Incidence and Prognosis of Bone Metastasis in Newly Diagnosed Differentiated Thyroid Carcinoma: A SEER Population-Based Study

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Abstract

Background: Clinical characteristics and sociodemographic of differentiated thyroid carcinoma (DTC) patients with bone metastasis (BM) remain unclear.

Methods: Data of patients with newly diagnosed DTC from 2010 to 2016 were retrieved from Surveillance, Epidemiology, and End Results (SEER) database. Incidence trend of BM in patients with DTC was explored by joinpoint regression. Multivariable logistic regression was utilized to figure out predictors of BM at initial presentation of DTC, and was further evaluated by receiver operator characteristics (ROC) analysis. Multivariable Cox regression was applied to reason out factors associated with overall survival and DTC-specific survival.

Results: A total of 67,176 patients with DTC were identified from the database, with 0.36% (244/67176) presenting BM at the time of diagnosis. The age-adjusted incidence of BM in DTC was relatively stable during study period with an average annual percentage change (AAPC) of 2.52. Multivariable logistic regression recognized eight factors as predictors of presence of BM among the entire cohort. Multivariable Cox regression indicated multiple metastatic sites, total thyroidectomy and radioisotopes as predictors for survival of patients.

Conclusions: The incidence of BM in DTC patients has been stable in recent years. Predictors and prognostic factors of BM in DTC patients were identified in this study.

Background

The overall incidence of thyroid carcinoma has been on the rise in recent decades[1], and it has been reported that the newly diagnosed thyroid carcinoma cases in 2018 was 567,233 worldwide[2]. Furthermore, new cases of thyroid carcinoma in 2020 will reach up to 52,890 in United States according to the newly published cancer statistics[3]. DTC is the most common type of thyroid cancer, as well as the most curable endocrine tumors with 10-year cancer-specific survival of more than 70%[4]. Distant metastasis in DTC was extremely rare and has been regarded as predictor for poor prognosis[5]. It has been demonstrated that 10-year overall survival rate of DTC patient with distant metastasis was less than 50%, lower than that of no metastasis[6].

Second to lung, bone was reported to be one of the most common sites for metastasis of thyroid carcinoma, and it was still of great challenge to improve the prognosis in DTC patients with BM [7]. Spine (34.6%), pelvis (25.5%), sternum and ribs (18.3%), extremities (10.2%), shoulder girdle (5.4%), and craniomaxillofacial (5.4%) were the most common sites of BM in DTC[8]. Although BM was associated with poor prognosis, early detection and administration of appropriate therapy could significantly alleviate suffering of patients[9]. Treatments including radiotherapy, chemotherapy, and surgery have been applied or reported to improve outcomes of DTC patients with BM[9–11]. For instance, chemotherapy drugs such as Zoledronic Acid has been demonstrated to be effective in reducing skeletal-

related events or delaying its appearance in patients with BM from DTC[7]. Moreover, bone stability of patients could be improved by using percutaneous osteoplasty combined with radioiodine therapy[12].

Early detection or prediction of BM in DTC was in urgent need for improving the prognosis as well as reducing unnecessary cost of patients. With early intervention, BM can be controlled or suppressed. Nevertheless, the promising data related to the incidence and prognosis of BM in newly diagnosed DTC, especially the population-based study, was extremely limited[9, 13, 14]. Even though characteristics of BM from DTC have been discussed in some case reports or reviews, we cannot reconcile these controversial observations to make a conclusion[15–17]. Thus, we extracted data from the SEER database from 2010–2016 to conduct this population-based analysis, aiming to identify the trend in incidence and investigate potential predictors and prognostic factors of BM in newly diagnosed DTC patients.

Methods

Data source

SEER database was one of the most authoritative cancer databases worldwide, which collected individual data of cancer patients from various regional cancer registries throughout the United States since 1973, covering approximately 30 percent of the U.S. population[18]. Data in SEER database was deemed reliable ascribe to rigorous quality control studies and various data assessments. We obtained data of information of eligible patients in this study by using the SEER*Stat software version 8.3.6 (Surveillance Research Program, National Cancer Institute, seer.cancer.gov/seerstat). The SEER database provided data of patients up to 2016 based on the Nov 2018 submission, and data on specific metastatic sites including lung, bone, liver and brain was available since 2010. Therefore, the study period was set between Jan 2010 to Dec 2016.

Study design and participants

Patients with BM of newly diagnosed DTC during 2010 to 2016 were initially enrolled in this study and then screened by following the inclusion criteria below. (1) Age more than 18 years old, (2) Diagnosis of DTC with positive histology conformation (ICD-O-3 histology code: 8050, 8052, 8260, 8330–8335 and 8340–8344) (3) DTC as the only primary cancer, (4) known survival status and time. Data of individual patient were excluded if there was no specific information of TNM system and bone or lung metastasis. In this study, variables collected through SEER database were composed of sociodemographic characteristics (year at diagnosis, age at diagnosis, race, gender, insurance situation and marital status), clinicopathological characteristics (laterality, histologic, American joint committee on cancer (AJCC) clinical stage, AJCC TNM classification, extraskelatal metastasis) and treatment-related information (surgical procedures, radiotherapy and chemotherapy). All data was confirmed by two independent authors (Lin Qi and Wenchao Zhang). Age was divided into 4 intervals (≤ 44 , 45–54, 55–64 and ≥ 65) based on the major age of onset. Race was classified into white, black and others. Year of diagnosis was stratified into two period (2010–2013 and 2014–2016). The primary endpoint in this study were overall

survival and cancer-specific survival, defined as time from onset to death caused by all reasons and cancer respectively. The study design with corresponding process was shown in Fig. 1.

