Original Article

Diffuse Sclerosing Variant Papillary Thyroid Carcinoma: Clinicopathological and Treatment Outcome Analysis of 44 Cases

Khalid Hussain AL-Qahtani[1], Mushabbab Al Asiri[2], Mutahir A Tunio[3], Naji J Aljohani[4], Yasser Bayoumi[5], Wafa AlShakwer[6]
[1]Department of Otolaryngology-Head & Neck Surgery, College of Medicine; Advanced Head & Neck Oncology, College of Medicine, King Saud University, Riyadh, Saudi Arabia
[2]Department of Radiation Oncology, Comprehensive Cancer Center, King Fahad Medical City, Riyadh, Saudi Arabia
[3]Department of Radiation Oncology, King Fahad Medical City, Riyadh, Saudi Arabia
[4]Department of Endocrinology and thyroid Oncology, King Fahad Medical City, Riyadh, Saudi Arabia
[5]Department of Radiation Oncology, NCI, Cairo University, Cairo, Egypt
[6]Department of Histopathology, Comprehensive Cancer Center, King Fahad Medical City, Riyadh, Saudi Arabia

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ABSTRACT

Objectives: Aim was to evaluate clinicopathological and treatment outcomes of diffuse sclerosing variant papillary thyroid carcinoma (DSV-PTC).
Design: Retrospective study
Setting: Two major tertiary care hospitals of Riyadh, Saudi Arabia
Material: Medical records of 1192 patients with confirmed papillary thyroid cancers (PTC), who were treated or followed up during the period of July 2000 and December 2012 were reviewed.
Main outcome measure: To evaluate the clinicopathologic features and treatment outcomes of patients with DSV-PTC and perform comparative analysis of DSV-PTC with classic-variant PTC (CV-PTC).
Results: A total of 44 cases (3.7%) of DSV-PTC were identified. DSV-PTC patients were younger than their CV-PTC ($p = 0.001$). The mean tumor size was larger in DSV-PTC as compared to CV-PTC ($p < 0.0001$). Advanced pathologic tumor (pT) stage and positive lymph nodes were more often present in DSV-PTC than in CV-PTC ($p < 0.0001$ and $p < 0.0001$ respectively). Median follow-up was 8.05 years (range: 1.62-11.4). Ten-year disease-specific survival (DSS) rates were lower in DSV-PTC (74.4%) than in CV-PTC (89.4%); $p = 0.001$.
Conclusion: DSV-PTC is more aggressive variant as compared to CV-PTC, and is associated with inferior DSS rates. An aggressive surgical approach followed by radioiodine therapy is warranted for these patients.

KEY WORDS: Papillary thyroid cancer, diffuse sclerosing variant, clinicopathologic features, treatment outcomes

INTRODUCTION

The incidence of differentiated thyroid cancers (DTC) especially papillary thyroid cancers (PTC) is increasing exponentially over the past years throughout the world with a wide geographic variation[1]. In the Kingdom of Saudi Arabia, PTC has become the second most common malignancy behind only breast cancer, accounting for more than 10% of all cancers among women[2]. Classical variant of PTC (CV-PTC) is the most predominant variant. This variant has an excellent outlook and prognosis. However, some other variants (follicular, macropapillary and encapsulated) also show a fairly good prognosis as CV-PTC, while some of variants appear to have a decidedly worse prognosis (tall cell and diffuse sclerosing) [3].

Diffuse sclerosing variant of PTC (DSV-PTC) is morphologically characterized by extensive squamous metaplasia, scattered microscopic tumor islands, diffuse fibrosis, calcification, abundant lymphocytic aggregation and innumerable psammoma bodies[4]. Compared to CV-PTC, the DSV-PTC is associated with greater incidence of cervical lymph node involvement and greater incidence of

Address correspondence to:
*Dr. Mutahar Ali Khairuddin Tunio, **MBBS, FCPS**, Assistant Consultant, Radiation Oncology Comprehensive Cancer Center, King Fahad Medical City, Riyadh, Saudi Arabia. Tel: +96612889999, Fax: +96612889999 Email: drmutahirtonio@hotmail.com, Ext:1050, Pager:5922*

distant metastases[5]. However, the probability of disease-specific survival (DSS) and overall survival (OS) after thyroidectomy, adjuvant modalities (radioiodine-131 therapy and neck irradiation) is not well characterized, because of rarity of this variant.

