

# Incidence and Survival of Thyroid Cancer with Lung Metastasis

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## Research

**Keywords:** Thyroid cancer, lung metastases, incidence, survival, Surveillance Epidemiology and End Results database

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# Abstract

**Background:** Thyroid cancer (TC) is a common malignancy. Lung metastasis is one of the top metastases for TC. The incidence and survival rates of TC with lung metastasis remain unclear.

**Methods:** Data on TC with lung metastasis and other site-specific metastases were extracted from the Surveillance, Epidemiology, and End Results (SEER) database. Chi-square tests were employed to compare the biological and clinical features of thyroid patients with different metastatic sites. Survival analysis was performed utilizing Kaplan-Meier analysis and log-rank tests. We used a Cox proportional hazards model for the multivariate analysis to identify prognostic factors of thyroid patients with lung metastases. Statistical significance was indicated by a two-tailed P value < 0.05.

**Results:** A total of 77322 patients suffering from TC with clear metastasis information were identified from 2010-2016. The probability of isolated lung metastasis was significantly higher than that of isolated distant metastasis to other sites among TC patients ( $P < 0.05$ ). Patients with isolated lung metastases had worse overall survival (OS) and thyroid cancer-specific survival (TCSS) than patients with bone metastasis only ( $P < 0.05$ ). There was a slight difference in thyroid cancer-specific survival between patients with lung metastasis and patients with liver metastasis ( $P=0.0496$ ), while there was no significant difference in overall survival. ( $P > 0.05$ ). There was no significant difference in OS or TCSS between patients with lung metastasis and those with brain metastasis ( $P > 0.05$ ). Multivariate analysis revealed that white race was associated with better outcomes in terms of both endpoints in the lung metastasis population.

**Conclusions:** The incidence of lung metastasis from TC was higher than that of other organ metastases. Thyroid cancer patients with isolated lung metastases have worse outcomes than patients with isolated bone metastases and liver metastases but are similar to brain metastases. There was the worst survival outcome in patients with multiorgan metastases.

## Background

Thyroid cancer (TC) is one of the most prevalent cancers. Although TC generally has a good prognosis, a subset of patients suffer metastasis, as indicated by some studies [1, 2]. The main locations of metastasis are the lung and bone[1]. As other experts have reported, the most likely location for TC metastasis may be the lung [1-3]. Information on the probability of lung metastasis compared with metastasis to other locations among TC patients and the impact of lung metastasis on survival is of increasing concern to scholars and patients and the general public. However, because TC with only lung metastasis had favorable long-term survival [3, 4], a large number of cohorts with follow-up data are needed to perform such a comparison. At present, there is no prospective randomized controlled study or even a sufficiently large sample study that may provide information on this topic. Population data are insufficient on the incidence rate and prognostic value of site-specific metastases for TC. The SEER database is helpful for this topic because of its sufficiently large patient population, relatively complete

datasets and follow-up data. Therefore, the purpose of this study was to review the performance of patients with metastatic TC registered in the SEER database, with a particular focus on the incidence and prognosis of lung metastasis.

## Methods

This study was based on the SEER database (Incidence-SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2018 Sub (1975-2016 varying)). We used SEER\*Stat software version 8.3.8 to retrieve the data in the SEER database. Since the study is based on an available database open to the public, it was exempt from institutional review board (IRB) approval.

### Data collection

We limited our search to the SEER database (2010-2016) because we could not obtain detailed information about distant metastasis sites of TC before 2010. In this study, we included cases with the site code ICD-O-3/WHO 2008 of “thyroid”, with a primary site of “thyroid gland”, and with a behavior code ICD-O-3 of “malignant”. We excluded TC patients without sufficient information about survival or the site of metastases, without information on the age at diagnosis, and those with a SEER cause-specific death classification of “N/A not first tumor”. We extracted the data from each case including race, sex, age at diagnosis, year at diagnosis, marital status, grade, histological type ICD-O-3, T stage, number of positive regional nodes, N stage, site of metastases, surgery of the primary lymph nodes, surgery of the distant lymph nodes (LNs) or other metastatic sites, SEER cause-specific death classification, vital status and survival time (months). In the current analysis, thyroid cancer-specific survival (TCSS) was defined as the time from diagnosis to death of TC. Due to the limitation of data composition in the SEER database in different years, T staging data were based on a combination of “derived AJCC T, 7th ed (2010-2015)” data and “derived SEER combined T” data. The cases diagnosed from 2010-2015 were based on “derived AJCC T, 7th ed (2010-2015)” data, and those diagnosed in 2016 were based on “derived SEER combined T” data. This is also applied to N stage and stage group data. Because of the lack of data on distant LN metastasis in the “mets at DX-distant LN” column, when the year of diagnosis was 2010-2015, we did not analyze information about distant LN metastasis. When we compared the survival of patients with different sites of metastases, patients without exact metastasis data were excluded.