Statistical analysis

Description analysis was utilized to present the overall view of frequency and age-adjusted incidence of BM in newly diagnosed DTC. Frequency was defined as the percentage of BM among the entire cohort or in the cases with distant metastasis. We principally focused on the entire cohort rather than the subset with metastatic disease because this was a population-based study. Sociodemographic, clinicopathological and treatment-related characteristics including year at diagnosis, age at diagnosis, race, gender, insurance situation, marital status, laterality, histologic, AJCC clinical stage, AJCC TMN classification, multifocality, extra skeletal metastases, surgery, radiation therapy and chemotherapy were employed to stratify the data. Survival data was expressed in the median with interquartile range. Incidence of DTC patients with BM were age adjusted to the 2000 US standard population and expressed per 1 000 000 person-years. Joinpoint Regression Analysis Program (version 4.7.0.0; National Cancer Institute) was used to calculate annual percentage change (APC) and corresponding 95% CIs to present the trend in incidence.

The differences in sociodemographic, clinicopathological and treatment characteristics were compared by Pearson's chi-squared test. Univariable and Multivariable logistic regression were applied to figure out possible predictors of BM and build the predicting models. Corresponding Odds ratio (OR) along with 95% confidence intervals (CI) were also presented. The models were further assessed by using the ROC curves. Meanwhile, the nomogram was established based on the significant predictors to predict the probability of BM in DTC patients. Furthermore, univariable and multivariable cox regression were conducted to identify prognostic factors for overall survival and cancer-specific survival in DTC patients with BM. Kaplan-Meier curves along with log-rank tests were created according to the significant prognostic factors. All statistical analyses were done among both the entire cohort and subset with metastatic disease and were conducted utilizing SPSS version 24 for Windows (IBM, Armonk, New York, USA). Survival curves were generated by GraphPad Prism 8. The nomogram was established using R version 3.5.3. Two-sided $P < 0.05$ was defined as statistical significance.

Results

Characteristics of enrolled patients

A total of 67,176 patients with DTC in United states during 2010 to 2016 were screened from SEER database based on the inclusion criteria. Among these patients, 702 (1.045%) patients were diagnosed with distant metastasis at initial presentation of DTC, including 323 men (46.01%) and 379 women (53.99%). BM accounts for 0.36% (244/67176) among entire group and 34.76% (244/702) among subset with all distant metastasis in DTC patients. The sociodemographic, clinicopathological and treatment characteristics of population in this study were present in Table 1. Patterns of distant metastasis to specific sites in DTC was listed in Supplemental table 1

Table 1
Clinical Characteristics of Patients with DTC with Identified BM at Diagnosis

Variable	Patients, No.			Proportion of BM, %		
	With DTC (n = 67176)	With Metastatic Disease (n = 702)	With BM (n = 244)	Among Entire Cohort	Among Subset with Metastatic Disease	Survival among Patients with BM, Median (IQR), mo
Year at diagnosis						
2010–2013	37542	367	122	0.32	33.24	47.00 (14.00–58.00)
2014–2016	29634	335	122	0.41	36.42	14.00 (5.00–23.25)
Age at diagnosis, Years						
18–44	27185	128	24	0.09	18.75	22.50 (10.25–47.00)
45–54	16284	112	35	0.21	31.25	33.00 (14.00–53.00)
55–64	13432	175	74	0.55	42.29	20.50 (6.00–39.50)
≥65	10275	287	111	1.08	38.68	19.00 (6.00–42.00)
Race						
White	53664	521	164	0.31	31.48	22.00 (7.00–47.00)

DTC, Differentiated Thyroid Carcinoma, BM, Bone Metastases, CI, Confidence Interval, IQR, Interquartile Range, NA, Not Applicable.

† including American Indians, Alaska Natives and Asian-Pacific Islanders.

‡ divorced, separated, single (never married), and widowed

§ according to the seventh edition of the AJCC Cancer Staging manual.

