Observational Study

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Metastatic site discriminates survival benefit of primary tumor surgery for differentiated thyroid cancer with distant metastases

A real-world observational study

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Abstract

The role of primary tumor surgery in the management of differentiated thyroid cancer (DTC) with distant metastases (DM) remains controversial. We aimed to explore the survival benefit of primary tumor surgery in patients with different metastatic sites.

A retrospective cohort study based on the SEER database was conducted to identify DTC patients with DM diagnosed between 2010 and 2016. Patients were divided into following 2 groups: surgery and non-surgery group. Propensity score weighting was employed to balance clinicopathologic factors between the 2 groups.

Of 3537 DTC patients with DM, 956 (66.0%) patients underwent primary tumor surgery while 493 (34.0%) patients did not. There were 798 all-cause deaths and 704 DTC-specific deaths over a median follow-up of 22 months. The weighted 3-year overall survival (OS) for the surgery group was 55.2%, compared to 27.8% ($P < .001$) for the non-surgery group. The magnitude of the survival difference of surgery was significantly correlated with metastatic sites ($P_{interaction} < .001$). Significant survival improvements in surgery group compared with non-surgery group were observed in patients with lung-only metastasis (adjusted HR = 0.45, $P < .001$), bone-only metastasis (adjusted HR = 0.40, $P < .001$), and liver-only metastasis (adjusted HR = 0.27, $P < .001$), whereas no survival improvement of surgery was found for patients with brain-only metastasis (adjusted HR = 0.57, $P = .059$) or multiply organ distant metastases (adjusted HR = 0.81, $P = .099$).

The survival benefit from primary tumor surgery for DTC patients with DM varies by metastatic sites. Decisions for primary tumor surgery of DTC patients with DM should be tailored according to metastatic sites.

Abbreviations: CI = confidence interval, DM = distant metastases, DSS = disease-specific survival, DTC = differentiated thyroid cancer, EBRT = external beam radiation therapy, FTC = follicular thyroid carcinoma, HR = hazard ratio, KPS = Karnofsky Performance Scale, NA = not available, NCCN = National Comprehensive Cancer Network, NCI = National Cancer Institute, NIS = sodium iodide symporter, OS = overall survival, PTC = papillary thyroid carcinoma, RAI = radioactive iodine, SEER = Surveillance Epidemiology and End Results, SRS = stereotatic radiosurgery, WBRT = Whole Brain Radiation Therapy.

Keywords: differentiated thyroid cancer, metastatic site, primary tumor surgery, survival

1. Introduction

Differentiated thyroid carcinoma (DTC), which includes papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), is one of the most curable cancers. In the majority of patients with DTC, the main cause of death is distant metastases (DM) rather than locoregional recurrence. There are 1% to 4% of DTC patients presenting with distant disease in initial diagnosis and additional 7% to 23% of patients developing metastatic disease in follow-up diagnosis.[1–3]

DTC with DM at initial diagnosis (primary DM) had markedly varying clinical outcomes from rapid progression and death to complete remission.[4–10] The difference of metastatic disease site was considered as a possible reason for inconsistent outcome. For

Editor: Eric Bush.

WD and GR contributed equally to this work and should be considered as co-first authors.

Ethical approval was reviewed and approved by the institutional review board at the Shaoxing Second hospital.

The authors declare that they have no competing interests.

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Ding W, Ruan G, Zhu J, Tu C, Li Z. Metastatic site discriminates survival benefit of primary tumor surgery for differentiated thyroid cancer with distant metastases: a real-world observational study. Medicine 2020;99:48(e23132).

Received: 27 March 2020 / Received in final form: 8 September 2020 / Accepted: 15 October 2020

