

## Clinicopathologic Features and Outcomes in Patients with Diffuse Sclerosing Variant of Papillary Thyroid Carcinoma

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### Abstract

**Background** Diffuse sclerosing variant (DSV) of papillary thyroid carcinoma (PTC) is a rare variant more common among younger patients.

**Materials and methods** Excluding patients with microcarcinoma, 5848 patients with PTC underwent initial surgery between 1995 and 2011. Twenty-two patients (0.4 %) were histologically diagnosed with DSV, of whom 20 (91 %) were <45 years old. We compared clinicopathologic characteristics and outcomes between patients with DSV and those with classical PTC <45 years old. Univariate analysis by the Kaplan–Meier method in relation to cause-specific survival (CSS) and disease-free survival (DFS) rates was performed with regard to the following variables: sex; anti-thyroglobulin antibody (TgAb) positivity; presence of distant metastasis; pathological lymph node metastasis; extra-thyroidal invasion; and pathological variant (classical vs. DSV).

**Results** The 20 patients with DSV <45 years old comprised 18 females and 2 males. Frequencies of TgAb, pN1b, and local recurrence were higher in the DSV group than in the classical PTC group. Ten-year CSS and DFS rates for PTC patients <45 years old were 99.7 and 88.6 % in the classical PTC group and 100 and 60.5 % in the DSV group. CSS rate did not differ between groups, but DFS rate was significantly lower in the DSV group than in the classical PTC group ( $p < 0.0001$ , log-rank test). Multivariate analysis identified DSV group and pN1b as prognostic factors for recurrence in young PTC patients.

**Conclusions** Most DSV patients were young and had a background of chronic thyroiditis. Outcomes for DSV were very good, but recurrence was more common than in classical PTC.

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## Introduction

Papillary carcinoma is the most common type of well-differentiated carcinoma of the thyroid. In 1985, Vickery et al. described a new variant of PTC, for which they proposed the term “diffuse sclerosis variant” [1]. According to the World Health Organization (WHO) classification, DSV tumors tend to occur in young patients and are characterized by diffuse involvement of one or both thyroid lobes, usually without formation of a dominant mass, and by extensive squamous metaplasia, numerous psammoma bodies, dense lymphocytic infiltration, and stromal fibrosis. DSV was recognized as a histological variant of PTC in 1988 [2].

Previous studies have demonstrated outcomes for DSV [2–26], with some suggesting high incidences of lymph node metastasis and lung metastasis, and thus a less favorable prognosis compared with classical PTC [3, 4, 8, 21, 23, 27]. Other reports have suggested that the prognosis for DSV is no different from that for classical PTC [6, 9, 12, 15, 19, 20, 22]. In Japan, Fujimoto et al. reported that all 14 of their DSV patients remained alive without distant metastasis as of a mean follow-up period of 16 years [6], while Fukushima et al. reported a better cause-specific survival (CSS) rate was better in DSV patients than in other PTC patients, whereas the disease-free survival (DFS) rate was lower [23]. Pediatric thyroid carcinoma patients show a higher incidence of recurrence and higher prevalence of lymph node metastasis and pulmonary metastasis [27]. To assess the biological aggressiveness of DSV, we retrospectively reviewed the medical records of patients with DSV treated in our hospital. PTC patients in this hospital are staged according to the TNM classification, and separate stage groupings are recommended for patients <45 and  $\geq$ 45 years old, because age influences the prognosis of PTC. We therefore compared clinicopathologic features and outcomes between DSV patients and classical PTC patients <45 years old.

## Materials and methods

### Patients

Between 1995 and 2011, a total of 5848 patients underwent initial surgery for PTC, excluding papillary microcarcinoma,

at Ito Hospital in Tokyo. Of these, 22 patients (0.4 %) were histologically diagnosed with DSV. All PTC patients underwent ultrasonography (US) and US-guided fine-needle aspiration (FNA) biopsy preoperatively. All 22 DSV patients were diagnosed on the basis of histological examination of surgical specimens, and lesions were classified according to the WHO classification of malignant tumors [2] and staged according to the TNM classification system of the Union for International Cancer Control. We compared clinicopathologic characteristics and prognosis between the 1194 patients who were <45 years old with the presence of lymph node metastasis (1174 classical PTC patients and 20 DSV patients), because most DSV patients (91 %) were <45 years old and all DSV patients showed the presence of lymph node metastasis. To match for N factor between these groups, patients showing positive results for pathological lymph node metastases (pN1) were selected, because all DSV patients showed the presence of pathological lymph node metastasis. Patients underwent central neck lymph node dissection (CND) as routine dissection when diagnosed with PTC preoperatively. Patients diagnosed preoperatively with lateral lymph node metastasis by US-guided FNA underwent lateral compartment neck dissection (level II–V) in addition to routine dissection of the central compartment (level VI). As a result, all DSV patients underwent CND and 17 patients underwent uni- or bilateral modified neck lymph node dissection (MND).

