Divergent Metastatic Patterns Between Subtypes of Thyroid Carcinoma Results From the Nationwide Dutch Pathology Registry

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Background: Metastatic disease is the main cause of cancer-related mortality in thyroid carcinoma (TC) patients. Clinical studies have suggested differences in metastatic patterns between the different subtypes of TC. This study systematically evaluates the metastatic patterns of different subtypes in TC patients.

Methods: A nationwide review of pathological records of all 650 patients diagnosed with a primary malignancy in the thyroid who underwent an autopsy between 1991 and 2010 was performed. Patients were selected from the Dutch pathology registry (PALGA).

Results: Metastatic disease was present in 228 (35.1%) patients and was found in 38.7%, 17.3%, 75.4%, and 47.8% of patients with follicular, papillary, anaplastic, and medullary types of TC, respectively (P < .0001). The majority of patients had more than 1 metastasis. The most common site of metastatic disease was the lung for papillary (79.7%), follicular (72.9%), and anaplastic (92.1%) carcinoma but not for medullary carcinoma (56.3%), P < .0001. Medullary carcinoma patients most frequently had metastases to the liver (81.3%). The combination of metastases also differed between subtypes.

Conclusion: There are major differences in metastatic patterns between different subtypes of TC. The patterns and frequencies identified in this autopsy study may reflect the underlying biology of metastatic thyroid cancer and have potential to influence future monitoring and treatment strategies depending on clinical correlations. (*J Clin Endocrinol Metab* 105: 1–8, 2020)

Thyroid carcinoma (TC) currently accounts for 2% of all new malignant neoplasms (1, 2). Due to the distinct clinical presentation, etiology and biological behavior TC cannot be regarded as a single entity but is generally classified as differentiated papillary carcinoma (PTC), follicular carcinoma (FTC), or undifferentiated/anaplastic carcinoma (ATC). Due to its distinct cellular origin, a separate entity is formed by the medullary TC (MTC). Papillary and follicular tumors arise from follicular epithelium and are diagnosed in 71% and 15% of cases, respectively (3). ATC is an undifferentiated subtype also originating from the follicular epithelial cells. It is found in 3% of TC patients and mainly occurs in older patients and is associated with a dismal prognosis (2, 4). MTC is found in 5% of patients and originates from C-cells (5). Knowledge on the dissemination pattern of patients with different subtypes has mainly been gathered from clinical observational retrospective

studies and mainly reflects the clinically manifest metastases. A systematic analysis of the differences in dissemination patterns between the different subtypes has not been undertaken and it is unclear whether this could have clinical implications.

Although most patients with differentiated TC have a good prognosis, metastatic disease is the main determinant for cancer-related mortality, especially in MTC and ATC patients (6–9). At the time of diagnosis approximately 0.8% to 11% of patients will have distant metastases and another 7% to 34% of patients treated for local disease will develop distant metastases during follow-up (7, 9–15). Previous clinical and autopsy studies have described the dissemination patterns of TC to a limited extent. These studies, comprising primarily PTC, demonstrated that differentiated TCs primarily metastasize to liver, lung, and lymph nodes (14, 16, 17). MTC is associated with a high rate of locoregional lymph node metastases and distant metastases may occur in the liver, lungs, and bone (5). An autopsy study that took all subtypes into account also reported on rarer metastatic sites, including the kidneys, heart, and abdomen (18). Unfortunately, these studies included small numbers of patients and mainly focused on well-differentiated non-MTCs.

This nationwide autopsy study aims to evaluate the patterns of metastatic spread of TC for different subtypes. We hypothesize that the various subtypes show differences in metastatic spread.

Materials and Methods

Patients

A review of pathological and autopsy records of patients diagnosed with a malignancy of the thyroid who underwent an autopsy between May 1981 and May 2016 in the Netherlands was performed. Patients were selected from the Nationwide Network and Registry of Histopathology and Cytopathology (PALGA) Group in the Netherlands (19). In this period, the proportion of included cases in PALGA increased to nationwide coverage in 1989. The rate of autopsies has been declining in the Netherlands, from 31.4% of all deaths in 1977 to 7.7% in 2011 (20). The individual reason to request autopsy could not be collected from the registry, but autopsies in the Netherlands are generally performed to determine the cause of death or to obtain additional information regarding the medical condition of the deceased. Forensic autopsies were not included. Patients were only included if whole body autopsy had been performed. The neurocranium was opened during autopsy in a minority of 193 patients. Ethical approval for this study was obtained from the PALGA institutional review board. The study was performed in accordance with the Declaration of Helsinki.

