RESEARCH

Pleural effusion as a novel prognostic factor in metastatic thyroid carcinoma

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Abstract

Objective: To identify novel prognostic risk factors and compare them with other known prognostic risk factors in follicular-cell-derived thyroid carcinoma (FDTC) with distant metastases.
Methods: A retrospective review was conducted of adult patients with metastatic FDTC seen at a tertiary care center between January 1990 and December 2010. A 15-year Kaplan–Meier survival estimate was created for overall survival (OS) and cancer-specific survival (CSS). Hazard ratios (HR) and *P* values from Cox proportional hazard models were used with a 95% CI.
Results: There were 143 patients (60.1% male, 39.9% female), of whom 104 (72.7%) patients had papillary, 30 (21.0%) had follicular, 5 (3.5%) had poorly differentiated, and 4 (2.8%) had Hürthle cell cancers. Median length of follow-up was 80.0 months (range 1.0–564.0). The 15-year mortality rate was 32.2% and cancer-specific mortality was 25.2%, with OS and CSS having the same risk factors. Lung was the most common site of metastases in 53 patients (37.1%), and patients with pleural effusions had significantly lower CSS (HR = 5.21, CI = 1.79–15.12). Additional risk factors for a decreased CSS included: older age upon diagnosis (>45 years, HR = 4.15, CI = 1.43–12.02), multiple metastatic locations (HR = 3.75, CI = 1.32–10.67), and incomplete/unknown tumor resection (HR = 2.35, CI = 1.18–4.67).
Conclusion: This study is the first to demonstrate that pleural effusion is a poor prognostic sign in patients with FDTC with distant metastases and compare this risk with other accepted prognostic variables.

Key Words
- pleural effusion
- prognostic factors
- metastatic thyroid cancer
- follicular cell derived thyroid cancer

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Introduction

Thyroid cancer is currently the third fastest rising cancer diagnosis in the United States. The National Cancer Institute indicates that there were 52,070 new cases of thyroid cancer diagnosed in 2019 and an estimated 52,890 newly diagnosed cases in 2020, representing 2.9% of all new cancer diagnoses in the United States (1). The incidence of thyroid carcinoma is 15.7 per 100,000 men and women per year and represents 0.4% of all cancer deaths currently. The incidence has increased significantly since 1975 going from 4.5 per 100,000 in 1975 to 15.7 per 100,000 in 2020, representing a 3.4-fold increase (1). The rise in incidence is mainly attributed to an increase in thyroid cancer detection secondary to increased imaging, increased detection of incidental thyroid tumors, and introduction of high-sensitivity ultrasonography detecting small subcentimeter lesions. Malignant pleural effusion currently has an estimated annual incidence of 150,000 in the USA, and it is expected that with the

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increase in new cancer diagnoses, this incidence would also increase (2, 3, 4).

Survival for low-risk thyroid cancer remains above 90% (1), and prognosis for patients with metastasis on presentation falls between 23.1 and 31% for 10-year survival (5, 6, 7). The majority of cases are low grade/stage upon diagnosis and seldom do patients present with distant metastasis, which have since made it difficult to assess which clinical characteristics have the largest effect on overall survival (OS) and cancer-specific survival (CSS). Significant risk factors that were identified for a decrease in survival included follicular thyroid cancer, age >45 years (8), cancer with metastasis to bone (5), increased tumor size (8) and tumor size >3 cm (5), and incomplete tumor resection (5, 8). In addition to extra-thyroid tumor spread, lymph node metastases, distant metastases and tall cell variants for PTC (8), other risk factors associated with a decrease in CSS were distant metastasis diagnosed before whole body scan, non-radioactive iodine (RAI) avidity, external beam radiation to distant metastases (6, 7), and a higher MACIS score (9). Treatment with RAI was previously found to be the single most powerful prognostic indicator for increased disease-free interval and significantly increased survival, while patients derived no benefit from treatment with external radiation (6). It is important to note that pleural effusion has not been studied with respect to these variables and its relative importance has never been quantified with respect to known prognostic variables in metastatic thyroid carcinoma.

The aim of this study was to identify the effect of novel prognostic variables (such as pleural effusion) on OS and CSS in comparison to known prognostic variables in patients with follicular-cell-derived thyroid carcinoma (FDTC) with distant metastases.

Methods

Patients

This study was approved by the Cleveland Clinic Foundation Institutional Review Board/Independent Ethics Committee (IRB/IEC) and was a retrospective review of patients (18 years and older) who presented to a tertiary referral center with FDTC between January 1, 1990 and December 31, 2010. Consent was determined to not be necessary and was waived given the minimal risk posed to patients for this study. Patients were identified with a diagnosis of thyroid cancer utilizing ICD-9 codes, then individual chart review was performed to ensure inclusion and exclusion criteria were met. Inclusion criteria included thyroid carcinoma with distant metastases and age greater than 18 years or older on presentation to the tertiary referral center. Patients excluded from analysis were those not followed at the tertiary referral center, those with insufficient data, and patients who had other types of concomitant cancer (e.g. breast, colon cancer). Additionally, medullary thyroid carcinoma patients were excluded. After manual chart review for exclusion criteria, 143 patients were included in the analysis (Supplementary Fig. 1, see section on supplementary materials given at the end of this article).