¶ combination of beam with implants or isotopes

Variable	Patients, No.			Proportion of BM, %		
Black	4685	61	35	0.75	57.38	23.00 (5.00–35.00)
Other†	8827	120	45	0.51	37.5	19.00 (6.00–46.50)
Gender						
Male	15085	323	103	0.68	31.89	22.00 (9.00–48.00)
Female	52091	379	141	0.27	37.2	21.00 (6.00–43.00)
Insurance situation						
Insured	65472	674	236	0.36	35.01	21.50 (7.00–47.00)
Uninsured	1704	28	8	0.47	28.57	33.00 (4.25–46.75)
Marital status						
Married	40859	381	138	0.34	36.22	22.00 (9.00–48.00)
Unmarried‡	22346	295	99	0.44	33.56	21.00 (5.00–44.00)
Unkonwn	3971	26	7	0.17	26.92	17.00 (17.00–35.00)
Laterality						

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Variable	Patients, No.			Proportion of BM, %		
Unilateral	66640	699	243	0.36	34.76	22.00 (7.00–47.00)
Bilateral	536	3	1	0.19	33.33	22.00 (7.00–46.50)
Histologic						
Papillary	63945	582	161	0.25	27.66	21.00 (7.00–41.50)
Follicular	3231	120	83	2.57	69.17	23.00 (7.00–49.00)
AJCC clinical stage§						
I	49301	0	0	0	NA	NA
II	4696	0	0	0	NA	NA
III	9021	0	0	0	NA	NA
IV	4158	702	244	5.87	34.76	22.00 (7.00–47.00)
AJCC T classification§						
T1	40294	101	44	0.11	43.56	25.50 (6.50–40.25)
T2	11168	82	42	0.38	51.22	26.50 (9.50–51.50)
T3	13838	263	91	0.66	34.6	26.00 (10.00–53.00)
T4	1876	256	67	3.57	26.17	11.00 (5.00–24.00)

DTC, Differentiated Thyroid Carcinoma, BM, Bone Metastases, CI, Confidence Interval, IQR, Interquartile Range, NA, Not Applicable.

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Variable	Patients, No.			Proportion of BM, %		
AJCC N classification§						
N0	51387	277	154	0.3	55.6	23.50 (8.00-50.25)
N1	15789	425	90	0.57	21.18	18.50 (6.00–33.00)
AJCC M classification§						
M0	66474	0	0	0	NA	NA
M1	702	702	244	34.76	34.76	22.00 (7.00–47.00)
Multifocality						
No	38843	337	128	0.33	37.98	19.50 (6.00-43.50)
Yes	28333	365	116	0.41	31.78	22.00 (8.50–47.00)
Extraskkeletal metastases to lung, liver and brain, No.						
0	66734	260	141	0.21	54.23	28.00 (14.00–53.00)
1	82	82	82	100	100	15.00 (6.00-29.50)
2	36	36	21	100	58.33	6.00 (4.00-8.50)
3	1	1	0	100	0	NA
Unkonwn	323	323	0	82.25	0	NA
DTC, Differentiated Thyroid Carcinoma, BM, Bone Metastases, CI, Confidence Interval, IQR, Interquartile Range, NA, Not Applicable.						
† including American Indians, Alaska Natives and Asian-Pacific Islanders.						
‡ divorced, separated, single (never married), and widowed						
§ according to the seventh edition of the AJCC Cancer Staging manual.						
¶ combination of beam with implants or isotopes						

Variable	Patients, No.			Proportion of BM, %		
Surgery						
No	568	87	38	6.69	43.68	6.00 (2.75–22.50)
Lobectomy	8904	33	10	0.11	30.3	16.00 (4.00–23.25)
Subtotal or near-total thyroidectomy	1758	18	1	0.06	5.56	NA
Total thyroidectomy	55946	564	195	0.35	34.57	25.00 (10.00–50.00)
Radiation therapy						
No	36712	171	43	0.11	25.15	7.00 (3.00–41.00)
Radiation beam or radioactive implants	1070	163	88	8.22	53.99	11.00 (5.00–30.25)
Radioisotopes	29293	348	97	0.33	27.87	27.00 (17.00–54.00)
Combination¶	100	20	16	16	80	35.00 (20.50–59.00)
Chemotherapy						
No	66990	638	224	0.33	35.11	22.00 (8.00–47.00)
Yes	186	64	20	10.75	31.25	7.00 (3.25–24.00)
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‡ divorced, separated, single (never married), and widowed						
§ according to the seventh edition of the AJCC Cancer Staging manual.						
¶ combination of beam with implants or isotopes						

Trends in DTC patients with specific distant metastasis are described in Supplemental table 2 and Fig. 2, with joinpoint regression denoted as trends 1 to 2. Incidence rates of BM in DTC patients remained relatively stable during the study period (from 1.23 [95%CI, 0.91 to 1.62] per 1 000 000 person-years in 2010 to 1.36 [95%CI, 1.06 to 1.74 per 1 000 000 person-years in 2016), with an AAPC of 2.52 (95% CI, -2.81 to 8.14, $P = 0.28$). Incidence rates of other specific distant metastasis including sites to lung, brain and livers also have been stable in recent years.

Predictors of BM in DTC patients

On Chi-square or Fisher's test, age at diagnosis, gender, race, marital status, histology, AJCC T classification, AJCC N classification, surgery, radiation therapy and chemotherapy showed significant difference among the entire cohort (Supplemental table 3). Within the entire cohort, proportion of older patients (age ≥ 65 years old) (45.4% vs 15.2%, $P < 0.001$), black race (14.3% vs 6.9%, $P < 0.001$), male gender (42.2% vs 22.4%, $P < 0.001$), unmarried patients (40.6% vs 33.2%, $P = 0.014$), follicular histology (34.0% vs 4.7%, $P < 0.001$), AJCC T4 staging (27.5% vs 2.7%, $P < 0.001$), AJCC N1 staging (36.9% vs 23.5%, $P < 0.001$), no surgery (15.6% vs 0.8%, $P < 0.001$), radiation beam or radioactive implants (36.1% vs 1.5%, $P < 0.001$), chemotherapy (8.2% vs 0.2%, $P < 0.001$) were associated with BM. Of note, P value of AJCC clinical stage between two groups was not calculatable because all BM patients were in AJCC 7th stage IV.

