Prognostic impact of vascular invasion in differentiated thyroid carcinoma: a systematic review and meta-analysis

Huy Gia Vuong^{1,2}, Tetsuo Kondo¹, Uyen N P Duong³, Thong Quang Pham², Naoki Oishi¹, Kunio Mochizuki¹, Tadao Nakazawa¹, Lewis Hassell⁴ and Ryohei Katoh¹

¹Department of Pathology, University of Yamanashi, Yamanashi, Japan, ²Department of Pathology, Cho Ray Hospital, Ho Chi Minh City, Vietnam, ³Pham Ngoc Thach University of Medicine, Ho Chi Minh City, Vietnam, and ⁴Department of Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA

Correspondence should be addressed to T Kondo
Email
ktetsuo@yamanashi.ac.jp

Abstract

Background: The role of vascular invasion (VI) as a prognostic marker in thyroid cancer is continuously debated among investigators. In this systematic review and meta-analysis, we aimed to investigate the association of VI with tumor recurrence and patient mortality in differentiated thyroid cancers (DTCs).

Methods: We searched five electronic databases for cases of DTC matching our criteria. Data of tumor persistence, locoregional recurrence (LRR), distant recurrence (DR) and overall recurrence/persistence (RP) were extracted and pooled into odds ratios (OR) and corresponding 95% confidence intervals (CIs) using random effect model. Pooled hazard ratio (HR) for disease-specific survival (DSS) was calculated using random effect model weighted by inverse variance method. Publication bias was examined by using Egger's test and funnel plot.

Results: From 1650 studies, we included 26 studies comprising 11 961 DTCs for meta-analyses. In DTC patients, we found significant associations of VI with tumor persistence (OR=2.75; 95% CI=1.46–5.18), LRR (OR=4.44; 95% CI=2.94–6.71), DR (OR=5.08; 95% CI=2.95–8.75), overall RP (OR=3.53; 95% CI=2.09–5.96) and worse DSS (HR=2.47; 95% CI=1.45–4.21). Our results also demonstrated that the presence of extensive VI is associated with a significantly higher risk for DR in follicular thyroid carcinomas as compared with focal VI.

Conclusion: Our study demonstrated a significant impact of VI on tumor recurrence and patient survival in DTC patients. The presence and extent of VI should be considered an adverse prognostic factor in DTCs.

European Journal of
Endocrinology
(2017) **177**, 207–216

Introduction

Thyroid carcinoma is the most common endocrine malignancy, and its incidence has been increasing over the years worldwide (1, 2). According to the World Health Organization (WHO) classification, thyroid cancer is classified into differentiated thyroid carcinoma (DTC), poorly differentiated thyroid carcinoma (PDTC) and undifferentiated thyroid carcinoma (UTC) (3). DTCs including papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC) and Hurthle cell carcinoma (HCC) account for 95% of thyroid cancer and have

more favorable prognosis as compared with PDTCs and ATCs (3).

DTCs usually exhibit indolent behavior with a 10-year survival rate of approximately 90–95% (1, 3, 4). Various clinicopathological factors have been reported to affect the patient outcomes such as older age, male gender, large tumor size, nodal or distant metastasis (5). VI is not a common event in DTCs which ranged from 2.5% to 52% (6, 7, 8). The rate of VI is higher in FTC than in PTC which can explain why FTC metastasizes to distant organs

more frequently than does PTC (7). The role of VI as a prognostic factor in DTC, however, remains controversial among literature studies (7, 9, 10).

In the current study, we aimed to conduct a systematic review and meta-analysis of observational studies to determine the impact of VI on tumor recurrence and disease-related mortality in patients with DTC.

Methods

Literature search

We searched for relevant articles in five electronic databases including PubMed, ISI Web of Science, Scopus, World Health Organization Global Health Library (WHO GHL) and Virtual Health Library (VHL) from inception to February 2017. The search terms were the following: (papillary OR follicular OR Hurthle OR differentiated OR well-differentiated) AND thyroid AND (carcinoma OR cancer) AND (vascular OR intravascular OR angioinvasive). Potential studies were also found by reviewing the citations within the included publications and reviews. Our study strictly followed the recommendation of Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement (11).

Selection criteria and abstract screening

We imported all search results from five electronic databases into Endnote (Thomson Reuters, PA, USA) and performed duplicate deletion. Two reviewers independently screened the titles and abstracts of included studies using the following inclusion criteria (i) retrospective or prospective observational studies and (ii) articles in which the authors investigated the association of VI with tumor RP or disease-related mortality in patients with DTC. We used the following criteria to exclude studies: (i) studies only reporting data on lymphatic invasion and had no data for VI, (ii) articles in which PDTCs or ATCs were included and extracted data of DTC not separately segregatable, (iii) review, (iv) case report, (v) conference, poster, proceeding paper, book, thesis and (vi) duplicated articles. Disagreements between two reviewers were resolved by discussion and consensus.

Full-text screening and data extraction

Full text of all potential articles was consecutively downloaded and screened independently by two

reviewers. Relevant data were extracted into a predefined data extraction form. We extracted the following data: institution, city, country, publication year, surgical time period, study design, number of events of tumor recurrence (LRR, DR, tumor persistence, overall RP) and disease-related death. Data of survival outcomes (DSS) and follow-up duration were also collected, if available. Disagreements between two reviewers were resolved again by discussion and consensus. In cases of insufficient data in the original papers or unpublished data, we tried to obtain potential data by contacting the authors via email.