Data collection process

Data were confirmed/refuted from the electronic research informatics with manual chart review for inclusion/exclusion criteria. Disputed results were discussed and agreed upon by all data collectors (D T B and G B G) and investigators (C N). The following demographic factors were collected: age, age ≥45 years, last recorded age, gender, race, history of neck radiation exposure, history of preexisting thyroid disease, last vital status, length of follow-up (months), and death due to disease. Death due to disease was defined as dying from the primary thyroid cancer or a direct complication of thyroid cancer, including expiring in hospice (if was transitioned to hospice for management of thyroid cancer), hypoxia from malignant pleural effusion, hypoxia from respiratory failure if determined to be from disease burden.

Statistical analysis

Categorical variables were summarized using frequencies and percentages, while continuous measures were reported with medians and ranges. Two separate univariate analyses were performed with primary outcomes of overall survival and cause-specific survival. The number of deaths and deaths due to cancer were summarized with frequencies and percentages, while 15-year Kaplan–Meier survival estimates were created for overall and cause-specific survival. Hazard ratios (HR) and *P* values from Cox proportional hazard models were used with 95% CI. A *P* value less than 0.05 was set as statistically significant. Multivariable models were fit using stepwise selection, with significance criteria of 0.05 to enter and remain in the model. Analysis was performed with SAS software (version 9.4; Cary, NC, USA).

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Results

Patient demographics

There were 143 patients who met study inclusion criteria after applying exclusion criteria (Supplementary Fig. 1). The median age at diagnosis was 59.0 years (9.0, 89.0), with patients who developed lung metastases and a pleural effusion being older at a median age of 75.0 (28.0, 89.0). The majority were male (60.1%) patients and the most common races represented were White (83.9%, $n=120$) and Black or African American (10.5%, $n=15$). The mean length of follow-up was 80.0 months (1.00, 564.0), with 32.2% being dead after 15 years of follow-up ($n=46$), with thyroid cancer being the most common cause of death ($n=36$). Patients who developed a pleural effusion had a median length of follow-up of 15.0 months (1.00, 432.00) (Table 1). Comparisons between the total cohort, patients with lung metastases with and without pleural effusion were compared and included in Tables 1 and 2.

Disease characteristics

The most common cancer type was papillary thyroid cancer (72.7%, $n=104$), with the most common histologic subtypes listed in Table 2. The median size of the tumor was 3.6 cm (0.2, 14.0), and 78.3% had complete resection of their tumor ($n=112$). The majority of patients did not have visible lung metastases on diagnosis (62.9%, $n=90$), but 37.1% of patients had developed lung metastases ($n=53$) during follow-up (Table 2). In the patients with lung

Table 1 Demographics summaries.

Factor	Total	Lung metastasis		*P*-value	Lung metastasis with pleural effusion		*P*-value
		No	Yes		No	Yes	
	($n=143$)	($n=90$)	($n=53$)		($n=43$)	($n=10$)	
Age at diagnosis	59.0 (9.0, 89.0)	58.0 (9.0, 81.0)	60.0 (13.0, 89.0)	0.11[b]	58.0 (13.0, 85.0)	75.0 (28.0, 89.0)	0.020[b]
Age > or = 45	107 (74.8)	67 (74.4)	40 (75.5)	0.89[c]	31 (72.1)	9 (90.0)	0.24[c]
Last Age	64.0 (24.0, 91.0)	65.0 (24.0, 91.0)	62.0 (26.0, 89.0)	0.76[b]	60.0 (26.0, 87.0)	78.0 (58.0, 89.0)	0.010[b]
Gender				0.96[c]			0.49[c]
Female	57 (39.9)	36 (40.0)	21 (39.6)		18 (41.9)	3 (30.0)	
Male	86 (60.1)	54 (60.0)	32 (60.4)		25 (58.1)	7 (70.0)	
Race				0.25[d]			0.58[d]
Pacific Islander	1 (0.70)	1 (1.1)	0 (0.0)		0 (0.0)	0 (0.0)	
Black or African American	15 (10.5)	6 (6.7)	9 (17.0)		6 (14.0)	3 (30.0)	
White	120 (83.9)	78 (86.7)	42 (79.2)		35 (81.4)	7 (70.0)	
More than one race	2 (1.4)	2 (2.2)	0 (0.0)		0 (0.0)	0 (0.0)	
Unknown/not reported	5 (3.5)	3 (3.3)	2 (3.8)		2 (4.7)	0 (0.0)	
History of neck radiation exposure				0.84[c]			0.99[d]
No	133 (93.0)	84 (93.3)	49 (92.5)		40 (93.0)	9 (90.0)	
Yes	10 (7.0)	6 (6.7)	4 (7.5)		3 (7.0)	1 (10.0)	
History of preexisting thyroid disease				0.10[d]			0.42[c]
None	121 (84.6)	79 (87.8)	42 (79.2)		42 (79.2)	35 (81.4)	
Graves' disease	2 (1.4)	2 (2.2)	0 (0.0)		0 (0.0)	0 (0.0)	
Hashimoto's thyroiditis	1 (0.70)	1 (1.1)	0 (0.0)		0 (0.0)	0 (0.0)	
Others	19 (13.3)	8 (8.9)	11 (20.8)		11 (20.8)	8 (18.6)	
Last vital status				0.70[c]			0.002[c]
Alive	97 (67.8)	60 (66.7)	37 (69.8)		34 (79.1)	3 (30.0)	
Dead	46 (32.2)	30 (33.3)	16 (30.2)		9 (20.9)	7 (70.0)	
Length of follow-up (months)	80.0 (1.00, 564.0)	99.5 (3.0, 564.0)	56.0 (1.00, 432.0)	<0.001[b]	64.0 (3.0, 210.0)	15.0 (1.00, 432.0)	0.015[b]
Death due to disease				0.11[d]			0.44[d]
Yes	36 (78.3)	21 (70.0)	15 (93.8)		9 (100.0)	6 (85.7)	
No	4 (8.7)	3 (10.0)	1 (6.3)		0 (0.0)	1 (14.3)	
Unknown	6 (13.0)	6 (20.0)	0 (0.0)		0 (0.0)	0 (0.0)	