http://dx.doi.org/10.1097/MD.0000000000023132

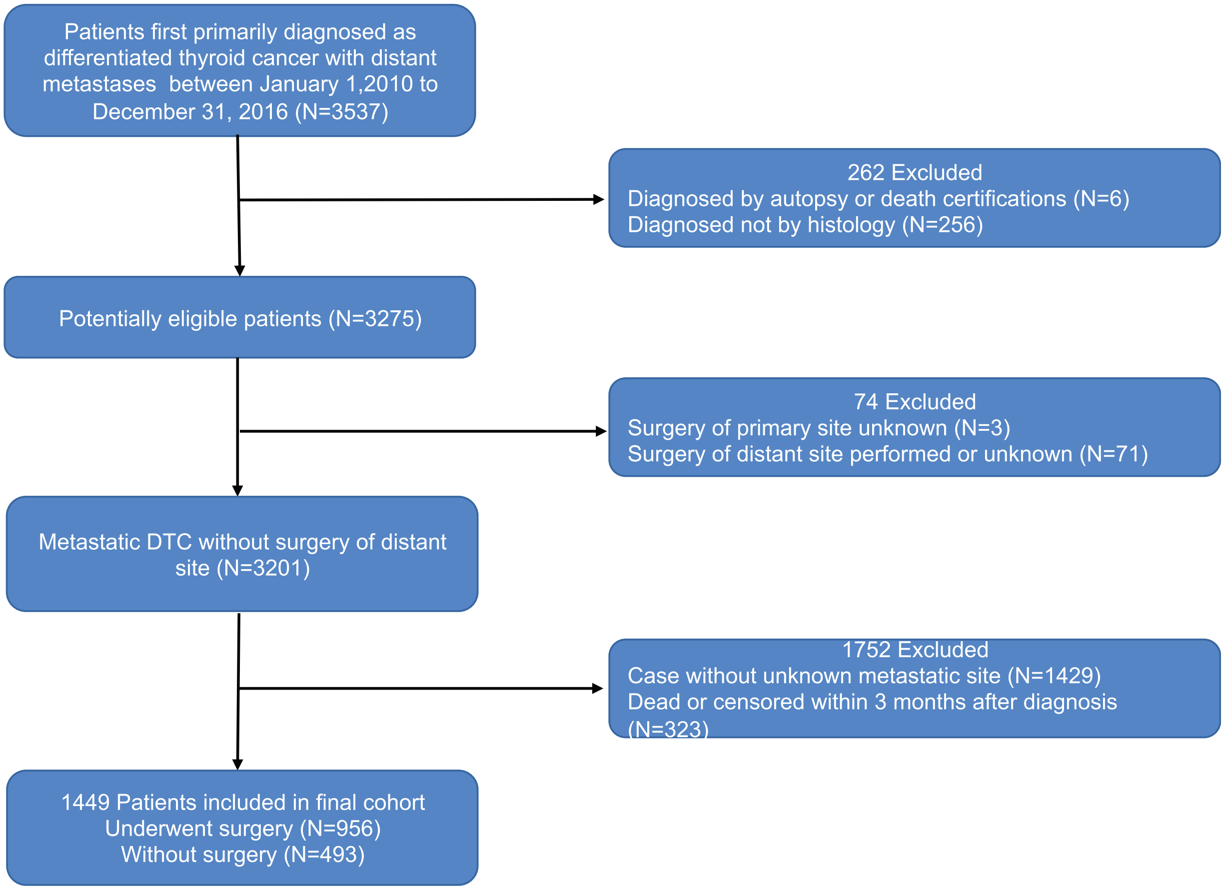


Figure 1. Flow diagram of patient population.

instance, the extrapulmonary metastases had been reported as a significant factor for poor prognosis.[4,7,8] Of note, the survival benefit of the removal of the primary tumor for patients with primary DM among those trials is controversial.

The aim of this real-world observational study was to explore the survival benefit of primary tumor surgery among patient subpopulations stratified by metastatic sites who presented with DM at initial diagnosis. We hypothesized that the local primary tumor surgery may confer a survival benefit to patients with low metastatic tumor burden.

2. Methods

2.1. Study design and data source

The Surveillance, Epidemiology, and End Results (SEER) database (http://seer.cancer.gov/) sponsored by the National Cancer Institute (NCI) covered 18 population-based registries, involving a large proportion (28%) of US people. We used the November 2018 SEER-18 submission for this retrospective longitudinal cohort study, which included patients from geographic regions covered as follows: Metropolitan Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Los Angeles, San Jose-Monterey, Utah, Rural and Greater Georgia, Alaska, Greater California, Kentucky, Louisiana, and New Jersey. We identified 3537 patients who were first initially diagnosed as DTC with DM between January 1, 2010, and December 31, 2016 (Fig. 1). We excluded patients only diagnosed by autopsy or death certifications and the ones without histological confirm. Patients receiving surgery for metastatic sits or unknown sites as well as cases with unknown metastatic sites were also excluded. At last, eligible 1449 DTC patients with primary DM were included in this study, and they were grouped according to whether they underwent primary tumor surgery (N=956) or not (N=493). This study was reviewed and approved by the institutional review board at the Shaoxing Second Hospital. It is also not considered as a human participant study, thus patient consent was not necessary.

