one alive with metastatic disease (23.9 months), and the remaining five alive with NED (median 18.3 months, average 24.5 months); 16.6% developed metastatic disease. Eleven were ≥ *55 years* at presentation: three alive with metastatic disease (median 27.7 months; average 42.4 months), two dead with metastatic disease (median and average 29.4 months); and six alive or dead with NED (median 28.8 months; average 21.2 months); 45.6% developed metastatic disease. Older age at presentation seems to influence overall outcome (too few cases for statistical evaluation).

Overall, nine patients were *female*: one died with metastatic disease (6.8 months), and the remaining eight are alive with NED (median 11.9 months, average 14.8 months); 11.1% developed metastatic disease. Eight patients were *male*: three alive with metastatic disease (median 27.7 months; average 42.4 months), two dead with metastatic disease (median and average 29.4 months), and six

alive or dead with NED (median 28.8 months; average 21.2 months); 45.6% developed metastatic disease. Males were more likely to develop metastatic disease.

Tumors were categorized using pT criteria: no pT1a or T1b tumors; three pT2 tumors: one male alive with disease (11.6 months) and two patients alive with NED (median and average 18.1 months); 33% developed metastatic disease. The remaining 14 patients all had pT3a/b tumors: five with metastatic disease (dead = 2; alive = 3; median 27.7 months; average 39.6 months); nine with NED (dead = 1; alive = 8; median 21.2 months; average 23.7 months), although one had metastatic lymph node disease at presentation; 42.9% developed metastatic disease. While this was a trend, size did not seem to influence outcome, as the patient with the smallest tumor died of metastatic disease in 12 months, and the patient with the largest tumor is alive with metastatic disease at 42.5 months.

Overall, seven patients had group I stage: one male is alive with metastatic disease (23.9 months), and the remaining six are alive with NED, although one had lymph node metastasis at presentation (median 19.7 months, average 25.9 months); 28.6% developed metastatic disease. Seven patients had group II stage: one male is alive with metastatic disease (27.6 months) and one is dead with metastatic disease (52.0 months), while the remaining five are with NED (alive = 4; dead = 1; median 24.8 months; average 18.9 months); 28.6% developed metastatic disease. Three patients had group III/IVA stage: two males are alive with metastatic disease (median and average 49.7 months), and one female is dead with metastatic disease (6.8 months); 100% developed metastatic disease.

Four patients had *extrathyroidal extension*: one female was alive without metastatic disease (1.8 months); three with metastatic disease: two alive (median and average 49.7 months), and one dead with disease (52 months); 75% developed metastatic disease.

An attempt was made to risk stratify based on Ki-67 labeling index, using 5% incremental cutoffs (0–4.9%; 5–9.9%; 10–14.9%; 15–19.9%). In the < 5% Ki-67 labeling index, one of three (33%) patients developed metastatic disease; in the 5–9.9% group, four of six (67%) patients developed metastatic disease; in the 10–14.9% group, two of six (33%) patients developed metastatic disease; and in the 15–19.9% group, one of two (50%) patients developed metastatic disease. Thus, no Ki-67 labeling index can meaningfully predict who may develop metastatic disease, although there is a trend to the development of metastatic disease with a higher labeling index.

PDTC

In the PDTC group, overall follow-up was a median of 27.7 months (average 29.5 months); 17 alive without evidence of disease (median 34.0 months; average 34.3 months); one dead without evidence of disease (4.7 months); two alive with metastatic disease (median and average 7.3 months), and four dead with metastatic disease (median 28.0 months; average 26.5 months). Overall, there were six patients with metastatic disease at last follow-up (median 15.5 months; average 20.1 months) and 18 patients without metastatic disease (median 33.4 months, average 32.6 months); overall 29.2% had developed metastatic disease (two patients had no evidence of disease after treatment for lymph node metastases at presentation). Five patients (20.8%) had metastatic disease at presentation, three to lymph nodes, two to lung, and one each to bone and mediastinum. Three patients had metastatic disease at last follow-up (alive = 1; dead = 2; median 4.9 months; average 18.3 months), and two were alive without metastatic disease (median and average, 8.7 months).