In the present study, we aimed to evaluate the clinicopathologic features and treatment outcomes including DSS in a large series of 44 patients with DSV-PTC and to compare them with a larger group of 532 patients with the CV-PTC; those were evaluated in the same period.

MATERIALS AND METHODS

After formal approval from the institutional ethical committee, medical records of 1192 patients with confirmed papillary thyroid cancers (PTC), who were treated or followed up in two major tertiary care hospitals of Riyadh, Saudi Arabia, during the period of July 2000 and December 2012 were reviewed retrospectively using computer based departmental database system. Patients with DSV-PTC were retrieved in following manner:

Demographic, clinicopathological and radiological variables

Demographic and clinical data including age at the diagnosis, gender, and symptomatology were reviewed. Different histopathological parameters, including the location of tumor, tumor size, multifocality, extrathyroidal extension (ETE), lymphovascular space invasion (LVSI), surgical margin status, and cervical lymph node status, distant metastasis at time of diagnosis and background thyroid tissue were also recorded. Patterns of different immunohistochemical panel including cytokeratin (CK) AE1/AE3, CK19, thyroid transcription factor-1 (TTF-1), thyroglobulin, S-100, and Ki-67 were noted down. Data from different imaging modalities, including ultrasonography, whole body I-131 scintigraphy (WBS), computed tomography (CT) scan of neck and chest, flourodeoxyglucose positron emission tomography (FDG-PET) was collected. Postoperative thyroid function tests (TFTs) and thyroglobulin (TG) levels were also reviewed. Data regarding different treatment modalities, including the type of surgery, neck dissection types, adjuvant radioactive iodine 131 (I-131), its dose regimens in millicurie (mCi) and the details of neck irradiation details (if given) were also recorded.

Statistical analysis

The primary endpoint was the disease specific survival (DSS). Secondary points were; the frequency of DSV-PTC, local recurrence free survival (LRFS), distant metastasis free survival (DMFS) and overall survival (OS). Comparison of DSV-PTC was