In our institution, routine radioiodine ablation therapy after initial surgery is not performed unless distant metastasis or massive extra-thyroidal extension and lymph node metastasis is clinically apparent at surgery, because the use of radioiodine ablation therapy has been limited in Japan. In the 1194 young patients, CSS rates were calculated and compared according to the following variables: sex; anti-thyroglobulin antibody (TgAb) positivity; presence of distant metastasis; presence of pathological lymph node metastasis (pN1a vs. pN1b); extra-thyroidal invasion; and pathological variant (classical PTC vs. DSV). DFS rate was also calculated for the 1152 young patients (classical PTC,  $n = 1134$ ; DSV,  $n = 18$ ) who did not show distant metastasis at presentation and who underwent locally curative surgery.

### Statistical analysis

The Kaplan–Meier method was used to calculate cumulative survival rate for patients from the date of diagnosis to the date of death or most recent follow-up examination. The impact of various factors on survival was analyzed using the log-rank test. Multivariate analyses of prognostic factors were based on Cox proportional hazards modeling.

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**Table 1** Clinical characteristics of the 20 cases with DSV <45 years old

Clinical characteristics	No.
Age (years)	
0–9	1
10–19	4
20–29	8
30–39	7
40–49	0
Sex	
Male	2
Female	18
TgAb or TPOAb	
Positive	15
Negative	5
Locations	
One lobe	12
Both lobes	8
Primary tumor at diagnosis	
T1	3
T2	9
T3	8
Distant metastasis at diagnosis	
Absent	18
Present	2
Lymph metastasis at diagnosis	
Absent	4
Present	16
Pathological lymph metastasis	
pN1a	3
pN1b	17
Extra-thyroidal invasion	
pEx0 or 1	18
pEx2	2

Values of  $p < 0.05$  were considered statistically significant. All statistical analyses were performed using JMP version 8.0 software (SAS Institute, Cary, NC, USA).

## Results

### Clinical features of DSV

Twenty PTC patients <45 years old were diagnosed with DSV, and their clinicopathologic characteristics are shown in Table 1. DSV patients comprised 18 females (90 %) and 2 males (10 %), and median age at diagnosis was 25 years (range 9–35 years). The most common initial manifestations were neck swelling (85 %) and general fatigue (10 %). One DSV patient (5 %) was receiving

pharmacotherapy for Graves' disease. Seventeen DSV patients (85 %) tested positive for TgAb or thyroid peroxidase antibody (TPOAb), and 2 DSV patients (10 %) were receiving pharmacotherapy for Hashimoto's thyroiditis. Thyroid functions at presentation were euthyroid in 17 patients (85 %), hypothyroid in 2 (10 %), and hyperthyroid in 1 (5 %).

Preoperative US showed that 8 DSV patients (40 %) had thyroid carcinomas in both thyroid lobes, and 12 (60 %) had thyroid carcinoma in only one lobe. All patients showed common US features such as heterogeneous echotexture, solid composition, ill-defined margins, and scattered microcalcifications. The sensitivity of PTC diagnosis by FNA was very high in our series (100 %). All DSV patients underwent initial surgery, comprising total thyroidectomy (TT) in 17 patients and lobectomy (LT) in 3 patients. All DSV patients underwent CND and 17 patients (85 %) underwent uni- or bilateral MND. All 20 DSV patients showed positive results for pathological lymph node metastasis. Radioiodine ablation therapy (RAT) was performed in 12 DSV patients, accounting for 71 % of patients who underwent total thyroidectomy. Two patients with lung metastasis at presentation were treated by total thyroidectomy and RAT ( $^{131}\text{I}$ , 100 mCi), of whom one achieved complete response. One patient remains alive as of 18 years postoperatively, and the other patient remains alive at 10 years postoperatively.

### Outcomes for young patients with DSV and classical PTC

We compared clinicopathologic characteristics between young patients in the DSV group and young patients in the classical PTC group (Table 2). Frequencies of TgAb, pN1b, and local recurrences were higher in patients with DSV than in those with classical PTC. Differences between groups in incidences of distant metastasis and extra-thyroidal extension were not significant.