2.2. Identification of key variables

The SEER*Stat software (version 8.3.6) was used to extract relevant information, including patient identification, age of diagnosis, year of diagnosis, gender, tumor size, regional lymph node status, race/ethnicity, marital status, distant metastatic site, histology type, nuclear grade, surgery, chemotherapy, radiation therapy, cause-specific death classification, other cause of death classification and survival months.

International Classification of Diseases for Oncology (ICD-O-3)[13] was adopted to identify the cancer site and histology type, and cases of papillary and follicular thyroid cancer were selected using the restrictions {ICD-O-3/WHO 2008=Thyroid} and {Histologic Type ICD-O-3=8050, 8260, 8340–8344, 8350, 8450–8460 (for papillary cancer), or Histologic Type ICD-O-3=8290, 8330–8335 (for follicular cancer)}. We placed Hurthle cell carcinoma (ICD-O-3=

8290) into the category of follicular carcinomas, as used in Lim et al study.[14,15] To investigate the benefit of primary tumor surgery on the basis of metastasis sites, the variable was categorized into single organ and multiple organ metastases. The single organ metastasis was further classified into bone-only, liver-only, lung-only and brain-only metastasis, and multiple organ metastases were classified into multiply organ metastases including brain or excluding brain.

2.3. Main outcome measure

The primary endpoint of this study was overall survival (OS) and DTC-specific survival (DSS). OS was defined as the time between diagnosis and death from any cause, and DSS was defined as the time between diagnosis and death from DTC. SEER defines mortality data based on the International Classification of Diseases Revisions 8 to 10, which categorized the cause of death as DTC-specific death and other-cause death.

2.4. Statistical analysis

For this study, we adopt the similar statistical analytic approaches with previous studies[16,17] that examined the benefit of interventions for breast cancer subsets. Clinicopathologic factors were compared between the surgery groups and non-surgery groups using Pearson χ^2 tests. Multiple imputation of missing data was performed by a multivariate logistic regression model, and 10 cycles were repeated to produce a final data set. Imputation model included these variables as follows: race (white, black, or others), marital status (single, separated and married), nuclear grade (I, II, III, IV), tumor size classification (0–2 cm, 2–4 cm, or>4 cm), and regional lymph node status (positive or negative).

Propensity score weighting was then used to balance patient characteristics between the surgery group and the non-surgery group.[18,19] we calculated the propensity scores based on patient age, year of diagnosis, race, gender, tumor size, regional lymph node status, marital status, distant metastatic site, histology type, nuclear grade, chemotherapy, radiation therapy through a logistic regression model for receipt of primary tumor surgery. From the model, the inverse predicted probability of breast surgery assignment was used to define weights for patients who received surgery (1/probability) and for those who did not receive surgery (1/[1 − probability]). Patient characteristics after propensity score adjustment are shown to be balanced in Table 1.

The hazard ratios for the DSS and OS of patients in the surgery group compared with patients in the non-surgery group were evaluated using propensity score weights for log-rank tests and Cox regression models. Hazard ratios (HRs) of OS and DSS were reported from multivariable models that adjusted for patient age, year of diagnosis, race, gender, tumor size, regional lymph node status, marital status, distant metastatic sites, histology type, nuclear grade, chemotherapy, radiation therapy. Similar procedures were also performed among subgroups defined by metastatic sites, and interaction tests were conducted using a likelihood ratio test to explore whether survival benefit conferred by surgery varied across subgroups.

In addition, to assess the stability of our results, we conducted a series of sensitivity analyses. First, the entire analyses were repeated after imputation unknown data using random survival forest methodology. Then, proportional subdistribution hazards model was used to calculated HR of OS and DSS between the surgery group and the non-surgery group after adjusting competing events[20] such as death from other causes. Second, we performed the analysis after restriction to patients in the SEER 9 registry, because the data in the SEER 9 registry are more accurate than the data in newer SEER registries.[21] Last, since age under 55 years is a

Table 1

Patient characteristics by weighted by propensity score.