Morphological and metastatic features

A total of 1335 patients with metastatic disease either to the thyroid or originating from the thyroid were identified. In

591 patients there was a metastasis to the thyroid gland and not a primary TC; these were excluded from further analyses. Tumor histology had been assessed by different pathologists in all cases. Only tumors that were classified as PTC, FTC, ATC, or MTC, were included ($N = 650$). For every patient data on gender, age, date of autopsy, date of primary tumor, and date of subsequent pathological examinations (eg, biopsies or metastasectomies) were available. Information on cause of death or further clinical data were not available in the PALGA database. Metastases that were found within 6 months after diagnosis of the primary tumor were considered synchronous. Lymph node metastases were considered distant if they were found outside the regional cervical or superior mediastinal lymph node regions.

Statistical analysis

The χ^2 test was used to compare demographics and tumor characteristics between both groups. All tests of significance were two-tailed: differences at P values of less than .05 were considered to be significant. Statistical analyses were performed with the statistical software package SPSS 20.0 (SPSS Inc, Chicago, Illinois, US). Survival was analyzed using overall survival data, which was determined as the interval between date of primary tumor and date of autopsy (only for patients in whom the primary tumor was diagnosed prior to autopsy).

Results

A total of 650 patients with a TC were included. PTC was found in 341 (52.5%) cases, FTC in 124 (19.1%), ATC in 118 (18.2%), and MTC in 67 (10.3%) cases.

Distant metastatic disease was present in 228 (35.1%) patients and was found in 38.7%, 17.3%, 75.4%, and 47.8% of patients with FTC, PTC, ATC, and MTC, respectively ($P < .0001$), Fig. 1A. Clinicopathological data of metastatic TC patients is presented in Table 1. The median age of the patients with distant metastatic disease was 70.5 (range 26–91) at the moment of diagnosis.

Distribution of distant metastases according to carcinoma type

The majority of patients with metastatic disease had more than 1 metastasis. In MTC patients, 81.2% had more than 1 metastasis versus 62.5%, 64.4%, and 66.3% in FTC, PTC, and ATC patients, respectively (Fig. 1A). There were considerable differences in the distribution of metastases across the subtypes (Table 2; Fig. 1B).