Statistics presented as Median (min, max) or *n* (column %).
P-values: [b]Kruskal–Wallis test; [c]Pearson's chi-square test; [d]Fisher's Exact test.

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Table 2 Thyroid summaries.

Factor	Total	Lung metastasis		*P*-value	Lung metastasis with pleural effusion		*P*-value
		No	Yes		No	Yes	
	(*n* = 143)	(*n* = 90)	(*n* = 53)		(*n* = 43)	(*n* = 10)	
Cancer type				0.21[d]			0.089[d]
Papillary thyroid cancer	104 (72.7)	62 (68.9)	42 (79.2)		36 (83.7)	6 (60.0)	
Follicular thyroid cancer	30 (21.0)	23 (25.6)	7 (13.2)		5 (11.6)	2 (20.0)	
Hürthle cell cancer	4 (2.8)	3 (3.3)	1 (1.9)		1 (2.3)	0 (0.0)	
Poorly differentiated cancer	5 (3.5)	2 (2.2)	3 (5.7)		1 (2.3)	2 (20.0)	
Histologic subtype: tall cell variant	20 (14.0)	7 (7.8)	13 (24.5)	0.005[c]	12 (27.9)	1 (10.0)	0.24[c]
Histologic subtype: follicular variant	32 (22.4)	15 (16.7)	17 (32.1)	0.033[c]	14 (32.6)	3 (30.0)	0.88[c]
Histologic subtype: diffuse sclerosing variant	4 (2.8)	3 (3.3)	1 (1.9)	0.99[d]	1 (2.3)	0 (0.0)	0.99[d]
Histologic subtype: oncocytic	6 (4.2)	4 (4.4)	2 (3.8)	0.99[d]	1 (2.3)	1 (10.0)	0.34[d]
Histologic subtype: cribriform morular	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Histologic subtype: solid variant	3 (2.1)	1 (1.1)	2 (3.8)	0.56[d]	1 (2.3)	1 (10.0)	0.34[d]
Histologic subtype: micropapillary (Hobnail)	2 (1.4)	0 (0.0)	2 (3.8)	0.14[d]	2 (4.7)	0 (0.0)	0.99[d]
Histologic subtype: encapsulated papillary	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Histologic subtype: insular	8 (5.6)	4 (4.4)	4 (7.5)	0.44[c]	2 (4.7)	2 (20.0)	0.16[d]
Histologic subtype: Warthin like	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Histologic subtype: Not stated	76 (53.1)	55 (61.1)	21 (39.6)	0.013[c]	15 (34.9)	6 (60.0)	0.14[c]
Largest tumor size known	97 (67.8)	56 (62.2)	41 (77.4)	0.061[c]	36 (83.7)	5 (50.0)	0.022[c]
Tumor size	3.6 (0.20, 14.0)	4.0 (0.20, 12.0)	3.0 (1.00, 14.0)	0.74[b]	3.0 (1.5, 14.0)	7.0 (1.00, 9.0)	0.60[b]
Completeness of surgery				0.53[c]			0.21[c]
Completely resected	112 (78.3)	72 (80.0)	40 (75.5)		34 (79.1)	6 (60.0)	
Incompletely resected	31 (21.7)	18 (20.0)	13 (24.5)		9 (20.9)	4 (40.0)	
Lung metastases: micronodules (up to 9 mm)	45 (31.5)	----	45 (84.9)		37 (86.0)	8 (80.0)	0.63[c]
Lung metastases: macronodules (>1cm)	19 (13.3)	----	19 (35.8)		13 (30.2)	6 (60.0)	0.077[c]
Lung metastases: diffuse miliary	2 (1.4)	----	2 (3.8)		2 (4.7)	0 (0.0)	0.99[d]
Number of micronodules							0.10[d]
0	3 (6.7)	----	3 (6.7)		1 (2.7)	2 (25.0)	
1–5 nodules	16 (35.6)	----	16 (35.6)		15 (40.5)	1 (12.5)	
6–10 nodules	6 (13.3)	----	6 (13.3)		5 (13.5)	1 (12.5)	
>10 nodules	20 (44.4)	----	20 (44.4)		16 (43.2)	4 (50.0)	
Number of macronodules							0.74[d]
0	1 (5.3)	----	1 (5.3)		0 (0.0)	1 (16.7)	
1–5 nodules	11 (57.9)	----	11 (57.9)		8 (61.5)	3 (50.0)	
6–10 nodules	4 (21.1)	----	4 (21.1)		3 (23.1)	1 (16.7)	
>10 nodules	3 (15.8)	----	3 (15.8)		2 (15.4)	1 (16.7)	
Laterality in lungs							0.29[c]
Unilateral	12 (22.6)	----	12 (22.6)		11 (25.6)	1 (10.0)	
Bilateral	41 (77.4)	----	41 (77.4)		32 (74.4)	9 (90.0)	
Mostly central lung metastases	5 (3.5)	----	5 (9.4)		5 (11.6)	0 (0.0)	0.57[d]
Mostly peripheral lung metastases	44 (30.8)	----	44 (83.0)		36 (83.7)	8 (80.0)	0.78[c]

(*Continued*)

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Table 2 Continued.

