

# The Differences in Distant Metastatic Patterns and Their Corresponding Survival Between Thyroid Cancer Subtypes

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## Research Article

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# Abstract

**Introduction:** Distant metastasis (DM) at presentation is one of the important prognostic factors in thyroid cancers. Dissemination patterns of different thyroid cancer subtypes are still controversial. This study aimed to systematically elucidate the metastatic patterns and their corresponding survival of each thyroid cancer subtype at time of diagnosis.

**Methods:** We accessed the Surveillance, Epidemiology, and End Results (SEER) database from 2010-2018 to search for primary thyroid cancers with DM at presentation (M1).

**Results:** We included 2,787 M1 thyroid cancers for statistical analyses and the incidence of DM at presentation was 2.4%. Lung was the most common metastatic site for anaplastic thyroid carcinoma (ATC), poorly-differentiated thyroid carcinoma (PDTC), papillary thyroid carcinoma (PTC), and oncocytic (Hurthle) cell carcinoma (HCC) whereas bone is the favorable disseminated site of follicular thyroid carcinoma (FTC) and medullary thyroid carcinoma (MTC). The risk of liver metastasis was highest in MTC while metastases to the brain were uncommon among thyroid cancer subtypes. Among M1 thyroid cancers, ATC showed the worst outcome while PTC and FTC exhibited a superior survival. Patients with multi-organ metastases had the worst survival whereas bone metastases were associated with a favorable outcome ( $p < 0.001$ ). We identified significant risk factors associated with multi-organ metastases including non-Caucasian race, large tumor diameter, ATC/FTC/MTC histology, and unifocality.

**Conclusion:** There are significant differences in DM patterns of thyroid cancer subtypes and their corresponding survival. These clinical data could be useful for clinicians to better evaluate risk stratification and predict patient outcomes.

## Introduction

Thyroid cancer is the most common type of endocrine cancer and its incidence has increased three-fold during the past 30 years [1]. Among thyroid cancers, papillary thyroid carcinoma (PTC) remains the most common histologic subtype, followed by follicular thyroid carcinoma (FTC), medullary thyroid carcinoma (MTC), poorly-differentiated thyroid carcinoma (PDTC), and anaplastic thyroid carcinoma (ATC). Most thyroid cancers have an indolent course with an estimated 5-year survival of more than 95%. However, a subset of thyroid cancers may behave aggressively with distant metastasis (DM) at time of diagnosis, which is the main prognostic factor for disease-specific mortality [2]. Several clinicopathological and molecular parameters have been demonstrated to be significant risk factors associated with this rare event [3–6]. Clinical data on the dissemination patterns and survival of thyroid cancers with DM at presentation have been primarily gathered from retrospective institutional experience. Nationwide or large population-based analyses on this topic are needed to understand its full clinical implications. Several studies have described the metastatic patterns of thyroid cancer variants, mainly differentiated thyroid cancers [7–10], with only a few studies focusing on MTC, PDTC, or ATC [11–13]. Unfortunately, the

number of included patients in these studies is relatively small and often limited to a specific subtype of thyroid cancer.

This study aimed to evaluate the DM patterns of different thyroid cancer subtypes and their impact on patient survival utilizing the Surveillance, Epidemiology, and End Results (SEER) program.

## Materials And Methods

We accessed the SEER 18 registries custom database to search for thyroid carcinomas from 2010–2018. The year 2010 was selected as the cut-off year because the metastatic location data were tabulated in the SEER database from this year onward. DM at presentation was categorized as M0 (without DM) and M1 (with DM). During this period, a total of 119,206 thyroid cancers were identified and we subsequently removed 6,256 cases with missing information for DM at presentation. Among 115,481 cases with available information, there were 2,787 cases (2.4%) with DM at presentation included for analyses. We extracted the following covariates: patient ID, age at diagnosis, gender, race, primary site, histology diagnosis, tumor diameter, nodal/distant metastasis, multifocality, sites of DM (bone, brain, liver, lung, distant nodes, and other sites), the extent of resection, radiotherapy, chemotherapy, overall survival (OS) time, OS status.

