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

A real-world observational study

Wu Ding, MD<br>Guodong Ruan, MD<br>Jianming Zhu, MD<br>Chuanjian Tu, MD<br>Zhian Li, MD

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 [Pinteraction < .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 = .999).

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.

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
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 sites 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=
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. Clinico-pathologic factors were compared between the surgery groups and non-surgery groups using Pearson χ² 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 (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 calculate 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
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, 936 (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 (83.4%, 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

| Characteristic | No-surgery group (N = 493) | Surgery group (N = 956) | P     |
|---------------|---------------------------|------------------------|------|
| Year of diagnosis |                           |                        |      |
| 2010          | 61 (12)                   | 174 (18)               | .003 |
| 2011          | 74 (15)                   | 161 (17)               | .10  |
| 2012          | 82 (17)                   | 178 (19)               | .85  |
| 2013          | 80 (16)                   | 145 (15)               | .91  |
| 2014          | 92 (19)                   | 161 (17)               | .25  |
| 2015          | 104 (21)                  | 137 (14)               |      |
| Age, years    |                           |                        |      |
| <55           | 95 (19)                   | 279 (29)               | <.001|
| ≥55           | 398 (81)                  | 677 (71)               |      |
| Race/ethnicity|                           |                        |      |
| 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|
| Yes           | 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          | 311 (63)                  | 703 (74)               | <.001|
| Yes           | 182 (37)                  | 253 (26)               |      |
| Brain         | 386 (78)                  | 925 (97)               | <.001|
| Yes           | 107 (22)                  | 31 (3)                 |      |
| Liver         | 390 (79)                  | 719 (75)               | .111 |
| Yes           | 103 (21)                  | 237 (25)               |      |
| Lung          | 228 (46)                  | 387 (40)               | .041 |
| Yes           | 265 (54)                  | 569 (60)               |      |

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

EBRT = external beam radiation therapy, NA = not available, RAI = radioactive iodine.
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,
compared to other groups. The 3-year DSS rate of brain metastases is worse than other sites.

Studies using the proportional subdistribution hazards model. Patients within SEER 9, and repeating analyses which included excluding patients with age under 55 years, restricted patients to SEER 9, and repeating analyses which included excluding patients with age under 55 years. These results were consistent with previous reports. [4,11,24]

Bone (17%), liver (17%), brain (5%) and multiple sites (19%). In this study, the site of metastases included lung (42%), bone (17%), liver (17%), brain (5%) and multiple sites (19%).

Outcomes. Distant metastasis from DTCs is usually slow-growing and patients presenting with distant metastasis have less favorable outcomes. Distant metastasis is the most common 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]

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

Figure 3. Hazard ratio comparing OS/DSS between surgery group and non-surgery group according to metastatic sites for patients with distant metastases. *(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.

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.\(^\text{[33]}\) Furthermore, some studies have suggested that the prognosis in patients who present initially with metastases versus those who subsequently develop metastases may be different.\(^\text{[7,11,12,32]}\) 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.\(^\text{[34]}\)

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.\(^\text{[35]}\) 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 younger 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.\(^\text{[32,34]}\)

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.\(^\text{[36]}\) It is obvious that brain metastases in the brainstem as well as with cranial neuropathy or vision changes could lead to a poor prognosis.\(^\text{[36,37]}\) 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% \((P<.001)\).\(^\text{[1]}\) 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\(^\text{[38]}\) and Izuim\(^\text{[39]}\) 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.
Formal analysis: WU DING, Guodong Ruan.
Funding acquisition: GR, JZ, CT, ZL, Zhian Li.
Investigation: WU DING, Jianming zhu.
Methodology: Guodong Ruan, Jianming zhu, Zhian Li.
Project administration: Jianming zhu, Zhian Li.
Resources: Guodong Ruan, Jianming zhu.
Software: WU DING, Chuanjian Tu.
Supervision: Jianming zhu, Chuanjian Tu, Zhian Li.
Validation: WU DING, Chuanjian Tu.
Visualization: Guodong Ruan, Jianming zhu, Chuanjian Tu.
Writing – original draft: WU DING.
Writing – review & editing: Zhian Li.
All authors have given final approval of the manuscript for submission and publication.