Factor	Total	Lung metastasis		*P*-value	Lung metastasis with pleural effusion		*P*-value
		No	Yes		No	Yes	
	(*n* = 143)	(*n* = 90)	(*n* = 53)		(*n* = 43)	(*n* = 10)	
Centrality of lung metastases unknown	4 (2.8)	----	4 (7.5)		2 (4.7)	2 (20.0)	0.16[d]
Visible metastases in bone				0.37[c]			0.060[c]
Yes	32 (22.4)	18 (20.0)	14 (26.4)		9 (20.9)	5 (50.0)	
No	111 (77.6)	72 (80.0)	39 (73.6)		34 (79.1)	5 (50.0)	
Visible metastases in brain	5 (3.5)	1 (1.1)	4 (7.5)	0.063[d]	3 (7.0)	1 (10.0)	0.99[d]
Visible metastases in liver	3 (2.1)	1 (1.1)	2 (3.8)	0.56[d]	1 (2.3)	1 (10.0)	0.34[d]
Visible metastases in kidney	1 (0.70)	0 (0.0)	1 (1.9)	0.37[d]	1 (2.3)	0 (0.0)	0.99[d]
Visible to other organs	11 (7.7)	4 (4.4)	7 (13.2)	0.058[c]	3 (7.0)	4 (40.0)	0.005[c]
Suppressed thyroglobulin post-RAI treatment done	28 (19.6)	14 (15.6)	14 (26.4)	0.11[c]	13 (30.2)	1 (10.0)	0.19[c]

Statistics presented as Median (min, max) or *n* (column %).
P-values: [b]Kruskal–Wallis test; [c]Pearson's chi-square test; [d]Fisher's Exact test.

metastases, a pleural effusion developed in ten patients, with eight being bilateral and two being unilateral (Table 2). The median MACIS score (9) upon diagnosis was 8.7 (4.5, 12.1), and all patients had AJCC seventh edition stage IVc disease (10) and were ATA high risk (11) (Table 3).

Risk factors for overall and cancer-specific survival

Significant risk factors were the same for OS and CSS with similar hazard ratios. Significant risk factors for decreased CSS included age ≥45 years (HR 4.15, CI = 1.43–12.02, $P = 0.009$), multisite metastases (HR 3.75, CI = 1.32–10.67, $P = 0.013$), incomplete tumor resection (HR 2.35, CI = 1.18–4.67, $P = 0.014$), visible metastases in bone (HR 3.20, CI = 1.49–6.88, $P = 0.003$), visible metastases in other organs (HR 2.27, CI = 1.12–4.60, $P = 0.022$), higher age at diagnosis (HR 1.06, CI = 1.03–1.08, $P < 0.001$), and higher MACIS score (HR 1.98, CI = 1.49–2.63, $P < 0.001$) (Tables 4, 5 and 6). The presence of visible lung metastases at diagnosis was found to have a decreased risk of mortality when compared to other sites of metastases (HR 0.49, CI = 0.25–0.97, $P = 0.042$) (Tables 4, 5 and 6). However, in patients who developed lung metastases and a pleural effusion, there was a significant decrease in OS (HR 5.74, CI = 1.97–16.73, $P = 0.001$) and CSS (HR 4.93, CI = 1.59–15.26, $P = 0.006$) (Tables 4, 5 and 6). Kaplan–Meier curves for 15-year OS and CSS, for OS and CSS by site of metastases, and the presence of pleural effusion are shown in Figs 1, 2 and 3.

Table 3 Staging summaries.

Factor	Total
	(*n* = 143)
MACIS score	8.7 (4.5, 12.1)
T	
x	33 (23.1%)
1a	2 (1.4%)
1b	2 (1.4%)
2	12 (8.4%)
3	44 (30.8%)
4a	45 (31.5%)
4b	5 (3.5%)
n	
0	28 (19.6%)
1a	10 (7.0%)
1b	78 (54.5%)
x	27 (18.9%)
M	
M1	143 (100.0%)
TNM stage	
IVc	143 (100.0%)
ATA risk stratification	
High	143 (100.0%)

Statistics presented as Median (min, max) or *n* (column %).

Multivariable analysis

Significant risk factors identified for decreased CSS included lung metastases with pleural effusion (HR 5.21, CI = 1.79–15.12, $P = 0.001$) and an increased MACIS score (HR 1.86, CI = 1.38–2.49, $P < 0.001$). A significant risk factor that was associated with an increase in CSS was radioactive iodine treatment (HR 0.23, CI = 0.09–0.65, $P = 0.005$) (Table 7). The median RAI treatment dose was 248 mCi (IQ1 112, IQ3 356.9, IQR of 244.9). Although, this association was not further explored, it is thought that patients with RAI-avid disease are more likely to have a better prognosis than those with RAI refractory disease as previously supported in the literature (7).

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Table 4 Univariate overall survival summary.