### Prognosis in DSV and classical PTC

Median overall follow-up after surgery was 9.0 years. None of the DSV patients died of their disease, whereas 3 patients with PTC died due to distant metastases. The overall 10-year CSS rate was 100 % in the DSV group and 99.7 % in the classical PTC group (Fig. 1). The present results showed no significant difference between the DSV and classical PTC groups in terms of CSS rate. In 1152 patients (1134 patients with classical PTC, 18 patient with DSV) who did not show distant metastasis at presentation and who underwent locally curative surgery, the 10-year DFS was 60.5 % in patients with DSV and 88.6 % in those with classical PTC (Fig. 2). The DFS rate was significantly

**Table 2** DSV vs. PTC in patients under 45 years old

	DSV ( <i>n</i> = 20)	Conventional PTC ( <i>n</i> = 1174)	<i>P</i> value
Sex (male/female)	2/18	178/996	NS
Median age (range)	26 (9–35)	33 (8–44)	NS
TgAb (negative/positive)	5/15	820/354	<0.0001
M at diagnosis (M0/M1)	18/2	1145/29	NS
pN (N1a/N1b)	3/17	613/561	0.001
pEx (0 or 1/ 2)	18/2	1039/135	NS
Surgery (complete/uncomplete)	20/0	1158/16	NS
Total thyroidectomy/others <sup>a</sup>	17/3	287/887	<0.0001
LN dissection (CND/ CND and MND <sup>b</sup> )	3/17	172/1002	NS
Local recurrence (negative/positive)	13/7	1044/114	<0.0001
Distant metastasis (M0/M1)	18/2	1125/49	NS

<sup>a</sup> Lobectomy and subtotal thyroidectomy

<sup>b</sup> Central or modified neck lymph node dissection

lower in the DSV than in the classical PTC group ( $p < 0.0001$ ). Seven patients (35 %) were diagnosed with lymph node recurrence, and all patients underwent re-operation (Table 3). The site of lymph node recurrence was the lateral compartment (level III and IV); of those, 5 patients (71 %) showed lymph node recurrences at the operation site. In DSV patients <45 years old, the median duration to recurrence after surgery was 1.4 years. Details of the eight patients who were diagnosed with distant metastasis or lymph node recurrence are shown in Table 3.

#### Prognostic factor for recurrence

In the 1152 young patients with PTC including DSV (classical PTC,  $n = 1134$ ; DSV,  $n = 18$ ) who did not show distant metastasis at presentation and who underwent locally curative surgery, we examined prognostic factors associated with recurrence, either of lymph node recurrence or distant metastases. Univariate analysis identified male sex, extra-thyroidal invasion (pEx2), lateral lymph node metastasis (pN1b), and histological type (DSV) as significant prognostic factors for recurrence (Fig. 3), whereas multivariate analysis only identified lateral lymph node metastasis (pN1b) and DSV as independent prognostic factors for recurrence (Table 4).

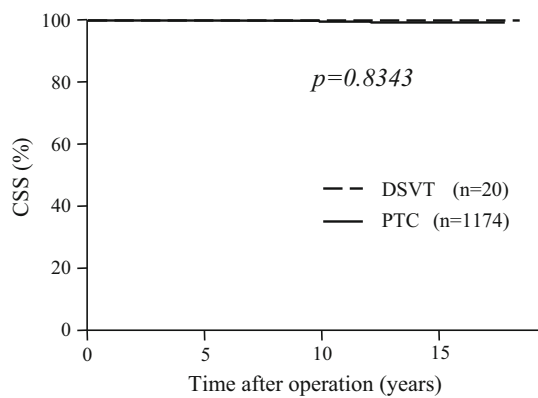
## Discussion

We examined a large series of 22 patients diagnosed with DSV over 16 years in our institution. Previous studies examining larger series of PTC patients have reported prevalence of DSV ranging from 0.74 to 5.3 % of PTC patients as a whole [19]. In our hospital, DSV accounted for 0.4 % of PTCs excluding microcarcinoma. The