The most common site of distant metastatic disease was the lung for PTC (79.7%), FTC (72.9%), and ATC (92.1%), but not for MTC (56.3%, $P < .0001$). In contrast, MTC patients most frequently had metastases to the liver (81.3%). Bone metastases were found in 40.6% of MTC patients and in only 15.7% of ATC patients ($P = .008$). Metastases to the heart were found in a notable 23.7% of PTC and 19.1% of ATC patients
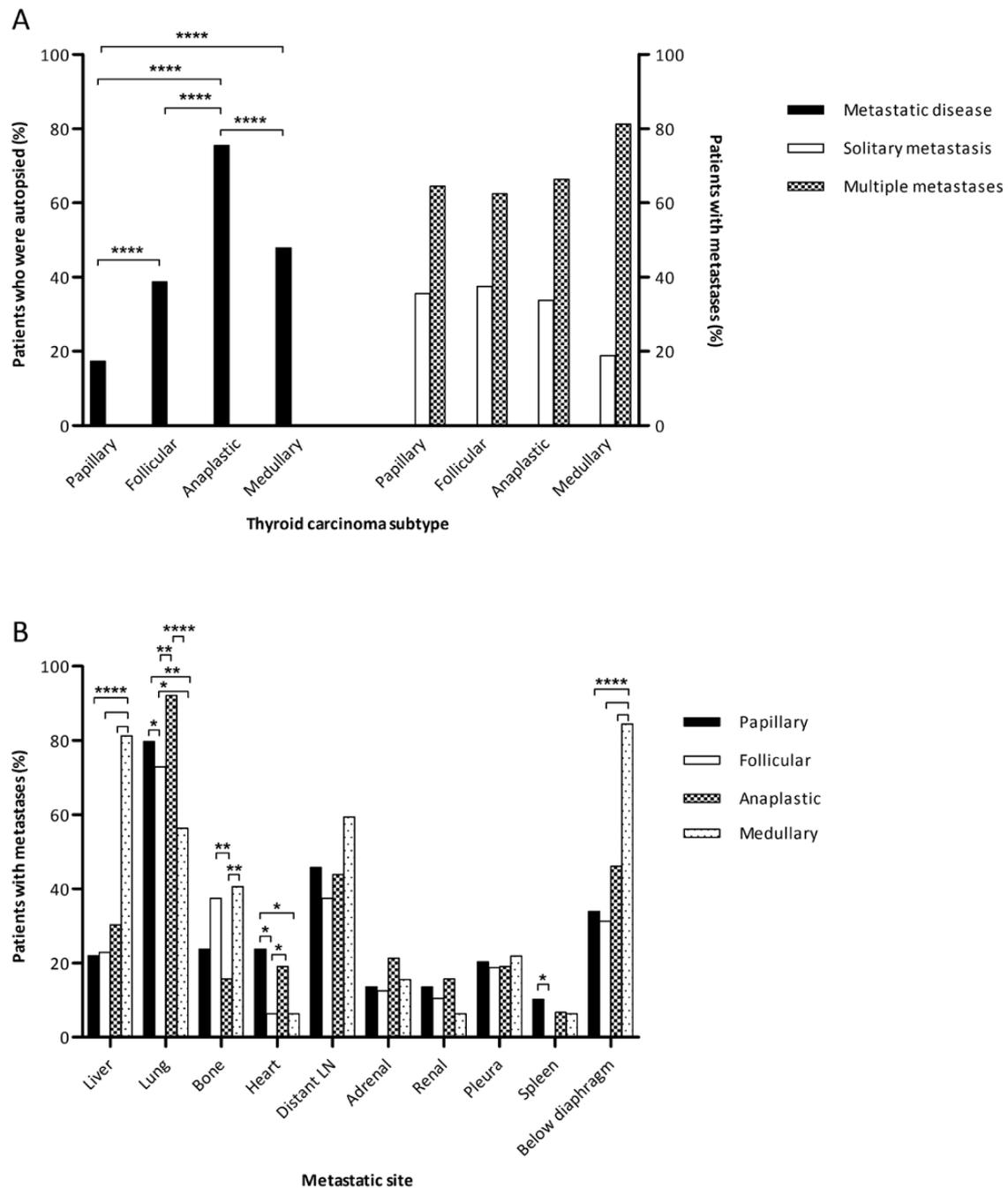
Figure 1. (A) Percentage of thyroid carcinoma patients with (i) distant metastatic disease and (ii) distribution of solitary versus multiple metastases for the different subtypes of thyroid carcinoma. (B) Distribution of distant metastases according to thyroid carcinoma type. Abbreviation: LN, lymph node. *$P \leq$ .05, **$P \leq$ .01, ***$P \leq$ .001, and ****$P \leq$ .0001.

compared with 6.3% in both MTC and FTC patients (P = .029). Interestingly, metastases to the pancreas were seen in 9.4% of MTC patients and in 6.7% of ATC patients. Metastases to the stomach were only seen in ATC patients (7.4% of cases). Metastases to distant lymph nodes were common and most often found in patients with multiple metastases. Only in 10% of patients with metastases to distant lymph nodes, this was the only metastatic site (N = 8). Metastases to distant lymph nodes were most commonly found in patients with lung

metastases (77.7%). Most of distant lymph nodes were indeed found adjacent to the lungs (ie, near the hilum of the lungs or within the mediastinum). Brain autopsy was performed in only 31 patients with metastatic disease, which rendered analyses on brain metastases not reliable.