References
1. Wang LY, Palmer FL, Nixon IJ, et al. Multi-organ distant metastases confer worse disease-specific survival in differentiated thyroid cancer. Thyroid 2014;24:1594–9.
2. Shaha AR, Shah JP, Loree TR. Differentiated thyroid cancer presenting initially with distant metastasis. Am J Surg 1997;174:474–6.
3. Cho SW, Choi HS, Yeom GJ, et al. Long-term prognosis of differentiated thyroid cancer with lung metastasis in Korea and its prognostic factors. Thyroid 2014;24:277–86.
4. Shoup M, Stopadianovic A, Nissam A, et al. Prognostic indicators of outcomes in patients with distant metastases from differentiated thyroid carcinoma. J Am Coll Surg 2003;197:191–7.

7
[5] Mihailovic J, Stefanovic L, Malesevic M, et al. The importance of age over radioiodine avidity as a prognostic factor in differentiated thyroid carcinoma with distant metastases. Thyroid 2009;19:227–32.
[6] Durante C, Haddy N, Baudin E, et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. J Clin Endocrinol Metab 2006;91:2892–9.
[7] Lee J, Soh EY. Differentiated thyroid carcinoma presenting with distant metastasis at initial diagnosis clinical outcomes and prognostic factors. Ann Surg 2010;251:114–9.
[8] Benbassat CA, Mchilis-Frish S, Hirsch D. Clinicopathological characteristics and long-term outcome in patients with distant metastases from differentiated thyroid carcinoma. World J Surg 2006;30:1088–95.
[9] Jonklaas J, SarlIs NJ, Livotfsky D, et al. Outcomes of patients with differentiated thyroid carcinoma following initial therapy. Thyroid 2006;16:1229–42.
[10] Huang IC, Chou FF, Liu RT, et al. Long-term outcomes of distant metastasis from differentiated thyroid carcinoma. Clin Endocrinol (Oxf) 2012;76:439–47.
[11] Haq M, Harmer C. Differentiated thyroid carcinoma with distant metastases: prognostic factors and outcome. Clin Endocrinol (Oxf) 2005;63:87–93.
[12] Sugitani I, Fujimoto Y, Yamamoto N. Papillary thyroid carcinoma with distant metastases: survival predictors and the importance of local control. Surgery 2008;143:35–42.
[13] Fritz APC, Jack A. International classification of diseases for Oncology. Geneva, Switzerland: World Health Organization; 2000.
[14] Lim H, Devesa SS, Sosa JA, et al. Trends in Thyroid Cancer Incidence and Mortality in the United States, 1974-2013. JAMA 2017;317:1338–48.
[15] Yang CQ, Gardiner L, Wang H, et al. Creating Prognostic Systems for Well-Differentiated Thyroid Cancer Using Machine Learning. Front Endocrinol (Lausanne) 2019;10:288.
[16] Kang W, Yang S, Zhu-Yoe L, et al. Metastatic pattern discriminates survival benefit of primary surgery for de novo stage IV breast cancer: a real-world observational study. Eur J Surg Oncal 2019;45:1364–72.
[17] Sagara Y, Freedman RA, Vaz-Luis I, et al. Patient prognostic score and associations with survival improvement offered by radiotherapy after breast-conserving surgery for ductal carcinoma in situ: a population-based longitudinal cohort study. J Clin Oncol 2016;34:1190–6.
[18] Stürmer T, Rothman KJ, Avorn J, et al. Treatment effects in the presence of unmeasured confounding: dealing with observations in the tails of the propensity score distribution—a simulation study. Am J Epidemiol 2010;172:843–54.
[19] Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. J Am Stat Assoc 1984;79:516–24.
[20] Fine JPGR. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;496–509.