	No. of Patients (%)	
Characteristic	No-surgery group (N=493)	Surgery group (N=956)
Year of diagnosis		
2010	68 (13.8)	156 (16.3)
2011	85 (17.2)	143 (15.0)
2012	82 (16.6)	169 (17.7)
2013	88 (17.9)	161 (16.8)
2014	78 (15.8)	169 (17.7)
2015	92 (18.7)	160 (16.7)
Age, years		
<55	148 (30.0)	254 (26.6)
≥55	345 (70.0)	702 (73.4)
Race/ethnic		
White	336 (68.2)	678 (70.9)
Black	90 (18.2)	131 (13.7)
Other*	67 (13.6)	147 (15.4)
Marital status		
Single	245 (49.7)	533 (55.8)
Separated	141 (28.5)	180 (18.8)
Married	107 (21.8)	243 (25.4)
Gender		
Male	168 (34.1)	351 (36.7)
Female	325 (65.9)	605 (63.3)
Histological type		
Papillary	424 (86.1)	846 (88.5)
Follicular	69 (13.9)	110 (11.5)
Grade		
I	92 (18.6)	105 (21.2)
II	106 (21.5)	105 (21.2)
III	211 (42.8)	377 (39.4)
IV	84 (17.1)	173 (18.2)
Tumor size (cm)		
≤2	73 (14.9)	173 (18.1)
2–4	125 (25.4)	215 (22.5)
>4	294 (59.7)	568 (59.4)
Regional node positive		
No	256 (52.0)	453 (47.4)
Yes	237 (48.0)	503 (52.6)
Radiation		
No	340 (69.0)	513 (53.7)
RAI	15 (3.1)	248 (25.9)
EBRT	138 (27.9)	195 (20.4)
Chemotherapy		
No	247 (50.1)	464 (48.5)
Yes	246 (49.9)	491 (51.5)
Bone		
No	349 (70.8)	666 (69.7)
Yes	144 (29.2)	290 (30.3)
Brain		
No	448 (90.9)	863 (90.3)
Yes	45 (9.1)	93 (9.7)
Liver		
No	356 (72.3)	727 (76.0)
Yes	137 (27.7)	229 (24.0)
Lung		
No	222 (45.0)	414 (42.3)
Yes	271 (55.0)	552 (57.7)

* American Indian/AK Native, Asian/Pacific Islander.

EBRT = external beam radiation therapy, RAI = radioactive iodine.

good prognosis factor no matter whether there is a distant metastasis, we excluded the patients with primary DM under the age of 55 years who often receive surgery for longer survival.

All p values were calculated from 2-sided tests with threshold of 0.05 to evaluate statistical significance of survival benefit by surgery, and all statistical analyses were performed using R software (version 3.6.1).

3. Results

3.1. Patient characteristics

We identified 3537 eligible DTC patients with DM at the time of initial treatment on the basis of our inclusion and exclusion criteria (Fig. 1). Of this cohort, 956 (66.0%) patients received the primary tumor surgery, and 493 (34.0%) patients did not. Clinicopathologic factors and SEER cancer registries according to receipt of primary tumor surgery were listed in Table 2. The final data after multiple imputations was exhibited in Table 1. Balance in patient characteristics was achieved after propensity score adjustments for estimating average treatment effect, as shown in Table 1. The proportion of patients with age under 55 years, earlier year of diagnosis (2010–2012), white, male, follicular, small tumor size, regional node negative, and nuclear grade was larger for the surgery group compared with the non-surgery group.

3.2. Sites of distant metastases

A total of 1747 sites of distant metastases were identified in the 3537 DTC patients with primary DM. Lung was the most common site of distant metastasis (834, 47.7%), followed by bone (435, 24.9%), liver (340, 19.5%) and brain (138, 7.9%) (Fig. 2). There are 1208 patients (83.4%) with single organ metastasis, and 241 patients (16.6%) with multiple organ metastases (Fig. 2).

3.3. Survival benefit of primary tumor surgery

After a median follow-up time of 22 months from diagnosis (interquartile range, 12–41 months), 704 patients (48.6%) died of DTC, while 94 patients (6.5%) died of other cancer causes. The 3-year OS rate weighted by inverse propensity score was 55.2% in the surgery group and 27.8% in the non-surgery group (log-rank test, $P<.001$; HR, 0.47; 95% CI, 0.43 to 0.52). The 3-year DSS rate weighted by inverse propensity score was 58.6% in the surgery group and 34.6% in the non-surgery group (log-rank test, $P<.001$; HR, 0.50; 95% CI, 0.45 to 0.56). The difference from the proportional hazard assumption in the Cox regression hazard model adjusting for age, race, marital status, gender, tumor size, regional lymph node status, nuclear grade, histological type, radiation, chemotherapy and metastasis sites was statistically significant ($P<.001$; adjusted HR for OS, 0.51; 95% CI, 0.46 to 0.56; $P<.001$; adjusted HR for DSS, 0.54; 95% CI, 0.48 to 0.60).

3.4. Survival benefit of primary tumor surgery according to metastasis sites

Among 1208 patients with single organ metastasis, there were 627 patients with lung metastasis, 253 patients with bone metastasis, 251 patients with liver metastasis, and 77 patients with brain metastasis. The magnitude of improved survival benefit among

Table 2

Patient characteristics by receipt of primary surgery.