Quality assessment and risk of bias analysis

We assessed the methodologic quality of included studies based on the Newcastle–Ottawa Scale (NOS) for quality of cohort studies in our meta-analyses (12). Stars were awarded for each cohort study (maximum nine stars) based on a developed checklist (12). In the second domain of outcome category, we awarded one star if the study had a median time of follow-up longer than five years, which was considered long enough for tumor recurrence and mortality to occur. In the last domain of outcome category, studies with the follow-up rate $\geq 80\%$ or description of those lost suggesting no difference from those followed were awarded one star. Studies awarded at least six stars were considered moderate- to high-quality studies and those with a NOS value of less than six were regarded low-quality studies.

Data analysis

We used Review Manager version 5.3 (Cochrane Collaborative, Oxford, UK) to analyze data. We calculated the pooled estimates of OR and its 95% CI to examine the association of vascular invasion with tumor recurrence (LRR, DR, tumor persistence and overall RP) by using random-effect modeling. We excluded the studies from the meta-analyses where there were no events in both arms because such studies do not provide any indication of either the direction or magnitude of the effect (13). Because survival rates at specific time points are known to be incompatible for meta-analyses of time-to-event data, pooled hazard ratio (HR) for DSS was calculated using the random model effect weighted by inverse variance method. HR and its 95% CI were directly collected from the original articles or indirectly estimated from Kaplan–Meier curves using the methods by Tierney *et al.* (14) Heterogeneity across studies was quantified by

the I^2 statistic, which measures the percentage of total variation across studies (15). Degree of heterogeneity across studies was classified as low, moderate and high with value of <25, 25–50 and >50%, respectively (16). Sources of heterogeneity were examined by using (i) subgroup analysis (PTC and FTC) and (ii) sensitivity analysis performed by excluding each of the included studies one at a time. Presence of publication bias was examined using Egger's regression test and funnel plot, investigated by MAVIS version 1.1.2—a R package (17). A P value less than 0.05 was considered as statistically significant publication bias.

Results

After importing results from five electronic databases and deleting duplicates, we found 1751 articles for title and abstract screening. We also found five additional articles by reading citations from the included studies and reviews. Following title and abstract screening step, we identified 39 potential articles to read full texts. We excluded 13 articles after carefully reading full texts, leaving 26 studies with a total of 8834 PTCs and 3127 FTCs that were included for final analysis (5, 7, 8, 9, 10, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38) (Fig. 1). Because HCC is considered a distinct variant of FTC in the WHO classification (3) and HCCs were only included in three studies by Van Heerden *et al.* (35), Ghossein *et al.* (24) and Xu *et al.* (38) respectively, the number of HCC cases was taken into account of FTC cases. Patients from

the studies by Kim *et al.* (26) and Ghossein *et al.* (24) could possibly overlap with patients from the studies by Kim *et al.* (8) and Xu *et al.* (38), respectively. We decided to select the study with higher number of cases for statistical analysis. Table 1 shows the detailed characteristics of each study.

For studies containing potential data, we contacted the authors via email to provide unreported HR and its 95% CI for effects of VI on DSS and we received responses from Sweden, USA and Japan with adequate information for the meta-analysis (32, 33, 38). Stenson *et al.* (32) and Sugino *et al.* (33) provided unadjusted HR and its 95% CI of VI on DSS from their FTC series. We received data of unadjusted HR and its 95% CI of VI on DSS in the study by Xu *et al.* (38) for the entire DTC population and subgroups of PTC and FTC.

Impact of VI on tumor persistence

We found separate data of tumor persistence in four of included studies, comprising 705 patients with DTCs. The pooled result demonstrated that VI was significantly associated with higher risk for tumor persistence (OR=2.75; 95% CI=1.46–5.18) (Fig. 2A). There was no heterogeneity across studies ($I^2=0\%$; p-heterogeneity=0.97).

Impact of VI on LRR

Separate data regarding impact of VI on LRR were found in ten studies, including 5018 patients with DTCs. In total, 15.6% DTC patients with VI and 2.7% of DTC patients without VI developed LRR during follow-up. DTCs with VI were associated with a significantly increased risk for LRR (OR=4.44; 95% CI=2.94–6.71) (Fig. 2B). Heterogeneity among included studies was not present ($I^2=0\%$; p-heterogeneity=0.60).

Impact of VI on DR

Ten studies comprising 1949 patients with DTCs provided relevant data regarding association of VI and DR. DR was identified in 13.9% and 2.2% of DTCs with and without VI during follow-up, respectively. The overall estimate showed a significant impact of VI on DR (OR=5.08; 95% CI=2.95–8.75) (Fig. 2C). Amount of heterogeneity among studies was low ($I^2=15\%$; p-heterogeneity=0.30). Excluding the study by Xu *et al.* (38) completely removed the heterogeneity among the included studies ($I^2=0\%$).

Figure 1

Study flowchart. VHL, Virtual Health Library; WHO GHL, World Health Organization Global Health Library.

Table 1 Characteristics of included studies.