### Statistical analysis

We used the chi-square test to compare the biological and clinical features of thyroid patients with different metastatic sites (liver, lung, bone, and brain). We used Kaplan-Meier analysis and log-rank testing for survival comparisons between those with isolated lung metastases, liver metastases, bone metastases and brain metastases and multiorgan metastases. We used a Cox proportional hazards model for the multivariate analysis to identify prognostic factors of thyroid patients with lung metastases. We also employed this method to compare the survival of patients with or without surgery of the primary site and surgery of the distant LNs or other metastatic sites; these analyses were performed separately for each organ metastasis site. In addition, we also compared

isolated lung metastases with lung metastases combined with one or more additional metastatic sites ( $\geq 2$  organs) for both endpoints with this method. The confidence interval (CI) was set to 95%. P values were considered statistically significant if a two-tailed p value  $< 0.05$ . Sas9.4 was used for all statistical analysis.

## Results

### Patient characteristics

A total of 77322 patients initially diagnosed with TC from 2010-2016 with known sites of distant metastases were included in our research. We summarize the biological and clinical features of different metastatic sites for all included patients. (Table 1 for lung metastases, Table S1 for other metastases)

A total of 998 (1.29%) patients were diagnosed with lung metastases, 514 (0.66%) patients were diagnosed with bone metastases, 152 (0.20%) patients were diagnosed with liver metastases, and 87 (0.11%) patients were diagnosed with brain metastases. A total of 1034 (1.33%) patients had single-organ metastases, while 326 patients (0.42%) had multiorgan metastases. Surgical resection of the primary lesion was performed in 543 (54.41%) patients, while surgery of the distant LN(s) or other metastatic site(s) was performed in 118 (11.82%) patients when lung metastases occurred.

### Survival outcomes

The OS and TCSS rates were compared according to the site of metastasis (Figure 1). Patients with isolated lung metastases had worse OS and TCSS than patients with isolated bone metastases ( $P < 0.0001$ ). There was a slight difference in TCSS between patients with lung metastasis and those with liver metastasis ( $P = 0.0496$ ), but there was no significant difference in OS (lung vs. liver metastases:  $P = 0.0584$ ). For both endpoints, there was no significant difference between patients with lung metastasis and those with brain metastases ( $P > 0.05$ ). Regardless of whether the patients had isolated lung metastasis, liver metastasis, bone metastasis or brain metastasis, isolated metastasis was related to better OS and TCSS than multiple metastases.

Hierarchical analysis revealed that there was a better outcome in patients with lung metastases if token surgery was performed either for primary or distant site(s) ( $P < 0.05$ ) (Figure 2). Surgery for primary lesions in patients with bone metastasis (Figure S1) showed the same survival advantage ( $P < 0.05$ ). There was no significant difference between the outcomes of patients with liver metastases (Figure S2) or the overall survival rates of those with brain metastases (Figure S3) with and without surgery of the distant site(s) (for the overall survival of liver metastases: surgery vs. no surgery:  $P = 0.13 > 0.05$ , for the thyroid cancer-specific survival of liver metastases: surgery vs. no surgery:  $P = 0.26 > 0.05$ , for the overall survival of brain metastases: surgery vs. no surgery:  $P = 0.05$ ).