Univariable logistic regression in the entire cohort figured out 10 statistically significant ($P < 0.05$) factors, including the age at diagnosis, race, gender, marital status, histology, AJCC T classification, AJCC N classification, surgery, radiation therapy and chemotherapy (Supplemental table 4). All these statistically significant factors were entered into the multivariable logistic regression. The multivariable logistic regression model of the predictors of presence of BM in DTC patients was constructed in Table 2. Age between 45 to 54 years (vs age between 18 to 44 years; OR: 2.562, 95%CI: 1.500 to 4.374, $P = 0.001$), age between 55 to 64 years (vs age between 18 to 44 years; OR: 5.644, 95%CI: 3.485 to 9.140, $P < 0.001$), age ≥ 65 years (vs age between 18 to 44 years; OR: 7.370, 95%CI: 4.589 to 11.838, $P < 0.001$), black race (vs white race; OR: 2.538, 95%CI: 1.675 to 3.847, $P < 0.001$), follicular histology (vs papillary histology; OR: 8.141, 95%CI: 5.809 to 11.409, $P < 0.001$), AJCC T2 staging (vs AJCC T1 staging; OR: 1.624, 95%CI: 1.032 to 2.557, $P = 0.036$), AJCC T3 staging (vs AJCC T1 staging; OR: 2.354, 95%CI: 1.582 to 3.503, $P < 0.001$), AJCC T4 staging (vs AJCC T1 staging; OR: 3.595, 95%CI: 2.169 to 5.958, $P < 0.001$), radiation beam or radioactive implants (vs no radiation therapy; OR: 25.477, 95%CI: 16.469 to 39.411, $P < 0.001$), radioisotopes (vs no radiation therapy; OR: 2.097, 95%CI: 1.420 to 3.097, $P < 0.001$), Combination radiation (vs no radiation therapy; OR: 70.766, 95%CI: 34.842 to 143.727, $P < 0.001$), chemotherapy (vs no chemotherapy; OR: 1.920, 95%CI: 1.008 to 3.656, $P < 0.001$) could serve as significant predictors of presenting BM in newly diagnosed DTC. Meanwhile, female gender (vs male gender; OR: 0.721, 95%CI: 0.540 to 0.963, $P = 0.027$), lobectomy (vs no surgery; OR: 0.071, 95%CI: 0.032 to 0.160, $P < 0.001$), subtotal or near-total thyroidectomy (vs no surgery; OR: 0.018, 95%CI: 0.002 to 0.144, $P < 0.001$), total thyroidectomy (vs no surgery; OR: 0.164, 95%CI: 0.096 to 0.279, $P < 0.001$) were significantly associated with lower possibility of BM in newly diagnosed DTC.

Table 2
Multivariable Logistic Regression for the Presence of BM at Diagnosis of DTC

Variable	Among entire cohort		Among subset with metastatic disease	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Age at diagnosis, Years				
18–44	Reference	NA	Reference	NA
45–54	2.562 (1.500–4.374)	0.001	1.969 (1.003–3.868)	0.049
55–64	5.644 (3.485–9.140)	< 0.001	2.619 (1.424–4.817)	0.002
≥65	7.370 (4.589–11.838)	< 0.001	1.865 (1.034–3.365)	0.038
Race				
White	Reference	NA	Reference	NA
Black	2.538 (1.675–3.847)	< 0.001	1.916 (1.003–3.662)	0.049
Other [†]	1.787 (1.242–2.571)	0.002	1.053 (0.650–1.704)	0.835
Gender				
Male	Reference	NA	NA	NA
Female	0.721 (0.540–0.963)	0.027	NA	NA
Marital status				
Married	Reference	NA	NA	NA
Unmarried [‡]	1.202 (0.897–1.611)	0.218	NA	NA
Unkonwn	0.579 (0.254–1.320)	0.194	NA	NA

DTC, Differentiated Thyroid Carcinoma, BM, Bone Metastases, OR, odds ratio, CI, Confidence Interval, NA, Not Applicable.

[†] including American Indians, Alaska Natives and Asian-Pacific Islanders.

[‡] divorced, separated, single (never married), and widowed

[§] according to the seventh edition of the AJCC Cancer Staging manual.