Patterns of metastasis

Fig. 2 illustrates the combinations of metastases according to TC subtype. Clearly, MTC most frequently metastasized to more than one site (81.2%). Metastases to the lung only

Table 1.   Clinicopathological features of patients with metastatic thyroid carcinoma diagnosed between 1991 and 2016

Features	Papillary 59	(%)	Follicular 48	(%)	Medullary 32	(%)	Anaplastic 89	(%)	P-value
Tumor diagnosed prior to autopsy									.057
Yes	37	62.7	37	77.1	27	84.4	71	79.8	
No	22	37.3	11	22.9	5	15.6	18	20.2	
Sex									
Women	35	59.3	26	54.2	15	46.9	59	66.3	.224
Men	24	40.7	22	45.8	17	53.1	30	33.7	
Age at diagnosis									
Median (range) years	69	(33–91)	70.5	(39–85)	62.5	(26–81)	73	(44–91)	
<45	4	6.8	1	2.1	6	18.8	1	1.1	.019
45–59	10	16.9	4	8.3	5	15.6	10	11.2	
60–74	25	42.4	24	50.0	13	40.6	40	44.9	
≥75	20	33.9	19	39.6	8	25.0	38	42.7	
Lymph node status									
positive	9	23.7	15	51.7	0	0	6	13.6	<.0001
negative	29	76.3	14	48.3	24	100	38	86.4	
unknown	21	-	19	-	8	-	45	-	
Number of metastases									
1	21	35.6	18	37.5	6	18.8	30	33.7	.310
>1	38	64.4	30	62.5	26	81.2	59	66.3	
Survival[a]									
Median (range) months	7	(0–207)	14	(0–262)	16	(0–324)	0	(0–29)	
Interval primary tumor and metastasis[a]									
Median (range) months	3	(0–207)	12	(0–262)	16	(0–324)	0	(0–28)	
Timing of metastases[a]									<.0001
Synchronous	19	51.4	21	56.8	17	63.0	64	90.1	
Metachronous	18	48.6	16	43.2	10	37.0	7	9.9	

[a]Only given for patients in whom the primary tumor was diagnosed prior to autopsy.

Table 2.   Distribution of Distant Metastases According to Thyroid Carcinoma Type

