Ann Surg Oncol (2023) 30:4761–4770
https://doi.org/10.1245/s10434-023-13589-y

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – ENDOCRINE TUMORS

Diffuse Sclerosing Papillary Thyroid Carcinoma: Clinicopathological Characteristics and Prognostic Implications Compared with Classic and Tall Cell Papillary Thyroid Cancer

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ABSTRACT

Background. The clinical behaviour and oncologic outcome of diffuse sclerosing papillary thyroid carcinoma (DS-PTC) is poorly understood. The objectives of this study were to compare the clinicopathological characteristics and oncological outcomes of DS-PTC to classic PTC (cPTC) and tall cell PTC (TC-PTC).

Methods. After institutional review board approval, 86 DS-PTC, 2,080 cPTC, and 701 TC-PTC patients treated at MSKCC between 1986 and 2021 were identified. Clinicopathological characteristics were compared by using chi-square test. Kaplan-Meier and log rank were used to compare recurrence-free survival (RFS), disease-specific survival (DSS), and overall survival (OS). DS-PTC patients were propensity matched to cPTC and TC-PTC patients for further comparison.

Results. DS-PTC patients were younger with more advanced disease than cPTC and TC-PTC ($p < 0.05$). Lymphovascular invasion (LVI), extranodal extension, and positive margins were more common in DS-PTC ($p < 0.02$). Propensity matching confirmed more aggressive histopathological features in DS-PTC. The median number of metastatic lymph nodes was significantly greater and DS-PTC metastases were RAI avid. DS-PTC 5-year RFS was 50.4% compared with 92.4% in cPTC and 88.4% in TC-PTC ($p < 0.001$). Multivariate analysis confirmed DS-PTC as an independent prognostic factor of recurrence. Ten-year DSS for DS-PTC was 100% compared with 97.1% in cPTC and 91.1% in TC-PTC. Differentiated high-grade, thyroid carcinoma DS had more advanced T-stage and worse 5-year RFS than DS-PTC.

Conclusions. DS-PTC presents with more advanced clinicopathological features than cPTC and TC-PTC. Large-volume nodal metastases and LVI are characteristic features. Almost half of patients develop recurrence despite aggressive initial management. Despite this, with successful salvage surgery DSS is excellent.

Papillary thyroid carcinoma (PTC) comprises 80% of thyroid cancers and typically has favourable recurrence and survival outcomes, with a 10-year disease-specific survival (DSS) of 98%.[1] Certain PTC subtypes that display more aggressive pathological and clinical behaviour are categorized as intermediate risk by the American Thyroid Association, including diffuse sclerosing, tall cell, columnar cell, solid, and hobnail subtypes.[2] Diffuse sclerosing papillary thyroid carcinoma (DS-PTC) is a rare subtype of PTC, first described by Vickery et al in 1985.[3] The reported incidence is 2–8% of PTC cases.[4] DS-PTC is characterized by diffuse involvement of one lobe or the entire thyroid gland with extensive lymphatic permeation, fibrosis, numerous

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First Received: 7 February 2023
Accepted: 13 March 2023
Published online: 8 May 2023

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psammoma bodies, squamous metaplasia, and associated chronic lymphocytic thyroiditis.[5,6]

DS-PTC occurs mostly in the second or third decades of life.[4,7–10] It is considered to carry a greater risk of extrathyroidal extension (ETE), lymphovascular invasion (LVI), metastases and recurrence in comparison to classic PTC (cPTC).[11] There is lack of definitive data in the literature regarding the prognostic significance of DS-PTC.[6] The American Thyroid Association reports a 93%, 10-year disease-specific survival in DS-PTC,[2] but it is unclear whether prognosis is equivalent or inferior to cPTC.[12–14] No large, single-center studies compare clinical and pathological data and oncological outcomes of DS-PTC to other PTC subtypes in the literature. Whether treatment regimens for surgery with or without adjuvant radioactive iodine should be modified in DS-PTC is unclear.

Tall cell (TC) PTC is the most common aggressive PTC subtype,[15] with a poorer distant recurrence-free survival and disease-specific survival (DSS) than cPTC.[16] Previous comparisons between TC-PTC and DS-PTC have not included histopathological features.[17]

The most current World Health Organisation (WHO) Classification of Thyroid Tumors (2022) defined differentiated high-grade thyroid carcinoma (DHGTC) as tumors with intermediate prognosis between well and undifferentiated (anaplastic) carcinomas.[18] These tumors retain the cytoarchitectural features of well differentiated thyroid carcinoma but harbor high mitotic count and tumor necrosis. Due to its rarity, no prior analysis has compared DHGTC, DS histotype (DHGTC-DS) to DS-PTC without tumor necrosis or marked mitotic count.

Incomplete knowledge of DS-PTC can lead to suboptimal management or inappropriate counselling of patients, so it is essential to accurately characterize this subtype. The objectives of this study were therefore to provide comprehensive clinical and histopathological characterization of DS-PTC in comparison to cPTC and TC-PTC using a large clinical and pathological dataset to better understand the patterns of presentation, treatment response, and oncologic outcomes.