Author	Institution	Histologic types	No. of patients		Mean age (years)	Median follow-up (months)	Number of events			
			With VI	Without VI			LRR	DR	Tumor persistence	Overall RP
Aida <i>et al.</i> (18)	Nippon Medical First School of Medicine	FTC	5	4	51.6	79.2	Yes	Yes	Yes	Yes
Akslen <i>et al.</i> (19)	Haukeland Hospital	PTC	24	149	46.0	87.6	No	No	No	No
Chereau <i>et al.</i> (20)	University Pierre and Marie Curie	PTC	71	2447	50.4	84	No	No	No	Yes
Collini <i>et al.</i> (9)	Istituto Nazionale Tumori	FTC	15	3	44.6	133	Yes	Yes	No	Yes
D'Avanzo <i>et al.</i> (21)	University of California, San Francisco	MIFTC	50	45	49.0	72	No	No	Yes	Yes
de Castro <i>et al.</i> (22)	Brazilian Cancer Care	PTC	26	33	47.0	120	No	No	Yes	Yes
Enomoto <i>et al.</i> (23)	Noguchi Thyroid Clinic	FTC	3	17	17.3	282	No	No	No	Yes
Falvo <i>et al.</i> (10)	University of Rome	PTC	39	361	45.5	79.2	Yes	Yes	No	No
Furlan <i>et al.</i> (7)	Mount Sinai Hospital	PTC	18	290	43.9	47.6	Yes	Yes	Yes	No
Gardner <i>et al.</i> (24)	Washington Hospital Center	FTC	17	33						
Ghossein <i>et al.</i> (25)	Memorial Sloan Kettering Cancer Center	PTC	31	379	39.0	66	Yes	Yes	No	No
Kim <i>et al.</i> (26)	Asan Medical Center	HCC	32	18	52.0	35.9	No	No	No	Yes
Kim <i>et al.</i> (27)	Samsung Medical Center	PTC	33	629	44.8 ^a	68	No	No	No	Yes
Kim <i>et al.</i> (8)	Samsung Medical Center	MIFTC	36	36	40.3	76.1	Yes	Yes	No	No
Lang <i>et al.</i> (28)	University of Hannover	FTC	106	98	45.0	55	No	No	Yes	Yes
Lee <i>et al.</i> (29)	Asan Medical Center	FTC	114	53	51.0	ND	No	No	No	No
Lee <i>et al.</i> (30)	Korea University Guro	MIFTC	39	127	ND	103.5	No	Yes	No	No
Marques <i>et al.</i> (31)	Instituto Portugues de Oncologica	PTC	10	194	48.1	35	Yes	No	No	Yes
Nishida <i>et al.</i> (32)	Multicenter	PTC	36	219	47	74	No	No	No	Yes
Stenson <i>et al.</i> (33)	Karolinska University Hospital	DTC	120	136	52.4	79.2	Yes	Yes	No	Yes
Sugino <i>et al.</i> (34)	Ito Hospital	MIFTC	36	22	50 ^a	140	No	No	No	No
Suh <i>et al.</i> (35)	Seoul National University	MIFTC	190	39	46 ^a	90	No	Yes	No	No
Van Heerden <i>et al.</i> (36)	Mayo Clinic	PTC	39	3342	45.6	67.2	Yes	Yes	No	Yes
Wong <i>et al.</i> (37)	Cedars Sinai Medical Center	FTC	45	20	56.3	11.1	Yes	Yes	No	No
		DTC	202	1414	46.1	11.8	No	No	No	Uni/
Wu <i>et al.</i> (38)	University of California, San Francisco	PTC	43	197	38 ^a	119	No	No	No	Multivariate
Xu <i>et al.</i> (39)	Memorial Sloan Kettering Cancer Center	PTC	20	204	45.8	72	Yes	Yes	No	Multivariate
		FTC	32	20					Yes	Univariate

Yes indicates that the study was evaluated for the corresponding factor; No indicates that the study was not evaluated for the corresponding factor.

^aMedium age.

DR, distant recurrence; DSS, disease-specific survival; HR, hazard ratio; LRR, locoregional recurrence; RP, recurrence/persistence; VI, vascular invasion; FTC, follicular thyroid carcinoma; PTC, papillary thyroid carcinoma; MIFTC, minimally invasive follicular thyroid carcinoma; ND, no description.

Figure 2

Forest plots of association of vascular invasion with (A) tumor persistence; (B) locoregional recurrence; (C) distant recurrence; (D) overall recurrence/persistence and (E) hazard ratio for disease-specific survival.

and the significant effect remained unaffected (OR=4.08; 95% CI=2.44–6.82).

Impact of VI on overall RP

We found 14 studies with 8053 DTC patients reporting relevant information of the association of VI and overall

RP. The pooled estimate demonstrated that VI significantly increased the risk for overall RP (OR=3.53; 95% CI=2.09–5.96) (Fig. 2D). The degree of heterogeneity across studies was high ($I^2=60\%$; p -heterogeneity <0.0001). It remained significant after removing each of included studies at a time but the statistical significance of effects was unaffected. The significant between-study heterogeneity

Clinical Study	H G Vuong and others	Vascular invasion in DTCs: a meta-analysis	177:2	212
----------------	----------------------	---	-------	-----

Table 2 Pooled results of subgroup analysis for tumor recurrence.

