Risk Patterns of Distant Metastases in Follicular, Papillary and Medullary Thyroid Cancer

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ABSTRACT

This study of 542 patients with follicular thyroid cancer, 366 patients with the follicular variant and 1452 patients with the classical variant of papillary thyroid cancer, and 819 patients with sporadic medullary thyroid cancer operated at a tertiary referral center aimed to determine risk patterns of distant metastasis for each tumor entity, which are ill-defined. On multivariable logistic regression analyses, lymph node metastasis consistently emerged as an independent risk factor of distant metastasis, yielding odds ratios (ORs) of 2.4 and 2.8 for follicular thyroid cancer and the follicular variant of papillary thyroid cancer, and ORs of 5.9 and 6.4 for the classical variant of papillary thyroid cancer and sporadic medullary thyroid cancer. Another independent risk factor consistently associated with distant metastasis, most strongly in follicular thyroid cancer and the follicular variant of papillary thyroid cancer (OR 3.5 and 4.0), was patient age >60 years. Altogether, 2 distinct risk patterns of distant metastasis were identified, which were modulated by other cancer type-dependent risk factors: one with lymph node metastasis as leading component (classical variant of papillary thyroid cancer and sporadic medullary thyroid cancer), and another one with age as leading component (follicular thyroid cancer and the follicular variant of papillary thyroid cancer). Distant metastasis was exceptional in node-negative patients with sporadic medullary thyroid cancer (1.7 %) and the classical variant of papillary thyroid cancer (1.4 %), and infrequent in node-negative patients with the follicular variant of papillary thyroid cancer (4.4 %). These findings delineate windows of opportunity for early surgical intervention before distant metastasis has occurred.

Introduction

Transformation of thyroid follicular cells and thyroid parafollicular C cells results in distinct types of cancer: follicular (FTC), papillary (PTC), and medullary (MTC) thyroid cancer [1]. Thyroid cancers display a broad spectrum of clinical behavior, ranging from small localized to widely metastatic malignancies.

Most thyroid cancers harbor mutations along the mitogen-activated protein kinase (MAPK) cellular signaling pathway [2]. This pathway, activated by mutually exclusive RET, BRAF, and RAS mutations in thyroid cancer, transmits growth signals from the cell membrane to the nucleus. These mutational events, playing an important part in gene expression and cell regulation, initiate cancer development. In some but not all thyroid cancers, tumor initiation is followed by tumor progression, depending on the accrual of more mutations. These somatic mutations enable the tumor to recruit further signal pathways [2].

Given this shared molecular background, growth and subsequent spread of different thyroid cancer types conceptually have commonalities, varying in magnitude by thyroid cancer type. Although clinically relevant, the impact of patient demographics, primary tumor, extrathyroid growth and nodal status on distant metastases has rarely been studied in more than one thyroid cancer

entity. Consequently, these relationships are poorly defined, limited by the infrequency of distant metastases in thyroid cancer.

The present comparative analysis was designed to determine risk patterns of distant metastases among patients with FTC, PTC (follicular and classical variants), and MTC.

Patients and Methods

Patient population

Included in the study were all patients with FTC, PTC, and sporadic MTC operated on between November 1994 and July 2021 at the authors' institution, a national referral center. Systematic lymph node dissection was carried out on clinical suspicion by ultrasonography, typically on evidence of enlarged nodes, or confirmation of nodal disease during clinical work-up or intraoperatively.

The present investigation, unlike previous research on metastatic and non-metastatic MTC [3], excluded carriers of RET germline mutations because these patients frequently are identified on family screening at asymptomatic stages.

Informed consent was obtained before each operation, which represented the standard of care in line with the practice guidelines of the German Association of Endocrine Surgery [4].

Histopathological analysis

Conventional staining (hematoxylin and eosin) and calcitonin immunohistochemistry were carried out on every surgical specimen. Histopathological diagnoses of thyroid cancer entities were based on World Health Organization criteria [5].

Primary tumor diameter was determined by direct measurements on the surgical thyroid specimens. When multiple primary tumors were present, only the largest tumor was considered.

All lymph node metastases were diagnosed using conventional histopathological methodology.

Distant metastases were diagnosed histopathologically and/or on unequivocal evidence on ultrasonography, computed tomography, magnetic resonance imaging, radioiodine scintigraphy, or positron emission tomography using 18-fluorodeoxyglucose or 18-fluorodopamine, or any combination thereof, regardless when it was noted.

For retrospective analysis of existing data sets from routine patient care, national law and applicable institutional regulations do not require institutional review board approval.