MATERIALS AND METHODS

Patient Selection

Institutional review board (IRB) approval and waiver of informed consent was obtained from Memorial Sloan Kettering Cancer Center (IRB Number: 16–160). The research was completed in accordance with the Declaration of Helsinki as revised in 2013. Retrospective review of a prospectively maintained database of 6260 patients undergoing surgery for thyroid malignancy between 1986 and 2015 at Memorial Sloan Kettering Cancer Center was performed. For our comparison of PTC subtypes, a total of 2080 cPTC, 701 TC-PTC, and 46 DS-PTC patients were identified from this database for inclusion. To increase the cohort, we also identified DS-PTC patients who had surgery from 2015 to 2021 and those who had initial surgery at an outside institution from pathology department records. All patients, including those who underwent surgery at an outside institution, had detailed histopathology review performed at our institution by a head and neck pathologist. Following exclusion of patients with insufficient clinical data, a total of 86 DS-PTC patients were included in the study population.

Tumor Definitions

Diffuse Sclerosing PTC

DS-PTC was confirmed by diffuse involvement of one or both lobes, marked tumor fibrosis, extensive lymphocytic infiltration, abundant psammoma bodies, squamous metaplasia, and clusters of tumor cells in cleft-like spaces consistent with lymphatic vessels (Fig. 1). A subset of DS-PTC cases were subclassified according to the WHO 2022 classification of endocrine tumors as DHGTC-DS if they harbored tumor necrosis and/or marked mitotic count (≥5 mitoses/2 mm^2 equivalent to ten high-power fields, 400x) in most microscopes.[18]

Classic PTC

A tumor was classified as cPTC if it had >1% papillary formations and was composed of cells showing the characteristic nuclear features of papillary carcinoma (irregular enlarged clear nuclei with grooves and pseudo-inclusions). Tumors were required to contain <30% tall cells and lack tumor necrosis or marked mitotic count (≥5 mitoses/2 mm^2).

Tall Cell PTC

A tumor was classified as TC-PTC if it contained 30% or more tall cells without tumor necrosis or marked mitotic count (≥5 mitoses/2 mm^2). Tall cells were defined as cells with height at least twice their width and having an eosinophilic cytoplasm with a low nuclear-cytoplasmic ratio. Nuclear features were characteristic of PTC.

Data Collection

Data were collected regarding patient clinical (sex, age), pathological (TNM stage, lymphatic and vascular invasion, ETE, surgical margin, multifocality, mitotic count, microscopic extranodal extension (ENE), tumor encapsulation, number of nodal metastases), and treatment (surgical procedure, adjuvant therapy, radioactive iodine) characteristics. TNM was defined according to the 8th Edition of the American Joint Committee on Cancer (AJCC) staging of thyroid carcinomas.[19]

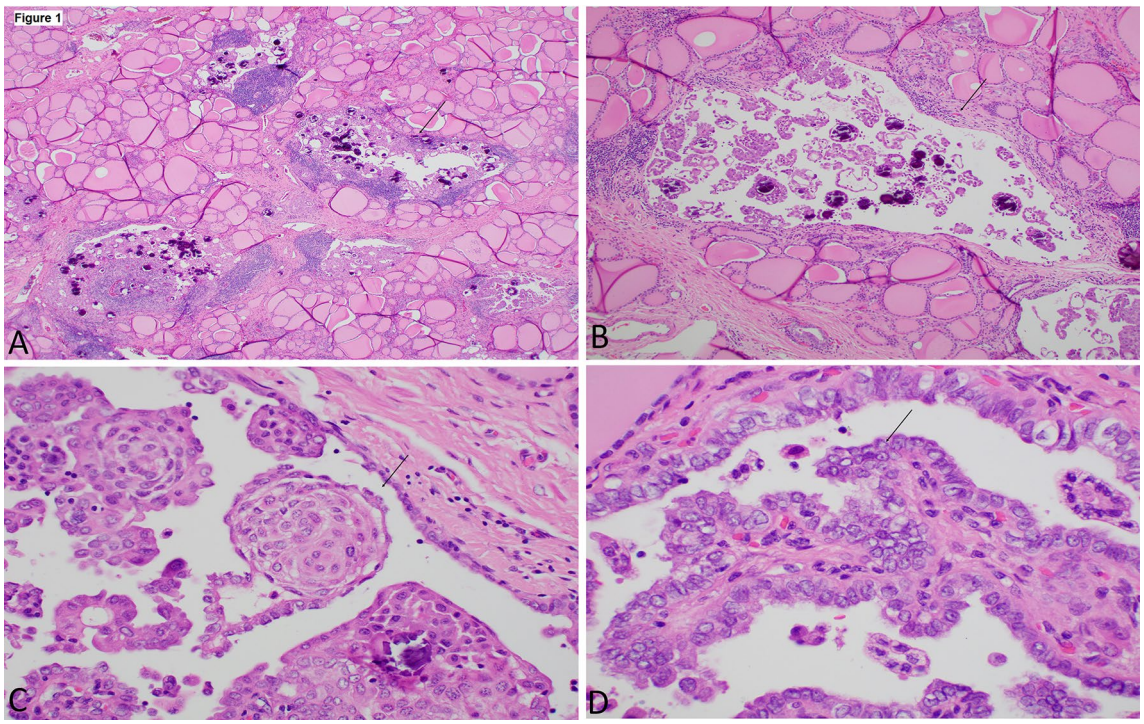

FIG. 1 Photomicrographs of a diffuse sclerosing papillary thyroid carcinoma. **A** Diffuse thyroid involvement by tumor (arrow) with chronic inflammation, fibrosis, and abundant psammoma bodies (40X). **B** Papillary tumor in a cleft like space (arrow) consistent with lymphatic (100X). **C** Squamous metaplasia is typically seen (arrow) (400x). **D** Nuclear features of papillary carcinoma in the form of clear, irregular, overlapping nuclei (arrow) (600x)