The overall survival of patients based on invasion is as follows:

a) The three patients with *non-invasive* tumors were all alive with NED (median 7.0 months; average 20.3 months);
b) The three patients with *minimally invasive* tumors were all were alive with NED (median 47.2 months; average 34.8 months);
c) The six patients with *encapsulated angioinvasive* tumors: one was dead with disease (34.8 months); the remaining five with NED (alive = 4; dead = 1; median 32.8 months; average 26.8 months); 16.7% of patients with encapsulated angioinvasive tumors developed metastatic disease.
d) The 12 patients with *widely invasive* tumors: two alive with disease (median and average 7.3 months); three dead with disease (median 21.3 months; average 23.7 months); and seven alive with NED (median 34.0 months; average 41.1 months); 41.7% of patients with widely invasive tumors developed metastatic disease.

Three patients were managed by surgery alone: all are with NED but only followed for a short duration, with one dead of metastatic small cell carcinoma (4.7 months): median 4.7 months, average 4.2 months. Seventeen patients had surgery followed by immediate radioablative iodine: three patients had metastatic disease at presentation (two patients with lymph node metastases; one with bone and lung metastases); two patients developed metastatic disease to lymph nodes, liver and bone 15 and 19 months after presentation. As a group, 13 were alive with NED (median 41.5 months; average 41.2 months); four were dead with metastatic disease (median 28.0 months; average 26.5 months); 29.4% developed metastatic disease. Three patients had surgery without radioablative iodine, but had external bean radiation ($n = 3$) in addition to chemotherapy ($n = 1$): two are

alive with NED (median and average, 19.6 months), and one is alive with metastatic disease (4.8 months); 67% developed metastatic disease. The remaining patient had surgery, radioablative iodine, and external beam radiation, and is alive with metastatic disease (9.8 months).

Overall, 11 patients were < 55 years at presentation: one alive with metastatic disease (4.8 months), two dead with metastatic disease (median and average 33.2 months), and eight alive with NED (median 24.7 months, average 32.7 months); 36.4% developed metastatic disease. Thirteen were ≥ 55 years at presentation: one alive with metastatic disease (9.8 months), two dead with metastatic disease (median and average 19.8 months); and 10 alive or dead with NED (median 34.5 months; average 32.6 months); 30.8% developed metastatic disease. Age at presentation did not seem to influence overall outcome.

Overall, 13 patients were female: 2 had metastatic disease at presentation; one patient died with metastatic disease (4.9 months), and the remaining 12 are with NED (alive = 11, dead = 1; median 33.4 months, average 32.2 months); 15.4% developed metastatic disease. Eleven patients were male: two were alive with metastatic disease (median and average 7.3 months), three were dead with metastatic disease (median 34.8 months; average 33.7 months), and six alive or dead without metastatic disease (median 36.4 months; average 33.3 months); 54.5% developed metastatic disease. Males were more likely to develop metastatic disease.

Tumors were categorized using pT criteria: one female with a T1b tumor was alive with NED (102.9 months); four pT2 tumors, all with NED (alive = 3; dead = 1; median 22.1 months; average 29.5 months); 0% developed metastatic disease. The remaining 19 patients all had pT3a/b tumors: two alive with metastatic disease (median and average 7.3 months), four dead with metastatic disease (median 28.0 months; average 26.5 months), and 13 alive with NED (median 34.0 months; average 28.1 months), although two had metastatic lymph node disease at presentation; 42.1% developed metastatic disease. Advanced size increased the risk of developing metastatic disease.

Overall, 10 patients had group I stage: one male is dead with metastatic disease (21.3 months), and the remaining nine are with NED, although one had lymph node metastasis at presentation (median 16.5 months, average 29.5 months); 20% developed metastatic disease. Twelve patients had group II stage: one male is alive with metastatic disease (4.8 months), three are dead with metastatic disease (median 34.8 months; average 28.2 months), while the remaining eight are alive with NED (median 42.5 months; average 35.9 months); 41.7% developed metastatic disease. Two patients had group III/IVA stage: one male is alive with metastatic disease (9.8 months), and one female is alive with NED (34.0 months); 50% developed metastatic disease. Advanced stage is associated with a higher risk of developing metastatic disease.