[¶] combination of beam with implants or isotopes

Variable	Among entire cohort		Among subset with metastatic disease	
Histologic				
Papillary	Reference	NA	Reference	NA
Follicular	8.141 (5.809–11.409)	< 0.001	3.237 (1.962–5.340)	< 0.001
AJCC T classification§				
T1	Reference	NA	Reference	NA
T2	1.624 (1.032–2.557)	0.036	1.177 (0.585–2.370)	0.648
T3	2.354 (1.582–3.503)	< 0.001	0.805 (0.465–1.396)	0.44
T4	3.595 (2.169–5.958)	< 0.001	0.495 (0.272–0.900)	0.021
AJCC N classification§				
N0	Reference	NA	Reference	NA
N1	1.312 (0.934–1.844)	0.117	0.399 (0.264–0.602)	< 0.001
Surgery				
No	Reference	NA	Reference	NA
Lobectomy	0.071 (0.032–0.160)	< 0.001	0.695 (0.261–1.850)	0.466
Subtotal or near-total thyroidectomy	0.018 (0.002–0.144)	< 0.001	0.043 (0.005–0.397)	0.043
Total thyroidectomy	0.164 (0.096–0.279)	< 0.001	0.743 (0.409–1.348)	0.328
Radiation therapy				

DTC, Differentiated Thyroid Carcinoma, BM, Bone Metastases, OR, odds ratio, CI, Confidence Interval, NA, Not Applicable.

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Variable	Among entire cohort		Among subset with metastatic disease	
No	Reference	NA	Reference	NA
Radiation beam or radioactive implants	25.477 (16.469–39.411)	< 0.001	4.349 (2.551–7.413)	< 0.001
Radioisotopes	2.097 (1.420–3.097)	< 0.001	1.298 (0.783–2.150)	0.311
Combination¶	70.766 (34.842–143.727)	< 0.001	13.171 (3.639–47.475)	< 0.001
Chemotherapy				
No	Reference	NA	NA	NA
Yes	1.920 (1.008–3.656)	0.047	NA	NA
DTC, Differentiated Thyroid Carcinoma, BM, Bone Metastases, OR, odds ratio, CI, Confidence Interval, NA, Not Applicable.				
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Moreover, ROC analysis was conducted to further assess the multivariable logistic regression models with significant predictors above. The multivariable logistic regression model of the entire cohort exhibited optimal performance with the value of AUC of 0.893 (Supplemental Fig. 1). Furthermore, the nomogram predicting the probability of BM in DTC patients was further established based on significant predictors identified through multivariable logistic regression (Fig. 3). Each variable had a corresponding score in the nomogram (Supplemental table 5). We could estimate the probability of undergoing amputation according to the total scores.

Survival Analysis

Findings above gave insight of BM incidence and prediction of presence in newly diagnosed DTC patients. In order to explore roles of these factors in prognosis of DTC patients with BM, we carried out the survival analysis. The univariable cox regression analysis for overall survival and cancer-specific survival in DTC patients with BM was present in Table 3. On multivariable analysis (Table 4) among the subset with BM, we identified three factors that were significantly associated with overall survival, including metastatic sites ≥ 2 (vs metastatic sites < 2 ; OR: 2.394, 95%CI: 1.376 to 4.164, $P = 0.002$), total thyroidectomy (vs no surgery; OR: 0.388, 95%CI: 0.224 to 0.673, $P = 0.001$), radioisotopes (vs no radiation

therapy; OR: 0.451, 95%CI: 0.216 to 0.941, $P = 0.034$). And factors linked with cancer-specific survival were diagnosis at 2014–2016 (vs diagnosis at 2010–2013; OR: 0.494, 95%CI: 0.270 to 0.904, $P = 0.022$), metastatic sites ≥ 2 (vs metastatic sites < 2 ; OR: 4.366, 95%CI: 2.259 to 8.435, $P < 0.001$), total thyroidectomy (vs no surgery; OR: 0.381, 95%CI: 0.202 to 0.720, $P = 0.003$). Overall survival estimates as stratified by metastatic site (Fig. 4A), surgery (Fig. 4B) and radiation therapy (Fig. 4C), and cancer-specific survival estimates as stratified by metastatic site (Fig. 4D), surgery (Fig. 4E), year at diagnosis (Fig. 4F) were illustrated in the Fig. 4.

Table 3

Univariable Analysis for Overall and Cancer-specific Survival in Patients with DTC diagnosed with BM

Variable	Overall Survival		Cancer-specific Survival	
	HR(95% CI)	P Value	HR(95% CI)	P Value
Year at diagnosis				
2010–2013	Reference	NA	Reference	NA
2014–2016	0.733 (0.437–1.230)	0.24	0.616 (0.348–1.089)	0.095
Age at diagnosis, Years				
18–44	Reference	NA	Reference	NA
45–54	0.642 (0.215–1.916)	0.427	0.471 (0.126–1.756)	0.262
55–64	1.227 (0.497–3.028)	0.657	1.352 (0.507–3.605)	0.546
≥65	1.685 (0.718–3.954)	0.23	1.657 (0.650–4.225)	0.29
Race				
White	Reference	NA	Reference	NA
Black	1.226 (0.669–2.247)	0.51	0.978 (0.479–1.997)	0.952
Other [†]	0.804 (0.430–1.502)	0.493	0.704 (0.345–1.437)	0.335
Gender				
Male	Reference	NA	Reference	NA
Female	1.014 (0.654–1.574)	0.95	1.122 (0.685–1.838)	0.649
Insurance situation				

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[†] including American Indians, Alaska Natives and Asian-Pacific Islanders.