Statistical Analysis

Oncological outcomes included OS, DSS, and recurrence free survival (RFS). Local, regional, and distant structural recurrence events were recorded. The OS, DSS, and RFS were calculated by using the Kaplan-Meier method. Differences in survival were assessed by using the log-rank test. Unadjusted and adjusted hazard ratios (HR) were calculated by using the Cox proportional hazards regression model. Factors found to be significant in univariable analysis were included in multivariable analysis. The follow-up interval was calculated in months from the date of initial curative surgery to death or last known status. All statistical analyses were completed using R version 4.2.0 (R Core Team, 2022). To select which DS-PTC, cPTC, and TC-PTC patients to include in propensity matching, we selected age, sex, T, N, and M stage as our propensity score-matching criteria to control for possible confounders. R package "MatchIt" and "Nearest Neighbor Matching" were used at a 1:1 ratio.[20] Greedy nearest-neighbor matching was used, where each treated unit is sequentially matched with k-nearest control units (*k = 1)* with the closest propensity score.

RESULTS

Clinicopathologic Features of DS-PTC Compared with cPTC and TC-PTC

Table 1 compares the clinicopathologic features of DS-PTC to cPTC and TC-PTC. Patients with DS-PTC were younger on average than both cPTC and TC-PTC ($p < 0.001$), with median age of 24, 44, and 50 years, respectively. The histogram in Supplementary Fig. S1 shows that DS-PTC predominantly presents younger than age 25 years. There was no difference in DS-PTC tumor and pathologic characteristics when comparing patients younger than age 55 years (N = 78) with patients older than age 55 years (N = 8) ($p > 0.05$). There was no significant difference in recurrence-free survival between the two age groups ($p = 0.59$).

DS-PTC patients were more likely to present with T2 or T3 disease compared with cPTC and TC-PTC patients ($p < 0.001$). Those with TC-PTC were more likely to present with T4 disease (3.6% DS-PTC; 3.9% cPTC; 12% TC-PTC). Gross ETE also was more common in TC-PTC than DS-PTC (24% vs. 10%; $p = 0.019$). DS-PTC patients were more likely to have positive margins (30% DS-PTC;

TABLE 1 Patient, histopathology and treatment characteristics for diffuse sclerosing PTC, classical ptc and tall cell PTC

Variable	Diffuse sclerosing PTC (n = 86)[1]	%[1]	Classical PTC (n = 2,080)[1]	%[1]	*p* value[2]	Tall cell PTC (n=701)[1]	%[1]	*p* value[2]
Age	24 (18,37)	NA	44 (24,55)	NA	< 0.001*	50 (39,59)	NA	< 0.001*
Sex								
Male	22	26%	627	30%	0.4	200	29%	0.6
Female	64	74%	1453	70%		501	71%	
pT stage								
T1	36	43%	1452	70%	< 0.001*	451	64%	< 0.001*
T2	27	32%	395	19%		87	12%	
T3	18	21%	151	7.3%		80	11%	
T4	3	3.6%	81	3.9%		83	12%	
pN stage								
N0	4	4.7%	1166	56%	< 0.001*	335	48%	< 0.001*
N1a	16	19%	507	24%		229	33%	
N1b	66	77%	406	20%		137	20%	
M stage								
M0	81	94%	2055	99%	0.006*	687	98%	0.047*
M1	5	5.8%	25	1.2%		14	2.0%	
Gross ETE								
No	52	90%	1829	88%	0.7	534	76%	0.019*
Yes	6	10%	251	12%		167	24%	
Microscopic ETE								
No	25	29%	1307	63%	< 0.001*	238	34%	0.4
Yes	61	71%	773	37%		463	66%	
Margin								
Negative	60	70%	1813	88%	< 0.001*	563	81%	0.017*
Positive	26	30%	245	12%		134	19%	
Multifocality								
No	0	0%	828	40%	< 0.001*	266	38%	< 0.001*
Yes	86	100%	1240	60%		430	62%	
LVI								
No	0	0%	1722	84%	< 0.001*	576	83%	< 0.001*
Yes	86	100%	321	16%		119	17%	
ENE								
No	46	58%	1701	87%	< 0.001*	570	83%	< 0.001*
Yes	33	42%	261	13%		106	17%	
Encapsulation[3]								
No	70	89%	688	34%	< 0.001*	399	60%	< 0.001*
Yes	9	11%	1320	66%		269	40%	
Surgery performed								
Total thyroidectomy	80	93%	1815	87%	0.11	632	90%	0.4
Less than total	6	7%	265	13%		69	10%	
Neck dissection								
Not performed	13	15%	1380	66%	< 0.001*	468	67%	< 0.001*
Performed	73	85%	700	34%		233	33%	
Central only	19	22%	294	14%		91	13%	
Lateral only	4	5%	109	5%		31	4%	
Central and lateral	50	58%	297	14%		111	16%	
RAI treatment								
Yes	79	93%	885	42%	< 0.001*	382	55%	< 0.001*
No	6	7%	1195	58%		319	45%	

[1]Median (IQR); n (%)

[2]Kruskal-Wallis rank-sum test; Pearson's chi-squared test

[3]Encapsulation refers to the main tumor nodule.