Metastatic site	Papillary N = 59	%	Follicular N = 48	%	Medullary N = 32	%	Anaplastic N = 89	%	P-value
Liver	13.0	22.0	11	22.9	26	81.3	27	30.3	**<.0001**
Lung	47.0	79.7	35	72.9	18	56.3	82	92.1	**<.0001**
Bone	14.0	23.7	18	37.5	13	40.6	14	15.7	**.008**
Heart	14.0	23.7	3	6.3	2	6.3	17	19.1	**.029**
Distant lymph nodes	27.0	45.8	18	37.5	19	59.4	39	43.8	.281
Adrenal	8.0	13.6	6	12.5	5	15.6	19	21.3	.486
Renal	8.0	13.6	5	10.4	2	6.3	14	15.7	.532
Pleura	12.0	20.3	9	18.8	7	21.9	18	20.2	.989
Spleen	6.0	10.2	0	0.0	2	6.3	6	6.7	.182
Brain	3.0	5.1	4	8.3	2	6.3	6	6.7	.927
Skin/subcutaneous tissue	4.0	6.8	2	4.2	0	0.0	2	2.2	.320
Pancreas	1.0	1.7	2	4.2	3	9.4	6	6.7	.377
Peritoneum	0.0	0.0	3	6.3	1	3.1	5	5.6	.283
Small intestine	1.7	2.0	2	4.2	0	0.0	0	0.0	.197
Large intestine	1.0	1.7	0	0.0	1	3.1	3	3.4	.604
Esophagus	0.0	0.0	0	0.0	0	0.0	2	2.2	.369
Ovary	0.0	0.0	0	0.0	0	0.0	1	1.1	.667
Omentum	1.0	1.7	0	0.0	0	0.0	1	1.1	.747
Stomach	1.0	1.7	1	2.1	0	0.0	7	7.9	.105
Uterus	2.0	3.4	0	0.0	1	3.1	1	1.1	.507
Mesentery	2.0	3.4	0	0.0	0	0.0	2	2.2	.481
Diaphragm	1.0	1.7	1	2.1	0	0.0	2	2.2	.867
Mouth/tongue	0.0	0.0	1	2.1	0	0.0	0	0.0	.288
Breast	0.0	0.0	0	0.0	1	3.1	2	2.2	.419
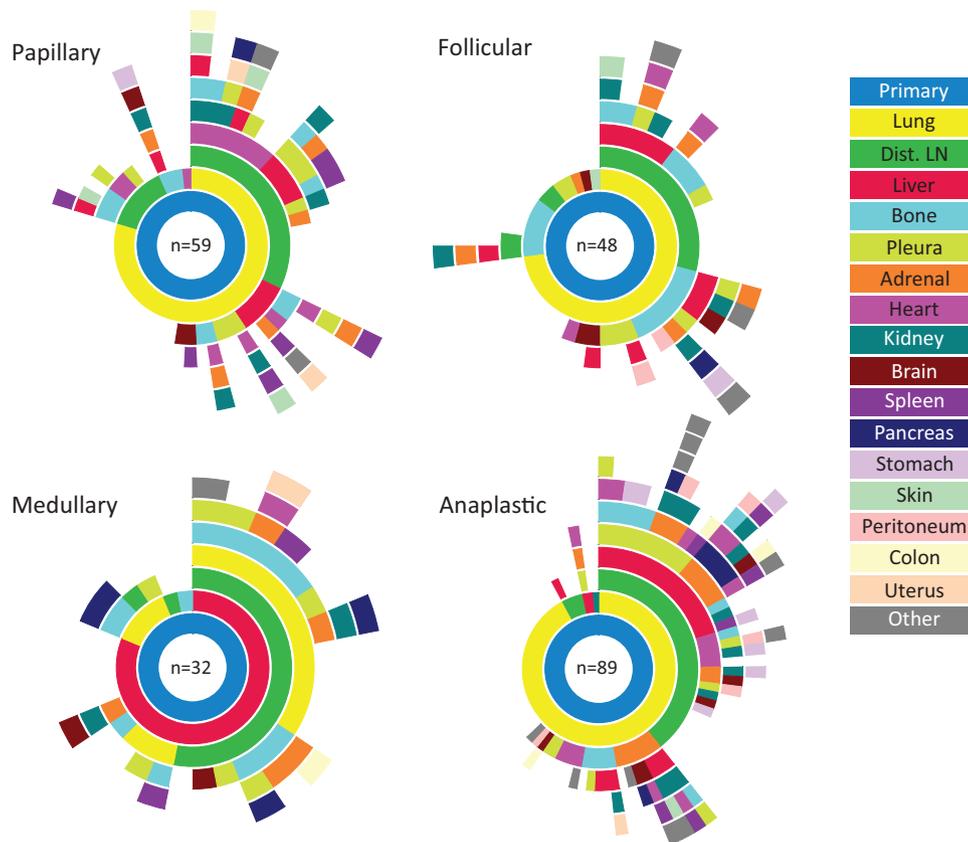
Figure 2. Combinations of distant metastases in thyroid carcinoma patients. Each ring represents a percentage of patients with a metastasis to a specific site. Combinations of metastases are stacked and ranked according to frequency of occurrence from the center to periphery. Abbreviation: Dist LN, distant lymph nodes.

were seen in 22.9% to 30.4% of PTC, FTC, and ATC carcinoma patients, whereas none of the MTC patients had a metastases to the lung only (P = .034). Liver metastases as the only site of metastatic disease was rare, it was not seen in patients with FTC and PTC, and only occurred in 15.4% of MTC patients and 3.7% of ATC patients.

Incidentally noted thyroid carcinoma

There were 359 patients in whom the pathological diagnosis of TC was first reported during autopsy. PTC was most commonly diagnosed at first during autopsy in 72.4% of patients versus 46.8%, 20.3%, and 44.8% of patients diagnosed with FTC, ATC, and MTC, respectively (P < .0001). Metastatic disease was found in 15.6% of patients (N = 56) in whom the pathological diagnosis of TC was first reported during autopsy (8.9% in PTC, 19.0% in FTC, 16.7% in MTC and 75.0% in ATC, P < .0001). The extent of metastatic disease varied among the subtypes. A single metastasis was found in PTC and FTC in 45.5% of patients, whereas multiple metastases were found in MTC and ATC in 80.0% and 77.8%, respectively (P = .344).