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[¶] combination of beam with implants or isotopes

Variable	Overall Survival		Cancer-specific Survival	
Insured	Reference	NA	Reference	NA
Uninsured	1.577 (0.576–4.317)	0.375	0.951 (0.233–3.890)	0.945
Marital status				
Married	Reference	NA	Reference	NA
Unmarried†	1.350 (0.866–2.103)	0.185	1.245 (0.759–2.041)	0.385
Unkonwn	0.516 (0.071–3.753)	0.513	0.601 (0.082–4.390)	0.615
Histologic				
Papillary	Reference	NA	Reference	NA
Follicular	0.884 (0.553–1.413)	0.607	0.954 (0.570–1.595)	0.856
AJCC T classification§				
T1	Reference	NA	Reference	NA
T2	0.952 (0.393–2.305)	0.913	0.945 (0.330–2.692)	0.912
T3	1.016 (0.484–2.133)	0.966	1.134 (0.476–2.702)	0.776
T4	3.020 (1.488–6.126)	0.002	3.478 (1.533–7.889)	0.003
AJCC N classification§				
N0	Reference	NA	Reference	NA
N1	1.904 (1.226–2.956)	0.004	2.020 (1.240–3.290)	0.005
Metastatic sites ≥ 2				

DTC, Differentiated Thyroid Carcinoma, BM, Bone Metastases, HR, hazard ratio, CI, Confidence Interval, NA, Not Applicable.

† including American Indians, Alaska Natives and Asian-Pacific Islanders.

‡ divorced, separated, single (never married), and widowed

§ according to the seventh edition of the AJCC Cancer Staging manual.

¶ combination of beam with implants or isotopes

Variable	Overall Survival		Cancer-specific Survival	
No	Reference	NA	Reference	NA
Yes	4.014 (2.510–6.402)	< 0.001	6.224 (3.512–11.028)	< 0.001
Multifocality				
No	Reference	NA	Reference	NA
Yes	0.903 (0.581–1.402)	0.649	0.746 (0.454–1.220)	0.242
Surgery				
No	Reference	NA	Reference	NA
Lobectomy	0.987 (0.423–2.303)	0.977	1.181 (0.494–2.824)	0.708
Subtotal or near-total thyroidectomy	8.427 (1.058–67.143)	0.044	8.871 (1.106–71.166)	0.04
Total thyroidectomy	0.205 (0.125–0.335)	< 0.001	0.218 (0.124–0.380)	< 0.001
Radiation therapy				
No	Reference	NA	Reference	NA
Radiation beam or radioactive implants	1.311 (0.747–2.300)	0.346	1.206 (0.646–2.253)	0.557
Radioisotopes	0.279 (0.141–0.553)	< 0.001	0.301 (0.143–0.633)	0.002
Combination¶	0.277 (0.081–0.947)	0.041	0.345 (0.099–1.203)	0.095
Chemotherapy				
No	Reference	NA	Reference	NA
Yes	3.756 (2.051–6.876)	< 0.001	4.076 (2.156–7.706)	< 0.001
DTC, Differentiated Thyroid Carcinoma, BM, Bone Metastases, HR, hazard ratio, CI, Confidence Interval, NA, Not Applicable.				
† including American Indians, Alaska Natives and Asian-Pacific Islanders.				
‡ divorced, separated, single (never married), and widowed				
§ according to the seventh edition of the AJCC Cancer Staging manual.				
¶ combination of beam with implants or isotopes				

Table 4

Multivariable Analysis for Overall and Cancer-specific Survival in Patients with DTC diagnosed with BM

Variable	Overall Survival		Cancer-specific Survival	
	HR(95% CI)	P Value	HR(95% CI)	P Value
Year at diagnosis				
2010–2013	NA	NA	Reference	NA
2014–2016	NA	NA	0.494 (0.270–0.904)	0.022
AJCC T classification§				
T1	Reference	NA	Reference	NA
T2	0.685 (0.273–1.716)	0.419	0.688 (0.233–2.031)	0.499
T3	0.684 (0.312–1.500)	0.343	0.596 (0.240–1.477)	0.264
T4	1.029 (0.439–2.413)	0.947	0.819 (0.308–2.180)	0.69
AJCC N classification§				
N0	Reference	NA	Reference	NA
N1	1.158 (0.701–1.913)	0.566	1.422 (0.809–2.498)	0.221
Metastatic sites ≥ 2				
No	Reference	NA	Reference	NA
Yes	2.394 (1.376–4.164)	0.002	4.366 (2.259–8.435)	< 0.001
Surgery				
No	Reference	NA	Reference	NA
Lobectomy	1.036 (0.430–2.498)	0.937	0.945 (0.367–2.433)	0.907
Subtotal or near-total thyroidectomy	3.428 (0.406–28.976)	0.258	2.131 (0.241–18.813)	0.496
DTC, Differentiated Thyroid Carcinoma, BM, Bone Metastases, HR, hazard ratio, CI, Confidence Interval, NA, Not Applicable.				
§ according to the seventh edition of the AJCC Cancer Staging manual.				
¶ combination of beam with implants or isotopes				