Characteristic	No. of Patients (%) No-surgery group (N=493)	No. of Patients (%) Surgery group (N=956)	P
Year of diagnosis			
2010	61 (12)	174 (18)	.003
2011	74 (15)	161 (17)	
2012	82 (17)	178 (19)	
2013	80 (16)	145 (15)	
2014	92 (19)	161 (17)	
2015	104 (21)	137 (14)	
Age, years			
<55	95 (19)	279 (29)	<.001
≥55	398 (81)	677 (71)	
Race/ethnic			
White	327 (66)	698 (73)	.036
Black	84 (17)	127 (13)	
Other*	82 (17)	130 (14)	
NA	0 (0)	1 (0)	
Marital status			
Single	100 (20)	189 (20)	.42
Separated	125 (25)	216 (23)	
Married	245 (50)	515 (54)	
NA	23 (5)	36 (4)	
Gender			
Male	198 (40)	309 (32)	.004
Female	295 (60)	647 (68)	
Histological type			
Papillary	449 (91)	835 (87)	.042
Follicular	44 (9)	121 (13)	
Grade			
I	25 (5)	92 (10)	<.001
II	36 (7)	100 (10)	
III	39 (8)	237 (25)	
IV	22 (4)	126 (13)	
NA	371 (75)	401 (42)	
Tumor size (cm)			
≤2	44 (9)	154 (16)	<.001
2–4	90 (18)	197 (21)	
>4	173 (35)	471 (49)	
NA	186 (38)	134 (14)	
Regional node positive			
No	168 (34)	447 (47)	<.001
Yes	250 (51)	452 (47)	
NA	75 (15)	57 (6)	
Radiation			
No	300 (61)	511 (53)	<.001
RAI	10 (2)	287 (30)	
EBRT	183 (37)	158 (17)	
Chemotherapy			
No	172 (35)	512 (54)	<.001
Yes	321 (65)	444 (46)	
Distant metastatic site			
Bone			
No	311 (63)	703 (74)	<.001
Yes	182 (37)	253 (26)	
Brain			
No	386 (78)	925 (97)	<.001
Yes	107 (22)	31 (3)	
Liver			
No	390 (79)	719 (75)	.111
Yes	103 (21)	237 (25)	
Lung			
No	228 (46)	387 (40)	.041
Yes	265 (54)	569 (60)	

* American Indian/AK Native, Asian/Pacific Islander.

EBRT = external beam radiation therapy, NA = not available, RAI = radioactive iodine.