Table 1 (continued)

Missing values excluded from count. Percents rounded. *Denotes significant *p* values

LVI lymphovascular invasion; *ENE* extranodal extension; *ETE* extrathyroidal extension

12% cPTC; 19% TC-PTC; $p < 0.005$). Multifocality was seen in 100% of DS-PTC, because by definition they diffusely involve one or both thyroid lobes, significantly more than cPTC (60%) and TC-PTC (62%) ($p < 0.001$). Significantly more tumor encapsulation was seen in cPTC and TC-PTC (11% DS-PTC; 66% cPTC; 40% TC-PTC; $p < 0.001$). Encapsulation in DS-PTC refers to the presence of capsule in the main tumor nodule.

N1b disease occurred in 77% of DS-PTC patients compared with 20% in TC-PTC and cPTC ($p < 0.001$). DS-PTC patients were more likely to have 20 or more cervical nodes positive for metastatic disease compared with cPTC and TC-PTC (33.7% (29/86) DS-PTC, compared with 3.4% (70/2080) of cPTC and 3.7% (26/701) of TC-PTC patients). A finding of microscopic ENE was more likely in DS-PTC (42% DS-PTC; 13% cPTC; 17% TC-PTC; $p < 0.001$), and 100% of DS-PTC tumors demonstrated lymphovascular invasion (LVI) compared with 15% of cPTC and 17% of TC-PTC ($p < 0.001$); 8.7% (6/69) of DS-PTC tumors had blood vessel invasion. There was no significant difference in regional or distant recurrence for DS-PTC with or without blood vessel invasion ($p = 0.89$ and 0.6). Distant metastases were present at diagnosis in 5.8% of DS-PTC compared with 1.2% of cPTC and 2% of TC-PTC ($p < 0.05$). All metastases on presentation in DS-PTC patients were pulmonary; 80% (4/5) of these patients with pulmonary metastases were younger than age 18 years (median age 17.07 years; range 6.88–29.52 years).

Treatment Characteristics

Table 1 shows the treatment of DS-PTC, cPTC, and TC-PTC; 93% of DS-PTC, 87% of cPTC, and 90% of TC-PTC underwent total thyroidectomy ($p > 0.05$). The percentage of patients undergoing therapeutic neck dissection was significantly higher in DS-PTC (85%) than TC-PTC (33%) and cPTC (34%) ($p < 0.001$). Most neck dissections in DS-PTC involved both the central and lateral compartments. Postoperative radioactive iodine (RAI) was used more frequently in DS-PTC (93%) patients compared with cPTC (42%) and TC-PTC (55%) ($p < 0.001$).

Survival and Recurrence Outcomes

The median follow-up for DS-PTC was 53 (range 1–247) months. The Kaplan-Meier plot in Fig. 2A illustrates the significantly increased risk of recurrence in DS-PTC patients compared with cPTC and TC-PTC ($p < 0.0001$). Patients with DS-PTC had a poorer 5-year, recurrence-free survival (RFS) compared with patients with cPTC and TC-PTC (50.4% 5-year RFS for DS-PTC; 92.4% cPTC; 88.4% TC-PTC). In DSPTC, the median time to locoregional recurrence was 36 months (interquartile range [IQR] 46 months); 82% (27/33) of patients with regional recurrence had recurrence in a neck level that had been dissected at initial surgery. These patients had a median number of 22 metastatic lymph nodes and 62.9% had ENE. Univariable analysis

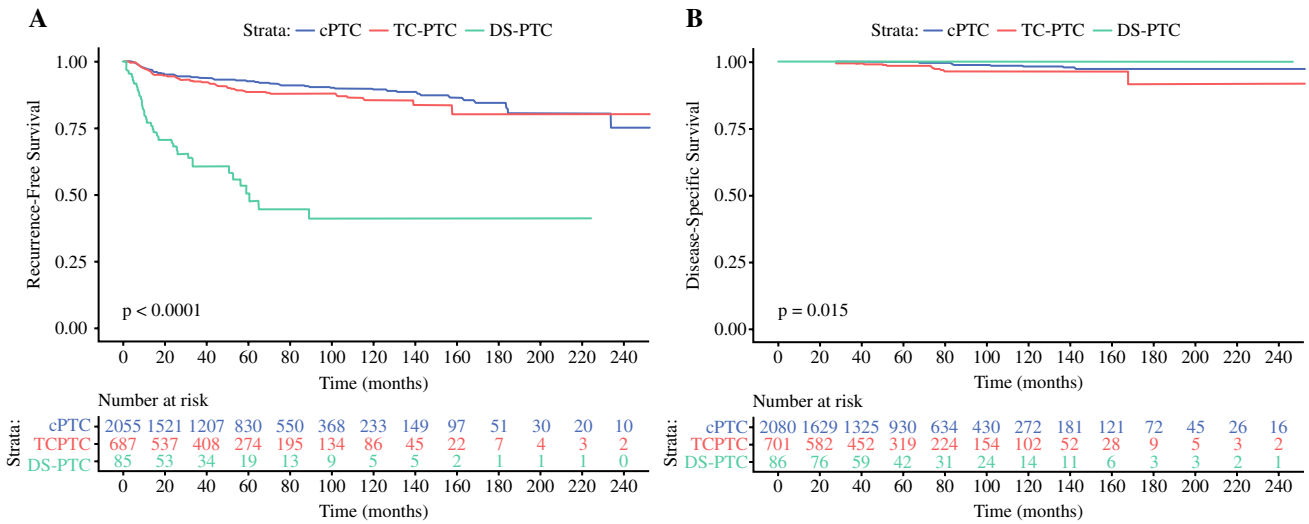

FIG. 2 Kaplan-Meier plot of recurrence-free survival **A** and disease-specific survival **B** stratified by histology