Nine patients had extrathyroidal extension: four with metastatic disease at last follow-up (alive = 2; dead = 2; median 7.3 months; average 10.2 months); five are alive with NED (median 34.0 months; average 44.7 months); 67% developed metastatic disease.

An attempt was made to risk stratify based on Ki-67 labeling index, using 5% incremental cutoffs (0–4.9%; 5–9.9%; 10–14.9%; 15–19.9%). In the < 5% Ki-67 labeling index, two of seven (29%) patients developed metastatic disease; in the 5–9.9% group, three of 10 (33%) patients developed metastatic disease; in the 10–14.9% group, one of three (33%) patients developed metastatic disease; and in the 15–19.9% group, two of four (50%) patients developed metastatic disease. Thus, no Ki-67 labeling index can meaningfully predict who may develop metastatic disease, although there is a trend toward development of metastatic disease with a higher labeling index.

Discussion

Follicular cell-derived carcinomas (follicular differentiation at the histological and/or immunohistochemical level) encompass a wide variety of different tumor types, with the two end point categories (differentiated and undifferentiated/anaplastic) generally easily recognized. Generally accepted criteria have been proposed and accepted for PDTC [13]. However, high grade differentiated follicular cell-derived carcinomas have only recently been proposed as a category based on tumor necrosis and/or increased mitoses of ≥ 5/2 mm^2 in a follicular cell-derived tumor lacking anaplastic features [3, 8, 10, 11, 14, 22, 23, 26–28]. Morphologic overlap can be seen between these two different high grade categories, including patterns of growth, cytomorphology, tumor necrosis, and increased mitoses, although the latter has a different cutoff between 3 and 5 mitoses/2 mm^2 (data extrapolated from 10 high power fields) for PDTC and HGDFCDTC, respectively.

These tumors are more likely to be seen in older patients (median overall 63 years), but without a sex predilection in this series [5, 6, 8]. Symptoms were usually present for less than 1 year, with incidentally identified tumors found in 5 patients overall. Nearly all patients had FNA investigation prior to surgery, but a significant proportion were interpreted as category II or III, an important note of caution about interpretation of FNA results in the setting of potentially large clinical masses. Multifocality was more frequent in PDTC (54%) than in HGDFCDTC patients (24%).

It is important to note that four patients in this series met the histologic criteria of the tumor categories, but had non-invasive tumors: one HGDFCDTC and three PDTCs. These patients have not been followed for a sufficient length of time as yet, although the one patient followed for 52.1 months

shows no evidence of metastatic disease or recurrence. Thus, it is important to recognize that either category has a small subset of non-invasive tumors that seem to have an indolent biologic behavior even though tumor necrosis and/or increased mitoses are identified [11, 26]. This is clearly a controversial area, but it is the author's bias to keep these cases in the carcinoma category at present, until a longer follow-up duration without any adverse events may suggest moving the completely encapsulated tumors to a lower risk category for classification purposes. Extrathyroidal extension (22% and 37.5%) and positive margin status (50% and 37.5%) were noted in both categories of HGDFCDTC and PDTC, respectively.