The comparison of the survival of patients with isolated lung metastasis and multiple-organ metastases, including lung metastasis, is shown in Figure 3. We found that there were significant differences in the

outcomes of patients with isolated lung metastasis and those with combined lung-liver metastasis and lung-brain metastasis. In contrast, the overall survival and thyroid cancer-specific survival were similar in patients with isolated lung metastasis and those with combined lung-bone metastasis. Similarly, there was no significant difference in the prognosis of combined lung-liver metastasis, lung-brain metastasis and metastasis of more than three organs, including the lung.

The multivariate analysis results shown in Table 2 revealed that white race was associated with better overall survival and thyroid cancer-specific survival in the population of patients with lung metastasis.

## Discussion

The main findings of this study were the incidence and prognostic value of the lung metastasis of TC compared with that of other site-specific metastases. This will help us to have a better-informed discussion with the patients concerned and help us understand the overall prospect of the disease. Moreover, survival data about whether surgical treatment of the primary or distant LN(s) or other metastatic site(s) is beneficial for TC lung metastasis and other organ metastases will help us make more appropriate clinical decisions about TC.

In our analysis, we found that white race patients had a survival advantage in terms of both overall survival and thyroid cancer-specific survival when lung metastases occurred. Referring to other studies [5, 6]. This may be explained by better social support, including Medicare. Some experts considered it an independent prognostic factor of recurrence and metastasis in thyroid cancers [7]. Regarding the intrinsic differences in tumor biology, genome and/or gene variation was also considered a possible explanation for the differences between races[8]. In addition, a small study using a microRNA expression profile reported that there were microRNA expression differences between races, which may also be related to the potential variation of tumors[9].

In this study, we found that lung metastasis from the thyroid was worse than bone metastasis, but it was still not as bad. In many kinds of cancer, bone metastasis generally has a relatively better prognosis[10] [11], but lung metastasis is not necessarily. Fortunately, as many other scholars have reported, pulmonary metastases may also have a better prognosis [4].

In our study, the prognostic advantage of surgery over a conservative approach for primary thyroid tumors was obvious among those with lung and other-organ metastases. However, for the treatment of metastatic sites, different strategies should be adopted for different locations of metastasis from the thyroid. Our studies have shown that patients with lung and bone metastases can benefit from surgical treatment of distant LN(s) or other metastatic site(s) in terms of both overall survival and disease-specific survival. This is similar to the general strategy for other metastatic cancers with better prognosis; that is, surgery for distant lesions may improve the prognosis[12] [13]. An important landmark publication is the 1997 report from Europe and North America, which indicated that the fewer the metastases and the longer the interval before their appearance, the longer the survival after metastasectomy[12] [13]. This

implied that tumors with a relatively good prognosis may have a longer postoperative survival for metastasectomy. This may be an encouraging inference for surgical management.

Notably, except for surgical information, other related treatment information was incomplete in the SEER database. The multivariate analysis of this study revealed that surgery, as an important part of treatment, played a significant role in the outcomes of metastatic TC, especially for lung metastasis and bone metastasis. This reveals that we should be active in the treatment of TC metastases.

Other studies have reported a propinquity trend that multiple-site metastases were associated with an increased risk of death[4]. However, after comparing the survival data of isolated lung metastasis with those of multiple-organ metastasis, including lung metastasis, a phenomenon was revealed: the prognosis of isolated lung metastasis from TC was similar to that of lung-bone metastasis from TC; conversely, there was a significant difference between the prognosis of isolated lung metastasis and other multiple-organ metastases, including lung metastasis ( $\geq 3$  organs). The cooccurrence of two metastatic lesions with a relatively good prognosis did not change the prognosis.

However, we have to consider the inherent difficulties of SEER database analysis, and the above results in particular should be cautiously interpreted. Therefore, prospective controlled studies are expected to evaluate the prognosis of patients, which could avoid many interference factors and allow further analysis. This work would take a long time to accumulate enough cases. Multicenter clinical studies or large-scale databases with more details may help us.

## Conclusions

Based on the SEER analysis, the lung is the most prevalent site of metastasis from the thyroid. Similar to brain metastasis, lung metastasis of TC had a worse outcome than liver or bone metastases. The worst survival outcome was observed in patients with multiorgan metastases. Further studies are needed to determine the exact subset of patients who may benefit from local treatment for primary lesions and/or metastatic sites.