Survival

The median age of all patients at death was 72 (range 25–100). Patients who were diagnosed with TC prior to autopsy were included in the survival analysis. The median overall survival was 58 months (range 6–262) in stage I, II, and III patients and 1 month (range 0–324) in stage IV patients. Patients with ATC had the worst survival with a median of 21 days (range 0–29 months) from date of initial diagnosis.

Discussion

Patients with differentiated TC have a good prognosis. The occurrence of metastatic disease, however, is one of the most important prognostic factors for survival in differentiated TC and MTC patients (6–9). Survival in ATC is mainly determined by its locally invasive behavior. This autopsy study on metastatic pattern recognition demonstrates major differences in metastatic patterns of different subtypes of TC, which may reflect the underlying biology of metastatic thyroid cancer.

Postmortem studies offer a possibility to register both the extent and location of metastatic disease in any type of cancer. Findings during autopsy may be considered the ultimate endpoint of disease, and limitations of imaging techniques for detecting metastases do not apply. Therefore, autopsy studies offer a unique method to study the pattern of metastatic spread and

can be considered the gold standard. The validity of data from autopsy studies has been confirmed in other cancer types where findings have been validated using independent clinical trial and population-based cohorts (21, 22). However, it is important to realize that metastatic lesions that were revealed during autopsy may not have influenced the clinical course, nor may they have required clinical intervention. Moreover, metastatic disease may not have been the cause of death for patients who were included in this study. As far as we are concerned, this is the largest study focusing on recognition of patterns of metastatic spread in different subtypes of TC.

In the autopsy cohort of the current study, metastatic disease was found in one-third of the patients with TC, with ATC being clearly overrepresented among the non-MTCs. The majority of patients had more than 1 metastasis, particularly in MTC. Lung metastases were most common in the non-MTCs and liver and bone metastases in the MTC. Solitary metastases were rare, with lung only metastases present in non-MTCs whereas liver only metastases were only present in the MTC and ATC. Metastases to distant lymph nodes only were very rare. Distant lymph node metastases were mostly present in the vicinity of the lungs and mediastinum and were accompanied by lung metastases.

Our study shows that many of the differentiated TCs, particularly PTCs, were not pathologically diagnosed during lifetime, which is not surprising. PTC has often been reported to be found as an incidental finding in both clinical and autopsy studies, and the disease often follows a relatively indolent clinical course (23). On the other hand, as shown in the current large autopsy study, metastases could be found in up to 17.3% and 38.7% of the patients with PTC and FTC, respectively. If metastatic disease was present, in two-thirds of the cases more than 1 metastatic site could be found, mostly lungs and bones. ATC on the other hand had rarely not been diagnosed during lifetime. Of these patients, the vast majority had synchronous metastases, and two-thirds had more than 1 metastatic site, which, in most of the cases, included the lungs. Rare metastatic locations were also found such as heart and pancreas. The number of cardiac metastases is seemingly high. Another autopsy study also revealed that cardiac metastases were found in 7% of patients with TC (N = 43) (18). This study focused on all types of cancer and did not further specify TC subtypes. It is unknown whether these metastases can be considered the main cause of death for these patients. In patients with ATC, single metastatic locations were very rare. MTCs also follow a different metastatic pattern with almost half of the

patients having evidence of metastases at the time of the autopsy and 81% of them at more than 1 site, most commonly the liver and bone.

Studies on distant metastases in TC are sparse due to its relatively rare occurrence. However, studies that have reported on metastatic disease, generally do not report on sites of metastatic disease nor on patterns of metastatic spread according to subtype. Moreover, in ATC in particular, in which survival is mainly compromised due to the locally invasive rapid growth of the tumor, metastases have not been studied well. A single institution review of 111 cases by Haq et al. (16) reported on differentiated TC patients with metastatic disease upon presentation. This study reported that lung only and bone only metastases were seen in 49% and 24% of patients, respectively. No more than 19% of patients had metastases at multiple sites. Another study by Lee et al. (14), reporting on 91 cases of metastatic disease found metastases in the lung only in 68.1% and at multiples sites in 15.4%. In the present study, between 62.5% and 81.2% of patients had distant metastases to more than 1 site. Although results from an autopsy study cannot be compared with a retrospective review of cases directly, it is not inconceivable that patients actually may suffer from metastatic disease at a more extensive level than clinically evident.