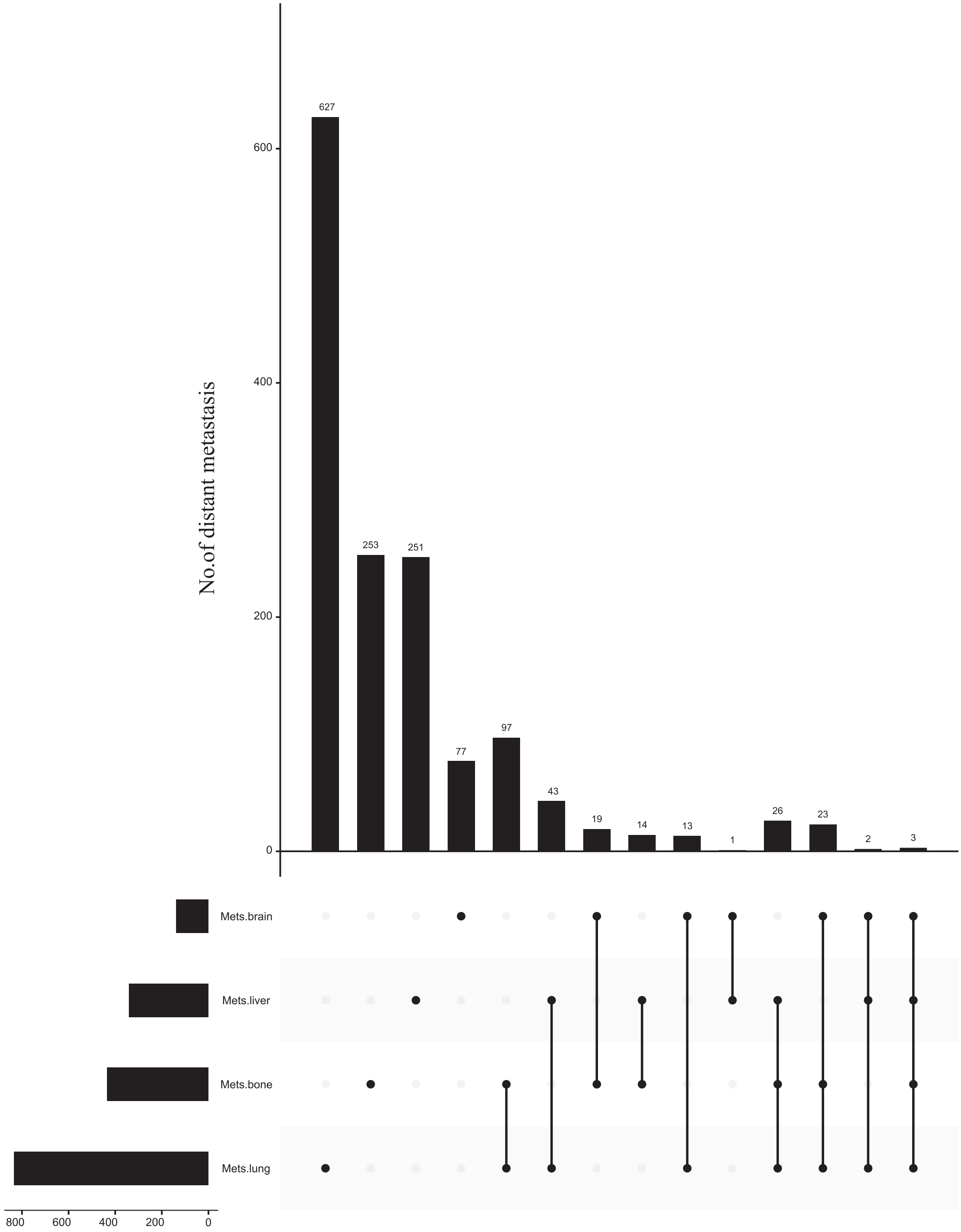
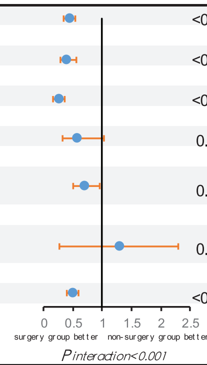


Figure 2. The distribution of metastatic sites in differentiated thyroid cancer patients with distant metastases.

patients receiving primary tumor surgery was significantly correlated with the metastatic site ($P_{\text{interaction for OS}}$ <.001; $P_{\text{interaction for DSS}}$ <.001). When examining the benefit of primary tumor surgery stratified by metastatic site, we found that, for the patients with lung, bone, or liver metastasis, the survival for the primary tumor surgery group was significantly better than that observed in the non-surgery group (lung: OS, HR, 0.45; 95% CI, 0.38–0.54, P < .001; DSS, HR, 0.50; 95% CI, 0.42–0.60; P < .001; bone: OS, HR, 0.40; 95% CI, 0.29–0.56, P < .001; DSS, HR, 0.35; 95% CI, 0.24–0.50; P < .001; liver: OS, HR, 0.27; 95% CI, 0.21–0.36, P < .001; DSS, HR, 0.21; 95% CI, 0.27–0.36; P < .001; Fig. 2). Nevertheless, there was no significant difference in OS or DSS among patients with brain metastasis (OS: HR, 0.57, 95% CI, 0.32–1.02, P = .059; DSS: HR, 0.59; 95% CI, 0.33–1.05,

Site of distant metastasis	No. of patients		Weighted 3-year OS (%)		Weighted Multivariable HR of OS*†	P	Weighted 3-year DSS (%)		Weighted Multivariable HR of DSS*†	P
	Non-surgery group	Surgery group	Non-surgery group	Surgery group			Non-surgery group	Surgery group		
Lung	162	465	41.5	41.8		<0.001	45.4	49.2		<0.001
Bone	89	164	61.1	61.9		<0.001	65.5	70.2		<0.001
Liver	55	196	28.8	38.4		<0.001	30.4	42.7		<0.001
Brain	60	17	22.8	36.2		0.059	24.0	36.2		0.073
Multiply organs metastases(excluding brain)	80	100	25.0	30.4		0.021	34.1	35.1		0.109
Multiply organs metastases(including brain)	47	14	53.0	30.6		0.644	54.9	33.1		0.566
Total	493	956	27.8	55.2		<0.001	34.6	58.6		<0.001