Table 1: Patients' characteristics

Variables	SCV- Papillary n (%)	Classic- Papillary n (%)	p-value
Total patients	44/576 (7.6)	532/576 (92.4)	< 0.0001
Age (years)			
≤ 45 years	38 (86.4)	345 (64.8)	
≥ 45 years	6 (13.6)	50 (35.2)	0.001
Gender			
Female	39 (88.6)	452 (84.9)	
Male	5 (11.4)	80 (15.1)	0.05
Type of surgery			
Near or total thyroidectomy	44 (100)	437 (82.1)	0.84
Lobectomy	-	95 (17.9)	
Lymph node surgery			
Central neck dissection	23 (52.3)	174 (32.7)	
Lateral neck dissection	11 (25.0)	102 (19.2)	0.05
Sampling	5 (11.4)	133 (20.8)	
None	5 (11.4)	123 (23.1)	
Mean size (cm)	4.5 (1-9.8) ± 2.1	2.7 (0.1-7) ± 1.9	< 0.0001
≤ 2 cm	4 (9.1)	408 (76.7)	
≥ 2 cm	40 (90.9)	124 (23.3)	
Location (dominant mass)			
Right lobe	18 (40.9)	171 (32.2)	
Left lobe	11 (25.0)	176 (37.8)	0.09
Isthmus	5 (11.4)	64 (12.4)	
Bilateral	10 (22.7)	121 (22.7)	
Multifocal			
Yes	12 (27.3)	239 (44.9)	< 0.0001
No	32 (72.7)	293 (55.1)	
ETE			
Yes	29 (65.9)	191 (35.9)	< 0.0001
No	15 (34.1)	341 (64.1)	
LVSI			
Yes	31 (70.5)	148 (27.8)	< 0.0001
No	13 (29.5)	384 (72.2)	
Surgical margins			
Positive	14 (31.8)	184 (34.6)	0.83
Negative	30 (68.2)	348 (65.4)	
Lymph node metastasis			
Yes	34 (77.3)	255 (47.9)	< 0.0001
N1a	31 (91.2)	165 (64.7)	
\N1b	3 (8.8)	90 (35.3)	
N0	10 (22.7)	277 (52.1)	
Background thyroid tissue			
Normal	19 (43.2)	253 (47.6)	
Multi-nodular goiter	6 (13.6)	122 (22.9)	
Lymphocytic thyroiditis	12 (27.3)	42 (7.9)	
Hashimotos' thyroiditis	7 (15.9)	115 (21.6)	0.04
Distant Metastasis at presentation	6 (13.6)	24 (4.5)	< 0.0001
pT staging			
T1	1 (2.2)	157 (29.5)	
T2	12 (27.3)	165 (31.0)	
T3	29 (65.9)	191 (35.9)	< 0.0001
T4	2 (4.5)	19 (3.6)	
Mean postoperative TG (ng/ml)	2.44 (0.1-42890)	2.39 (0.1-34550)	0.62
I-131 dose			
30 mCi	-	54 (10.2)	
100 mCi	4 (9.1)	199 (37.4)	
150-200 mCi	40 (90.9)	279 (52.4)	< 0.0001
RT to Neck	1 (2.2)	13 (2.4)	0.73

*Mean age in SCV-PTC 34.5 years (18-54); SD ± 8.63 and mean age in CV-PTC 43.2 (8-71); SD ± 12.3

I-131 = radioactive iodine 131, N= number, SD = standard deviation, ETE= extra-thyroidal extension, LVSI = lymphovascular space invasion, pT= primary tumor, TG= thyroglobulin, mCi= millicurie, RT= radiation therapy

performed with CV-PTC those were evaluated in the same period.

Local recurrence was defined as, clinically or radiologically detectable recurrences in the thyroid bed or in cervical lymph nodes, and distant metastasis was defined as, clinically or radiologically detectable disease outside the neck. The DSS was defined as, the duration between the completion of treatment date and the date of documented disease reappearance/ relapse, death from cancer and/or last follow-up (censored). The OS was defined as, the duration between the completion of treatment date and the date of patient death or last follow-up (censored). Chi-square test, Student's t test, or Fisher exact tests were used to determine the differences in various clinical variables. Multivariate logistic regression was done using Cox proportional hazards modeling. Probabilities of LRFS, DMFS, DSS and OS were shown with the Kaplan-Meier method and the comparisons for various survival curves were performed using log rank. All statistical analyses were performed using the computer program SPSS version 16.0.

RESULTS

Among the 1192 PTC patients in our departmental database, 44 (3.7%) patients were found to have DSV-PTC, while 532 patients (44.6%) had CV-PTC. The study cohort was predominantly consisted of female gender (85.3%). The female to male ratio was slightly higher in DSV-PTC (7.6) as compared to CV-PTC (5.6) with $p = 0.05$. The majority of patients had near or total thyroidectomy (n = 481, 83.5%); only 95 (17.9%) patients underwent lobectomy. All DSV-PTC patients (100%) underwent near or total thyroidectomy. Prophylactic central neck dissection (pCND) was performed in 23 in DSV-PTC cases (52.3%) and 174 CV-PTC cases (32.7%) $p = 0.05$. Positive lymph nodes were more often present in DSV-PTC (77.3%) than in their counterpart ($p < 0.0001$). The mean tumor size was 4.5 cm in DSV-PTC while mean tumor size was 2.7 cm in CV-PTC ($p < 0.0001$). Advanced pathologic tumor (pT) stage and distant metastasis at time of diagnosis was higher in DSV-PTC as compared to CV-PTC ($p < 0.0001$, $p < 0.0001$ respectively). Other clinicopathological features are described in Table 1.

