Diffuse Sclerosing Variant of Papillary Thyroid Carcinoma Is Associated With Aggressive Histopathological Features and a Poor Outcome: Results of a Large Multicentric Study

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Context: Diffuse sclerosing variant (DSV) is a rare and aggressive subtype of papillary thyroid carcinoma (PTC).

Objective: The objective of the study was to investigate the clinicopathological features and prognosis of DSV patients and compare these findings with all other PTCs and high-risk PTCs.

Design and Setting: The data of patients who underwent surgery for DSV and PTC between 2003 and 2014 in seven surgical departments specialized in endocrine surgery were reviewed.

Patients: Fifty-six DSV patients were included (mean age 32.6 $\pm$ 12.5 y; 46 [82%] female) and were compared with 2945 non-DSV PTCs and 48 high-risk PTCs.

Results: Forty-six DSV patients (82%) were pT3, 43 (77%) had an extrathyroidal extension, and 54 (96%) had lymph node metastasis, including 48 patients with involvement in the lateral compartment (86%). During the follow-up period of 4.3 $\pm$2.3 years, 19 patients (34%) had a recurrence, including 18 patients with an ipsilateral lateral compartment recurrence. The only prognostic factor for recurrence in the multivariate analysis was extranodal extension (odds ratio 3.4 [1.1; 10.8]). The 7-year recurrence-free survival (RFS) was 63%. The RFS was significantly worse in patients with DSV than in other PTC patients (hazard risk 8.5 [5.2; 13.9], $P < .0001$) and were similar to the RFS of high-risk PTCs (hazard risk 1.1 [0.6; 2.2], $P = .5$).

Conclusion: DSV patients share the same recurrence rate as high-risk PTC patients. Despite aggressive surgical approaches, the recurrence rate within the first 5 years requires a careful ongoing surveillance, similar to the follow-up of high-risk PTC patients. **(*J Clin Endocrinol Metab* 101: 4603–4610, 2016)**

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Abbreviations: ATA, American Thyroid Association; BMI, body mass index; DSV, diffuse sclerosing variant; HR, hazard risk; LN, lymph node; LND, lymph node dissection; OR, odds ratio; PTC, papillary thyroid carcinoma; RFS, recurrence-free survival; TNM, tumor node metastasis; US, ultrasound.

Diffuse sclerosing variant (DSV) is a rare histological form of papillary thyroid carcinoma (PTC) with a prevalence of 0.7%–6.6% among patients with PTC (1–3). It was originally described in 1985 by Vickery et al (4) and was recognized as a morphological variant of PTC by the World Health Organization in 1988 (5). Despite the limited number of cases, DSV is recognized to have specific characteristics, a high female to male ratio, and a young patient age (6). They are also considered to have aggressive pathological features, such as bilateral lesions, extrathyroidal extension, and lymph node (LN) metastasis. However, it remains unclear whether DSV patients share a similar risk of recurrence and disease-specific mortality with other PTCs (2, 7–10). The prevalence of distant metastasis in the literature is also very debatable and ranges from 5% to 60%, with mostly pulmonary involvement. Data from these studies appear heterogeneous, probably because of the small number of patients with DSV and the differences in diagnostic and therapeutic management.

The objectives of this study were to describe the clinicopathological characteristics of patients with DSV and to report their outcomes in a large multicentric study. We compared clinicopathological features and outcomes of DSV patients with all other PTCs and with high-risk PTCs according to the American Thyroid Association (ATA) classification (10) (macroscopic invasion of tumor into the perithyroidal soft tissues, distant metastases, and any metastatic lymph node > 3 cm in largest dimension), including a comparison of recurrence-free survival (RFS) and cancer-related death.

Materials and Methods

Patients

A retrospective multicentric study of 56 patients surgically treated for DSV was performed from 2003 to 2014 in seven academic hospitals. The participating hospitals were high-volume referral centers in endocrine surgery. Data for all patients who underwent surgical treatment for PTC including DSV were collected into prospective databases. The charts of patients were reviewed and analyzed retrospectively. This study was approved by the French-speaking Association of Endocrine Surgeons, and the National Cancer Institute does not require institutional review board for this study oversight. Each DSV diagnosis was reconfirmed by an expert pathologist who retrospectively reviewed histological slides. DSVs are characterized by six nonspecific morphological criteria that all must be observed: a diffuse involvement of at least one thyroid lobe, with multifocal grayish white lobulated lesions; fibrous stroma; diffuse or nodular lymphocytic infiltration; abundant psammoma bodies; squamous metaplasia areas; and numerous micropapillary infiltrations within dilated lymphatics (4, 11, 12) (Supplemental Figure 1).