The Chi-squared and Wilcoxon rank-sum tests was used to compare clinical parameters between groups. For survival analyses, Kaplan-Meier analysis and Cox regression analysis were run to analyze all-cause mortality differences between M1 groups. Hazard ratio (HR) and corresponding 95% confidence interval (CI) were computed. All *p*-values are two-sided and a value of less than 0.05 was considered statistically significant. Statistical analyses were performed using R, version 3.6.1 (The R Foundation, Vienna, Austria).

## Results

### The characteristics of M1 thyroid cancers

ATC was the histologic subtype with the highest rate of DM at presentation (50.1%), followed by PDTC (21.7%), MTC (10.5%), FTC (5.7%), HCC (3.6%), and PTC (1.2%).

Thyroid cancer patients with DM at time of diagnosis presented at an older age and with a large tumor diameter. Females were slightly more common than males. PTC was the most common histologic subtype, followed by ATC and FTC. Nearly half of the cases were unresectable and diagnosed by biopsy only. The characteristics of the patient cohort are described in Table 1.

Table 1  
 Characteristics of thyroid cancers with DM at presentation

<b>Parameter</b>	<b>All cases (n = 2787)</b>
<b>Age</b>	
Mean (SD)	64.6 (16.6)
Median [Range]	67.0 [5-100]
<b>Sex</b>	
Female	1546 (55.5)
Male	1241 (44.5)
<b>Race</b>	
American Indian	24 (0.8)
Asian	386 (13.9)
Black	190 (10.4)
Caucasian	2076 (74.8)
<b>Histology</b>	
PTC	1282 (50.7)
FTC	317 (12.5)
HCC	76 (3.0)
MTC	208 (8.2)
PDTC	38 (1.5)
ATC	532 (21.0)
Others	78 (3.1)
<b>Size</b>	
Mean (SD)	47.8 (34.1)
Median [Range]	43.0 [0–53]
<b>Multifocal</b>	
Multifocal	742 (38.4)
Unifocal	1188 (61.6)
Abbreviations: ATC, anaplastic thyroid carcinoma; FTC, follicular thyroid carcinoma; HCC, Hurthle cell carcinoma, MTC, medullary thyroid carcinoma; NOS, not otherwise specified; PDTC, poorly-differentiated thyroid carcinoma; PTC, papillary thyroid carcinoma; SD, standard deviation;	

Parameter	All cases (n = 2787)
<b>Regional nodal involvement</b>	
No	1329 (55.7)
Yes	1058 (44.3)
<b>Extent of surgery</b>	
Biopsy	1202 (43.3)
Thyroidectomy, NOS	42 (1.5)
Thyroidectomy, Subtotal	210 (7.6)
Thyroidectomy, Total	1321 (47.6)
<b>Radiotherapy</b>	
No	1207 (43.3)
Yes	1580 (56.7)
<b>Chemotherapy</b>	
No	2234 (80.2)
Yes	553 (19.8)
Abbreviations: ATC, anaplastic thyroid carcinoma; FTC, follicular thyroid carcinoma; HCC, Hurthle cell carcinoma, MTC, medullary thyroid carcinoma; NOS, not otherwise specified; PDTC, poorly-differentiated thyroid carcinoma; PTC, papillary thyroid carcinoma; SD, standard deviation;	

## Dissemination patterns of M1 thyroid cancer subtypes

Among PTC, HCC, PDTC, and ATC, the lungs were the most common site for DM whereas bone metastases were most frequently observed in FTC and MTC ( $p < 0.001$ ). The proportion of liver metastases was remarkably higher in MTC (42.7%) as compared to other histologic subgroups ( $p < 0.001$ ) (Fig. 1). On the other side, distant node involvement mainly occurred with MTC (37.4%), PTC (30.5%), and ATC (27.9%).

About 27.6% of patients were documented with metastases to multiple organs at the time of diagnosis. MTC (40.6%) and ATC (32.8%) most frequently metastasized to more than one site at presentation. Metastases to lung alone were seen in 53.2%, 49.1%, and 47.4%, of ATCs, PTCs, and PDTCs, respectively whereas bone metastases as the only site of metastatic disease was found in 43.1% of FTCs and 26.5% of HCC. Single organ dissemination to the liver was generally uncommon; they were identified in 20.3% of MTCs but only occurred in 0–5% of other subtypes. Brain metastases alone were also extremely rare in thyroid cancers.