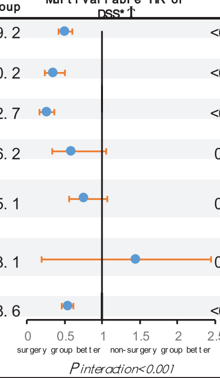


Figure 3. Hazard ratio comparing OS/DSS between surgery group and non-surgery group according to metastatic sites for patients with distant metastases. (*) Weighted by inverse propensity score. (†) Multivariate analysis adjusted by patient age, year of diagnosis, race, gender, tumor size, regional lymph node status, marital status, distant metastatic sites, histology type, nuclear grade, chemotherapy, radiation therapy. DSS = disease specific survival, HR = hazard ratio, OS = overall survival.

$P=.073$; Fig. 3). Also, similar results were found in patient with multiple organ metastases including brain metastasis (OS: HR, 0.77, 95% CI, 0.26–2.30, $P=.644$; DSS: HR, 0.69; 95% CI, 0.19–2.45, $P=.566$; Fig. 3). However, the eye-catching thing is that when we observed the OS and DSS benefit of primary tumor surgery for DTC patients with multiple organ metastases excluding brain metastasis, there was a significant difference in OS while no difference in DSS (OS: HR, 0.70, 95% CI, 0.51–0.95, $P=.021$; DSS: HR, 0.77, 95% CI, 0.56–1.06, $P=.109$, Fig. 3).

We observed similar findings after performing a sensitivity analyses which included excluding patients with age under 55 years, restricting patients within SEER 9, and repeating analyses using the proportional subdistribution hazards model.

4. Discussion

Although DTC is a disease with a generally good outcome, DTC patients presenting with distant metastasis have less favorable outcomes. Distant metastasis from DTCs is usually slow-growing compared with other malignancies, but some patients with these conditions still die from disease-specific causes. For this reason, many risk stratification algorithms consider such cases to be highly risky. Because of the higher possibility of poor outcome, current treatment guidelines advocate an aggressive management with surgery and postoperative radioactive iodine (RAI) therapy.[22,23] This treatment consists of total thyroidectomy, neck dissection as indicated by the detection of disease in the central and/or lateral neck and following RAI therapy in most patients.

Distant metastasis of DTC may affect the prognosis of patients, and the prognostic value of distant metastatic site has been widely studied. In this study, the site of metastases included lung (42%), bone (17%), liver (17%), brain (5%) and multiple sites (19%). These results were consistent with previous reports.[4,11,24] Furthermore, a number of studies showed that the prognosis of patients was related to the location of metastases.[4,7,8] In this study, patients with brain metastases have a worst outcome compared to other groups. The 3-year DSS rate of brain metastasis from DTC was 28.7%, the lung metastasis was 45.9%, the liver metastasis was 40.9%, and the bone metastasis was 50.4%. This finding based on this real-world study were consistent with prior study.[12] This may be due to a possible heterogeneous treatment effect of primary tumor surgery as metastatic sites varied.

DM is undoubtedly the most common primary cause of death in cancer including DTC while other characteristics of DTC in the high-risk group, such as invasion to surrounding organs or anaplastic transformation in the neck lesion, can also become fatal. Haq et al reported that lesser surgery (biopsy or nodulectomy) of the primary tumor in patients with DM was associated with worse survival compared to radical surgery.[11] Our findings indicated that definitive local primary tumor surgery of patients with only-brain metastasis produced no significant survival benefit over non-operative management, but a significant survival improvement for surgery was observed in DTC patients with other single organ metastasis. For patients with multiply organ distant metastases, surgery could also increase DSS in patients without brain metastasis, whereas surgery produced no OS or DSS benefit for patients with brain metastasis. These results demonstrated that individualized decisions for primary tumor surgery of primary DM patients should be tailored on the basis of metastatic sites. Although there were no widely-accepted guidelines existing on the management of metastatic thyroid carcinoma, patients who underwent surgical resection had significantly longer survival than their counterparts in this study. We thus conclude that the presence of DM alone cannot automatically exclude the indication of aggressive local radical resection to clear margins.