## Declarations

### Ethics approval and consent to participate

All SEER data were accessed with approval from the SEER database and, as such, this article does not contain any studies with human participants or animals performed by any of the authors.

### Consent for publication

Not applicable

### Availability of data and materials

The datasets analysed during the current study are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests.

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### Authors' contributions

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Supervision: Kefeng Lei.

Writing – original draft: Miaochun Zhong, Kefeng Lei.

Writing – review & editing: Xianghong He, Lingfei Cui, Kefeng Lei.

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This manuscript was edited for proper English language, grammar, punctuation, spelling, and overall style by some experts at American Journal Experts. This assistance was funded by the study sponsor.

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## Tables

Table 1 Clinical features of TC patients with or without and lung metastasis.



Variable	Lung metastasis			Chi-square P value
	Yse	No	Total	
	(N=998)	(N=76,324)	(N=77,322)	
Age				
				<0.0001
≥55	249(24.95%)	50,765(66.51%)	51,014(65.98%)	
<55	749(75.05%)	25,559(33.49%)	26,308(34.02%)	
Race				
				<0.0001
White	745(74.65%)	60,807(79.67%)	61,552(79.60%)	
Black	100(10.02%)	5413(7.09%)	5513(7.13%)	
Unknown	4(0.40%)	1308(1.71%)	1312(1.70%)	
Others	149(14.93%)	8796(11.52%)	8945(11.57%)	
Sex				
				<0.0001
Male	458(45.89%)	17,547(22.99%)	18,005(23.29%)	
Female	540(54.11%)	58,777(77.01%)	59,317(76.71%)	
Married				0.5408
Married	4(0.40%)	177(0.23%)	181(0.23%)	
Unmarried	994(99.60%)	76,145(99.77%)	77,139(99.76%)	
Unknown	0(0.00%)	2(0.00%)	2(0.00%)	
Grade				
				<0.0001
GradeI	74(7.41%)	14,684(19.24%)	14,758(19.09%)	
GradeII	39(3.91%)	2748(3.60%)	2787(3.60%)	
GradeIII	104(10.42%)	754(0.99%)	858(1.11%)	
GradeVI	295(29.56%)	492(0.64%)	787(1.02%)	
Unknown	486(48.70%)	57,646(75.53%)	58,132(75.18%)	
Histologic ICD-O-3				