## Risk factors for multi-organ metastases at presentation

Table 2 shows the correlation of single- and multi-organ metastases with various clinical parameters. Large tumor diameter, non-Caucasian race, ATC/FTC/MTC histology, and unifocal tumors were significant risk factors for the presence of multi-organ metastases at presentation. Other clinical covariates including age, gender, and regional nodal metastasis were not associated with increased risk for multi-organ spread.

Table 2  
Risk factors for multi-organ metastases at presentation

Parameters	Multi-organ metastases (n = 716)	Single-organ metastases (n = 1877)	p-value
<b>Age</b>			0.91
Median [IQR]	67.0 [58.0; 76.0]	67.0 [56.0; 77.0]	
<b>Sex</b>			0.71
Female	388 (54.2)	1034 (55.1)	
Male	328 (45.8)	843 (44.9)	
<b>Race</b>			0.021
Caucasian	509 (71.1)	1409 (75.1)	
Non-Caucasian	207 (28.9)	468 (24.9)	
<b>Size</b>			< 0.001
Median [IQR]	54.0 [30.0; 77.0]	42.0 [25.0; 68.0]	
<b>Histology</b>			< 0.001
PTC	245 (38.3)	925 (53.9)	
FTC	95 (14.9)	204 (11.9)	
HCC	20 (3.1)	48 (2.8)	
MTC	82 (12.8)	120 (7.0)	
PDTC	11 (1.7)	27 (1.6)	
ATC	167 (26.1)	342 (19.9)	
Others	19 (3.0)	49 (2.9)	
<b>Regional nodal involvement</b>			0.541
No	56 (18.7)	192 (20.5)	
Yes	244 (81.3)	744 (79.5)	
<b>Primary tumor multifocality</b>			0.028
Multifocal	162 (34.1)	536 (40.0)	
Unifocal	313 (65.9)	805 (60.0)	
Abbreviations: ATC, anaplastic thyroid carcinoma; FTC, follicular thyroid carcinoma; HCC, Hurthle cell carcinoma, IQR, interquartile range; MTC, medullary thyroid carcinoma; NOS, not otherwise specified; PDTC, poorly-differentiated thyroid carcinoma; PTC, papillary thyroid carcinoma;			

# Survival patterns of M1 thyroid cancer subtypes

Stratified by histologic type, metastatic ATC patients had the worst survival with a median OS of 2 months whereas metastatic PTC and FTC/HCC conferred the most favorable outcome (median OS of 26.0 and 24.0 months, respectively) ( $p < 0.001$ ). Metastatic MTC and PDTC had an intermediate median survival of 12.0 and 15.0 months, respectively (Fig. 2).

Patients presenting with DM to multiple organs were associated with a dismal outcome in comparison to those presenting with DM to only one site (HR = 1.810; 95% CI = 1.624–2.017;  $p < 0.001$ ). Stratified by metastatic sites, patients with multi-organ metastases had a statistically comparable survival with brain metastases alone (median OS of 5 months versus 14.0 months, respectively;  $p = 0.158$ ), but had a shortened survival in comparison to the liver (median OS of 15.0 months;  $p < 0.001$ ), lung (median OS of 9.00 months;  $p < 0.001$ ), and bone (median OS of 26.5 months;  $p < 0.001$ ) (Fig. 3). Metastases to the brain alone had a statistically comparable prognosis with metastases to the liver ( $p = 0.461$ ) or lung alone ( $p = 0.791$ ). On the other side, metastases to bone alone showed an improved outcome compared to liver ( $p = 0.016$ ), lung ( $p < 0.001$ ), and brain alone ( $p = 0.011$ ). Patients with DM to another location alone, mainly to distant nodes also had a statistically comparable outcome (median OS of 18.0 months) compared to those with bone metastases alone ( $p = 0.101$ ) and exhibited a superior outcome in comparison to metastases to brain ( $p = 0.007$ ), liver ( $p = 0.015$ ), lung ( $p < 0.001$ ), and multiple sites ( $p < 0.001$ ).

Multivariate Cox regression analysis adjusted for patient age, gender, race, histology, and the extent of DM at diagnosis demonstrated that older patient age (HR = 1.029; 95% CI = 1.025–1.033), ATC histology (HR = 7.937; 95% CI = 6.944–9.091), and multi-organ involvement (HR = 1.735; 95% CI = 1.541–1.953) negatively impacted the OS of M1 thyroid cancers.