showed ENE (hazard ratio [HR] 2.63, 95% confidence interval [CI] 1.24-5.57, $p = 0.012$) and number of positive lymph nodes as a continuous variable (HR 1.03, 1.01–1.05, $p = 0.005$) to be risk factors for locoregional recurrence in DSPTC patients (n = 86). Number of 95% CI positive lymph nodes was an independent risk factor for locoregional recurrence after multivariable analysis (HR = 1.03, 95% CI 1.00-1.06, $p = 0.041$) (Supplementary Table S1). Despite the high rate of recurrence, 10-year, disease-specific survival (DSS) was 100% in DS-PTC, with no patients dying of disease. In comparison, 10-year DSS was 97.1% cPTC and 91.1% in TC-PTC. The Kaplan-Meier plot in Fig. 2B demonstrates the significantly worse DSS in cPTC and TC-PTC compared with DS-PTC ($p = 0.015$).

Recurrence occurred in 45.3% (39/86) of DS-PTC patients; regional recurrence predominated. The distribution of recurrence is shown in Supplementary Fig. S2; 40.7% (35/86) developed locoregional recurrence, and 7% (6/86) developed distant recurrence (five lung and one bone metastases). Five-year regional RFS for DS-PTC was 56% compared with 93.7% for cPTC and 90.3% for TC-PTC ($p < 0.0001$; Fig. 3a). The 5-year local recurrence-free survival for DS-PTC was poorer than cPTC and TC-PTC (89.5% DS-PTC; 98.9% cPTC; 98.3% TC-PTC) (Fig. 3b). The overall local recurrence rate for DS-PTC was 10.4% (9/86); 1.1% for cPTC (24/2182), and 1.7% for TC-PTC (12/701).

Survival Outcomes after Propensity-Matching Analysis

To adjust for the effect of advanced TNM stage in DS-PTC patients, we performed propensity-matching analyses. 84 DS-PTC patients were propensity-matched to 84 cPTC and 84 TC-PTC patients on age, sex, T, N, and M stage (Table 2). Supplementary Figs. S3 and S4 show reduced variability in standardized mean differences pre- and post-propensity matching. Supplementary Figs. S5 and S6 show successful propensity matching of selected variables of interest. DS-PTC continued to demonstrate a greater rate of microscopic ETE, LVI, multifocality, and positive margins than cPTC ($p \leq 0.006$). DS-PTC had a significantly increased likelihood of LVI and multifocality ($p < 0.001$) than TC-PTC. There was no difference between the groups in gross ETE or microscopic ENE. The RFS was significantly worse for DS-PTC compared with cPTC and TC-PTC after propensity matching ($p < 0.0001$; Figs. 4a and 4b). Propensity-matching analysis using age, sex, and T stage as the matching variables gave median number of metastatic lymph nodes as 11.5, 2, and 3 for DS-PTC, cPTC, and TC-PTC respectively ($p < 0.05$).

Prognostic Factors of Recurrence-free Survival

Table 3 lists variables affecting RFS for the combined cohort of DS-PTC, cPTC, and TSV-PTC. On univariate analysis, age ($p < 0.05$), female sex, T-stage, cervical nodal metastases, gross ETE, microscopic ETE, positive margins, LVI, and microscopic ENE conferred worse RFS ($p < 0.001$). Patients with DS-PTC histology were more than seven times more likely to recur than cPTC (HR 7.57; $p < 0.001$). Multivariate analysis confirmed a histological diagnosis of DS-PTC as an independent prognostic factor of recurrence ($p < 0.001$).