Preoperative diagnosis

All patients underwent a neck ultrasound (US) by specialized radiologists or endocrinologists before surgery. US features were recorded according to the internal composition, echogenicity, margin, calcification, and shape. DSV was suspected in case of massive and bilateral neoplastic involvement of the thyroid gland, diffuse scattered microcalcification, and numerous lymph node metastases (Supplemental Figure 2). Fine-needle aspiration biopsy was performed under US guidance for patients with a suspicious tumor.

Surgery

The operative management was homogeneous because the seven surgical departments including patients are among the teams that systematically perform central and ipsilateral lateral lymph node dissection (LND). All patients who were initially diagnosed for PTC (including DSV) with preoperative ultrasound-guided fine-needle aspiration cytology, or with a positive frozen section during surgery, underwent total thyroidectomy with central LND (level VI) and ipsilateral lateral (levels III and IV) compartment LND. A therapeutic LND of the invaded compartment (level II, contralateral lateral compartment) was performed in any patient with LN metastasis preoperatively suspected. We collected patient demographic data (age, sex, and body mass index [BMI]), preoperative investigations, and operative details. The following data were obtained from pathological examination: tumor size, number of tumors, bilaterality, extrathyroidal extension, vascular invasion, and pathological tumor staging in accordance with the seventh edition of the American Joint Committee on Cancer pathological tumor node metastasis (TNM) staging system. For patients with LND, we collected for each LN neck compartment, the number of resected LNs, the number of LN metastases, and the presence of an extranodal extension of positive LNs. We also calculated the LN ratio by dividing the number of positive LNs by the total number of LNs removed in central and lateral compartments. Complications after surgery were also documented. During the postoperative course, recurrent laryngeal nerve palsy was considered permanent if there was no proof of recovery using laryngoscopy within 6 months of surgery. Serum calcium concentration was assessed on postoperative day 1 and repeated on postoperative day 2 if the first result was less than 2 mmol/L. Hypoparathyroidism was considered permanent if the patient required oral calcium supplements and vitamin D for 6 months or more with a plasma PTH level less than 8 pg/mL.

Radioactive iodine therapy

Patients with DSV and high-risk PTC (according to ATA classification) received 100 mCi (3.7 GBq) of radioactive iodine after thyroid hormone withdrawal for 4 weeks. Lower-risk (intermediate) patients received 30 mCi (1.1 GBq) or 100 mCi with the use of recombinant human TSH, and low-risk PTCs were managed without radioiodine treatment.

Follow-up and recurrence

Follow-up information was obtained from databases containing patient medical records. A standardized procedure was used for patient follow-ups, including check-ups under TSH stimulation at 6 and 12 months and then annually thereafter. After 7 years of follow-up, periodic correspondence with patients or their referring physicians was set up to occur every 3

years. Physical examination, neck US, and serum thyroglobulin (Tg) measurements after stimulation or under suppressive treatment were routinely performed during the follow-up. The locoregional recurrence was assessed by fine-needle aspiration biopsy of LN and/or isolated and repeatedly elevated serum Tg levels (>10 ng/mL after L-thyroxine withdrawal in the absence of interfering antibodies).

Comparison between DSV, all other PTCs, and high-risk PTCs

Data from patients with DSV were compared with those obtained from 2945 consecutive non-DSV PTC patients (see Table 1) and 48 consecutive high-risk PTC patients (see Table 3) according to the ATA classification (10) treated during the same study period (2003–2014). We compared clinicopathological characteristics and outcomes in terms of disease recurrences, distant metastases, RFS, and cancer-related death.