Statistical analysis

For statistical analysis, the software package SPSS version 25 (IBM, Armonk, New York, USA) was used. Categorical data are given as absolute and relative frequencies and were tested with the two-tailed Fisher's exact test. Continuous data are presented as means with 95 % confidence intervals and were compared by analysis of variance (ANOVA) or Student's *t*-test, as appropriate. Multivariate logistic regression models were fitted for each thyroid tumor type, using the same set of clinical variables. The level of statistical significance (all values were two-tailed) was set at $p \leq 0.05$.

Results

Clinical characteristics of the study population

During the study period, 542 patients with FTC, 366 patients with the follicular variant and 1452 patients with the classical variant of PTC, and 819 patients with sporadic MTC underwent thyroid surgery at the authors' institution. The clinical characteristics of these 4 groups of thyroid cancer patients are detailed in ▶ **Table 1**.

Multivariable logistic regression analysis on distant metastasis

On comparative multivariable logistic regression analysis (▶ **Table 2**), lymph node metastasis consistently emerged as an independent risk factor of distant metastasis, yielding odds ratios (ORs) of 2.4 and 2.8 for FTC and the follicular variant of PTC, and ORs of 5.9 and 6.4 for the classical variant of PTC and sporadic MTC. Another independent risk factor consistently associated with distant metastasis, most strongly in FTC and the follicular variant of PTC (OR 3.5 and 4.0), was patient age > 60 years.

Primary tumor size > 40 mm and referral for reoperation were independent risk factors of distant metastases in patients with sporadic MTC (ORs 5.4 for tumors > 60 mm and 3.2 for tumors 41–60 mm, and 1.7 for reoperation) and the classical variant of PTC (ORs 3.7 for tumors > 60 mm and 2.7 for tumors 41–60 mm, and 2.1 for reoperation), but not in patients with FTC and the follicular variant of PTC.

Also independently associated with distant metastases was extrathyroid extension in MTC (OR 4.4) and the follicular variant of PTC (OR 3.4), and male sex in FTC (OR 2.0) (▶ **Table 2**).

Primary tumor size by lymph node and distant metastasis

When stratified by lymph node and distant metastasis, the follicular and classical variants of PTC and sporadic MTC were comparable in primary tumor size (▶ **Table 3**).

Node-positive PTC (follicular and classical variants) and MTC were 31.1, 33.2 and 35.2 mm large in the presence, and 27.5, 24.5 and 23.5 mm large in the absence of distant metastasis.

Node-negative PTC (follicular and classical variants) and MTC were 36.0, 47.8 and 42.0 mm large in the presence, and 18.6, 12.6 and 15.0 mm large in the absence of distant metastasis.

Distant metastases were frequent in FTC (41.4 %, or 41 of 99 node-positive patients vs. 19.1 %, or 65 of 341 node-negative patients), but less so in the follicular variant of PTC (14.2 %, or 22 of 155 node-positive patients vs. 4.4 %, or 9 of 205 node-negative patients); the classical variant of PTC (11.0 %, or 77 of 700 node-positive patients vs. 1.4 %, or 9 of 647 node-negative patients); and sporadic MTC (23.1 %; 104 of 450 node-positive patients vs. 1.7 %, or 5 of 301 node-negative patients).

Discussion

The present comparative analyses of 4 thyroid cancer entities identified 2 distinct risk patterns of distant metastasis, which were modulated by other cancer type-dependent risk factors: one with lymph node metastasis as leading component (classical variant of PTC and

▶ **Table 1** Clinical characteristics of the study population.

		Follicular	Papillary		Medullary (sporadic)
			Follicular variant	Classical variant	
No. of patients		542	366	1452	819
Age at thyroidectomy, years, mean [95 % CI]		55.1 [53.8; 56.4]	47.1 [45.3; 48.9]	45.3 [44.4; 46.2]	52.1 [51.2; 53.1]
Sex, no. of male patients		220 (40.6)	127 (34.7)	467 (32.2)	376 (45.9)
No. of patients referred for reoperation		362 (66.8)	163 (44.5)	698 (48.1)	394 (48.1)
Largest primary tumor size, mm, mean [95 % CI]		44.1 [41.8; 46.4] (*n = 440*)	22.8 [20.7; 24.8] (*n = 338*)	19.5 [18.6; 20.5] (*n = 1347*)	21.9 [20.6; 23.1] (*n = 751*)
No. of patients with extrathyroid extension		189 (36.4) (*n = 519*)	109 (30.0) (*n = 363*)	502 (35.1) (*n = 1432*)	181 (22.6) (*n = 801*)
No. of patients with lymph node metastases		118 (21.8)	153 (41.8)	778 (53.6)	514 (62.8)
No. of lymph node metastases, mean [95 % CI]		2.0 [1.3;2.8] (*n = 441*)	5.3 [4.1;6.5] (*n = 291*)	7.5 [6.9; 8.1] (*n = 1182*)	10.1 [9.0; 11.3] (*n = 760*)
No. of dissected nodes, mean [95 % CI]		19.2 [17.1; 21.3] (*n = 441*)	31.1 [27.4; 34.8] (*n = 291*)	35.2 [33.4; 37.0] (*n = 1182*)	54.4 [52.1; 56.6] (*n = 760*)
No of patients with node dissection	central	415 (76.6)	277 (75.7)	1092 (75.3)	728 (89.9)
	ipsilateral lateral	146 (26.9)	139 (38.0)	656 (45.2)	641 (78.6)
	contralateral lateral	38 (7.0)	45 (12.3)	264 (18.2)	504 (61.5)
No. of patients with	distant metastasis, any	143 (26.4)	36 (9.8)	107 (7.4)	134 (16.4)
	lung metastasis	113 (20.8)	32 (8.7)	96 (6.6)	79 (9.6)
	bone metastasis	57 (10.5)	27 (1.9)	18 (1.2)	45 (5.5)
	liver metastasis	8 (1.5)	0 (0)	3 (0.2)	68 (8.3)
	brain metastasis	7 (1.3)	0 (0)	2 (0.1)	4 (0.5)