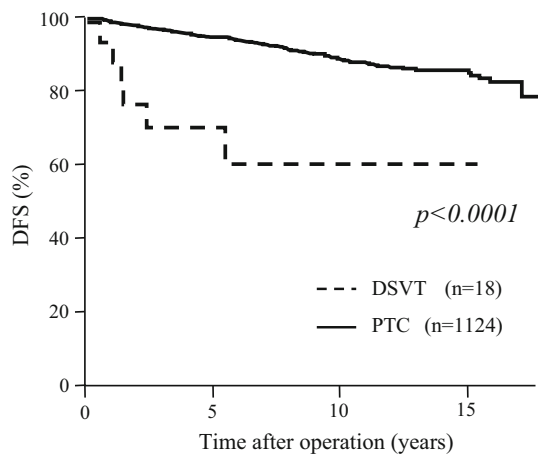
prevalence of DSV was lower in our series than in other previous studies. Previous reports of DSV exclusive of case reports are summarized in Table 5. Koo et al. reported DSV as the most prevalent subtype of pediatric papillary carcinoma PTC in their series [25]. The mean age of DSV patients in our study was 27.6 years (range 9–59 years), similar to that of DSV patients in previous studies. We therefore studied outcomes in subgroups of young patients <45 years old, because age is thought to influence the prognosis of DSV.

Preoperative neck US may be helpful in detecting intra-thyroidal extension and lymph node metastases in DSV patients. The US features of DSV were heterogeneous echotexture, solid composition, ill-defined margins, scattered microcalcifications with a “snowstorm” appearance, and various echogenicities [28]. In this study, all patients showed the US features of scattered microcalcifications. Eight (40 %) patients showed intra-thyroidal extension of bilateral lobes. Sixteen (80 %) patients showed positive findings for lymph node metastases on preoperative US. The sensitivity of PTC diagnosis by FNA was very high in our series (100 %). DSV can be diagnosed preoperatively based on a combination of typical imaging findings and cytological examination. The sensitivity of PTC diagnosis by FNA was very high in our series (100 %). DSV can be diagnosed preoperatively based on a combination of typical imaging findings and careful cytological examination.

In our series, 91 % of DSV patients complained of neck swelling, and 85 % tested positive for TgAb or TPOAb and showed a background of chronic lymphocytic thyroiditis. In one previous study, approximately 30 % of DSV patients tested positive for TgAb [20], while in another study, a higher percentage of DSV patients were TgAb-positive (DSV 72 vs. PTC 42 %) [23]. In the present series, TgAb-positive results were seen in a higher proportion of DSV



**Fig. 1** CSS curves of the DSV group and conventional PTC group. No significant difference between groups was evident



**Fig. 2** Comparison of disease-free survival (DFS) rates between the DSV and conventional PTC groups. DFS rate was significantly lower in the DSV group than in the conventional PTC group ( $p < 0.0001$ , log-rank test)

patients (85 %) than among patients with classical PTC (30 %). Clinically, DSV is sometimes misdiagnosed as Hashimoto's thyroiditis due to the diffuse enlargement of the thyroid lobes. Early correct diagnosis and surgical treatment of DSV is required.

In our institution, the standard operation for patients with PTC was hemi-thyroidectomy or total thyroidectomy and CND, even for N0 patients. The indications for total thyroidectomy are intra-thyroidal metastasis, extra-thyroidal invasion, maximum tumor diameter more than 4 cm, presence of distant metastasis, and presence of lymph node metastasis on preoperative US-guided FNA. Patients diagnosed with DSV preoperatively were recommended total thyroidectomy. Patients diagnosed preoperatively with lymph node metastasis on US-guided FNA underwent additional uni- or bi-lateral MND. In this series, total thyroidectomy was performed in 85 % of DSV patients. Lobectomy was performed in a few DSV patients when the primary tumor was located in only one lobe. All DSV patients underwent CND, and 86 % also underwent MND. During follow-up (median, 9 years), lymph node recurrence was diagnosed in 40 % of young DSV patients, and re-operation was performed in all such cases.

The lung has been the most common site of distant metastasis in reports of DSV in the literature, and the mean incidence of distant metastasis reported in DSV is 14.9 % [19]. In our own study, 2 DSV patients (10 %) showed lung metastasis at presentation. Both M1 patients were treated by total thyroidectomy as the initial surgical procedure, followed by RAT. Both patients showed positive  $^{131}\text{I}$  uptake into lung metastases and one achieved complete remission with 5 administrations of RAT. We recommend initial surgery and subsequent RAT.