Statistical analysis

Quantitative data were expressed as the mean ± SD or the median (range). Qualitative data were represented as a percentage or frequency. DSV patients were compared with classical and high-risk PTC patients using Student's *t* tests for quantitative data and χ^2 tests for qualitative data. A multivariate logistic regression analysis was performed to define the independent factors between DSV and PTC patients. The RFS was estimated for the DSV patients using the Kaplan-Meier estimator. The follow-up time was censored based on the date of the last event, which was recurrence, death, or the last visit. To avoid bias, follow-ups were censored after 7 years because our follow-up protocol stops after this time. The prognosis factors were tested using Cox proportional-hazards regression. In addition, the RFS and cancer-related death was compared between DSV patients, all other PTCs, and high-risk PTC patients using Cox proportional-hazards regression. All tests were two sided at the 5% level of significance. Statistical analyses were performed using SAS software (version 9.4; SAS Institute).

Results

Clinical features of DSV

During the study period, 56 patients underwent surgery for DSV. Their mean age was 32.6 ± 12.5 years; eight patients (14%) were aged older than 45 years. The patient group included a high prevalence of female patients (n = 46, 82%). Table 1 summarizes the clinicopathological fea-

Table 1. Clinicopathological Features of DSV (n = 56) Versus Other PTC (n = 2945)

Variable	DSV (n = 56)	Non-DSV PTC (n = 2945)	*P* Value
Sex, female	46 (82)	2355 (80)	.8
Age, y	32.6 ± 12.5	50 ± 11.9	<.0001
BMI	23.4 ± 4.0	25.2 ± 5.3	.001
Size of the largest tumor, mm	25.5 ± 20.2	12.3 ± 8.7	<.0001
Tumors, n	17.1 ± 14.7	2.4 ± 1.8	<.0001
Bilaterality	45 (80)	721 (24)	<.0001
Extrathyroidal extension	43 (77)	666 (23)	<.0001
Vascular invasion	25 (41)	130 (4)	<.0001
TNM T staging			<.0001
1	8 (14)	1945 (66)	
a	2	1463	
b	6	482	
2	2 (4)	251 (9)	
3	46 (82)	724 (25)	
4	0	25 (1)	
Distant metastases at diagnosis	2 (4)	27 (1)	.04
Lymph node dissection	56 (100)	1791 (61)	<.0001
Prophylactic	12 (21)	1477 (50)	
Therapeutic	44 (79)	314 (11)	
TNM N staging			
0	2 (4)	944 (53)	
1	54 (96)	552 (31)	<.001
1a	6 (11)	225 (13)	
1b	48 (86)	327 (18)	
Number of resected LN	34.4 ± 21.4	20 ± 10.3	<.001
Number of total involved LN	14.9 ± 12.2	1.9 ± 2.5	<.0001
Central	8.6 ± 7.3	1.7 ± 1.9	
Lateral	6.7 ± 6.0	1.5 ± 1.6	
Ratio (N1/N resected) total	0.44 ± 0.23	0.2 ± 0.13	<.0001
Central	0.69 ± 0.34	0.32 ± 0.31	
Lateral	0.32 ± 0.24	0.16 ± 0.14	
Size of the largest node, mm	20 ± 15	10 ± 8	<.0001
Extranodal extension	23 (49) (n = 47)	162 (31) (n = 523)	.0146

Values in parentheses are percentages unless indicated otherwise; values are mean ± SD.