Variable	*n*	Events	15-year survival % (95% CI)	Cox univariate hazard ratio (95% CI)	Cox univariate wald *P*-value	Cox univariate overall *P*-value
Age > or = 45						0.003
No	36	7 (19%)	89.6 (78.2, 100.0)	1.00 (REF)		
Yes	107	39 (36%)	47.5 (33.0, 62.0)	4.15 (1.61, 10.70)	0.003	
Papillary cancer						0.14
Papillary thyroid cancer	104	30 (29%)	65.9 (54.0, 77.8)	1.00 (REF)		
Other thyroid cancer	39	16 (41%)	44.8 (22.1, 67.5)	1.59 (0.86, 2.95)	0.14	
Metastasis location						0.015
Lung only	45	6 (13%)	82.2 (67.3, 97.0)	1.00 (REF)		
Bone only	12	1 (8%)	90.9 (73.9, 100.0)	0.65 (0.08, 5.42)	0.69	
Other/multisite	86	39 (45%)	49.4 (36.3, 62.6)	3.08 (1.30, 7.30)	0.011	
Multiple locations						0.003
No	58	7 (12%)	83.2 (70.1, 96.3)	1.00 (REF)		
Yes	85	39 (46%)	49.1 (36.0, 62.2)	3.42 (1.52, 7.67)	0.003	
Completeness of surgery						0.005
Tumor completely resected	112	27 (24%)	67.0 (54.9, 79.2)	1.00 (REF)		
Tumor incompletely resected	31	19 (61%)	39.4 (19.2, 59.7)	2.40 (1.31, 4.39)	0.005	
Visible metastasis to lung						0.84
No	22	6 (27%)	74.6 (55.2, 94.1)	1.00 (REF)		
Yes	121	40 (33%)	58.1 (46.1, 70.1)	1.09 (0.46, 2.60)	0.84	
Visible metastasis to bone						0.007
No	74	14 (19%)	76.1 (64.0, 88.2)	1.00 (REF)		
Yes	69	32 (46%)	45.1 (29.5, 60.6)	2.42 (1.28, 4.57)	0.007	
Visible metastasis in other organs						0.019
No	80	16 (20%)	74.7 (63.1, 86.2)	1.00 (REF)		
Yes	63	30 (48%)	46.5 (30.6, 62.4)	2.08 (1.13, 3.85)	0.019	
Age at diagnosis	143	46 (32%)	59.8 (48.9, 70.8)	1.06 (1.03, 1.08)	<0.001	
Last known age	143	46 (32%)	59.8 (48.9, 70.8)	1.031 (1.009, 1.054)	0.006	
MACIS score	143	46 (32%)	59.8 (48.9, 70.8)	2.03 (1.58, 2.62)	<0.001	<0.001

Key: 'REF' stands for reference value (set at 1.00) in Cox univariate hazard ratio analysis.

Pleural effusion characteristics

Patients who developed a pleural effusion were further examined in which 70% died during this 15-year study period. Half of the patients had exudative pleural effusions, and within this group, four out of the five had pleural fluid cytology that was positive for malignant cells (40% were cytology positive). In the two patients who did not have an exudative pleural effusion or positive cytology, one died from the acute onset of a pleural effusion attributed to metastatic disease (Table 8). Patients with a pleural effusion survived a duration of 0.1–82.8 months, and the patients who survived longer had RAI-avid disease (Table 8).

Discussion

This study aimed to evaluate the impact of pleural effusion on OS and CSS in patients with FDTC and distant metastases and compare this novel risk factor to other well-known prognostic variables. This is the first study to investigate pleural effusion as a prognostic variable in metastatic follicular-cell-derived thyroid carcinoma, and with this information, providers can inform patients about their prognosis more effectively. Outside of lymph nodes, the lung is the most common site of distant metastases (12), and it is important for providers to be aware that if a patient develops a pleural effusion in the setting of lung metastases, this portends a worse prognosis than any other prognostic variable.

Prior studies have demonstrated that increased age (and age ≥45 years), multisite metastases, osseous metastasis, incomplete tumor resection, and a higher MACIS score were associated with poor prognosis in patients with thyroid carcinoma (2, 3, 4, 8). In addition to these prognostic variables, distant metastases and increasing tumor size were identified as independent poor prognostic risk factors for follicular thyroid cancer (5, 8). Our data are consistent with these previous findings with similar OS and CSS hazard ratios compared to what was previously reported. Malignant pleural effusion has previously been

Table 5 Univariate cancer-specific survival summary.