Variable	Overall Survival		Cancer-specific Survival	
Total thyroidectomy	0.388 (0.224–0.673)	0.001	0.381 (0.202–0.720)	0.003
Radiation therapy				
No	Reference	NA	Reference	NA
Radiation beam or radioactive implants	1.318 (0.740–2.345)	0.348	1.064 (0.560–2.023)	0.849
Radioisotopes	0.451 (0.216–0.941)	0.034	0.537 (0.238–1.209)	0.133
Combination¶	0.403 (0.114–1.427)	0.159	0.534 (0.143–1.988)	0.349
Chemotherapy				
No	Reference	NA	Reference	NA
Yes	1.523 (0.783–2.963)	0.215	1.786 (0.866–3.684)	0.116
DTC, Differentiated Thyroid Carcinoma, BM, Bone Metastases, HR, hazard ratio, CI, Confidence Interval, NA, Not Applicable.				
§ according to the seventh edition of the AJCC Cancer Staging manual.				
¶ combination of beam with implants or isotopes				

Discussion

Incidence of BM in DTC was relatively lower compared with that in other malignant cancers such lung cancer[19] and breast cancer[20, 21]. Besides, BM often occurs in medullary and undifferentiated thyroid cancer[22], and limited characteristics about BM in DTC have been reported. Despite several case reports and cohort studies[23–25], little was known about its incidence, risk factor and prognosis in DTC. In this population-based study, we analyzed the trend in incidence, survival, risk factors and prognostic factors of BM in newly diagnosed DTC patients, aiming to promote understanding on the current situation and the association between clinical pattern and BM. To the best of our knowledge, this study included largest sample size of DTC patients with BM compared with previous ones.

In the present study utilizing SEER database, BM accounts for 0.36% (244/67176) among entire group and 34.76% (244/702) among subset with metastatic diseases in newly diagnosed DTC patients, which was lower than the proportion (2.0%) in study of Yoriyhis et al.[9] and the proportion (5.51%) in study of Marie-odile et al.[26] Sample size in these two studies was relatively small and they only included patients in a single institution; therefore the results in the above studies were not representative. In

addition, the above two studies were conducted with data in early period, while our study focused on patients diagnosed during 2010 to 2016. With the advancement of screening methods, early detection of asymptomatic thyroid cancer and timely interventions such as surgery have substantially enhanced the prognosis of thyroid tumor patients. Therefore, the frequency of bone metastases in DTC patients may have reduced compared with early decades.

To explore the trend of incidence of BM in DTC patients, Jointpoint regression analysis was introduced, and result indicated that the age-adjusted incidence of BM in DTC was relatively stable during study period, which was not reported before. Besides, incidence of thyroid cancer was in constant increasing during 1974 to 2013 in United States[1].

By using multivariable logistic regression, we recognized predictors of BM in newly diagnosed DTC. Older age, black race, male gender, follicular histology, more advanced T stage, radiation therapy, no surgery, and chemotherapy were significantly associated with presence of BM in DTC patients at diagnosis. In a meta-analysis that enrolled 34 articles with 73,219 patients, age ≥ 45 years, male gender, and follicular histology were demonstrated to be significant predictors of distant metastasis, which was consistent with our analysis [27]. Follicular thyroid cancer was characterized with higher invasion and distant metastasis compared with papillary thyroid cancer; therefore BM rate was higher correspondently[28]. According to a population analysis included patients with DTC during 1988–2009 in SEER database, patients with distant metastasis tended to have received radiation therapy and not to have had surgery[29]. However, as it was discussed, SEER database did not provide information about specific anatomic sites of distant metastasis at that time, so the detailed data for BM was not gettable in their analysis.

Furthermore, the optimal performance of multivariable logistic regression model in the entire cohort was authenticated by ROC analysis, in which the AUC value was 0.893. Besides, the nomogram established in this study is an efficient tool to help doctors decision-making owing to its user-friendly interface and optimal predictive ability. Nevertheless, we were not capable of figuring out the most common site for BM because there was no data documented in SEER database until now.

Prognostic factors for overall survival and cancer-specific survival of DTC patient with BM was analyzed using the multivariable Cox model. Results revealed that patients with multiple metastatic sites have higher hazard ratio for overall survival and cancer-specific survival, which was in coherence with previous studies[10, 30]. Meanwhile, significant decrease in the hazard ratio for overall survival and cancer-specific survival was found in patients with total thyroidectomy and radioisotopes radiation therapy. Surgery was the mainstay of therapy for thyroid cancer patients, especially in patients without distant metastasis[31]. Surgical options include thyroid total thyroidectomy or lobectomy, and it was still in controversy on how to choose optimal surgical procedure because of the difficulty in balancing surgical effect and complication[32]. Total thyroidectomy reduces recurrence and allows early detection of recurrence in the neck using ultrasonography compared with lobectomy, thereafter improving the prognosis compared with others. The most used radioisotope in DTC was radioiodine, but its using was still of wide divergence, partially due to the lack of evident prospective randomized controlled trials[33]. Patients with BM could