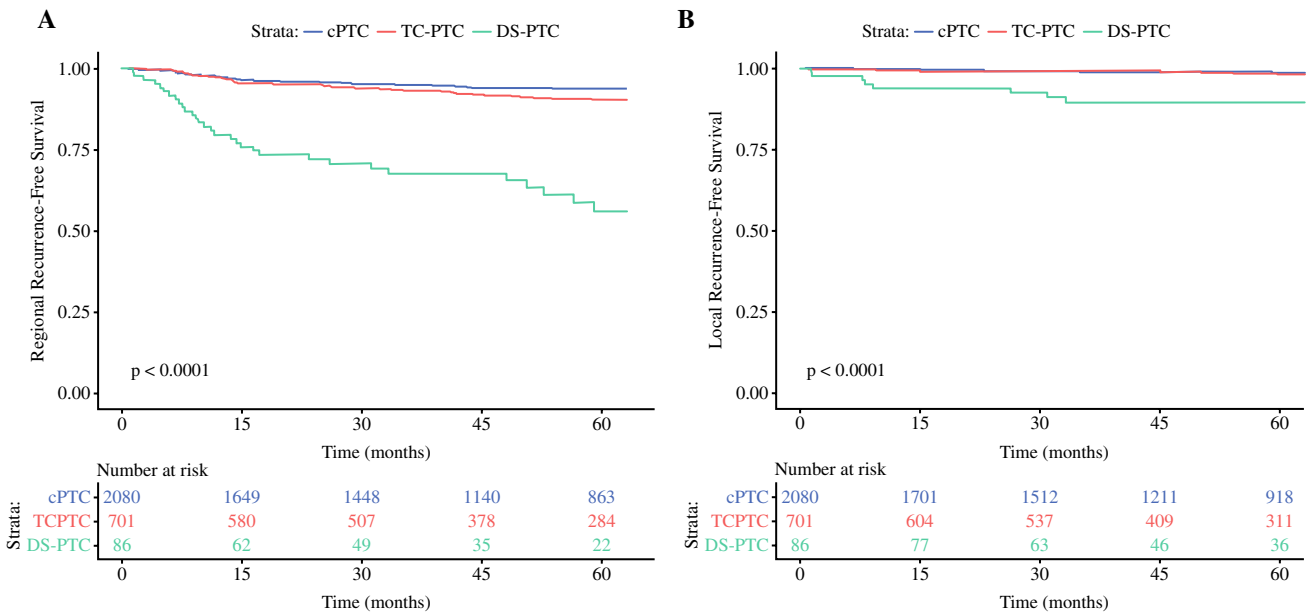

FIG. 3 Kaplan-Meier plot of 5-year regional recurrence-free survival **A** and 5-year local recurrence-free survival **B**

TABLE 2 Comparison of pathology characteristics for classical and tall cell PTC propensity matched to diffuse sclerosing PTC

Variable	Classical PTC ($n = 84$)[1]	Diffuse Sclerosing PTC ($n = 84$)	p value[2]	Tall cell PTC (n = 84)[1]	Diffuse sclerosing PTC ($n = 84$)	p value[2]
Gross ETE						
No	78 (93%)	50 (89%)	0.5	72 (86%)	50 (89%)	0.5
Yes	6 (7.1%)	6 (11%)		12 (14%)	6 (11%)	
Microscopic extension						
No	39 (46%)	24 (29%)	0.006*	23 (46%)	24 (29%)	0.9
Yes	45 (54%)	60 (71%)		61 (54%)	60 (71%)	
Margin						
Negative	66 (89%)	59 (70%)	0.003*	67 (82%)	59 (70%)	0.084
Positive	8 (11%)	25 (30%)		15 (18%)	25 (30%)	
Multifocality						
No	32 (38%)	0 (0%)	< 0.001*	31 (37%)	0 (0%)	< 0.001*
Yes	52 (62%)	84 (100%)		53 (63%)	84 (100%)	
LVI						
No	60 (72%)	0 (0%)	< 0.001*	69 (83%)	0 (0%)	< 0.001*
Yes	23 (28%)	84 (100%)		14 (17%)	84 (100%)	
Extranodal extension						
No	44 (59%)	45 (58%)	0.9	53 (65%)	45 (58%)	0.4
Yes	30 (41%)	32 (42%)		29 (35%)	32 (42%)	
Encapsulation3						
No	35 (43%)	72 (89%)	< 0.001*	48 (59%)	72 (89%)	< 0.001*
Yes	47 (57%)	9 (11%)		33 (41%)	9 (11%)	

LVI lymphovascular invasion

[1]Percents may not add up to 100 due to rounding. Missing observations excluded from counts