Subgroup	No. of studies	No. of patients	OR	95% CI	P value	I ² (%)
PTC						
LRR	5	4553	5.95	3.51–10.08	<0.0001	0
DR	3	967	8.11	3.46–18.98	<0.0001	0
Tumor persistence	2	356	2.76	0.98–7.80	0.05	0
Overall RP	6	7011	3.36	1.49–7.59	0.004	71
FTC						
LRR	5	209	4.73	1.28–17.45	0.02	0
DR	7	606	3.76	1.67–8.47	0.001	0
Tumor persistence	3	349	2.78	1.27–6.07	0.01	0
Overall RP	6	510	2.76	1.17–6.53	0.02	28

CI, confidence interval; DR, distant recurrence; FTC, follicular thyroid carcinoma; LRR, locoregional recurrence; OR, odds ratio; PTC, papillary thyroid carcinoma; RP, recurrence/persistence.

was caused mainly by the studies by Marques *et al.* (30), Xu *et al.* (38) and Suh *et al.* (34). Excluding these three studies simultaneously resulted in completely removing the heterogeneity among included studies ($I^2=0\%$; p -heterogeneity=0.59) and the overall effect slightly decreased but remained significant (OR=2.11; 95% CI=1.49–3.00).

Impact of VI on DSS

In 26 included studies, we found relevant data of HR for DSS or sufficient data to estimate HR for DSS in only four studies (5, 8, 36, 37). We received three replies from USA, Sweden and Japan containing adequate data on unadjusted HR for DSS for the pooled analysis (32, 33, 38). We used random effect model weighted by inverse variance method to pool HR for DSS and the pooled result demonstrated that VI significantly increased the risk of disease-related mortality in DTC patients with VI compared with DTC patients without VI (HR=2.47; 95% CI=1.45–4.21) (Fig. 2E). There was a moderate amount of heterogeneity between the included studies ($I^2=45\%$; p -heterogeneity=0.09). After excluding the study by Stenson *et al.* (32), there was no heterogeneity among the studies ($I^2=0\%$; p -heterogeneity=0.42) and the pooled

estimate remained significant with an increased effect size (HR=3.02; 95% CI=1.94–4.68).

Subgroup analyses

To further explore the sources of heterogeneity among studies, we performed subgroup analysis with regard to the impact of VI on recurrence and survival in PTC and FTC subgroup. Association of LRR, DR and overall RP with VI in each subgroup is summarized in Table 2.

In PTCs, the pooled results showed that VI significantly increased the risk of LRR, DR and overall RP. However, VI was not associated with a higher risk for tumor persistence (Table 2 and Supplementary Fig. 1, see section on supplementary data given at the end of this article). In FTC subgroup, effects of VI on tumor persistence, LRR, DR and overall RP were all associated with a significantly increased risk (Table 2 and Supplementary Fig. 2).

We carried out an additional analysis to further examine the prognostic effect of extensive VI (≥ 4 VI foci) in FTCs and found eligible data in four studies (9, 27, 28, 38). Our results demonstrated that the presence of extensive VI increases the risk for DR 26 times as compared with FTCs with focal VI (<4 VI foci) (OR=26.38; 95% CI=7.67–90.78; $I^2=54\%$).

Table 3 Pooled results of subgroup analysis for DSS.

Subgroup	No. of studies	No. of patients	HR for DSS	95% CI	I ² (%)
HR calculation method					
Unadjusted HR	5	2358	2.16	1.19–3.91	50
Adjusted HR	3	2066	2.75	1.44–5.25	12
Histologic type					
PTC	3	637	5.70	2.63–12.37	0
FTC	4	543	1.38	0.87–2.21	0
MIFTC	3	452	1.70	0.64–4.52	50

CI, confidence interval; FTC, follicular thyroid carcinoma; HR, hazard ratio; MIFTC, minimally invasive follicular thyroid carcinoma; PTC, papillary thyroid carcinoma.

Subgroup analyses for DSS were also performed by HR calculation method (unadjusted HR and adjusted HR) and histologic type (PTC, entire FTC population and minimally invasive FTC (MIFTC)). Subgroups of unadjusted and adjusted HR both showed significantly adverse effects of VI on DSS (Table 3). When histologically dividing into subgroups of PTC and FTC, only the pooled result of PTC was associated with worse impact on DSS. On the other hand, in subgroups of FTC and MIFTC, VI showed no significant effect on DSS (Table 3 and Supplementary Fig. 3). Between-study heterogeneity

significantly decreased and was almost absent in subgroup analyses.

Risk of bias assessment and quality of studies

All included studies were retrospective studies. The number of stars awarded to each of included studies ranged from five to eight stars. All studies but two were considered to be of moderate to high quality. Details of given stars within domains of Selection, Comparability and Outcome for all included studies were described in Table 4.

Table 4 Newcastle–Ottawa quality assessment scale for cohort studies.