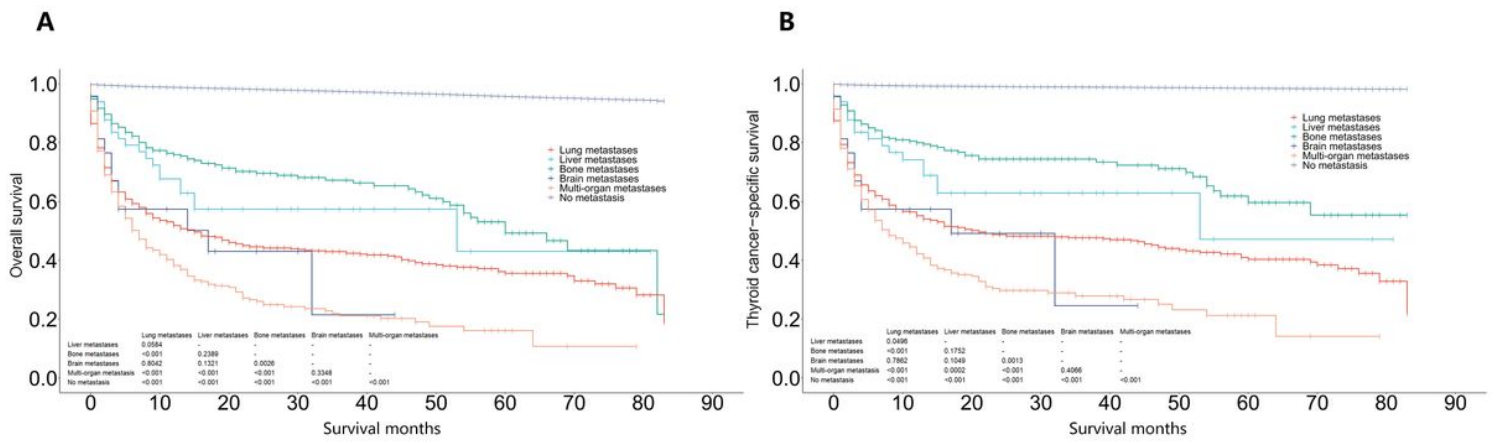
				<0.0001
Carcinoma,undiff.,NOS	215(21.54%)	327(0.43%)	542(0.70%)	
Follicular adenocarcinoma,NOS	99(9.92%)	3632(4.76%)	3731(4.83%)	
Medullary carcinoma,NOS	39(3.91%)	1186(1.55%)	1225(1.58%)	
Oxyphilic adenocarcinoma	28(2.81%)	1338(1.75%)	1366(1.77%)	
Papillary & follicular adenoca.	137(13.73%)	26,399(34.59%)	26,536(34.32%)	
Papillary adenocarcinoma,NOS	312(31.26%)	40,869(53.55%)	41,181(53.26%)	
Papillary carcinoma,NOS	10(1.00%)	1686(2.21%)	1696(2.19%)	
Others	158(15.83%)	887(1.16%)	1045(1.35%)	
Stage group				
				<0.0001
I	0(0.00%)	53,510(70.11%)	53,510(69.20%)	
II	92(9.22%)	5540(7.26%)	5632(7.28%)	
III	0(0.00%)	9761(12.79%)	9761(12.62%)	
VI	896(89.78%)	4989(6.54%)	5885(7.61%)	
Unknown	10(1.00%)	2524(3.31%)	2534(3.28%)	
T				
				<0.0001
T0	6(0.60%)	107(0.14%)	113(0.15%)	
T1	47(4.71%)	43,527(57.03%)	43,574(56.35%)	
T2	48(4.81%)	12815(16.79%)	12,863(16.64%)	
T3	209(20.94%)	15,575(20.41%)	15,784(20.41%)	
T4	560(56.11%)	2420(3.17%)	2980(3.85%)	
Tx	128(12.83%)	1880(2.46%)	2008(2.60%)	
N				
				<0.0001
N0	279(27.96%)	56,099(73.50%)	56,378(72.91%)	
N1	613(61.42%)	18,044(23.64%)	18,657(24.13%)	

Nx	106(10.62%)	2181(2.86%)	2287(2.96%)	
M				<0.0001
M0	0(0.00%)	75,590(99.04%)	75,590(97.76%)	
M1	988(99.00%)	603(0.79%)	1591(2.06%)	
Mx	10(1.00%)	131(0.17%)	141(0.18%)	
Regional				<0.0001
Positive	407(40.78%)	17,729(23.23%)	18,136(23.46%)	
Negative	75(7.52%)	23,536(30.84%)	23,611(30.54%)	
Unknown	516(51.70%)	35,059(45.93%)	35,575(46.01%)	
Surgery of the primary				<0.0001
Yes	543(54.41%)	74,221(97.24%)	74,764(96.69%)	
No	454(45.49%)	2067(2.71%)	2521(3.26%)	
Unknown	1(0.10%)	36(0.05%)	37(0.05%)	
Surgery of other Reg Dis				<0.0001
Yes	118(11.82%)	1025(1.34%)	1143(1.48%)	
No	879(88.08%)	75,177(98.50%)	76,056(98.36%)	
Unknown	1(0.10%)	122(0.16%)	123(0.16%)	

Table 2 Multivariate analyses of overall survival and thyroid cancer-specific survival in TC patients with lung metastasis.