Table 2: Disease specific survival according to different prognostic factors

Variables	DSV - PTC				CV - PTC			
	5 year DSS (%)	p-value	10 year DSS (%)	p-value	5 year DSS (%)	p-value	10 year DSS (%)	p-value
Age								
≤ 45 years	93.9		81.8		97.6		95.1	
≥ 45 years	85.7	0.061	57.1	0.037	94.5	0.72	84.4	0.06
Gender								
Female	93.8		71.3		96.6		91.5	
Male	96.8	0.76	80.4	0.065	96.8	0.81	95.3	0.73
Multifocal								
Yes	90.2		64.3		95.2		90.9	
No	96.7	0.72	82.9	0.001	90.0	0.72	88.3	0.60
Lymph node surgery								
Neck dissection								
Yes	96.8		81.8		97.6		95.1	
No	83.3	0.90	57.0	0.001	94.5	0.90	91.7	0.08
Lymph node status								
N0	96.0		71.8		97.6		80.1	
N1	83.3	0.001	53.8	0.001	94.5	0.67	91.7	0.04
Surgical margins								
Positive	96.6		80.4		86.3		84.0	
Negative	96.8	0.60	85.3	0.091	93.2	0.64	87.9	0.60
ETE								
Yes	92.9		57.1		94.5		80.1	
No	96.2	0.63	80.4	0.001	97.6	0.90	90.2	0.01
LVSI								
Yes	92.3		58.5		94.5		80.1	
No	96.3	0.82	80.9	0.001	97.6	0.71	95.3	0.01
Mean postoperative TG								
≤ 2 ng/ml	96.6		83.4		93.2		91.7	
>2 ng/ml	89.5	0.93	85.5	0.95	87.9	0.63	80.1	0.04

DSV-PTC = Diffuse sclerosing variant of papillary thyroid cancer, CV = classical variant, yr = year, DSS = disease specific survival, SD = standard deviation, ETE = extra-thyroidal extension, LVSI = lymphovascular space invasion, TG = thyroglobulin

Table 3: Univariate and multivariate Model of various prognostic factors for disease specific survival in whole cohort

Variable	All patients			
	Univariate analysis		Multivariate analysis	
	RR (95% CI)	p-value	RR (95% CI)	p-value
Age				
≤ 45 years	1.04 (0.7 - 1.3)		1.06 (0.8 - 1.3)	
≥ 45 years	1.34 (1.0 - 2.0)	0.6	1.25 (1.0 - 1.9)	0.6
Gender				
Female	1.07 (0.9 - 1.4)		1.05 (0.7 - 1.3)	
Male	1.05 (0.7 - 1.3)	0.6	1.40 (1.2 - 1.6)	0.05
Lymph node surgery /Neck dissection				
Yes	1.30 (1.1 - 1.7)		2.00 (1.6 - 2.4)	
No	2.70 (1.6 - 4.5)	< 0.0001	2.82 (2.4 - 4.6)	< 0.0001
Histopathologic variants				
Classical	1.05 (0.7 - 1.2)		1.20 (0.8 - 1.6)	
Diffuse Sclerosing	2.80 (1.6 - 3.9)	< 0.0001	2.70 (1.5 - 3.4)	< 0.0001
Multifocal				
Yes	1.93 (1.2 - 2.2)		1.44 (0.9 - 1.7)	
No	1.00 (1.0 - 1.2)	0.9	1.07 (0.9 - 1.3)	0.82
Surgical margins				
Positive	1.10 (0.9 - 1.4)		1.20 (0.8 - 1.6)	
Negative	1.07 (0.9 - 1.4)	0.7	1.17 (0.6 - 1.2)	0.68
ETE				
Yes	4.2 (3.5 - 5.1)		3.31 (1.7 - 4.2)	
No	1.05 (0.7 - 1.1)	< 0.0001	1.17 (0.9 - 1.4)	< 0.0001
LVSI				
Yes	2.3 (1.7 - 2.9)		1.91 (1.7 - 2.8)	
No	1.2 (0.9 - 1.3)	0.02	1.05 (0.9 - 1.4)	0.03
Lymph nodes				
Positive	4.75 (3.7 - 7.8)		3.84 (3.4 - 6.9)	
Negative	1.17 (0.9 - 1.4)	< 0.0001	1.01 (0.8 - 1.4)	< 0.0001