## Discussion

Thyroid cancers, especially differentiated thyroid cancers, generally have a good prognosis and show a good response to initial thyroidectomy. DM at presentation is not a common event in thyroid cancers and its incidence ranges from 3–15% in published literature [14, 15, 7]. It has been well established as one of the leading adverse events in thyroid cancers [2]. Published studies on DM in thyroid cancers are limited given its relatively rare occurrence and most of these studies solely focused on a specific subtype of thyroid cancers such as differentiated thyroid cancer (DTC), MTC, PDTC, or ATC. Additionally, studies reporting DM data less frequently reported the locations of metastatic spread limiting the understanding of the dissemination patterns and differences in patient survival between thyroid cancer subtypes with DM. This study accessed a large population-level database and demonstrated that each thyroid cancer subtype has a unique remote spread pattern and survival.

The lung and bone have been shown as the most common site of DM in DTCs [16, 8, 17]. Sugino et al. reported an equal rate of 33% for single-organ metastases to the lung or bone in minimally invasive FTCs presenting with DM while simultaneous metastases to numerous sites were documented in about 25% of



cases [16]. Another single institution reported an incidence of 48%, 24%, and 19% of metastatic DTC metastasizing to lung only, bone only, and multiple sites, respectively [8]. For MTCs, the most common disseminated sites were liver and bone [18]. ATC is the most lethal form of thyroid cancer and DM is a frequent event among these neoplasms. Besic et al. reported that 78% of metastatic ATCs were seen in the lung, followed by intrathoracic lymph nodes while bone metastases were uncommon [19]. In a recent nationwide study on autopsy of thyroid cancer patients, there were major differences in hematogenous spread patterns between thyroid cancer subtypes with the lung being the most frequent site for DTC and ATC whereas MTC more likely metastasized to the liver [20]. Our results affirmed that each thyroid cancer histological subtype has a distinctive metastatic pattern. Some of our findings differed from known patterns reported in prior clinical studies. This information is extremely helpful for clinicians to further guide the search for metastatic disease when the histological diagnosis has been confirmed.

Besides metastases to remote organs, our results also highlighted that spread to distant lymph nodes was not uncommon in M1 thyroid cancers, particularly MTC, PTC, and ATC. These findings emphasize that metastatic spread to distant locations is not always driven through the hematogenous pathway, but also through the lymphatic channels. The risk of DM is known to be associated with nodal involvement [21]. Unfortunately, we were unable to investigate the location distribution of distant node metastases since these data are not included in the SEER database.

The prognostic impact of different metastatic sites in thyroid cancers with DM is still controversial. It is of clinical interest to accurately evaluate the risk stratification of these patients. Our study demonstrated that thyroid cancer patients with metastases to multiple sites have the worst prognosis. This prognostic information is useful during patient counseling and may help clinicians consider additional local or systemic therapies. These high-risk patients might be suitable candidates for future clinical trials on novel targeted therapies. Wang et al. reported an estimated 5-year OS of 77.6% in DTCs with single-organ metastases and only 15.3% in those with multi-organ spread [22]. In this study, we also demonstrated that metastatic thyroid cancers did not have a universally similar outcome. Metastatic ATC had the worst outcome compared to MTC, PDTC, or DTC with an estimated 1-year OS of less than 5%. Therefore, it is important to determine the accurate histological diagnosis and the extent of DM at time of diagnosis. We also found several important risk factors associated with multi-organ metastases at presentation including non-Caucasian race and ATC/MTC/FTC histology. Additionally, large solitary thyroid cancers might have a higher risk for multi-organ involvement than smaller ones with multiple foci. These data are crucial to alert clinicians to search for multi-organ metastases in high-risk patients to better assess patient outcomes.