Variable	*n*	Events	15-year survival % (95% CI)	Cox univariate hazard ratio (95% CI)	Cox univariate wald *P*-value	Cox univariate overall *P*-value
Age > or = 45						0.009
No	36	6 (17%)	89.6 (78.2, 100.0)	1.00 (REF)		
Yes	101	30 (30%)	56.5 (41.8, 71.2)	4.15 (1.43, 12.02)	0.009	
Papillary cancer						0.089
Papillary thyroid cancer	101	23 (23%)	73.6 (63.3, 84.0)	1.00 (REF)		
Other thyroid cancer	36	13 (36%)	49.6 (25.2, 74.0)	1.83 (0.91, 3.65)	0.089	
Metastasis location						0.023
Lung only	44	4 (9%)	85.1 (70.9, 99.3)	1.00 (REF)		
Bone only	12	1 (8%)	90.9 (73.9, 100.0)	0.94 (0.10, 8.54)	0.96	
Other/multisite	81	31 (38%)	57.4 (44.0, 70.8)	3.75 (1.32, 10.67)	0.013	
Multiple metastatic locations						0.005
No	57	5 (9%)	85.7 (73.1, 98.2)	1.00 (REF)		
Yes	80	31 (39%)	57.1 (43.7, 70.5)	3.90 (1.51, 10.08)	0.005	
Completeness of surgery						0.014
Tumor completely resected	107	21 (20%)	74.6 (64.2, 85.0)	1.00 (REF)		
Tumor incompletely resected	30	15 (50%)	45.4 (23.4, 67.5)	2.35 (1.18, 4.67)	0.014	
Visible metastasis on lung						0.98
No	21	5 (24%)	79.3 (61.1, 97.6)	1.00 (REF)		
Yes	116	31 (27%)	65.4 (53.8, 77.1)	1.01 (0.39, 2.65)	0.98	
Visible metastasis on bone						0.003
No	71	9 (13%)	81.8 (70.2, 93.4)	1.00 (REF)		
Yes	66	27 (41%)	51.9 (36.0, 67.9)	3.20 (1.49, 6.88)	0.003	
Visible metastasis on other organs						0.022
No	78	12 (15%)	78.3 (66.9, 89.6)	1.00 (REF)		
Yes	59	24 (41%)	54.9 (38.4, 71.4)	2.27 (1.12, 4.60)	0.022	
Age at diagnosis	137	36 (26%)	66.9 (56.2, 77.5)	1.06 (1.03, 1.08)	<0.001	<0.001
Last known age	137	36 (26%)	66.9 (56.2, 77.5)	1.030 (1.005, 1.055)	0.018	0.018
MACIS score	137	36 (26%)	66.9 (56.2, 77.5)	1.98 (1.49, 2.63)	<0.001	<0.001

Key: 'REF' stands for reference value (set at 1.00) in Cox univariate hazard ratio analysis.

Table 6 Univariate analyses of overall survival and cancer-specific survival in patients with lung metastases.

Variable	*n*	Events	15-year survival % (95% CI)	Cox univariate hazard ratio (95% CI)	Cox univariate wald *P*-value	Cox univariate overall *P*-value
Overall survival:						
Lung micronodules (≤9 mm)						0.42
No	8	3 (38%)	68.6 (32.1, 100.0)	1.00 (REF)		
Yes	45	13 (29%)	0.0 (0.0, 0.0)	1.86 (0.41, 8.30)	0.42	
Lung macronodules (≥1 cm)						0.056
No	34	6 (18%)	0.0 (0.0, 0.0)	1.00 (REF)		
Yes	19	10 (53%)	39.9 (13.2, 66.6)	2.74 (0.97, 7.70)	0.056	
Pleural effusion						0.001
No	43	9 (21%)	68.8 (50.7, 86.8)	1.00 (REF)		
Yes	10	7 (70%)	20.0 (0.0, 53.6)	5.74 (1.97, 16.73)	0.001	
Cancer-specific survival:						
Lung micronodules (≤9 mm)						0.47
No	8	3 (38%)	68.6 (32.1, 100.0)	1.00 (REF)		
Yes	45	12 (27%)	0.0 (0.0, 0.0)	1.75 (0.39, 7.89)	0.47	
Lung macronodules (≥1 cm)						0.10
No	34	6 (18%)	0.0 (0.0, 0.0)	1.00 (REF)		
Yes	19	9 (47%)	42.4 (14.5, 70.3)	2.43 (0.84, 7.02)	0.10	
Pleural effusion						0.006
No	43	9 (21%)	68.8 (50.7, 86.8)	1.00 (REF)		
Yes	10	6 (60%)	22.9 (0.0, 60.8)	4.93 (1.59, 15.26)	0.006	

Key: 'REF' stands for reference value (set at 1.00) in Cox univariate hazard ratio analysis.

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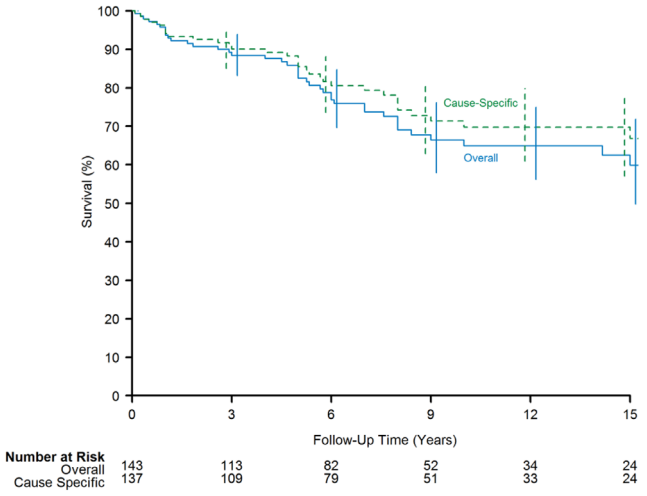

Figure 1
Kaplan–Meier curve for 15-year overall- and cause-specific survival is shown among all patients.