I-131 = radioactive iodine 131, RR = relative risk, CI = confidence interval, ETE = extra-thyroidal extension, LVSI = lymphovascular space invasion

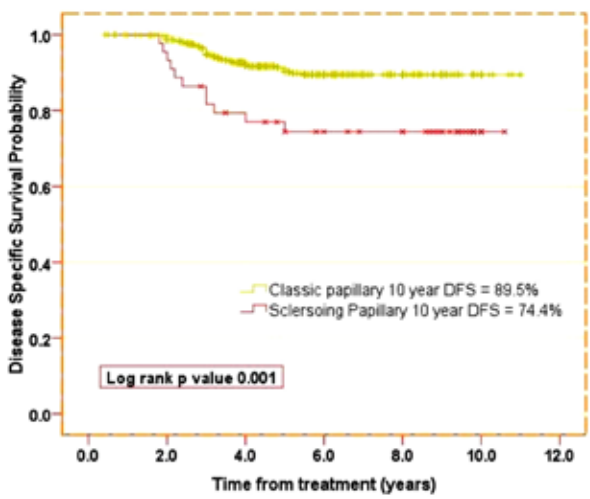

Fig 1: Kaplan-Meier curves of disease specific survival (DSS) according to classical and diffuse sclerosing variants of papillary thyroid cancer

Locoregional recurrences, distant metastasis, overall survival and disease specific survival rates

A median follow-up period was 8.05 years (range: 1.62-11.4). For the whole cohort (CV-PTC and DSV-PTC), the 10 year LRFS, DMFS and OS rates were 91.7%, 91.0% and 98.6% respectively and the 10 years DSS rates were 81.95%.

A total of 32 local recurrences (5.56%) were observed; 7/44 (15.9%) in DSV-PTC patients and 25/532 (6.77%) in CV-PTC patients (*p <0.0001*). The pattern of local recurrences was: 12/32 patients (37.5%) had disease in thyroid bed only (DSV-PTC; 3 patients, CV-PTC; 9 patients) and 20/32 (62.5%) developed cervical lymphadenopathy (DSV-PTC; 9 patients, CV-PTC; 11 patients). Combined locoregional and distant metastasis were seen in 5/44 (11.4%) DSV-PTC patients and 13/532 (3.2%) in CV-PTC patients. The isolated locoregional recurrences were salvaged by surgery (lateral neck dissection

for 10 patients, and completion thyroidectomy for 4 patients) followed by I-131 ablation (12 patients). Distant metastasis were seen in 5/44 (11.4%) in DSV-PTC patients and 26/532 (4.9%) in CV-PTC patients (*p <0.0001*). All DSV-PTC had metastases in the lungs. All distant metastases were salvaged by I-131 ablation and palliative irradiation for bony lesions (three CV-PTC patients). In DSV-PTC patients, time to initial local recurrence was 1.8 years and time to initial distant metastasis was 2.0 years. The 10 year DSS rates were 89.5% vs. 74.4% in CV-PTC and DSV-PTC patients respectively (*p = 0.001*) Fig. 1. The 5 and 10 year DSS rates in CV-PTC and DSV-PTC patients according to different variables are summarized in Table 2. No transformation to squamous cell carcinoma or death was reported in our series of DSV-PTC patients.