In addition to surgery, radiotherapy or RAI therapy have been widely adopted to treat DTC patients with distant metastases. In our study, the benefit of surgical intervention of locally disease was limited in patients with brain metastasis. For those patients, RAI, an important systemic therapy for DTC patients with metastases, may be used as an available form of treatment.[25] Unfortunately, based on current case reports and retrospective series, the uptake of RAI by cranial metastatic lesions is quite low, with a reported range from 0% to 25% of cases,[26–30] and a possible explanation may be because of decreased expression of the sodium iodide symporter (NIS) or diminished membrane targeting of NIS in metastatic lesions.[31] Furthermore, some studies have suggested that the prognosis in patients who present initially with metastases versus those who subsequently develop metastases may be different.[7,11,12,32] The patients presenting initially with metastases appear to have relatively favorable outcomes compared with the patients developing metastases after initial treatment. This result may due to the patients with initial distant metastasis are "treatment-nonresistant", in particularly with respect to RAI, and therefore strongly RAI avid.[24]

As is well-known, age of diagnosis of the initial cancer is known to be a valuable prognostic factor for the recurrence and the mortality of DTC.[33] The current series multivariate analysis identified age as an independent risk factor for bad prognostic feature. In our study, the results showed that compared to those older than 55 years, patients younger than 55 years had a higher survival rate (3-year DSS 52% vs 45%, respectively). Advanced age, as a negative factor of prognosis, is mainly directly related to tumor differentiation and hence RAI avidity. Nixon et al stressed that age was associated with RAI avidity. Higher rates of RAI avidity in younger patients could bring a good outcome, while loss of RAI avidity may produce a poor outcome.[32,34]

In addition, the number and the location of metastases also affect the prognosis of DTC patients with primary DM. Al-Dhahri et al underlined that brain metastasis occurs more frequently in the cerebral hemispheres, and other sites of intracranial metastasis are the cerebellum, brainstem and pituitary.[35] It is obvious that brain metastases in the brainstem as well as with cranial neuropathy or vision changes could lead to a poor prognosis.[36,37] In addition, patients with multiple cranial metastases seemed to suffer a worse outcome than patients with a single metastasis. Surgical resection of metastatic disease can enhance local disease control and improve the quality of life. The NCCN guideline recommended that surgical resection followed by whole brain radiation therapy (WBRT) or stereotactic radiation Therapy (SRS) plus WBRT was appropriate for patients who had stable systemic disease or were newly diagnosed, while WBRT or SRS was advisable for patients who had multiple (>3) metastatic lesions. Understandably, patients with multiple organ metastases often have a worse OS or DSS. The study reported by Wang et al found that the 5-year survival rate in patients with DM limited to 1 organ system was 77.6%, whilst that in patients who develop second organ involvement by DM was just 15.3% ($P<.001$).[1] This was probably because that those patients with multiple organs involvement were not operated due to the high metastatic burden and poor performance status. The Karnofsky Performance Scale (KPS) is an assessment tool for functional impairment. In the American Society for Radiation Oncology evidence-based guideline, KPS was used as a prognostic factor for brain metastasis. They defined a KPS score of over 70 points as having a good prognosis. Akiba[38] and Izumi[39] highlighted that a KPS score over 70 points was a good prognosis factor for metastasis of brain tumor.

Few studies evaluated the primary tumor surgery benefit varied by metastatic sites for DTC with distant metastases, thus this study could narrow the gap. However, several limitations also should be noticed. Besides the extent and site of metastatic disease, additional effect modifiers such as surgical resection margins, timing of surgery, type of systemic treatment administered prior to surgery, and coding errors may influence the effect of surgery. We were unable to completely control these potential modifier effects in this retrospective study due to lack of the information of those variables in the SEER database. Despite propensity score weighting was used in this study, the selection bias, such as younger age, better performance status, smaller size of primary tumor, and good response to prior systemic therapy may still have influenced the decision to perform surgery, which may decrease the reliability of this retrospective study. Additionally, the SEER program only included 4 site-specific distant metastases at the initial diagnosis, and we could not obtain further details involving the other sites of distant metastases.

5. Conclusion

Survival benefit produced by primary tumor surgery for DTC with primary DM varies by metastatic sites. Local primary tumor surgery for DTC patients with lung metastasis, liver metastasis, and bone metastasis were associated with better survival, whereas no survival benefit was observed among patients with only brain metastasis or multiply organ distant metastases along with brain metastasis. Thus, decisions for primary tumor surgery of DTC patients with primary DM should be tailored according to metastatic site.

Acknowledgments

Sincerely thanks to Yingli Lin for supporting this paper, and Wu Ding would like to take this opportunity to ask, "Miss. Lin, will you spend the rest of your life with me?"

Author contributions

Conceptualization: WU DING, Guodong Ruan.
Data curation: WU DING, Guodong Ruan, JZ, CT.
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Visualization: Guodong Ruan, Jianming zhu, Chuanjian Tu.
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All authors have given final approval of the manuscript for submission and publication.

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