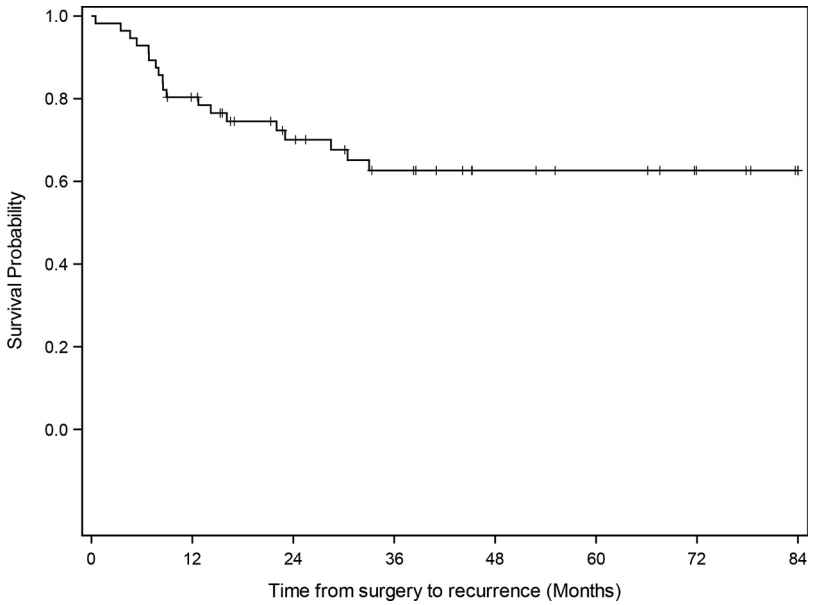

Figure 1. RFS of DSV patients (n = 56).

tures of the cohort. Palpable lymphadenopathy at presentation was found in six patients (11%).

Thyroid carcinoma was suspected on preoperative US and confirmed by preoperative ultrasound-guided fine-needle aspiration cytology in 48 patients (86%). DSV was suggested preoperatively in only eight of these patients based on any of the following US and/or cytological findings: hyperechogenicity (n = 42), diffuse scattered microcalcification (n = 28), ill-defined margins (n = 19) or cervical LN metastasis (n = 34), numerous psammoma bodies, and extensive lymphatic infiltration on cytological examination (n = 2). Eight other patients had a positive frozen section of a macroscopic suspicious nodular lesion discovered during surgery.

At the time of the initial diagnosis, 46 patients (82%) were pT3, including 43 (77%) with extrathyroidal extension. Forty-five patients (80%) had bilateral tumors.

All patients underwent thyroidectomy and central LND. An ipsilateral lateral LND was also performed on the side of the largest primary tumor in 53 patients (95%) including level II in nine patients. Thirty-nine patients (70%) had associated contralateral lateral LND, including the level II in four patients. Fifty-four patients (96%) had lymph node metastasis (N1), all of whom had central compartment involvement. In patients with lateral LND, 48 (91%) had ipsilateral involvement and 26 (67%) had contralateral involvement. The median number of the lymph nodes involved was four (range 0–17) in the ipsilateral compartment and two (range 0–12) in the contralateral lateral compartment. Metastatic LN with extracapsular extension was found in 49% of DSV patients. Two patients had lung metastasis at the time of presentation.

Thirty-one patients (51%) developed postoperative complications: 27 patients had postoperative hypocalcemia, including 25 patients with transient and two (4%) with permanent hypoparathyroidism; recurrent laryngeal nerve palsy was diagnosed in six patients, which was transient in three patients and permanent in the other three patients (5%).

Table 2. Univariate Analysis of Risk Factors for Recurrence in Patients With DSV

Variable	HR (95%CI)	Univariate Analysis *P* Value
Sex, male	2.11 (0.76; 5.88)	.15
Age	1.01 (0.97–1.05)	.71
BMI	0.99 (0.89–1.11)	.87
Bilaterality	2.6 (0.6; 11.28)	.20
Extracapsular extension	1.02 (0.37; 2.83)	.98
Vascular invasion	1.86 (0.67; 5.12)	.23
Tumors, n	0.98 (0.94–1.03)	.42
Size of largest tumor	1 (0.98–1.03)	.76
Size of largest LN	1 (0.96–1.04)	.94
Number of involved LN, total	1.03 (1–1.07)	.11
Central	1.06 (1–1.13)	.05
Lateral	1.07 (0.99–1.15)	.10
LN ratio, total	2.89 (0.44–18.87)	.27
central	1.81 (0.58–5.69)	.31
lateral	1.25 (0.19–8.13)	.81
Extranodal extension	3.45 (1.1; 10.84)	.03

LN ratio is the number of positive LNs by the total number of LNs removed.