[2]Wilcoxon rank-sum test; Pearson's chi-squared test; Fisher's exact test

[3]Encapsulation refers to the main tumor nodule

*Denotes significant p values

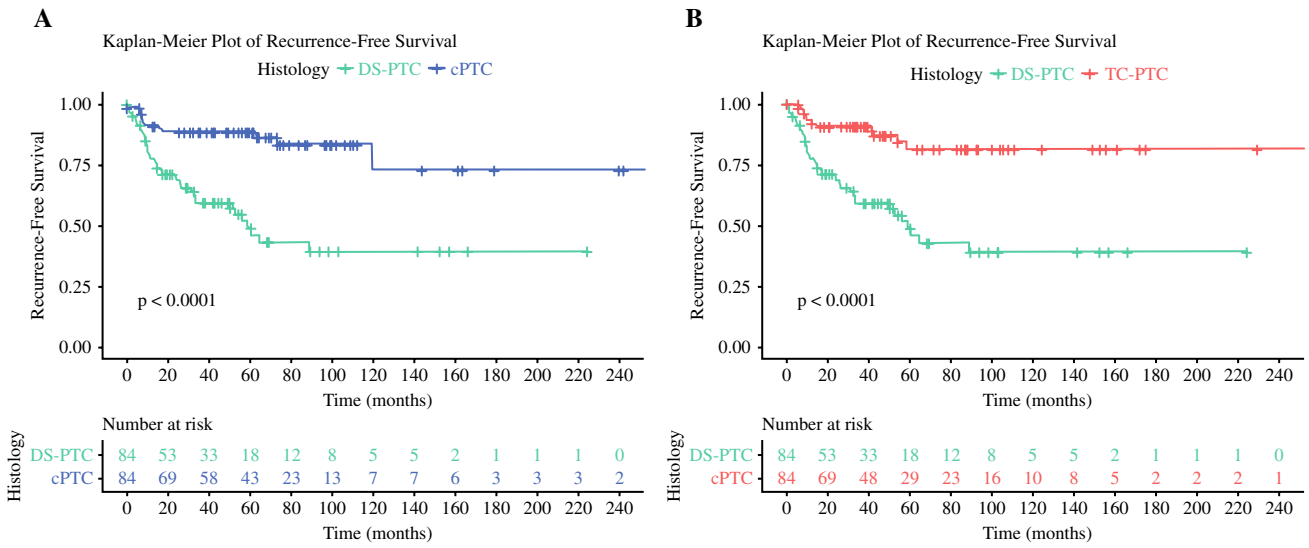

FIG. 4 Recurrence-free survival of propensity matched cPTC and DS-PTC cohorts **A** and propensity-matched TC-PTC and DS-PTC cohorts **B**

TABLE 3 Univariable and multivariable analysis of recurrence-free survival for diffuse sclerosing, classical, and tall cell PTC (N = 2,867)

Factor	Variable	Univariate analysis			Multivariate analysis		
		HR[1]	95% CI[1]	*p* value	HR[1]	95% CI[1]	*P* value
Age	(Cont)	0.99	0.98, 1.00	0.023*	1.00	0.99, 1.01	0.5
Sex	Male	REF	REF	< 0.001*			0.3
	Female	0.65	0.50, 0.83		0.84	0.62, 1.14	
T stage	T1/2	REF	REF	< 0.001*			0.2
	T3/4	2.95	2.27, 3.84		1.38	0.84, 2.28	
N stage	N0	REF	REF	< 0.001*			< 0.001*
	N1a/N1b	4.18	3.06, 5.69		2.28	1.46, 3.56	
Histology	cPTC	REF		< 0.001*	2.39		0.008*
	DS-PTC	7.57	5.29, 10.8			1.26, 4.54	
	TC-PTC	1.33	0.99, 1.77	0.056	1.13	0.80, 1.58	0.5
Gross ETE	No		REF	< 0.001*			0.4
	Yes	2.60	1.98, 3.41		1.26	0.76, 2.08	
Microscopic ETE	No	REF	REF	< 0.001*			0.5
	Yes	3.02	2.29, 3.98		1.16	0.78, 1.71	
Margins	Negative	REF	REF	< 0.001*			0.017*
	Positive	2.86	2.19, 3.73		1.54	1.08, 2.19	
Multifocality	No	REF		< 0.001*			0.8
	Yes	1.80	1.36, 2.39		1.03	0.73, 1.45	
LVI	No	REF	REF	< 0.001*			0.8
	Yes	2.44	1.88, 3.16		0.96	0.66, 1.39	
ENE	No	REF	REF	< 0.001*			0.073
	Yes	4.14	3.17, 5.39		1.40	0.97, 2.03	
Positive LN	(Cont)	1.06	1.05, 1.06	< 0.001*	1.02	1.01, 1.04	0.006*

[1]*HR* hazard ratio; *CI* confidence interval. Unknown observations excluded from analysis.

[2]*NA* not attempted multivariate analysis for variables not significant in univariate analysis.

ETE extrathyroidal extension; *LVI* lymphovascular invasion; *ENE* extranodal extension *Denotes significant p-values

Prognostic Factors of Recurrence-free Survival in Patients with DS-PTC Alone

In DS-PTC alone, microscopic ENE was the only factor that conferred worse RFS ($p < 0.05$). There were no independent prognostic factors of RFS on multivariate analysis.

Management of Recurrence in DS-PTC

DSS was excellent in DS-PTC despite the high incidence of recurrence, meaning patients were successfully salvaged; 51.5% (17/33) of patients with regional recurrence had salvage neck dissection, and 33.3% (11/33) with regional recurrence were able to be observed due to small-volume disease. Five of nine (55.5%) patients with local recurrence also were able to be observed. Multiple, locoregional recurrences occurred in four patients (4/86, 4.7%). Three patients had at least two locoregional recurrences that were treated with neck dissection on each occasion. One patient had two separate locoregional recurrences that were observed.

Comparison Between DS-PTC Lacking High-Grade Features and DHGTC-DS Histotype

Nine of 86 (10.5%) patients were subcategorised as DHGTC-DS due to tumor necrosis or marked mitotic count (≥5 mitoses/2 mm^2). Supplementary Table S2 compares the clinicopathologic features of DS-PTC lacking high-grade features to DHGTC-DS. DHGTC-DS presented with more advanced T-stage ($p = 0.007$), increased likelihood of gross ETE ($p = 0.029$), and increased mitotic count ($p = 0.006$). Median number of positive nodes was 35 in DHGTC-DS compared with 13 in DS-PTC ($p = 0.051$). Five-year RFS was 38.9% in DHGTC-DS and 51% in DS-PTC ($p = 0.19$).

Radioactive Iodine Avidity of DS-PTC

RAI avid lymph node metastases were identified on post-therapy radioactive iodine scan in 33% (24/72), whereas 80% (4/5) of patients with distant metastases demonstrated RAI avid disease. RAI uptake occurred in 44% (4/9) of

DHGTC-DS patients with regional metastases and 100% (2/2) of DHGTC-DS patients with distant metastases.