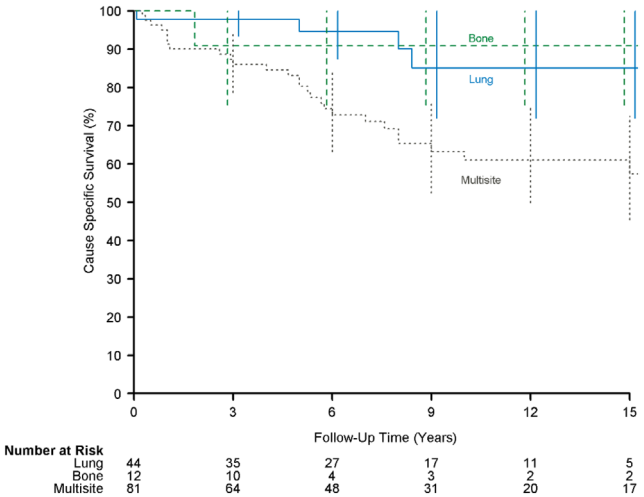

Figure 2
Kaplan–Meier curve for 15-year cause-specific survival by site is shown among all patients.

demonstrated to be associated with poor outcomes in other types of malignancy (12, 13, 14, 15, 16). It is noted that malignant pleural effusion complicates the clinical course in 0.6% of adult patients with papillary thyroid cancer and greatly shortens survival time in all cases (17, 18, 19, 20, 21, 22, 23, 24, 25, 26). Our data support these studies, and we further demonstrated that the hazard ratio was highest for patients with lung metastases who developed a pleural effusion, when compared to other prognostic variables. In our study, lung metastases with development of pleural effusion had a hazard ratio higher than the second worst prognostic variable's hazard ratio (age ≥45 years). With the significance of pleural effusion having a higher hazard ratio than other variables, details of these patients were further sought.

When examining our data closely, 70% of all cases that developed a pleural effusion died within 15 years, and the survival after development of pleural effusion was from 0.1 to 82.8 months with a median survival of 15 months. This is similar to prior studies that found pleural effusion preceded death by a median of 10–11 months (17, 18). Specifically, most patients were dying from respiratory failure or a complication of fluid accumulation (e.g. pneumonia). What is surprising is that two-thirds of the patients who survived had cytology-proven malignant pleural effusions (with the remaining case not having their fluid sampled). This may be that, in these scenarios, the patients underwent multiple interventions (thoracentesis, pleurX drains, thoracotomy) or more aggressive therapeutic interventions (tyrosine kinase inhibitors, multikinase inhibitors).

In 2014 and 2015, it was reported that the tyrosine kinase inhibitor sorafenib and the multikinase inhibitor lenvatinib increase progression-free survival in patients with RAI-refractory metastatic thyroid carcinoma (27, 28). Since that time, there has been a case report demonstrating a notable decrease in a malignant pleural effusion after treatment with sorafenib in RAI-refractory follicular thyroid carcinoma (29) and a subsequent report of rapid pleural effusion accumulation after discontinuation of lenvatinib (30). This is important to note, as it seems that currently available therapeutic options have the potential to improve the prognostic outcomes of patients who have metastatic thyroid carcinoma, that is, radioiodine

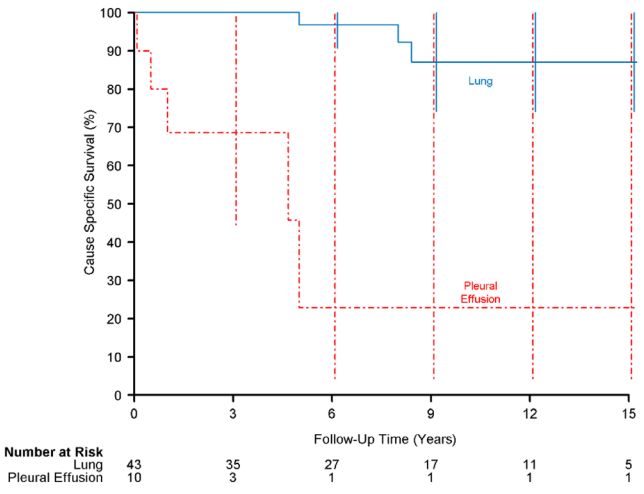

Figure 3
Kaplan–Meier curve for 15-year cause-specific survival in patients with lung metastases with and without pleural effusion.

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Table 7 Multivariable overall survival and cancer-specific survival analyses.

Variable	*n*	Events	15-year survival % (95% CI)	Cox multivariable hazard ratio (95% CI)	Cox univariate wald *P*-value (*n*=143)	Cox univariate overall *P*-value (*n*=143)
Overall survival analysis:						
Lung metastasis at presentation						0.002
No	90	30 (33%)	62.3 (49.7, 74.8)	1.00 (REF)		
Yes, without pleural effusion	43	9 (21%)	68.8 (50.7, 86.8)	0.60 (0.26, 1.41)	0.24	
Yes, with pleural effusion	10	7 (70%)	20.0 (0.0, 53.6)	4.42 (1.68, 11.62)	0.003	
Undetectable thyroglobulin post RAI treatment						0.049
No	115	36 (31%)	62.7 (51.1, 74.4)	1.00 (REF)		
Yes	28	10 (36%)	45.8 (15.6, 76.0)	2.168 (1.003, 4.686)	0.049	
RAI treatment						< 0.001
No	12	7 (58%)	0.0 (0.0, 0.0)	1.00 (REF)		
Yes	131	39 (30%)	62.7 (51.4, 74.1)	0.18 (0.07, 0.47)	< 0.001	
MACIS score	143	46 (32%)	59.8 (48.9, 70.8)	1.96 (1.51, 2.55)	< 0.001	< 0.001
Cancer-specific survival analysis:						
RAI treatment						0.005
No	12	6 (50%)	0.0 (0.0, 0.0)	1.00 (REF)		
Yes	125	30 (24%)	69.9 (59.1, 80.7)	0.23 (0.09, 0.65)	0.005	
Lung metastasis at presentation						0.008
No	84	21 (25%)	71.2 (59.0, 83.4)	1.00 (REF)		
Yes, without pleural effusion	43	9 (21%)	68.8 (50.7, 86.8)	1.05 (0.44, 2.50)	0.92	
Yes, with pleural effusion	10	6 (60%)	22.9 (0.0, 60.8)	5.21 (1.79, 15.12)	0.002	
MACIS score	137	36 (26%)	66.9 (56.2, 77.5)	1.86 (1.38, 2.49)	< 0.001	< 0.001