Outcomes and prognostic factors of recurrence

The mean (± SD) follow-up period was 4.3 ± 2.3 years (median 3.8 y; range 0.8–7 y). No patient was lost to follow-up. A recurrence was diagnosed in 19 patients (34%), and the 7-year RFS of DSV patients was 63% (Figure 1). The mean delay to recurrence was 26 ± 1.5 months. One patient had an exclusive recurrence in the central compartment. Eighteen patients had recurrence in the ipsilateral lateral compartment, including six patients with contralateral lateral LN involvement (three of these patients had no contralateral LND at initial surgery) and one patient with metastatic central LNs. In 11 patients, the recurrence involved level II LNs (seven of these patients had no level II LND at the initial operation). The 19 patients with locoregional recurrence underwent reoperation, except three patients with advanced disease (lung and mediastinal metastases). Selective single-level II dissection

Table 3. Clinicopathological Features of DSV (n = 56) Versus High-Risk PTC (n = 48)

Variable	DSV (n = 56)	High Risk PTC (n = 48)[a]	*P* Value
Sex, female	46 (82)	35 (73)	.30
Age, y	32.6 ± 12.5	53.8 ± 15.7	<.001
BMI	23.4 ± 4.0	24.9 ± 3.1	.20
Size of the largest tumor, mm	25.5 ± 20.2	28.2 ± 16.9	.20
Tumors, n	17.1 ± 14.7	6.6 ± 6.1	<.0001
Bilaterality	45 (80)	24 (50)	.001
Extrathyroidal extension	43 (77)	41 (85)	.30
Vascular invasion	25 (41)	11 (23)	.02
Metastases at diagnosis	2 (4)	24 (50)	<.0001
TNM T staging			
1	8 (14)	5 (10)	
2	2 (4)	1 (2)	
3	46 (82)	17 (35)	
4	0	25 (52)	
LN dissection	56 (100)	48 (100)	
Prophylactic	12 (21)	19 (40)	
Therapeutic	44 (79)	29 (60)	
Central compartment	56 (100)	47 (100)	
Lateral compartment	53 (95)	44 (92)	
TNM N staging			
0	2 (4)	12 (25)	
1	54 (96)	36 (75)	.001
1a	6 (11)	6 (13)	
1b	48 (86)	30 (63)	
Resected LNs, n	34.4 ± 21.4	29.7 ± 17.8	.60
Total involved LNs, n	14.9 ± 12.2	7.4 ± 5.9	<.0001
Ratio (N1/N resected) total	0.44 ± 0.23	0.24 ± 0.17	<.0001
Central	0.69 ± 0.34	0.37 ± 0.32	
Lateral	0.32 ± 0.24	0.23 ± 0.15	
Size of the largest node, mm	20 ± 15	24 ± 10	.50
Extranodal extension	23 (49) (n = 47)	28 (44) (n = 41)	.10

Values in parentheses are percentages unless indicated otherwise; values are mean ± SD.

[a] High-risk PTCs are defined by the ATA risk stratification system (2015): macroscopic invasion of tumor into the perithyroidal soft tissues (gross extra thyroidal extension), distant metastases, and pathological N1 with any metastatic lymph node greater than 3 cm in largest dimension.

was performed in two patients through a small incision in the upper neck, seven patients underwent lateral neck dissection (levels II, III and IV) along the sternocleidomastoid muscle, and central and lateral LND were performed through a collar incision in the remaining seven cases. Eight patients had two or more reoperations.

The only prognostic factor for recurrence in the univariate and multivariate analyses was extranodal extension (odds ratio [OR] 3.4 [1.1; 10.8]) (Supplemental Figure 3). The number of centrally involved LNs was also associated with an increasing risk of recurrence ($P = .045$) in the univariate analysis but not in the multivariate analysis (Table 2).

At the end of follow-up, distant metastases occurred in 7% of our cohort, which included two patients at presentation and two additional patients 6 and 7 months after initial thyroid resection (three lung and one mediastinal metastases).

One patient with locoregional recurrence and lung metastases occurring 6 months after surgery died from DSV evolution 17 months after thyroidectomy.

Comparison of DSV (n = 56) with non-DSV PTC (n = 2945)

Table 1 shows the results of the comparison between DSV and all other PTC patients. Using a multivariate regression logistic analysis, the independent factors were age (OR 0.95 [0.92; 0.98]), number of tumors (OR 1.03 [1.01; 1.05]), size of the largest tumor (OR 1.04 [1.02; 1.06]), bilaterality (OR 3.92 [1.55; 9.92]), size of the largest node (OR 4.02 [1.56; 10.33], tumor extension in the perithyroid tissue (OR 4.92 [2.49; 9.73]), and vascular invasion (OR 5.66 [2.46; 13.02]).