* Statistically significant after Bonferroni correction for multiple testing within each column; Values in parentheses denote column percentages; CI: Confidence interval.

sporadic MTC), and another one with age as leading component (FTC and the follicular variant of PTC).

These multivariable logistic regression analyses were based on the assumption that distant metastasis had already taken place by the time of thyroidectomy, as implied in the concept of metastatic dormancy [6]. Distant metastases primarily affected the lungs, which receive the entire cardiac output and have the densest capillary bed in the body [7].

Tumor cells invading normal tissues probably are also capable of metastasizing [8]. Metastatic spread occurs when a malignant cell becomes detached from the primary cancer, moves through the lymphatic and/or hematogenous system, and invades and successfully colonizes a lymph node or distant organ. Only a very small proportion of all tumor cells that becomes separated from the primary tumor winds up in the capillary bed of an organ that provides a microenvironment favorable to tumor growth and implantation [8]. This hypothesis explains why distant metastatic thyroid cancers overall are much larger at thyroidectomy when compared to nonmetastatic thyroid cancers (▶ **Table 3**).

FTC and the follicular variant of PTC produced strikingly similar results on multivariable analysis, setting these cancers apart from the classical variant of PTC and from sporadic MTC (▶ **Table 2**). On the genomic level, FTC and the follicular variant of PTC have more in common than the follicular and classical variants of PTC, which currently are classified together [9]. This observation prompted calls for reclassification of follicular-patterned tumors to reunite FTC with the follicular variant of PTC. The present data would support such reclassification.

Interestingly, patient age >60 years was positively correlated with distant metastasis in FTC and PTC, but inversely in sporadic MTC. Indeed, follicular thyroid cells, falling into the category of '*deterministic tumors*', are more susceptible to environmental factors than parafollicular C cells, which belong to the category of '*replicative tumors*' in which replication errors are the principal cause of cancer [10].

Despite the advent of more powerful diagnostic and imaging technologies since the 1990s [11], thyroid tumors were twice as large in patients with FTC than in patients with the follicular or classical variants of PTC or sporadic MTC (means of 44.1 mm vs. 22.8, 19.5 and 21.9 mm) and developed more frequently distant metastases (26.4 % vs. 9.8, 7.4 and 16.4 %) in this study (▶ **Table 1**). This observation may reflect difficulties in distinguishing follicular adenoma from follicular cancer, aggravated by the high prevalence of goiter in Germany [12]. Altogether, lymph node metastasis, a hallmark of the classical variant of PTC and sporadic MTC, may have triggered thyroid investigations earlier in these patients than in patients with FTC.

Smaller distant metastases, evading even the most sophisticated imaging technology, arguably may have been missed in all

▶ **Table 2** Comparative multivariable logistic regression analysis on distant metastasis† in thyroid cancer.