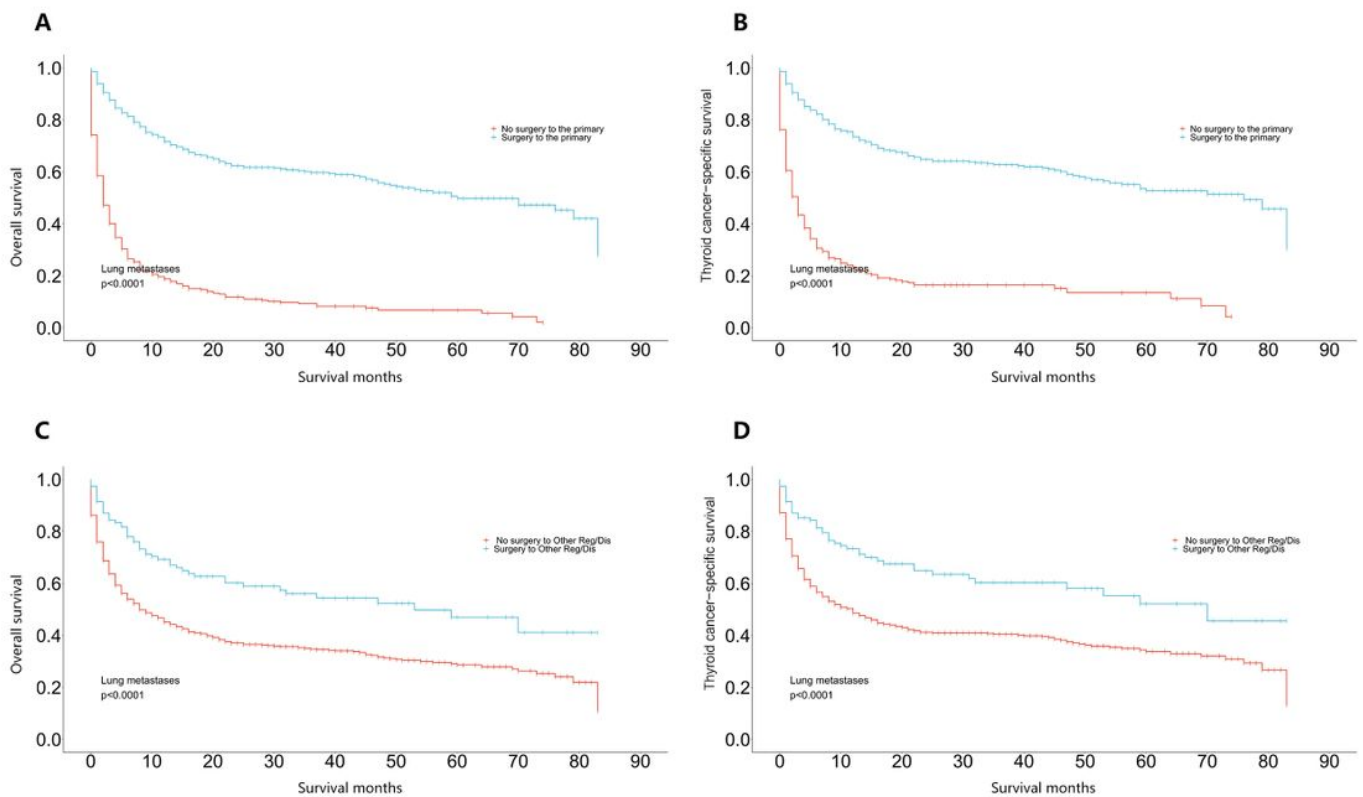
Variable		Overall survival		Thyroid cancer-specific survival	
		Hazard ratio(95%CI)	p value	Hazard ratio(95%CI)	p value
Age	<55	1.00(reference)		1.00(reference)	
	≥55	0.86(0.69~1.07)	0.1668	0.94(0.77~1.16)	0.5869
Race	White	1.00(reference)		1.00(reference)	
	Black	1.47(1.06~2.04)	0.0220	1.49(1.11~2.01)	0.0087
	Others	1.28(0.95~1.71)	0.1011	1.24(0.95~1.63)	0.1097
	Unknown	9.98(3.63~27.46)	0.0000	10.26(3.93~26.78)	0.0000
Gender	Male	1.00(reference)		1.00(reference)	
	Female	0.95(0.77~1.16)	0.6077	0.94(0.78~1.14)	0.5509
Married	Married	1.00(reference)		1.00(reference)	
	Unmarried	29.11(0.00~NA)	0.5482	18.60(0.02~NA)	0.4108
T	T0	1.00(reference)		1.00(reference)	
	T1	1.02(0.39~2.64)	0.9705	1.03(0.43~2.48)	0.9396
	T2	1.11(0.43~2.87)	0.8256	1.12(0.47~2.68)	0.7978
	T3	0.90(0.36~2.23)	0.8184	0.88(0.39~2.03)	0.7720
	T4	0.80(0.32~1.97)	0.6229	0.84(0.37~1.93)	0.6828
	Tx	0.64(0.24~1.71)	0.3730	0.67(0.28~1.61)	0.3671
N	N0	1.00(reference)		1.00(reference)	
	N1	1.13(0.89~1.43)	0.3147	1.21(0.97~1.52)	0.0849
	Nx	1.14(0.71~1.82)	0.5795	1.25(0.84~1.86)	0.2787
SP	No	1.00(reference)		1.00(reference)	
	Yes	27.78(0.00~NA)	0.9128	17.95(0.00~NA)	0.8770
	Unknown	19.16(0.00~NA)	0.9225	8.75(0.00~NA)	0.9075
SD	No	1.00(reference)		1.00(reference)	
	Yes	1.07(0.82~1.40)	0.6254	1.12(0.86~1.44)	0.3970