During the follow-up, the risk of recurrence was significantly higher in DSV patients than in other PTC patients (34% and 5%, respectively; hazard risk [HR] 8.5 [5.2; 13.9], $P < .0001$, Figure 2). The cancer-related death rate was lower in non-DSV patients than in DSV patients (0.2% vs 1.8%. $P = .03$).

Comparison of DSV (n = 56) with high-risk PTC (n = 48)

Patients with DSV were significantly younger than high-risk PTC patients ($P < .001$), and the number of

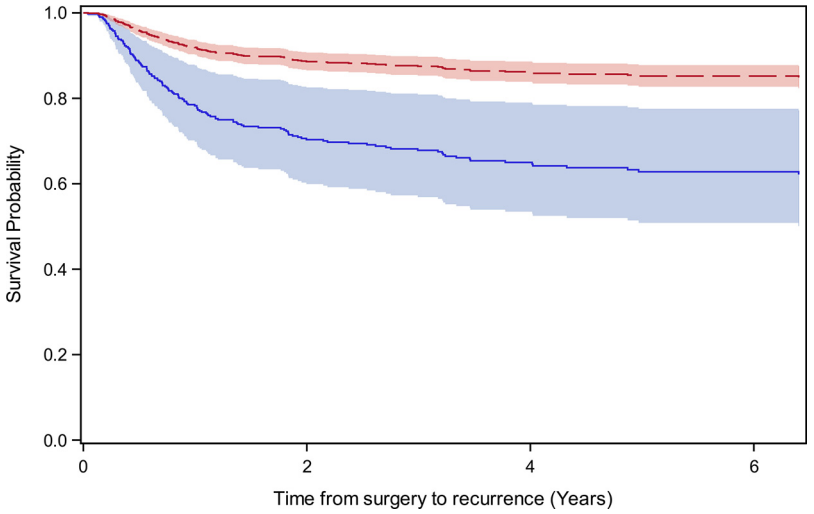

Figure 2. Comparison of RFS rates between the DSV (blue curve) and other classical PTC groups (red curve).

tumors, bilaterality, and vascular invasion were significantly greater in DSV patients (Table 3). The rate of LN metastases was significantly lower than in patients with DSV ($P = .001$) with a ratio N1 to resected LN significantly higher in these patients ($P < .0001$). The prevalence of distant metastases at diagnosis was also lower in patients with DSV (n = 24; 50% vs n = 2; 16%, $P < .0001$).

Using a multivariate regression logistic analysis, independent factors between DSV and high-risk PTC patients were age (OR for DSV 1.26 [0.42; 1.76]), the number of tumors (OR 4.71 [2.01; 11.04]), bilaterality (OR 3.02 [1.56; 9.33]), and LN involvement (OR 1.3 [0.9; 2.1]).

The mean (±SD) follow-up period for high-risk PTC patients was 3.8 ± 2.5 years (median 3.6 y; range 0.1–7 y). The risk of recurrent disease was not significantly different for DSV patients than for high-risk PTC patients (n = 19 [34%] vs n = 13 [27%], respectively; HR 1.1 [0.6; 2.2], $P = .5$) (Figure 3), although the cancer-related death rate was higher in high risk-PTC patients (n = 5, 10%) than in DSV patients (1.8%, $P = .05$).

Furthermore, after excluding patients with distant metastases at the time of thyroid carcinoma diagnosis (24 patients in the high-risk PTC group and two patients in the DSV group), the risk of recurrent disease was slightly higher in DSV patients than in high-risk PTC patients (17 of 54 [31%] vs 5/f 24 [21%], respectively), but this difference did not reach significance ($P = .2$). The cancer-related death rates were also equivalent between the two groups (n = 1; 4% for M0 high-risk PTC patients vs n = 1; 1.8% for M0 DSV PTC; $P = .5$).