Independent variable		Follicular			Papillary						Medullary (sporadic)		
					Follicular variant			Classical variant					
		n‡ = 441	Odds ratio [95 % CI]	p	n‡ = 337	Odds ratio [95 % CI]	p	n‡ = 1346	Odds ratio [95 % CI]	p	n‡ = 765	Odds ratio [95 % CI]	p
Lymph node metastasis	present	99	2.4 [1.4; 4.1]	0.001	132	2.8 [1.1; 7.2]	0.033	700	5.9 [2.7; 12.5]	<0.001	458	6.4 [2.4; 16.7]	<0.001
	absent	342	1		205	1		646	1		307	1	
Largest primary tumor size, mm	>60	96	1.4 [0.6; 3.2]	0.422	17	1.7 [0.4; 8.4]	0.505	46	3.7 [1.6; 8.8]	0.003	28	5.4 [2.1; 14.2]	0.001
	41–60	105	1.4 [0.6; 3.1]	0.430	34	2.4 [0.7; 8.7]	0.178	105	2.7 [1.4; 5.3]	0.003	61	3.2 [1.5; 6.6]	0.002
	21–40	170	1.0 [0.5; 2.2]	0.917	102	2.0 [0.7; 5.5]	0.165	320	1.4 [0.8; 2.5]	0.221	237	1.9 [1.1; 3.3]	0.015
	≤20	70	1		184	1		875	1		439	1	
Extrathyroid extension	present	139	1.1 [0.6; 1.8]	0.843	92	3.4 [1.4; 8.2]	0.007	447	1.4 [0.9; 2.3]	0.170	163	4.4 [2.7; 7.3]	<0.001
	absent	302	1		245	1		899	1		602	1	
Referral for reoperation	yes	277	1.3 [0.8; 2.2]	0.255	181	1.4 [0.6; 3.5]	0.416	668	2.1 [1.3; 3.6]	0.004	345	1.7 [1.0; 2.8]	0.041
	no	164	1		156	1		678	1		422	1	
Sex	male	185	2.0 [1.3; 3.3]	0.004	120	1.6 [0.7; 3.8]	0.261	438	1.2 [0.8; 1.9]	0.525	350	1.2 [0.8; 2.0]	0.431
	female	256	1		217	1		908	1		415	1	
Age at thyroidectomy, years	>60	177	3.5 [1.4; 8.5]	0.006	81	4.0 [1.3; 12.5]	0.016	310	1.8 [1.0; 3.2]	0.050	247	0.4 [0.2; 0.7]	0.002
	41–60	194	2.4 [1.0; 5.7]	0.052	147	1.8 [0.6; 5.0]	0.261	493	1.2 [0.7; 2.2]	0.567	358	0.5 [0.3; 0.8]	0.007
	≤40	70	1		109	1		543	1		160	1	

†330 patients (106, 31, 86, and 110, respectively) had metastatic events; ‡ Patients with information on all examined variables; CI: Confidence interval.

▶ **Table 3** Primary tumor size† by lymph node and distant metastasis in thyroid cancer.

	Follicular	Papillary		Medullary (sporadic)
		Follicular variant	Classical variant	
Patients with node-positive tumor, n = 1404 (244 patients with and 1160 patients without distant metastasis)	99 (41/58)	155 (22/133)	700 (77/623)	450 (104/346)
Tumor with distant metastasis: largest primary tumor size, mm, mean [95 % CI]	50.5 [43.4; 57.6]	31.1 [23.2; 39.1]	33.2 [27.8; 38.6]	35.2 [31.4; 39.1]
Tumor without distant metastasis: largest primary tumor size, mm, mean [95 % CI]	49.2 [42.5; 56.1]	27.5 [24.2; 30.8]	24.5 [23.1; 25.9]	23.5 [21.7; 25.3]
Size difference, mm, mean [95 % CI]	1.3 [–8.6; 11.4]	3.6 [–4.6; 11.9]	8.7 [2.8; 14.1]	11.7 [7.5; 16.0]
p	0.796	0.383	0.003	< 0.001
Patients with node-negative tumor, n = 1494 (88 patients with and 1406 patients without distant metastasis)	341 (65/276)	205 (9/196)	647 (9/638)	301 (5/296)
Tumor with distant metastasis: largest primary tumor size, mm, mean [95 % CI]	49.4 [43.2; 55.6]	36.0 [17.8; 54.2]	47.8 [24.3; 71.3]	42.0 [–7.8; 91.8]
Tumor without distant metastasis: largest primary tumor size, mean [95 % CI]	40.8 [38.0; 43.6]	18.6 [16.0; 21.2]	12.6 [11.6; 13.7]	15.0 [13.5; 16.4]
Size difference, mm, mean [95 % CI]	8.6 [2.1; 15.0]	17.4 [4.7; 30.1]	35.2 [11.7; 58.7]	27.0 [–22.7; 76.8]
p	0.009	0.007	0.009	0.206

†Based on 2898 patients with information on primary tumor size; Values in parentheses denote patients with/without distant metastasis. Owing to rounding, not all numbers add up; CI: Confidence interval.

4 groups of patients. Such non-differential misclassification, rendering metastatic and non-metastatic patients more alike, typically works to level, not to augment, differences that may exist among the 4 thyroid cancer entities.

Conclusions

Distant metastasis was exceptional in node-negative patients with sporadic MTC (1.7 %) and the classical variant of PTC (1.4 %), and infrequent in node-negative patients with the follicular variant of PTC (4.4 %). These findings delineate windows of opportunity for early surgical intervention before distant metastasis has occurred.

Conflict of Interest

The authors declare that they have no conflict of interest.

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