This is the first study that generated insight into metastatic spread of ATC in a nationwide population using autopsy data. There are, however, limitations due to the retrospective nature of this study, as well as the type of study and therefore the findings should be interpreted with caution. First, patients included in an autopsy studies do not reflect the general population, since autopsy is regularly chosen when the patient died postoperatively or had an unexpected clinical course. In the current study, this is reflected by a relatively high number of patients with ATC and a high proportion of male patients. Autopsy studies may reveal metastatic lesions that are clinically not necessary relevant and may be less common. However, given the histopathological confirmation of each of the metastases, they generate insight into the possible patterns of metastatic spread, which is becoming increasingly important in the era in which targeted therapeutic modalities and imaging are evolving. Findings from this study have the potential to influence future monitoring and treatment strategies depending on clinical correlations.

Data from previous autopsy studies have been validated with clinical trial data and population-based cohorts, which supports validity of observed metastatic patterns (21, 22). Moreover, it is important to realize that patients may have died of other causes than

cancer and that disease may have progressed when untreated, limiting the possibility of survival analyses. Furthermore, it has not been possible to review the pathological diagnosis of each individual patient or to retrieve additional information, such as regional lymph node status of the primary tumor. The poorly differentiated TC, which was recognized as a distinct entity in 2004 by the World Health Organization Classification of Endocrine Tumors, was not classified as a separate entity in this study because it has not been registered as such in the PALGA nationwide database. Variations in interpretation may have resulted in misclassification, and this cannot be corrected for. It may be possible that there is an underestimation of the number of metastatic lesions in the autopsy study, since metastatic sites outside of the routinely examined regions (eg, long bones) may have been missed during autopsy. Brain autopsy was only performed in 199 patients, which unequivocally has led to an underestimation of brain metastases. This bias, however, applies to all TC subtypes.

It is known that tumor subtype, tumor differentiation, and presence of metastases are important prognostic factors in differentiated TC (9, 14, 24). Moreover, patients with multiple affected sites at presentation are associated with a worse survival compared with others (16). Approximately half of patients who die from metastatic TC die due to respiratory failure from pulmonary metastases or due to suffocation from airway compression (25). There is some evidence suggesting that surgical removal of a solitary or low number of distant metastases may lead to long-term remission or be curative (16, 26, 27). Nevertheless, it is important to realize that well differentiated non-MTCs benefit from iodine-131 treatment and that survival in patients with distant metastases is better in patients with iodine avidity (14). On the other hand, screening for presence of metastases at other potential locations than clinically obvious could help better tailoring the treatment decisions in patients with known metastases.

The underlying mechanisms for differences in metastatic patterns between the TC subtypes are not clear. The results from our study indicate that metastatic spread to distant sites is foremost through the hematogenous pathway, but most probably also through the lymphatic pathway as distant lymph nodes were affected in 37.5% to 59.4% of metastatic patients. Unfortunately, we were not able to evaluate the metastatic pattern according to the lymph node status of the primary tumor since data on local lymph node status were missing in up to two-thirds of patients. Jeon et al. (13) reported in 2014 that the cumulative risk of distant metastasis in PTC patients is related to the location of involved regional lymph nodes in patients with an odds ratio of 6.1 and 27.01 for N1a and N1b respectively, when compared with N0. Another study suggested that numerical categories of lymph node metastases correlated with the risk for lung metastasis development (28). These findings are suggestive of a certain biological behavior in which tumor cells more easily migrate when regional lymph nodes are affected.

This study has demonstrated that different TC subtypes disseminate to different sites according to divergent patterns, which can differ from the known patterns reported in clinical studies. This may be related to differences in biological behavior of metastatic thyroid cancer. These findings have potential to influence future monitoring and treatment strategies depending on clinical correlations and substantiate the need to take carcinoma subtype into account during follow-up. The findings warrant to include carcinoma subtype as a stratification factor in future research initiatives on metastatic TC.

Additional Information

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