There are gaps of knowledge on why thyroid cancers have distinctive spread patterns. Our results support the premise that different thyroid cancer subtypes may have different underlying biology and tumorigenesis. Several molecular biomarkers are associated with an increased risk for hematogenous spread in thyroid cancers including *TERT* promoter, *RET*, *PLEKHS1*, and *TP53* mutations [6, 4, 23]. The distinct genetic landscape of each subtype might explain why different tumor cell types favor distant migration to a specific organ. Oncogenic mutations in the *BRAF* kinase gene have been shown to

cooperate in the pathogenesis and development of lung metastases in melanomas [24]. *BRAF* mutation is the most predominant activating mutation in PTC and ATC, which could explain why these two entities likely develop lung metastases. Coexisting occurrence of *BRAF* and *TERT* promoter mutations, which is commonly seen in ATC and PDTC, could enhance the risk of DM at presentation [25, 26]. ATC carries the highest tumor mutation burden among thyroid cancers resulting in the high likelihood of developing DM in these neoplasms [27].

Our study is the largest study to date providing data on disseminated locations of thyroid cancer subtypes with DM. Besides the outlined clinical importance, it is also essential to discuss the limitations of this study. Firstly, we could not avoid the certain selection biases inherent to retrospective patient collection and nature and design of population-level databases. Next, data on DM during follow-up and recurrence-free survival were not available for analysis. A few studies have outlined the differences between thyroid cancers presenting with DM at diagnosis versus developing DM during follow-up [16, 28]. In the SEER database, metastases to rare distant sites such as adrenal glands, pancreas, kidney, or peritoneum are also not documented which could limit or confound the extent of our analyses.

In conclusion, this study demonstrated that different thyroid cancer subtypes remotely spread to specific organs and have unique metastatic patterns, which are important for patient counseling and mortality risk stratification. Given the relatively frequent occurrence of multi-organ metastases in thyroid cancers with DM at presentation and its adverse impact on patient outcome, clinicians should consider searching for additional metastases according to each specific histology and confounding risk factors.

## **Declarations**

### **Ethics approval and consent to participate**

Not applicable

### **Consent for publication**

Not applicable

### **Availability of data and material**

Not applicable

### **Competing interest**

The authors declare no conflicts of interest.

### **Funding**

This study receives no funding support.

## Authors' contributions

HGV: conceptualization, data curation, formal analysis, investigation, methodology, project administration, software, validation, writing-original, review, and editing

KML: data curation, formal analysis, investigation, methodology, writing-review, editing

LH: data curation, formal analysis, investigation, writing-review, editing

TK: data curation, formal analysis, investigation, writing-review, editing

KK: data curation, formal analysis, investigation, writing-review, editing

All authors have read and approved the manuscript.

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Not applicable

**Disclosure:** The authors declare that the research was conducted in the absence of any commercial and financial relationships that could be construed as a potential conflict of interest

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## Tables

Table 1. Characteristics of thyroid cancers with DM at presentation

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<b>Chemotherapy</b>	
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Abbreviations: ATC, anaplastic thyroid carcinoma; FTC, follicular thyroid carcinoma; HCC, Hurthle cell carcinoma, MTC, medullary thyroid carcinoma; NOS, not otherwise specified; PDTC, poorly-differentiated thyroid carcinoma; PTC, papillary thyroid carcinoma; SD, standard deviation;

Table 2. Risk factors for multi-organ metastases at presentation



Parameters	Multi-organ metastases (n = 716)	Single-organ metastases (n = 1877)	p-value
<b>Age</b>			0.91
Median [IQR]	67.0 [58.0; 76.0]	67.0 [56.0; 77.0]	
<b>Sex</b>			0.71
Female	388 (54.2)	1034 (55.1)	
Male	328 (45.8)	843 (44.9)	
<b>Race</b>			0.021
Caucasian	509 (71.1)	1409 (75.1)	
Non-Caucasian	207 (28.9)	468 (24.9)	
<b>Size</b>			<0.001
Median [IQR]	54.0 [30.0; 77.0]	42.0 [25.0; 68.0]	
<b>Histology</b>			<0.001
PTC	245 (38.3)	925 (53.9)	
FTC	95 (14.9)	204 (11.9)	
HCC	20 (3.1)	48 (2.8)	
MTC	82 (12.8)	120 (7.0)	
PDTC	11 (1.7)	27 (1.6)	
ATC	167 (26.1)	342 (19.9)	
Others	19 (3.0)	49 (2.9)	
<b>Regional nodal involvement</b>			0.541
No	56 (18.7)	192 (20.5)	
Yes	244 (81.3)	744 (79.5)	
<b>Primary tumor multifocality</b>			0.028
Multifocal	162 (34.1)	536 (40.0)	
Unifocal	313 (65.9)	805 (60.0)	