This study has reinforced the histological differences of the underlying tumor category, recognizing the convoluted nuclei and insular architecture may still be a challenge when distinguishing solid subtype of PTC from PDTC, but solid subtype PTC does not have tumor necrosis and/or increased mitoses. OFTC may be especially challenging when necrosis or degeneration is being evaluated, as degeneration is a common development in this tumor category [8, 9, 16]. Still, identifying cellular swelling, cell membrane rupture, ghost cell/nuclear outlines with associated nuclear debris and inflammation are reproducible histological criteria to support unequivocal tumor necrosis. While exceptions exist, 97.6% of tumors in this series had tumor necrosis, while 15 (36.6%) tumors had mitoses of $< 5/2$ mm^2 and 10 (24.4%) had a Ki-67 labeling index of $< 5\%$, suggesting that identification of tumor necrosis is a much more reliable and reproducible histologic feature in high grade thyroid follicular cell-derived carcinomas than an elevated mitotic count/labeling index [5, 6, 8, 10, 16]. As such, it must be emphasized that careful evaluation of all thyroid gland follicular cell-derived neoplasms is critical to accurate classification. It is significant that any tumor necrosis, no matter how limited or small in extent, qualifies for the feature and there is no size or volume criterion for this feature [8, 9, 14, 16]. Therefore, by extension, the more of the tumor evaluated the more likely one is to feel confident in its inclusion/exclusion, and thus classifying the tumor correctly [5, 8, 10]. Clearly, either feature of tumor necrosis or increased mitoses was used to classify HGDFCDTC, but all cases in this series had tumor necrosis, and thus would have qualified for the category no matter the mitotic count/proliferation index. Others have suggested that Ki-67 labeling index of $\geq 4\%$ or $\geq 10\%$ was an independent prognostic factor [6, 10], although not achieved in this study: 42.9% of patients developed metastatic disease with a Ki-67 labeling index of $< 4\%$ versus 35.3% with $\geq 4\%$ labeling index. While necrosis and increased mitoses are not interchangeable with only one required, it seems that a specific cutoff or Ki-67 labeling index is not as significant as tumor necrosis. Furthermore, the median Ki-67 labeling index of 6.9 and 8.3% (range of 0–27% including both categories) in PDTC and HGDFCDTC, respectively, is lower than has been previously reported [6, 8, 10], and stratification in various risk categories based on Ki-67 labeling was not reproducible in this series, as suggested by others [8].

Tumor necrosis and increased mitoses (counted or Ki-67 labeling index) may be seen in both high grade tumor categories, with only one needed in either tumor category [8, 13, 16]. In this series, only one case had a mitotic count of $< 3/2$ mm^2, but had necrosis in the HGDFCDTC group, while two cases had a mitotic count of $< 3/2$ mm^2 in the PDTC group, but also had necrosis. While the outcomes for well differentiated follicular cell-derived carcinomas with 4 mitoses/2 mm^2 and without necrosis have not been specifically evaluated (this category is currently undefined)[14, 29], and so the arbitrary cutoff of 5 mitoses has not been evaluated specifically by sequential increases in mitoses/2 mm^2 when compared to outcome. However, based on the findings in this cohort, there is no difference in those tumors with 4 mitoses/2 mm^2, because they all had concurrent tumor necrosis. Perhaps to harmonize criteria a little more effectively, it may be prudent to use the same mitotic count criterion of $\geq 3/2$ mm^2 for classification of both tumor types rather than $\geq 5/2$ mm^2 for the HGDFCDTC group [10, 16]. Still, further evaluation of a cohort of differentiated follicular cell-derived carcinomas with 4 mitoses/2 mm^2 without tumor necrosis could be evaluated and their outcome compared to this cohort to make a more definitive recommendation. No matter, it does not seem that a Ki-67 proliferation index adds any additional prognostic value in these tumors at this point. There is a correlation of the individual case mitotic rate and Ki-67 proliferation index, but when evaluated as a group, no specific Ki-67 labeling index predicts metastatic disease, although there was a trend to higher Ki-67 proliferation indices suggesting metastatic disease development.

High grade tumors, whether HGDFCDTC (18%) or PDTC (21%), have similar rates of initial metastases at presentation, and slightly different rates of developing later metastases although in a relatively short interval from initial presentation. There was no difference in the rate of initial lymph node metastases between the groups (11.7% for HGDFCDTC versus 12.5% for PDTC), a finding that is different from other authors [3, 5]. Overall, 41.2% of HGDFCDTC group and 29.2% of PDTC developed metastases at any time in their disease course. These initial metastatic rates are similar to previously published reports of about 25% [9]. Furthermore, distant metastases were seen in 35.3% (6/17) of the HGDFCDTC group and 20.8% (5/24) of the PDTC group at any point in their follow-up, lower than the rates of up to 83% reported in the literature [5, 9, 14], but supporting a higher rate of metastases in the HGDFCDTC group as a whole.