Author	Number of stars awarded in each domain			Study quality
	Selection	Comparability	Outcome	
Aida <i>et al.</i> (18)	3	0	3	Moderate
Akslen <i>et al.</i> (19)	3	1	3	High
Chereau <i>et al.</i> (20)	3	0	3	Moderate
Collini <i>et al.</i> (9)	3	0	3	Moderate
D'Avanzo <i>et al.</i> (21)	3	0	3	Moderate
de Castro <i>et al.</i> (22)	3	0	3	Moderate
Enomoto <i>et al.</i> (23)	3	0	3	Moderate
Falvo <i>et al.</i> (10)	3	1	3	High
Furlan <i>et al.</i> (7)	3	0	2	Low
Gardner <i>et al.</i> (24)	3	1	3	High
Ghossein <i>et al.</i> (25)	3	0	3	Moderate
Kim <i>et al.</i> (26)	3	0	3	Moderate
Kim <i>et al.</i> (27)	3	0	3	Moderate
Kim <i>et al.</i> (8)	3	0	3	Moderate
Lang <i>et al.</i> (28)	3	0	3	Moderate
Lee <i>et al.</i> (29)	3	0	3	Moderate
Lee <i>et al.</i> (30)	3	0	2	Low
Marques <i>et al.</i> (31)	3	0	3	Moderate
Nishida <i>et al.</i> (32)	3	0	3	Moderate
Stenson <i>et al.</i> (33)	3	0	3	Moderate
Sugino <i>et al.</i> (34)	3	0	3	Moderate
Suh <i>et al.</i> (35)	3	0	3	Moderate
Van Heerden <i>et al.</i> (36)	3	0	3	Moderate
Wong <i>et al.</i> (37)	3	0	3	Moderate
Wu <i>et al.</i> (38)	3	2	3	High
Xu <i>et al.</i> (39)	3	0	3	Moderate

Publication bias

Egger's regression test and funnel plot were used to examine the presence of publication bias. Observation of funnel plots did not reveal strong indication of publication bias among the set of studies included in the meta-analyses. Egger's regression test of all effects did not suggest any evidence of publication bias (data not shown). We did not analyze publication bias among subgroups because this method is known to be unreliable for meta-analyses of small numbers of included studies (39).

Discussion

DTC is the major histologic type and accounts for more than 95% of thyroid cancer (3). Most of DTCs generally show good response to initial treatment. However, a subset of DTCs behave aggressively, develop metastases or recurrence and are associated with a higher rate of mortality. There have been a number of studies investigating the prognostic factors for DTCs, and some factors have been proposed as adverse prognostic factors such as age over 45, tumor size exceeding 4 cm, the presence of extrathyroidal extension, lymph node metastasis and distant metastasis (5, 40, 41). The role of VI to predict adverse outcome in DTC has been an ongoing debate (5, 8, 32, 38, 40, 41). Our study is the first meta-analysis to help clarify this debate and confirm the prognostic implication of VI in DTCs.

In our study, we comprehensively reviewed five electronic databases and investigated the association of VI with DTC patient outcomes. Our results demonstrate that the presence of VI in DTCs is not only associated with an increased risk for tumor recurrence or persistence but also significantly associated with an adverse impact on patient DSS. Our findings strongly support the latest ATA guidelines in which DTCs with VI are classified

Clinical Study	H G Vuong and others	Vascular invasion in DTCs: a meta-analysis	177:2	214
----------------	----------------------	--	-------	-----

as ATA intermediate risk, while DTCs without VI are regarded as ATA low risk (42). However, the three-tiered ATA classification did not specifically address the risk of tumor recurrence associated with each histologic type. In subgroup analysis of our meta-analysis, the presence of VI is both associated with a significantly increased risk for LRR, DR and overall RP in both PTC and FTC patients (Table 2). As a result, pathologists should assess the presence and extent of VI in all specimen blocks during histopathological examination because the presence of even one focus of VI can enhance the recurrence risk for patients and influence the management and follow-up schedule. The risk for tumor persistence is heterogeneous between histologic subgroups with the insignificant pooled results in patients with PTC. But, this result should be interpreted with caution because of the small number of included studies and patients (Table 2).

In addition to the presence of VI, the extent of VI (number of VI foci) also merits concern from thyroid specialists. A few studies reported that FTCs with a greater extent of VI (≥ 4 foci of VI) are associated with poorer outcome (24, 38, 43). Our results demonstrated that FTCs with extensive VI (≥ 4 VI foci) are associated with a significantly increased risk for distant metastasis during follow-up as compared to tumors with focal VI (< 4 foci). In the ATA 2009 guidelines, the degree of VI in FTC was not included in the risk stratification system (44). But, this prognostic variable was supplemented in the ATA 2015 guidelines in which FTCs with extensive VI (≥ 4 VI foci) are classified as ATA high risk (42). Our results further support the latest ATA guidelines and warrant the need of careful evaluation for the presence and degree of VI in thyroid cancer.

Our primary and subgroup analyses also indicate that the presence of VI in DTCs is an independent and adverse risk factor on DTC patients' survival (Table 3). The significant overall estimate of HR for DSS is mostly attributable to the PTC population. When we separate into each histologic subgroup, there are heterogeneities in pooled results regarding impact of VI on DSS. The presence of VI is only associated with a significantly unfavorable effect on DSS in PTC patients, but this effect is not significant in FTC patients (Table 3). The different criteria in diagnosis of PTC and FTC might be an appropriate explanation for this difference. In previous years before the latest consensus regarding new term of 'non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)' (45), the diagnosis of PTC mostly relies on the characteristic nuclear features and

many cases of non-invasive encapsulated follicular variant PTCs (FVPTC) might be included in PTC series in our study. Meanwhile, the presence of at least VI and/or capsular invasion is required for the diagnosis of FTC. Hence, the survival of patients in group of PTCs without VI might be much better than patients in group of PTCs with VI and results in higher HR ratio in PTC subgroup.