Key: 'REF' stands for reference value (set at 1.00) in Cox multivariable hazard ratio analysis.

refractory, in addition to help resolve and prevent the re-accumulation of pleural effusion in these patients. This, in addition to addressing limitations from this study, may be an important future area of study.

One limitation of this study is that it is a retrospective study and there are inherent limitations in data that are available to be collected. Specifically, some patients did not have complete data, such as underlying thyroid disease upon presentation, and also the pathological subtype was not always present or obtainable for our pathologists to review. This latter concern is a considerable limitation in our study, as in these circumstances, we had to rely on interpretation from the referring outside institution for their pathological interpretation and did not have access to the histologic subtype. A second limitation of this study was that this study did not utilize socioeconomic status, access to care, or the Eastern Cooperative Oncology Group (ECOG) performance status as variables. This may have affected our results as patients with low socioeconomic status, limited access to care, and a low ECOG performance status would likely contribute to a decreased OS and CSS. A third limitation of this study is that the IRB was written prior to the publication of the AJCC eighth edition for staging of malignancy, and therefore, the AJCC seventh edition staging system was used. This is unlikely to have an effect on our results, as our database included patients who were diagnosed or had presented between the years 1990 and 2010, and it is recommended that all newly diagnosed cases through December 31, 2017 continue to be staged by tumor registries according to the seventh edition staging system (31). A fourth limitation is that comparisons involving patients with pleural effusion had limited power and may be subject to influence by individual patient response. Therefore, these findings may be further validated with external corroboration and future studies with a larger cohort to ensure these findings are reliable.

Conclusion

Utilizing a 15-year retrospective chart review of patients presenting with FDTC and distant metastases, our study sought to identify and quantify the importance of novel

Table 8 Characteristics of patients with malignant pleural effusion.

Pathological variant	Months with effusion	RAI Avid?	Effusion laterality	Type of effusion	Cytology	Sampled? (VATS/ thoracotomy/ thoracoscopy)	Vital status	Cause of death
Papillary thyroid carcinoma	0.1	No	Unilateral	Exudative	Positive	Autopsy/cytology	Dead	Hemothorax
Papillary thyroid carcinoma – follicular variant	1.5	No	Bilateral	Exudative	Negative	Thoracentesis	Dead	Respiratory failure due to acute effusion development
Follicular thyroid carcinoma	5.5	Yes	Bilateral	N/A	N/A	No	Dead	Brain metastases leading to seizures and neurologic decline
Papillary thyroid carcinoma	82.8	Yes	Bilateral	Exudative	Positive	Thoracentesis	Alive	N/A
Papillary thyroid carcinoma – tall cell variant	5.7	Yes	Bilateral	N/A	N/A	No	Dead	Shortness of breath due to metastatic lung lesions and development of acute development of effusion
Papillary thyroid carcinoma	9.4	Unknown	Bilateral	Exudative	Positive	Thoracentesis	Dead	Ventricular tachycardia leading to cardiac arrest
Papillary thyroid carcinoma	1.2	Unknown	Bilateral	Exudative	Positive	Thoracentesis	Alive	N/A
Poorly differentiated thyroid carcinoma – oncocytic, insular and follicular variants	13.4	Yes	Bilateral	N/A	N/A	No	Alive	N/A
Poorly differentiated thyroid carcinoma – follicular variant, solid variant and insular variant	6.7	Yes	Unilateral	Transudative	Negative	Thoracentesis	Dead	Sepsis initially from pneumonia, then developed atrial fibrillation with rapid ventricular response with volume overload. This led to hypoxia, shortness of breath and pursuit of hospice
Follicular thyroid carcinoma	0.2	No	Bilateral	N/A	N/A	No	Dead	Mass effect from tumor compressing the trachea

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prognostic variables on OS and CSS. In this study, pleural effusion, in addition to age ≥45 years, multisite metastases, incomplete tumor resection, visible metastases in bone, age at diagnosis, and a higher MACIS score were identified as significant risk factors for decreased overall- and cancer-specific survival. Pleural effusion is a novel prognostic finding and is associated with a more significant decrease in OS and CSS compared to other known prognostic variables in patients with FDTC with distant metastases.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EC-20-0193.

Declaration of interest

C N has no direct conflict of interest. C N is a member on the advisory committee or review panels for Exelixis and Nevro Corporation. The other authors have nothing to disclose.

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Author contribution statement

D T B contributed to data collection and wrote the manuscript. G B G designed the study and edited the manuscript. E F edited the manuscript. J F B performed the statistical analyses. C N designed the study and edited the manuscript.

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