benefit from radioiodine in both suppressing the progression of tumor and reducing recurrence of primary carcinoma as we concluded. It was testified in some retrospective studies that application of radioiodine could improve survival of DTC patients[9, 34, 35] as well as BM patients[36]. Especially, radioiodine therapy was effective in the ablation of thyroid remnant after surgery[37]. External beam radiation therapy (EBRT) was not associated with positive outcomes in our analysis. Inversely, a retrospective study enrolled 74 BM patients has demonstrated that EBRT significantly increased survival[38]. Nevertheless, EBRT was reported to have acute toxicities such as esophageal stricture, so it was used under relatively strict indication[39]. Besides, combining radioiodine and external beam radiation therapy seems advantageous in some cases[40]. However, the treatment effect of total thyroidectomy and radioiodine in DTC patients with BM need to be further explored in the future study. Other factors did not exhibit prognostic value in our analysis, but their role has been demonstrated in other studies. Older age, higher T stage, positive lymph node, and black race were predictors of positive outcome[24, 25]. Further study is necessary to shed light on their prognostic value in BM.

Although this was a population-based study that enrolled largest cohort of DTC patients with BM, limitations in this study was unneglectable. Because it was a retrospective study based on current database record, some parameters were unavailable. Firstly, the further detailed information of BM like specific sites was not available in SEER database, which limited further analysis. Secondly, onset of BM during follow-up period was not presented and we only had information on synchronous metastasis, so the incidence may be underestimated. Thirdly, more detailed information about radiation or chemotherapy such as chemotherapy regimens, doses, and the specific number of cycles were not recorded in SEER database. Fourthly, except the survival, other outcomes such as complications of exposures or interventions were not reported. We could only assess the prognosis by survival data. Finally, data on specific metastatic sites including lung, bone, liver and brain was available in SEER database since 2010, leading to some inevitable bias. Therefore, more convincing clinical studies especially the randomized clinical trials were necessitated in the future.

In summary, results of this population-based study highlighted the incidence, predictors and prognostic factors of BM in newly diagnosed DTC patients. The age-adjusted incidence of BM in DTC was relatively stable during study period. Older age, male gender, black race, follicular histology, more advanced T staging, no surgery, radiation therapy, and chemotherapy were significant predictors for the presence BM in DTC patients. Thus, timely, and appropriate screenings for patients with these risk factors are recommended. Moreover, in DTC patients with BM, presence of total thyroidectomy and radioisotopes radiation therapy exhibited significant benefit on overall survival (OS) and cancer-specific survival (CSS) while multiple metastatic sites could serve as indicator of poor prognosis, which provided evidence for clinical practice.

List Of Abbreviations

DM: distant metastasis

DTC: differentiated thyroid carcinoma

BM: bone metastasis

SEER: Surveillance, Epidemiology, and End Results

ROC: receiver operating characteristic

APCC: average annual percentage change

AUC: value of area under curve

AJCC: American joint committee on cancer

APC: annual percentage change

OR: odds ratio

CI: confidence intervals

EBRT: external beam radiation therapy

OS: overall survival

CSS: cancer-specific survival

Declarations

Ethics approval and consent to participate

Not applicable

Consent to publication

Not applicable

Availability of data and materials

The datasets generated and/or analyzed during the current study are available in the [Surveillance, Epidemiology, and End Results (SEER)] repository, [seer.cancer.gov].

Competing interests

Zhihong Li and Chao Tu are members of the editorial board of BMC cancer. Other authors declare that they have no competing interests.

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Authors' contributions

LQ and WCZ conceived and designed the work. Material preparation, data collection and analysis were performed by LQ, WCZ, XLR, and CQL. The first draft of the manuscript was written by LQ and WCZ, and all authors commented on previous versions of the manuscript. CT and ZHL contributed to article drafting, critical revision and final approval of the version to be published. All authors read and approved the final manuscript.

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Figures

SEER*Stat Database: Incidence - SEER 18 Regs Custom Data
(2010-2016 varying)

Patients with newly
diagnosed thyroid
cancer (N=91975)

Excluded
1. Age <18 years old (N=1044);
2. Not the primary cancer (N=12427);
3. Diagnosis without positive histology
confirmation (N=2697);
4. Without specific information of TNM
system (N=4860);
5. Diagnosis without ICD-O-3 histology
code of DTC (N=3552);
6. Diagnosis with unknown bone and lung
metastases (N= 219);

Eligible patients with
newly diagnosed DTC
(N=67176)

Patients with DTC
diagnosed with BM.
(N=244)

Patients with DTC
diagnosed without BM.
(N=66932)

Exploring incidence of BM in patients with DTC

Univariable and multivariable logistic regression models

Development of nomogram for predictors

Univariable and multivariable Cox regression models

Kaplan-Meier curves and log-rank tests

Figure 1

Study design

Figure 2

Trends in annual incidence rates of DTC with different distant metastasis to specific sites

Figure 3

Nomogram for predictors of presence of BM in the patients with DTC

Figure 4

Kaplan-Meier survival curves presenting OS and CSS of in Patients with DTC diagnosed with BM. (A) OS between metastasis sites ≥ 2 and ≤ 1 . (B) OS in different surgery approaches. (C) OS in different radiation methods. (D) CSS between metastasis sites ≥ 2 and ≤ 1 . (E) CSS in different surgery approaches. (F) CSS in different radiation methods.

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