Kim *et al.* (8) found an association of VI with increased mortality rate in minimally invasive but not in widely invasive FTCs and suggested that MIFTC be separated into two groups according to the presence or absence of VI. This finding, however, was not found in other MIFTC series (32, 33), and our pooled analysis could not establish a significant association between VI and poorer outcome in MIFTCs (Table 3). Although our pooled analysis indicates an insignificant effect of VI on FTC patient's survival, the presence and extent of VI in FTCs do need to be carefully examined and reported in histopathological report due to its significant association with increased risk for tumor recurrence or persistence in FTCs.

The diagnosis of microscopic VI has been an ongoing controversy in surgical histopathology and it is an important criterion in the diagnosis of FTC (3). Classic criteria for diagnosis of microscopic VI have been well described previously (3, 46, 47), and these strict criteria should be used for the diagnosis of VI on routine histopathological examination to avoid artifactual displacement of tumor cells (47). Our study has a limitation that not all included studies reported or described the criteria for diagnosis of VI and it could raise heterogeneity among the included studies. Nonetheless, the significant heterogeneity among included studies of the overall effects are present in only a few of pooled results and the pooled results remain statistically significant following the sensitivity analysis, thus reflecting a good stability of our analyses. Another limitation is that all of included studies were retrospective studies so selection biases are inevitable.

To summarize, our current study demonstrated the prognostic importance of VI as a predictor of tumor recurrence in both PTCs and FTCs and its association with unfavorable patient outcomes in PTCs. The presence and extent of VI in DTCs should be considered an adverse prognostic factor and needs to be carefully assessed on histopathological examination for accurate risk stratification, management and follow-up.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-17-0260>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Acknowledgements

The authors specially thank Dr Inga-Lena Nilsson (Karolinska University Hospital, Sweden), Dr Ronald Ghossein, Dr Bin Xu (Memorial Sloan Kettering Cancer Center, USA) and Dr Kiminori Sugino (Ito Hospital, Japan) for their generous help to calculate necessary data for pooled analysis.