Discussion

This is the first report that investigated the clinicopathological features and prognosis of DSV in a large multicentric study. DSV has a strong tendency for extrathyroidal extension (77%), lateral LN involvement (86%), and a high incidence of recurrence (34%). We found that the presence of extranodal extension was the only independent prognostic factor for recurrence in the multivariate analysis. The risk of recurrence was significantly higher in DSV patients than for all other PTC patients (HR 8.5 [5.2; 13.9], $P < .0001$) but not when compared with high-risk PTC (HR 1.1 [0.6; 2.2], $P = .5$).

The preoperative diagnosis of DSV remains difficult. In the present study, DSV was preoperatively suspected in only 17% of patients by US or fine-needle aspiration biopsy. DSV can also mimic chronic thyroiditis, which is suggested by diffuse enlargement of the thyroid lobes, resulting in a delayed diagnosis. Repeated fine-needle aspiration should be carried out to improve the preoperative diagnosis of DSV (13). However, recent technical improvements of thyroid US and cytology contributed to an increasing rate of preoperative diagnosis of DSV over the past decade (3).

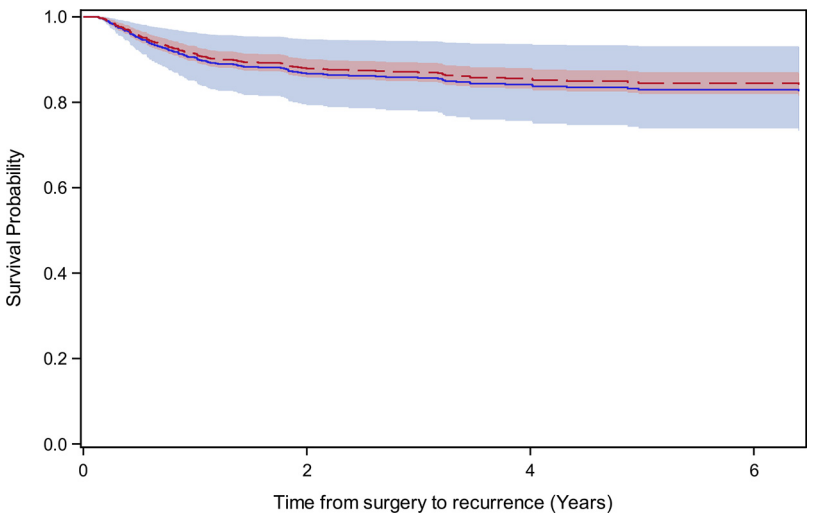

Figure 3. Comparison of RFS rates between the DSV (blue curve) and high-risk PTC groups (red curve).

In our large cohort, we found worse clinicopathological features of DSV than those described in previous studies (2, 8, 9, 12), with young patients, high number of tumors, bilaterality, vascular invasion, and lymph node metastases that were more frequent in DSV than in high-risk PTC patients. This is in contradiction with the results reported by Regalbuto et al (14), who found similar clinicopathological features, except for extrathyroidal extension, between 24 DSV and 123 high-risk PTC patients. The comparison of this study between DSV and high-risk PTC are questionable because high-risk PTC was defined as any patient with at least one of the following characteristics: tumor size greater than 4 cm, advanced grading, bilaterality, extrathyroidal extension, or locoregional or distant metastases. These high-risk PTCs were quite indolent and are not validated by any current guidelines. Consequently, the conclusion of the authors that recurrence or persistent disease at the first postsurgery follow-up was higher in DSV patients than in other high-risk PTC patients (44% vs 24%; $P < .05$) is quite questionable. LN involvement in DSV patients of this study was also lower (50%) than that in the present study (96%). This difference was likely because LND was carried out in only 18 of the 34 patients (53%) for the central neck compartment and six (18%) for the lateral compartment in that study. In our series, a systematic central and ipsilateral lateral LND showed a high propensity to detect locoregional metastases for patients with DSV, including 86% N1b. We also observed that 58% of the DSV recurrences were located in level II, although it is possible that these LNs were already metastatic at the initial presentation in the patients with negative preoperative US findings. Our results suggest that level II should be included systematically in any initial therapeutic LND when DSV is suspected. Moreover, 80% of our patients had bilateral tumors on definitive pathology, including 67% of patients who had an associated contralateral lateral LN involvement of the largest primary tumor. Consequently, we believe that an initial bilateral extended LND should be recommended to expect a reduced locoregional persistence/recurrence rate of DSV. However, aggressive treatments and salvage therapy remain to be determined, although they seem to be effective.