Prognostic Factors

The results of Cox regression Model using univariate and multivariate analysis for DSS to predict important prognostic factors are shown in Table 3. Important prognostic factors found were; sclerosing variant (*p < 0.0001*), lymph node dissection (*p < 0.0001*), ETE (*p < 0.0001*), LVSI (*p = 0.03*) and nodal status (*p < 0.0001*).

DISCUSSION

DSV-PTC is rare aggressive variant, and according to several reports, the prevalence of DSV-PTC of all papillary carcinomas has been reported to be 0.3% to 5.3%[6]. In this large series of DSV-PTC patients, we were able to determine overall ten years DSS rates of 74.4% after aggressive treatment by near or total thyroidectomy followed by I-131 therapy in the majority of cases in our cohort. These results are in consistent with similar reported data[3,5,7,8,9]. However, one series found that the prognosis of DSV-PTC was similar to CV-PTC[10]. The poor outcome in our series can be justified by (a) larger tumors (mean: 4.5 cm Vs. 3.6 cm); (b) predominant elderly population (mean: 34.5 years vs. 29 years) and (c) few patients received external beam irradiation (1 Vs. 4) in our cohort. However, in our series no cancer related death was reported, in contrary to studies by Thompson LD, *et al* (4.5%), Koo JS, *et al* (3.6%) and Lam AK, *Lo CY* (6.7%).[3,8,10]

Malignant transformation of squamous metaplasia to squamous cell carcinomas (SCC) of thyroid, albeit very rare have been reported in few DSV-PTC case reports and series[11]. Thompson LD, *et al* have reported one (4.5%) squamous cell carcinoma in a series of 22 DSV-PTC patients[3]. In our series, although no case of DSV-PTC transformed SCC was observed, but to differentiate DSV-PTC transformed SCC from primary SCC of thyroid needs extensive work up. Primary SCC lacks psammoma bodies, extensive lymphocytic thyroiditis, the presence of characteristic PTC and appears at older age[12,13]. Although not reported in our series, another rare entity that shall be differentiated from DSV-PTC is the primary mucoepidermoid carcinoma (MEC) and sclerosing mucoepidermoid carcinoma with eosinophilia (SMECE) of the thyroid. MEC consists of nests of epidermoid or even squamous appearance and mucin-containing cysts and in MECE, there is extensive fibrosis with eosinophilic leukocytes enriched stroma with background of chronic lymphocytic thyroiditis and extensive fibrosis[14,15]. Similar to DSV-PTC, MEC and MECE are TTF-1 and P-cadherin immunoreactive, however MEC and MECE lacks extensive lymphovascular space invasion (LVSI), psammoma bodies, and extensive cervical lymph node metastasis as compared to DSV-PTC[16].

In our series, none of DSV-PTC patient had history of radiation exposure, as related literature has suggested possible epidemiologic link between radiation exposure and the development of DSV-PTC[4,17].

Lymph node involvement was the most significant independent risk factor for recurrence in our cohort of DSV-PTC patients. Failure of I-131 therapy to minimize the risk of locoregional recurrence in lymph node positive DSV-PTC is an indicator of underlying tumor burden in neck and this supports the hypothesis of extensive prophylactic central and lateral neck dissection during thyroidectomy in such patients[10]. However, there is potential increased risk of hypoparathyroidism associated with central neck dissection.

Strengths of our study are; (a) according to our knowledge, this is the largest series of DSV-PTC to date and (b) comparative analysis was performed with CV-PTC. However, limitations of our study were (a) it was retrospective, and (b) potential selection bias could not be ruled out.

CONCLUSION

DSV-PTC is rare variant and we should be familiar with the clinicopathological features and treatment outcomes of this variant. Long terms outcomes can be achieved by aggressive surgical approaches (neck dissection) and adjuvant modalities (I131 therapy and neck irradiation).

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