Previous studies comparing DSV with classical PTC have reported a similar predilection of DSV for females, younger age at tumor presentation, and higher incidences

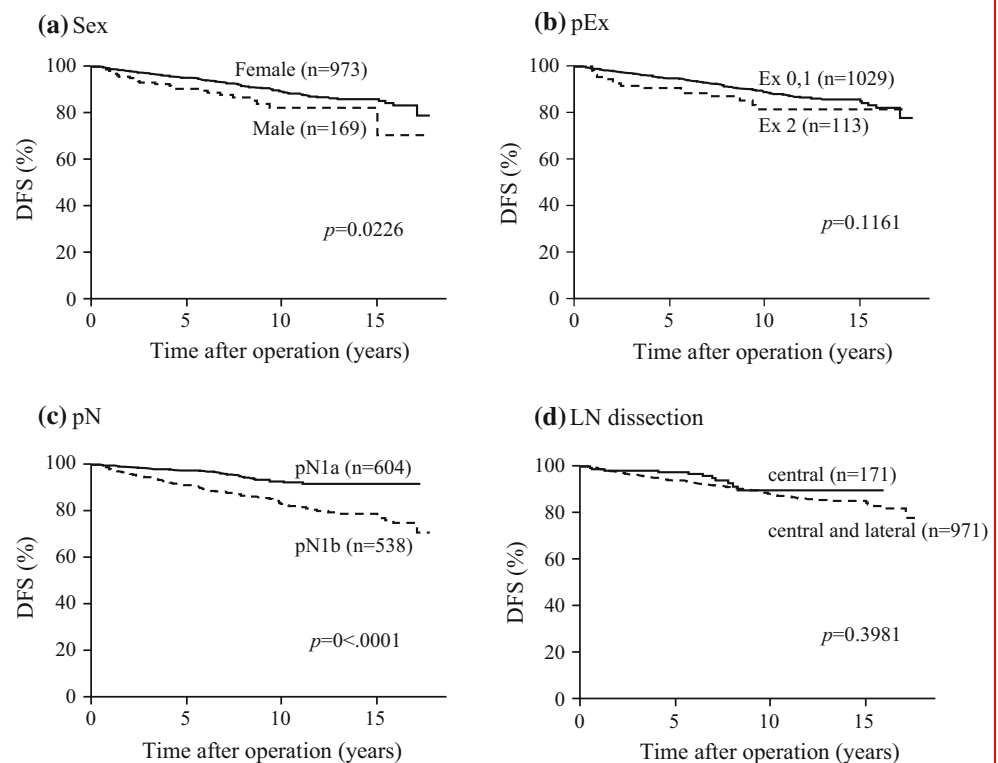
**Table 3** The Clinical characteristics and treatments of the 8 young DSV patients with distant metastasis or recurrence

No.	Age	Sex	M	pEx	pN	Surgery	Recurrence	Other treatment	Outcome
1	13	F	1(Lung)	1	1b	TT <sup>a</sup> + bil MND	Absent	RAI	Alive (18 years)
2	21	F	0	0	1b	TT + bil MND	LN (6 years)	Reoperation	Alive (13 years)
3	21	M	0	0	1b	TT+bil MND	LN (1 years)	RAI, reoperation	Alive (12 years)
4	16	F	0	0	1b	LT+uni MND	LN (1 years)	Reoperation	Alive (12 years)
5	26	F	1(Lung)	1	1b	TT+bil MND	LN (1 years)	RAI, reoperation	Alive (10 years)
6	25	F	0	0	1b	LT+uni MND	LN (2 years)	RAI, reoperation	Alive (10 years)
7	31	F	0	2	1b	TT+bil MND	LN (1 years)	RAI, reoperation	Alive (9 years)
8	35	F	0	0	1a	TT+CND	LN (1 years)	RAI, reoperation	Alive (7 years)

<sup>a</sup> Total thyroidectomy

<sup>b</sup> Lobectomy

**Fig. 3** **a** Comparison of DFS rates between female and male. **b** Comparison of DFS rates between patients with pEx 0 or 1 and pEx2. **c** Comparison of DFS rates between patients with pN1a and pN1b. **d** Comparison of DFS rates between patients with central compartment dissection, and those with both central and lateral compartment dissection



**Table 4** Multivariate analysis to identify prognostic factors for recurrence related to clinicopathological characteristics

Factor	Risk ratio	95 % CI	P value
Sex (male)	1.55	0.94–2.42	0.08
pN (pN1b)	2.28	1.53–3.48	0.0004
Histological type (DSV)	5.84	2.43–11.91	<0.0001

CI confidence interval

of cervical lymph node involvement and lung metastasis [3, 4, 6, 19, 20, 22, 23]. Regalbuto et al. reported finding that DSV patients have a poorer prognosis than low-risk PTC patients and can be assimilated into patients with high-risk PTC [26]. The present study found that DSV has a higher incidence of lymph node metastasis and extra-thyroidal extension, but the frequency of distant metastasis did not differ from that in other PTCs. We found that the DFS rate of DSV patients was significantly lower than that of classical PTC patients. We also performed multivariate analysis to identify prognostic factors for recurrence, showing the histological type of DSV as an independent prognostic factor. Patients with DSV are classified as a high-risk group in PTC. Initial surgical treatment with total thyroidectomy and subsequent RAT are recommended and long-term follow-up is required for this group of patients.