Abbreviations: ATC, anaplastic thyroid carcinoma; FTC, follicular thyroid carcinoma; HCC, Hurthle cell carcinoma, IQR, interquartile range; MTC, medullary thyroid carcinoma; NOS, not otherwise specified; PDTC, poorly-differentiated thyroid carcinoma; PTC, papillary thyroid carcinoma;

# Figures

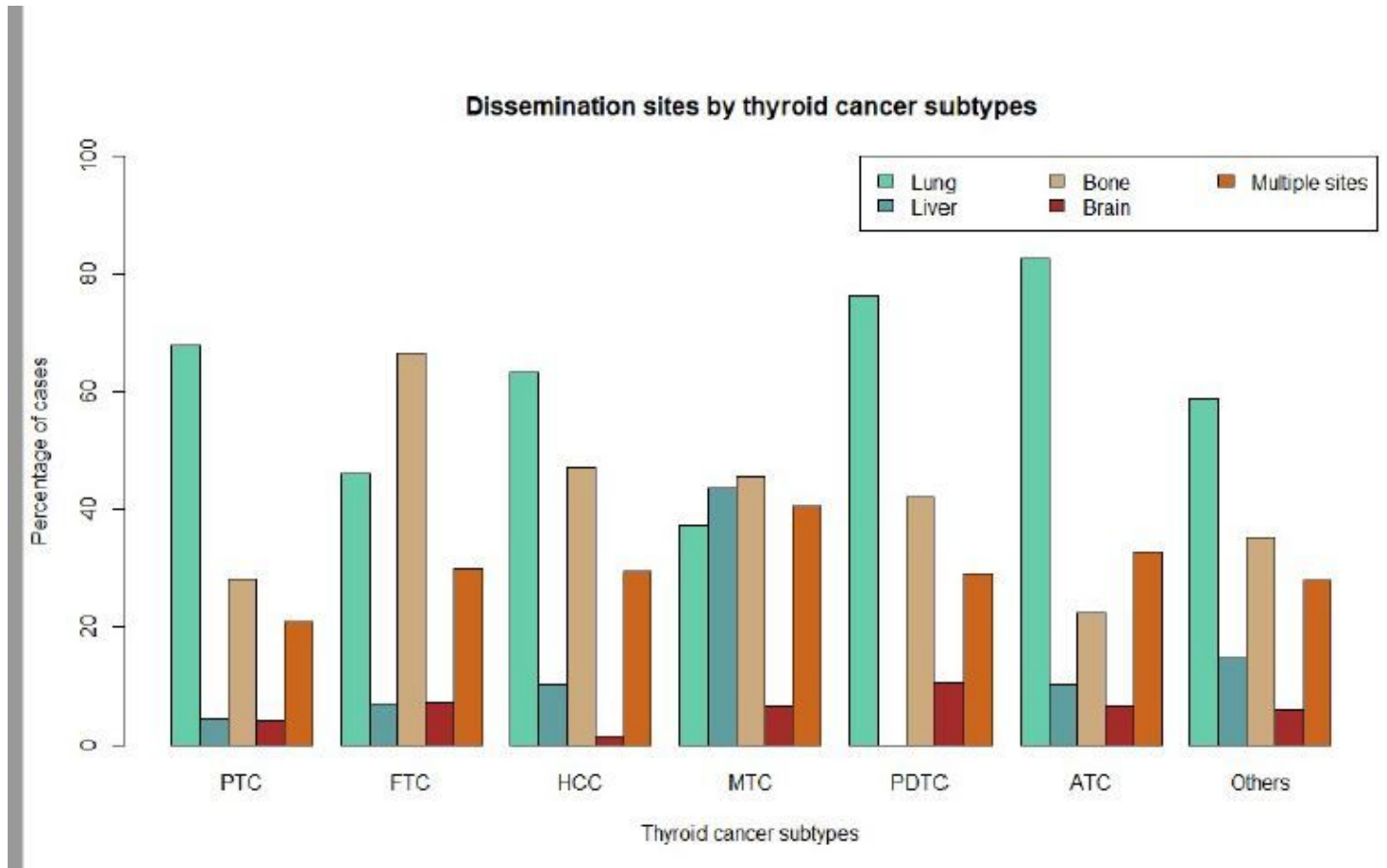
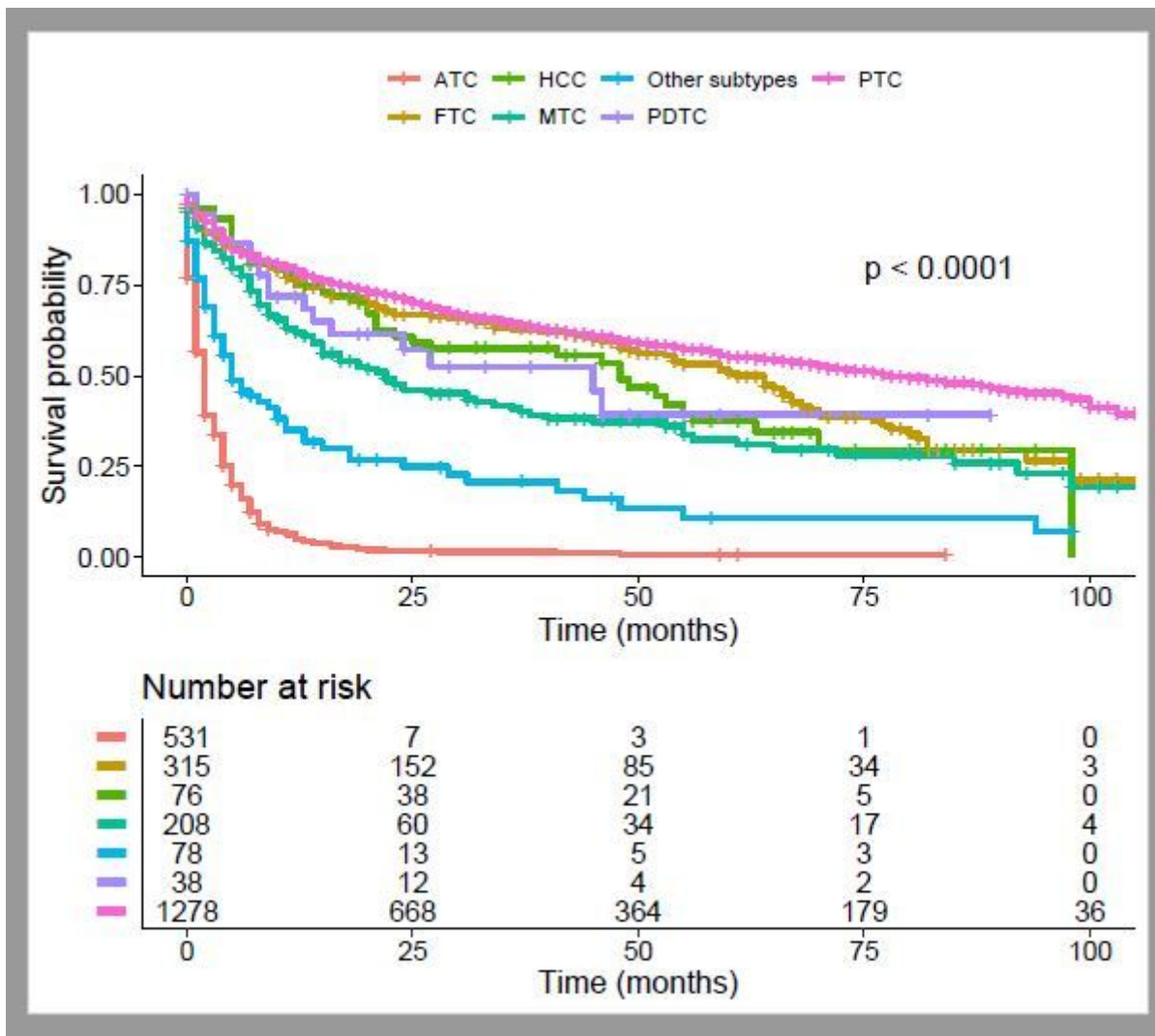