References

- Davies L & Welch HG. Current thyroid cancer trends in the United States. *JAMA Otolaryngology: Head and Neck Surgery* 2014 **140** 317–322. (doi:10.1001/jamaoto.2014.1)
- Kilfoy BA, Zheng T, Holford TR, Han X, Ward MH, Sjodin A, Yaquin Z, Bai Y, Zhu C, Guo GL *et al.* International patterns and trends in thyroid cancer incidence, 1973–2002. *Cancer Causes and Control* 2009 **20** 525–531. (doi:10.1007/s10552-008-9260-4)
- De Lellis, Lloyd R, Heitz P & Eng C. World Health Organization classification of tumours. In *Pathology and Genetics of Tumours of Endocrine Organs*. Lyon, France: IARC Press, 2004.
- Lerch H, Schober O, Kuwert T & Saur HB. Survival of differentiated thyroid carcinoma studied in 500 patients. *Journal of Clinical Oncology* 1997 **15** 2067–2075. (doi:10.1200/JCO.1997.15.5.2067)
- Akslen LA, Myking AO, Salvesen H & Varhaug JE. Prognostic importance of various clinicopathological features in PTC. *European Journal of Cancer* 1992 **29A** 44–51. (doi:10.1016/0959-8049(93)90574-y)
- Cao J, Hu JL, Chen C, Wang QL, Fang XH, Zhang Y & Ge MH. Vascular invasion is an independent prognostic factor for distant recurrence-free survival in papillary thyroid carcinoma: a matched-case comparative study. *Journal of Clinical Pathology* 2016 **69** 872–877. (doi: 10.1136/jclinpath-2015-203547)
- Furlan JC, Bedard YC & Rosen IB. Clinicopathologic significance of histologic vascular invasion in papillary and follicular thyroid carcinomas. *Journal of the American College of Surgeons* 2004 **198** 341–348. (doi:10.1016/j.jamcollsurg.2003.11.012)
- Kim HJ, Sung JY, Oh YL, Kim JH, Son YI, Min YK, Kim SW & Chung JH Association of vascular invasion with increased mortality in patients with minimally invasive follicular thyroid carcinoma but not widely invasive follicular thyroid carcinoma. *Head and Neck* 2014 **36** 1695–1700. (doi:10.1002/hed.23511)
- Collini P, Sampietro G & Pilotti S. Extensive vascular invasion is a marker of risk of relapse in encapsulated non-Hurthle cell follicular carcinoma of the thyroid gland: a clinicopathological study of 18 consecutive cases from a single institution with a 11-year median follow-up. *Histopathology* 2004 **44** 35–39. (doi:10.1111/j.1365-2559.2004.01729.x)
- Falvo L, Catania A, D'Andrea V, Marzullo A, Giustiniani MC & De Antoni E. Prognostic importance of histologic vascular invasion in papillary thyroid carcinoma. *Annals of Surgery* 2005 **241** 640–646. (doi:10.1097/01.sla.0000157317.60536.08)
- Moher D, Liberati A, Tetzlaff J, Altman DG & PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Medicine* 2009 **6** e1000097. (doi:10.1371/journal.pmed.1000097)
- Wells GA, Shea B & O'Connell D. *The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses*. Ottawa: Ottawa Hospital Institute, 2011.
- Higgins JP & Green S (eds). *Cochrane Handbook for Systematic Reviews of Interventions*. West Sussex, England: John Wiley & Sons, 2008.
- Tierney JF, Stewart LA, Ghersi D, Burdett S & Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007 **8** 16. (doi:10.1186/1745-6215-8-16)
- Higgins JP & Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002 **21** 1539–1558. (doi:10.1002/sim.1186)
- Ioannidis JP, Patsopoulos NA & Evangelou E. Uncertainty in heterogeneity estimates in meta-analyses. *BMJ* 2007 **335** 914–916. (doi:10.1136/bmj.39343.408449.80)
- Hamilton WK, Aydin B & Mizumoto A. MAVIS: Meta Analysis via Shiny. R package version 1.1.2, 2016. (Available at <http://kylehamilton.net/shiny/MAVIS/>)
- Aida N, Yamada N, Asano G & Tanaka S. 3-D analysis of vascular and capsular invasion in thyroid follicular carcinoma. *Pathology International* 2001 **51** 425–430. (doi:10.1046/j.1440-1827.2001.01221.x)
- Chereau N, Tresallet C, Noullet S, Godiris-Petit G, Tissier F, Leenhardt L & Menegaux F. Does the T1 subdivision correlate with the risk of recurrence of papillary thyroid cancer? *Langenbeck's Archives of Surgery* 2016 **401** 223–230. (doi:10.1007/s00423-016-1399-y)
- D'Avanzo A, Treseler P, Ituarte PH, Wong M, Streja L, Greenspan FS, Siperstein AE, Duh QY & Clark OH. Follicular thyroid carcinoma: histology and prognosis. *Cancer* 2004 **100** 1123–1129. (doi:10.1002/cncr.20081)
- de Castro TP, Waissmann W, Simoes TC, de Mello RC & Carvalho DP. Predictors for papillary thyroid cancer persistence and recurrence: a retrospective analysis with a 10-year follow-up cohort study. *Clinical Endocrinology* 2016 **85** 466–474. (doi:10.1111/cen.13032)
- Enomoto K, Enomoto Y, Uchino S, Yamashita H & Noguchi S. Follicular thyroid cancer in children and adolescents: clinicopathologic features, long-term survival, and risk factors for recurrence. *Endocrine Journal* 2013 **60** 629–635. (doi:10.1507/endocrj.EJ12-0372)
- Gardner RE, Tuttle RM, Burman KD, Haddady S, Truman C, Sparling YH, Wartofsky L, Sessions RB & Ringel MD. Prognostic importance of vascular invasion in papillary thyroid carcinoma. *Archives of Otolaryngology: Head and Neck Surgery* 2000 **126** 309–312. (doi:10.1001/archotol.126.3.309)
- Ghossein RA, Hiltzik DH, Carlson DL, Patel S, Shaha A, Shah JP, Turtle RM & Singh B Prognostic factors of recurrence in encapsulated Hurthle cell carcinoma of the thyroid gland: a clinicopathologic study of 50 cases. *Cancer* 2006 **106** 1669–1676. (doi:10.1002/cncr.21825)
- Kim JM, Kim TY, Kim WB, Gong G, Kim SC, Hong SJ & Shong YK. Lymphovascular invasion is associated with lateral cervical lymph node metastasis in papillary thyroid carcinoma. *Laryngoscope* 2006 **116** 2081–2085. (doi:10.1097/01.mlg.0000242118.79647.a9)
- Kim WW, Hur SM, Kim SH, Lee SK, Kim S, Oh YL, Choe JH, Lee JE, Kim JH, Nam SJ *et al.* Prognostic factors and treatment in follicular thyroid carcinoma. *Journal of the Korean Surgical Society* 2010 **78** 149–156. (doi:10.4174/jkss.2010.78.3.149)
- Lang W, Choritz H & Hundeshagen H. Risk factors in follicular thyroid carcinomas. A retrospective follow-up study covering a 14-year period with emphasis on morphological findings. *American Journal of Surgical Pathology* 1986 **10** 246–255. (doi:10.1097/0000478-198604000-00003)

Clinical Study	H G Vuong and others	Vascular invasion in DTCs: a meta-analysis	177:2	216
----------------	----------------------	---	-------	-----