Various limitations must be considered in interpreting the results of this retrospective study. First, surgical strategies for the extent of thyroidectomy in PTC patients remain controversial in Japan. In 2010, a guideline for thyroid tumor was created by the Japan Association of Endocrine Surgeons and the Japanese Society of Thyroid Surgery [29]. As we have mentioned before, the indications for total thyroidectomy in our institution are a little different from them. In this study, all DSV patients were diagnosed with PTC by fine-needle aspiration and 17 DSV patients (85 %) underwent total thyroidectomy because DSV was suspected preoperatively. Only 3 patients underwent lobectomy, because the primary tumors were located in only one lobe. The present study showed no remnant thyroidal recurrence in DSV patients.

This was attributed to strong selection bias in the selection of total thyroidectomy or lobectomy. Further investigation is needed to appropriately determine indications for the extent of thyroidectomy.

Second, the validity of the radioiodine ablation therapy after initial surgery cannot be compared between classical PTC patients and DSV patients, because the indications for RAT in Japan are limited to patients with the presence of extra-thyroidal invasion, massive lymph node metastasis, or distant metastasis. Follow-up of patients with DSV for a long time is necessary to investigate the biological characteristics of this pathology.

**Table 5** Data from studies of DSV in the literature

No.	Study (year)	Number of patients	Mean age (range)	Sex (M/F)	Distant metastases	Recurrence	Mean follow-up, years (range)	Disease-related death
1	Carcangiu (1989)	15	29.3 (9–63)	3/12	3 (Lung)	8	7.7 (2–13)	0
2	Wu (1989)	3	38.0 (33–46)	1/2	1 (Bone)	1	NR (1–5)	0
3	Soares (1989)	10	34.7 (10–67)	1/9	5 (Lung)	5	NR (3–14)	1
4	Fujimoto (1990)	14	19.6 (10–28)	0/14	0	3	16 (1–31)	0
5	Mizukami (1990)	3	41.7 (32–60)	0/3	1 (lung)	0	NR	1
6	Hayashi (1990)	4	29.2 (1742)	0/4	0	0	NR	0
7	Schroder (1990)	2	22.0 (10–34)	0/2	0	0	2 and 13 (2–13)	0
8	Gomez-Morales (1991)	4	19.5 (11–27)	1/3	0	1	NR	0
9	Macak (1993)	5	27.2 (15–36)	0/5	0	0	NR (3–9)	0
10	Moreo Egea (1994)	4	32.2 (23–48)	2/2	0	2	7.8 (6–10)	0
11	Albareda (1998)	7	23.0 (12–34)	2/5	1 (Lung)	2	6.4 (1–12)	0
12	Chow (2003)	8	27.4 (11–48)	2/6	1 (Lung)	1	8 (1.4–15.2)	0
13	Thompson (2005)	22	18 (6–19)	8/14	NR	2	16.3 (1.5–31)	1
14	Lam (2006)	15	29 (10–57)	2/13	2 (Lung, brain)	5	11.6 (1.5–28.5)	0
15	Falvo et al (2006)	83	40	24/59	6	13	7.6 (4–10)	3
16	Fukushima (2010)	35	30.4 ±13.0	5/30	4 (3 Lung, 1 Lung + brain)	9	NR	2
17	Koo (2010)	49	24.9 (6–66)	11/38	4	8	NR	NR
18	Concetto Regalbuto (2011)	34	43.2 (15–78)	4/30	1	15	50 mo (12–127 mo)	0
19	Our study (2013)	22	27 (9–59)	2/20	2 (Lung)	6	9	0

## Conclusions

DSV was more common in younger PTC patients. A high proportion of DSV patients tested positive for TgAb and showed a background of chronic lymphocytic thyroiditis. Outcomes for DSV patients were very good, similar to those for classical PTC, but lymph node recurrence was more common than with classical PTC.

**Conflict of interest** The authors have no conflict of interest to declare.

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