It seems in this group of patients, the histology features are useful in confirming a follicular cell-derived neoplasm that is not anaplastic, but that it is the tumor necrosis and/or increased mitoses that is more significant in predicting which cases may develop metastatic disease, rather than the tumor subtype [16]. As the extent of invasion increases, so does the risk of developing metastatic disease, as would be predicted. In both groups, the non-invasive tumors and the minimally invasive tumors showed that all patients were alive with NED at last follow-up. Within the encapsulated angioinvasive category, 28.6% of patients with HGDFCDTCs developed metastatic disease compared to 16.7% with PDTCs. This was significantly higher in the widely invasive tumor category, with 50% of patients with HGDFCDTCs developing metastatic disease and 41.7% with PDTCs. Thus, angioinvasive and widely invasive tumors are more likely to show metastatic disease compared to non-invasive or minimally invasive tumors, no matter which category the tumor was placed into [3, 5, 9, 10, 14, 22, 26]. Male patients also had a higher risk of developing metastatic disease than females, although this finding is not reported by some authors [6, 10, 12]. Advanced tumor size and higher tumor stage also was more likely to be associated with metastatic disease development overall [3, 10, 14]. However, there was no difference in median pT category between HGDFCDTC and PDTC [12], as suggested by others [3]. Extrathyroidal extension was associated with a higher risk of developing metastatic disease [14, 22], although it is of interest that it was not a common finding (HGDFCDTC 23.5%; PDTC 37.5%), as has been suggested by other authors up to 70% [3, 22]. Age of $\geq$ 55 years also seemed to be associated with developing metastatic disease, although only a trend in the PDTC category in this group [6, 12, 16]. Still, these findings are similar to those of other authors who have identified similar results [6, 10].

The molecular findings in this series are similar to those previously reported for the various tumor types, with driver mutations of the underlying carcinoma type for the differentiated follicular derived tumors including *RAS*, *BRAF*, *PIK3CA*, *PPARγ*, *PTEN, CDKN2C*, *ARID1A*, and *PIK3R1* genes, with *TERT* promoter mutations recognized as a later development [26, 30]. Tumors in this series was not evaluated specifically or uniquely for these mutations and so additional information is not herein reported [26, 30].

Conclusion

The high grade follicular cell-derived carcinoma group can be meaningfully separated into HGDFCDTC and PDTC categories based on current criteria, recognizing some differences in the clinical presentation between the groups. Tumor necrosis seems to be the criterion common to both categories. Extent of invasion (non-invasive, minimally invasive, angioinvasive, widely invasive) correlates strongly with developing metastatic disease. While additional evaluation of selected follicular cell-derived carcinomas with 4 and 5 mitoses/2 mm^2 without necrosis would be required, it may be practical to use $\geq$ 3 mitoses/2 mm^2 as the criterion for both tumor categories, while keeping the remaining criteria for PDTC unchanged. The Ki-67 labeling index does not independent of the mitotic count yield any added prognostic value.

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Availability of Data and Material Availability of data and material is possible upon reasonable request, deidentified for maintenance of anonymity and compliance with IRB approval.

Code Availability Not applicable. Presented as abstract #5, Poster Board #22, at the Los Angeles, CA, 109th United States and Canadian Academy of Pathology Annual meeting, March 22, 2022, morning Endocrine Pathology session.

Declarations

Ethics Approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional Review Board of Southern California Permanente Medical Group, IRB#5968.

Consent to Participate Consent to participate was waived by the IRB due to the retrospective nature of the work without therapeutic alterations.

Consent for Publication Consent for publication was obtained from all individual participants for whom identifying information is uniquely included in this manuscript.

Conflict of Interest The author declares no competing interests.

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