[21] Walker GV, Giordano SH, Williams M, et al. Muddy water? Variation in reporting receipt of breast cancer radiation therapy by population-based tumor registries. Int J Radiat Oncol Biol Phys 2013;86:686–93.
[22] Luster M, Aktolun C, Amendoeira I, et al. European Perspective on 2015 American Thyroid Association Management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: proceedings of an interactive international symposium. Thyroid 2019;29:7–26.
[23] Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid 2016;26:1–33.
[24] Sampson E, Brierly JD, Le I.W, et al. Clinical management and outcome of papillary and follicular (differentiated) thyroid cancer presenting with distant metastasis at diagnosis. Cancer 2007;110:1451–6.
[25] Haugen BR, Kane MA. Approach to the thyroid cancer patient with extracervical metastases. J Clin Endocrinol Metab 2010;95:987–93.
[26] Lee HS, Yoo H, Lee SH, et al. Clinical characteristics and follow-up of intracranial metastases from thyroid cancer. Acta Neurochir (Wien) 2015;157:2185–94.
[27] Sato F, Urano T, Shibuya H, et al. Prognosis after brain metastasis from differentiated thyroid carcinoma. World J Surg 2016;40:574–81.
[28] McWilliams RR, Giannini C, Hay ID, et al. Management of brain metastases from thyroid carcinoma: a study of 16 pathologically confirmed cases over 25 years. Cancer 2003;98:336–62.
[29] Salvati M, Prati A, Rocchi G, et al. Single brain metastasis from thyroid cancer: report of twelve cases and review of the literature. J Neurooncol 2001;51:33–40.
[30] Misaki T, Iwata M, Kasagi K, et al. Brain metastasis from differentiated thyroid cancer in patients treated with radioiodine for bone and lung lesions. Ann Nucl Med 2000;14:111–4.
[31] Spitzweg C, Bible KC, Hoffbauer LC, et al. Advanced radioiodine-refractory differentiated thyroid cancer: the sodium iodide symporter and other emerging therapeutic targets. Lancet Diabetes Endocrinol 2014;2:830–42.
[32] Nixon II, Whitcher MM, Palmer FL, et al. The impact of distant metastases at presentation on prognosis in patients with differentiated carcinoma of the thyroid gland. Thyroid 2012;22:884–9.
[33] Brierley J, Tsang R, Panzarella T, et al. Prognostic factors and the effect of treatment with radioactive iodine and external beam radiation on patients with differentiated thyroid cancer seen at a single institution over 40 years. Clin Endocrinol (Oxf) 2005;63:418–27.
[34] Ruesco-Eizaguirre G, Gutierrez-Martinez P, Garcia-Cabazas MA, et al. The oncogene BRAF V600E is associated with a high risk of recurrence and less differentiated papillary thyroid carcinoma due to the impairment of Nax/B-targeting to the membrane. Endocr Relat Cancer 2006;13:257–69.
[35] Al-Dhahir SF, Al-Amro AS, Al-Shakwer W, et al. Cerebellar mass as a primary presentation of papillary thyroid carcinoma: case report and literature review. Head Neck Oncol 2009;1:23.
[36] Jakola AS, Gulati S, Nerland US, et al. Surgical resection of brain metastases: the prognostic value of the graded prognostic assessment score. J Neurooncol 2011;105:573–81.
[37] Villi S, Weber DC, Moretones C, et al. Validation of the new Graded Prognostic Assessment scale for brain metastases: a multicenter prospective study. Radiat Oncol 2011;6:23.
[38] Akiba T, Kunieda E, Kogawa A, et al. Re-irradiation for metastatic brain tumors with whole-brain radiotherapy. Jpn J Clin Oncol 2012;42:264–9.
[39] Izumi J, Watanabe O, Koga M, et al. Stereotactic irradiation for brain metastases: analysis of prognostic factors in survival. Akita J Med 2011;38:49–55.