DISCUSSION

Robust data regarding DS-PTC is lacking due to the rarity of this histological subtype. Large population-level analyses have been undertaken,[10,11] whereas meta-analyses have shown heterogenicity in findings and opposing survival outcomes.[4,5] No previous studies have compared matched cohorts of DS-PTC, cPTC, and TC-PTC with DS-PTC subjected to a meticulous histopathologic examination.

In our study, patients with DS-PTC presented at a median age of 24 years, which supports data demonstrating DS-PTC patients present during the third decade of life.[4,9] Our data support previous literature that shows that DS-PTC typically presents with more advanced disease than cPTC.[8,10–12,14,21] In addition, the number of metastatic nodes was significantly greater than in cPTC and TC-PTC. This pattern reflects the strong tendency for LVI in DS-PTC, predominantly to the lymphatic vessels.[6] The LVI rate of 100% is more than double the rate cited in previous literature.[11,22] Accompanied by a greater rate of N1b disease and ENE, this results in DS-PTC patients requiring more extensive surgery. Previous comparisons of DS-PTC and TC-PTC have not included histopathological features except in the pediatric population.[23] Our study has shown DS-PTC to have a significantly greater rate of LVI, ENE, and positive margins than in TSV-PTC. Significantly more tumor encapsulation was seen in cPTC and TC-PTC, a characteristic that infers more indolent behaviour.

A 5% rate of distant metastases at presentation is similar to that reported in the literature.[9] However, the overall recurrence rate of 45.3% is significantly higher than previously cited.[9,11] Most recurrence occurred in regional lymph nodes and 82% (27/33) of these occurred in a previously dissected neck level. These patients had a high nodal burden and 62.9% rate of ENE at initial surgery, suggesting that large number of positive lymph nodes and incidence of ENE are important factors in DSPTC recurrence. This was confirmed by univariable and multivariable analysis, which showed ENE and increasing number of positive nodes to be risk factors for locoregional recurrence in DS-PTC (Supplementary Table S1).

DS-PTC has not been shown to be an independent risk factor for recurrence until now. We have shown through multivariate analysis that a diagnosis of DS-PTC has a hazard ratio of 7.57 for recurrence ($p < 0.001$). Close surveillance after initial treatment is therefore required to identify recurrence and implement salvage surgery if necessary.

Meta-analysis of 641 patients with DS-PTC inferred that DS-PTC prognosis is similar to cPTC when managed with aggressive treatment protocols.[9] However, results are conflicting in other meta-analyses, SEER studies, and single-center studies.[9–11,13,24,25] Excellent DSS in our study may be due to the tendency for DS-PTC to affect adolescents and young adults. However, young patients with DS-PTC (<55 years) had similar outcomes and histopathologic features to older counterparts in this study. Other factors, such as the unique molecular profile of DS-PTC (which is different from cPTC), may therefore play a role. The molecular profile of DS-PTC is characterized by increased RET rearrangements but fewer *BRAFV600E* mutations; the latter is associated with poor outcome in PTC.[18,26–28] *NCOA4::RET* fusions have been associated with advanced-stage and persistent disease, *CCDC6::RET* fusions with disease remission.[26,27] Further genetic studies are required to assess the effect of *RET* fusions on oncologic outcomes. In our study, three patients had multiple recurrences despite adjuvant RAI and repeat salvage neck dissections. Such patients may benefit from the option of RET targeted treatments in the future.

There are no previous reports regarding RAI avidity of DS-PTC. Our study shows that regional and distant metastases in DS-PTC can concentrate RAI on postsurgical scans. Recurrence is typically treated with salvage surgery. However, management of recurrence has not been addressed in the literature. We have shown that active surveillance of small-volume, nonprogressive disease is acceptable. Comparison between DHGTC-DS and DS-PTC is a novel analysis in this study. DHGTC-DS tumors had more advanced T-stage and incidence of gross ETE. However, the difference in 5-year RFS was not significant. Further studies are required to improve understanding of differences in genetics, histopathology, and survival between the two groups.

Our study has several limitations that warrant consideration. This is a retrospective review and is therefore susceptible to the inherent biases associated with such data. The inclusion of patients that had initial treatment at outside institutions improves the statistical power of our study but adds potential variability in radiological workup.

CONCLUSIONS

Our study illustrates the unique clinical and pathological characteristics of DS-PTC that distinguish it from cPTC and TC-PTC. The diagnosis of DS-PTC alone is an independent prognostic factor for recurrence, meaning accurate histological diagnosis is essential in the treatment and outcome of patients with aggressive cPTC subtypes. Large-volume nodal metastases and LVI are characteristic features of DS-PTC, and almost half of patients develop recurrence despite aggressive initial management. Nevertheless, DSS is favourable compared with cPTC and TC-PTC after successful salvage surgery.

SUPPLEMENTARY INFORMATION The online version contains supplementary material available at https://doi.org/10.1245/s10434-023-13589-y.

ACKNOWLEDGMENT Daniel Scholfield was supported by The Dowager Countess Eleanor Peel Trust and The Colledge Family Memorial Fellowship Fund to undertake a Research Fellowship for 12 months.

FUNDING Research reported in this publication was supported in part by the Cancer Center Support Grant of the National Institutes of Health/National Cancer Institute under award number P30CA008748.

DISCLOSURE The authors have no commercial or financial interests to disclose.

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