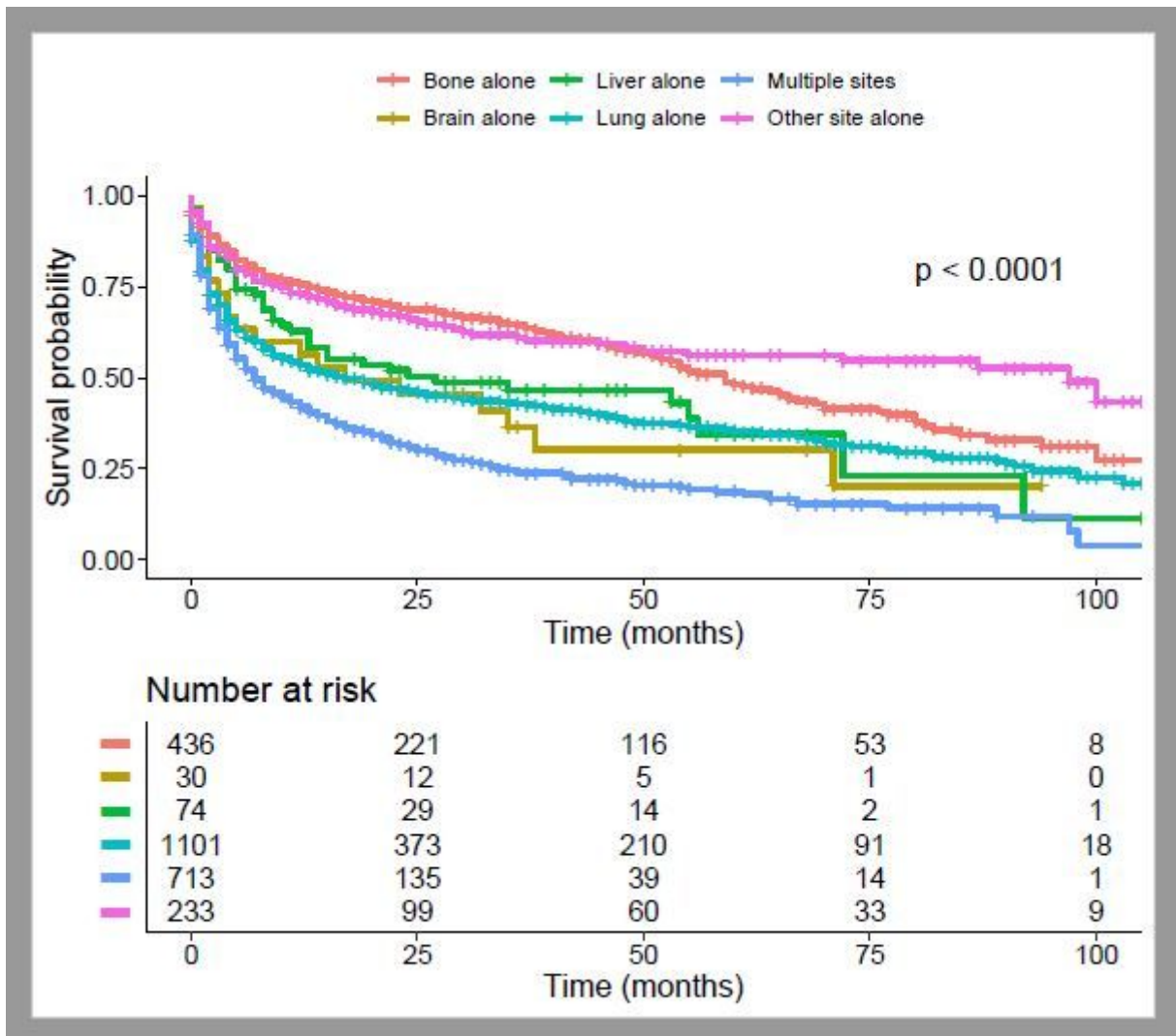
Figure 1

Histogram showing the percentages of metastatic sites of different thyroid cancer subtypes



**Figure 2**

Kaplan-Meier curve illustrating the overall survival of different thyroid cancer subtypes with DM at time of diagnosis



**Figure 3**

Kaplan-Meier curve illustrating the prognostic impact of metastatic sites on overall survival of thyroid cancers with DM at presentation