In previous studies, Chow et al (1) and Lam and Lo (9) showed that the prognosis of DSV was not worse than that in a whole cohort of PTC. However, because of the small number of patients in these series (8 and 15 patients, respectively), it is difficult to draw any undisputable conclusion for the prognosis of this PTC variant. The most recent study from Akaishi et al (8) did not reveal significant differences in terms of survival, despite a higher recurrence rate in 20 DSV patients than in an entire cohort of PTC patients (35% vs 10%, $P < .001$). Similar findings were also reported in previous studies (2, 6, 7), and we confirmed in our series this increasing risk in DSV patients when compared with all other PTC patients, not only for locoregional recurrence, but also we found that the cancer-related death rate was lower in non-DSV patients than in DSV patients (1.8% vs 10%, $P = .05$), showing the histological type of DSV as an independent prognostic factor for survival for PTC patients.

Although a more aggressive outcome is usually accepted in patients with DSV when compared with those in other PTCs, the difference between the prognosis of DSV and high-risk PTC remains unknown. In the present study, we found that the RFS rate of DSV patients was equivalent to that of high-risk PTC patients (34% and 27%). We therefore believe that DSV leads to a poor prognosis for recurrence and could justify its classification as a high-risk pathological entity.

The cancer-related death was significantly higher in high-risk patients than DSV patients. A possible explanation is that we included all PTC patients with distant metastases in the high-risk group according to ATA classification, and the prevalence of distant metastases (M1) was significantly higher in that group than in DSV patients (50% vs 7%, $P < .001$). However, no difference in cancer-related death was observed after excluding M1 patients at diagnosis between the two groups (4% for M0 high-risk PTC vs 1.8% for M0 DSV PTC patients, $P = .5$). The low rate of distant metastases observed in our series occurring during the follow-up of DSV patients could be explained by the extensive initial surgical management completed with a systematic postsurgical radioactive iodine treatment and a careful follow-up, although we could not demonstrate in the present study the impact of such a management on survival. However, a systematic lateral LND should be useful to decide adjuvant therapy with radioiodine ablation, and could reduce the risk of persistent/recurrent loco regional disease and the morbidity of reoperation (15, 16).

Metastatic LN with extracapsular extension was the only independent predictor factor for recurrence in the multivariate analysis. Several studies have found this factor for prognosis of PTC (17–19,) and propose that extranodal involvement should be incorporate in classification systems. To the best of our knowledge, this is the first study that demonstrated its impact in DSV patients.

The morbidity rate was relatively high in this series (51%), but it was in most cases transient and the permanent rates of hypocalcemia (4%) and recurrent laryngeal nerve palsy (5%) are of total thyroidectomy with LND for advanced thyroid carcinoma (20). Furthermore, central compartment reoperation may lead to higher rates of mor-

bidity, including 46% of hypocalcemia and 18% of recurrent laryngeal nerve palsy in the study of Roh et al (21). Consequently, the recurrence pattern may urge endocrine surgeons to routinely perform adequate primary surgery and, at least, central lymph node clearance for DSV at initial surgery.

Our study has some limitations including its retrospective nature. Most of postoperative Tg levels were lacking, and we were unable to give any relevant information about radioactive iodine avidity, especially the response to radioactive iodine of metastatic foci in patients with distant metastases. In the same way, the relatively short follow-up of 4.3 years is also a limit for analyzing survival. Because DSVs are rare and recently described tumors, our study may still be underpowered to document more subtle differences with other PTC patients. Despite these limitations, it is one of the largest studies to date.

Conclusion

Patients with DSV present aggressive clinicopathological features with high rates of bilateral locoregional nodal disease. Despite extensive surgical approach, the recurrence rate remains high within the first 5 years, similar to high-risk PTC, requiring careful ongoing surveillance. Overall, at presentation and on follow-up, patients have low rates of distant metastases and cancer-related death.

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