- 28 Lee YM, Lee YH, Song DE, Kim WB, Sung TY, Yoon JH, Chung KW & Hong SJ. Prognostic impact of further treatments on distant metastasis in patients with minimally invasive follicular thyroid carcinoma: verification using inverse probability of treatment weighting. *World Journal of Surgery* 2017 **41** 1144. (doi:10.1007/s00268-017-3879-9)
- 29 Lee E, Jung W, Woo JS, Lee JB, Shin BK, Kim HK, Kim A & Kim BH. Tumor sprouting in papillary thyroid carcinoma is correlated with lymph node metastasis and recurrence. *Korean Journal of Pathology* 2014 **48** 117–125. (doi:10.4132/KoreanJPathol.2014.48.2.117)
- 30 Marques P, Leite V & Bugalho MJ. Retrospective analysis of 255 papillary thyroid carcinomas ≤ 2 cm: clinicohistological features and prognostic factors. *European Thyroid Journal* 2014 **3** 258–263. (doi:10.1159/000369133)
- 31 Nishida T, Katayama SI & Tsujimoto M. The clinicopathological significance of histologic vascular invasion in differentiated thyroid carcinoma. *American Journal of Surgery* 2002 **183** 80–86. (doi:10.1016/S0002-9610(01)00843-1)
- 32 Stenson G, Nilsson IL, Mu N, Larsson C, Lundgren CI, Juhlin CC, Hoog A & Zedenius J. Minimally invasive follicular thyroid carcinomas: prognostic factors. *Endocrine* 2016 **53** 505–511. (doi:10.1007/s12020-016-0876-y)
- 33 Sugino K, Kameyama K, Ito K, Nagahama M, Kitagawa W, Shibuya H, Ohkuwa K, Yano Y, Uruno T, Akaishi J *et al.* Outcomes and prognostic factors of 251 patients with minimally invasive follicular thyroid carcinoma. *Thyroid* 2012 **22** 798–804. (doi:10.1089/thy.2012.0051)
- 34 Suh YJ, Kwon H, Kim SJ, Choi JY, Lee KE, Park YJ, Park DJ & Youn YK. Factors affecting the locoregional recurrence of conventional papillary thyroid carcinoma after surgery: a retrospective analysis of 3381 patients. *Annals of Surgical Oncology* 2015 **22** 3543–3549. (doi:10.1245/s10434-015-4448-9)
- 35 van Heerden JA, Hay ID, Goellner JR, Salomao D, Ebersold JR, Bergstralh EJ & Grant CS. Follicular thyroid carcinoma with capsular invasion alone: a nonthreatening malignancy. *Surgery* 1992 **112** 1130–1136; discussion 1136–1138.
- 36 Wong RM, Bresce C & Braunstein GD. Comparison with published systems of a new staging system for papillary and follicular thyroid carcinoma. *Thyroid* 2013 **23** 566–574. (doi:10.1089/thy.2012.0181)
- 37 Wu M-H, Shen WT, Gosnell J & Duh Q-Y. Prognostic significance of extranodal extension of regional lymph node metastasis in papillary thyroid cancer. *Head and Neck* 2015 **37** 1336–1343. (doi:10.1002/hed.23747)
- 38 Xu B, Wang L, Tuttle RM, Ganly I & Ghossein R. Prognostic impact of extent of vascular invasion in low-grade encapsulated follicular cell-derived thyroid carcinomas: a clinicopathologic study of 276 cases. *Human Pathology* 2015 **46** 1789–1798. (doi:10.1016/j.humpath.2015.08.015)
- 39 Ioannidis JP & Trikalinos TA. The appropriateness of asymmetry tests for publication bias in meta-analyses: a large survey. *CMAJ* 2007 **176** 1091–1096. (doi:10.1503/cmaj.060410)
- 40 Shah JP, Loree TE, Dharker DE, Strong EF, Begg CF & Vlamis V. Prognostic factors in differentiated carcinoma of the thyroid gland. *American Journal of Surgery* 1992 **164** 658–661. (doi: 10.1016/S0002-9610(05)80729-9)
- 41 Loree TR. Therapeutic implications of prognostic factors in differentiated carcinoma of the thyroid gland. *Seminars in Surgical Oncology* 1995 **11** 246–255. (doi:10.1002/ssu.2980110310)
- 42 Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M *et al.* 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* 2016 **26** 1–133. (doi: 10.1089/thy.2015.0020)
- 43 O'Neill CJ, Vaughan L, Learoyd DL, Sidhu SB, Delbridge LW & Sywak MS. Management of follicular thyroid carcinoma should be individualized based on degree of capsular and vascular invasion. *Annals of Surgical Oncology* 2011 **37** 181–185. (doi: 10.1016/j.ejso.2010.11.005)
- 44 Puxeddu E & Filetti S. The 2009 American Thyroid Association Guidelines for management of thyroid nodules and differentiated thyroid cancer: progress on the road from consensus- to evidence-based practice. *Thyroid* 2009 **19** 1145–1147. (doi:10.1089/thy.2009.1601)
- 45 Nikiforov YE, Seethala RR, Tallini G, Baloch ZW, Basolo F, Thompson LD, Barletta JA, Wenig BM, Al Ghuzlan A, Kakudo K *et al.* Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma: a paradigm shift to reduce overtreatment of indolent tumors. *JAMA Oncology* 2016 **2** 1023–1029. (doi:10.1001/jamaoncol.2016.0386)
- 46 Nikiforov YE, Biddinger PW & Thompson LD (eds). *Diagnostic Pathology and Molecular Genetics of the Thyroid: A Comprehensive Guide for Practicing Thyroid Pathology*. Philadelphia, Pennsylvania: Lippincott Williams & Wilkins, 2012.
- 47 Mete O & Asa SL. Pathological definition and clinical significance of vascular invasion in thyroid carcinomas of follicular epithelial derivation. *Modern Pathology* 2011 **24** 1545–1552. (doi:10.1038/modpathol.2011.119)

Received 30 March 2017

Revised version received 15 May 2017

Accepted 30 May 2017