## Figures



**Figure 1**

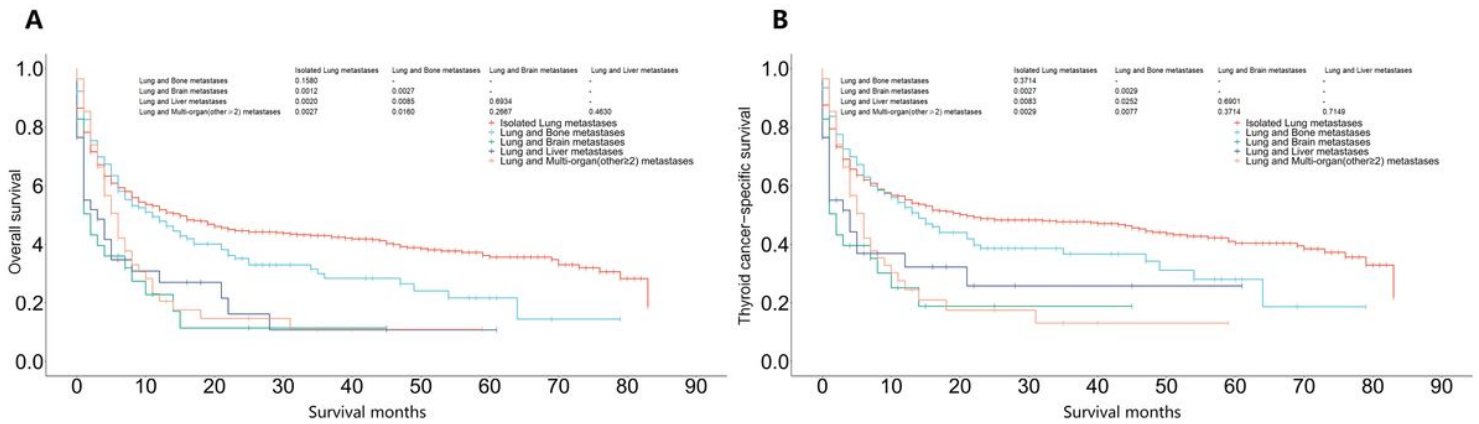
Kaplan-Meier curve of overall survival (A) and thyroid cancer-specific survival (B) according to the site of metastasis.



**Figure 2**

Kaplan-Meier curves of overall survival and thyroid cancer-specific survival according to whether or not surgery of the primary TC lesion and distant metastatic lymph nodes (LN) or lung metastasis: (A) overall survival for patients with isolated lung metastasis with or without surgery of the primary tumor; (B)

thyroid cancer-specific survival for patients with isolated lung metastasis with or without surgery of the primary tumor; (C) overall survival for patients with isolated lung metastasis with or without surgery of distant metastatic LN or lung metastasis; (D) thyroid cancer-specific survival for patients with isolated lung metastasis with or without surgery of distant metastatic LN or lung metastasis.



**Figure 3**

Kaplan-Meier curve of overall survival (A) and thyroid cancer-specific survival (B) according to the site of metastasis (isolated lung metastasis versus lung metastasis combined with one or more additional metastatic sites ( $\geq 2$  organs)).

## Supplementary Files

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