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Impact of distant metastasis on overall survival and cancer specific survival of elderly patients with differentiated thyroid cancer

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Distant metastases are common in most elderly patients, because elderly patients are diagnosed with advanced thyroid cancer due to delayed diagnosis. There is still few specific real-world data regarding prognosis in the elderly with differentiated thyroid cancer (DTC). The purpose of this study is to evaluate the prognostic factors and survival rate of elderly DTC patients with metastasis. This retrospective study included 14,603 elderly patients diagnosed with DTC from 2010 to 2015, including 447 patients with distant metastasis via the Surveillance, Epidemiology and End Results (SEER) database. The prognostic factors of overall survival (OS) and cancer-specific survival (CSS) in elderly DTC patients with metastasis or non-metastasis were determined by univariate and multivariate analysis. Age, primary site operation, radiotherapy, chemotherapy and tumor size are associated with OS and CSS in elderly DTC patients with distant metastasis. Compared with the patients without surgery, patients with total thyroidectomy showed significantly better OS. For the elderly DTC patients, radiotherapy was associated with improving OS and CSS. Chemotherapy increased the risk of death. For elderly DTC patients, early identification of distant metastasis, total thyroidectomy and radiotherapy are associated with better prognosis.

Keywords Differentiated thyroid carcinoma, Metastasis, Prognosis, Elderly, Surgery, Radiotherapy, Chemotherapy

Thyroid cancer (TC) is one of the most common endocrine tumors, and the prevalence of TC has gradually increased in recent years[1]. More than 90% of the cases with TC present as differentiated thyroid cancer (DTC), which included papillary and follicular subtypes. In general, DTC is associated with a good prognosis, only about 10-15% of DTC patients have distant metastasis or later, who have the worst survival prognosis[2,3]. It is important to note that age is an important factor affecting the prognosis of DTC, especially elderly DTC patients older than 60 years, the survival rate is significantly reduced. This may be due to the increased frequency of distant metastases in the elderly, its prognostic problems, advanced disease at diagnosis, and associated comorbidities[4,5]. Moreover, the delay in diagnosis as a potential etiology for distant metastases is more present in elderly, as often patients who were born younger would not have had widespread access to ultrasonography (given that this became more mainstream in the last 30–40 years) and would be less likely to have nodules/cancer appreciated on imaging performed for other reasons.

Furtherly, Distant metastasis of different sites and the treatment adopted all affect the survival rate of elderly DTC patients. In terms of metastatic sites, brain metastases are rare relative to lung metastases, but in the case of early detection, prognostic survival may be improved[6,7]. From the point of treatment, TC of distant metastases is usually palliative, with surgery and radioactive iodine therapy. In patients with low-risk DTC, both lobectomy and total thyroidectomy have similar oncologic outcomes in terms of recurrence-free and overall survival. Radioactive iodine (RAI) and active monitoring are also options[8]. Elderly DTC with metastases belong to the high-risk group, with tumors that are less iodine-addicted and have poor prognostic characteristics compared with those found in young adults. This may reduce the effect of radioactive iodine therapy in elderly patients with DTC[6,7].

At present, the research on DTC mainly focus on young patients, but there are few studies on elderly patients with DTC, especially those with metastasis. The 2015 ATA guidelines state that the prognosis of thyroid cancer with distant metastases depends on a variety of factors, including the patient's age at diagnosis, and

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that appropriate surgery and radiation therapy can significantly relieve disease symptoms. Chemotherapy has performed poorly in the treatment of thyroid cancer and may be effective in RAI-refractory DTC patients with metastasis. However, for the elderly, there are few studies on the impact of these interventions on survival[9]. A univariate analysis of prognostic factors for distant metastases in elderly patients with DTC found that type of pathology, extrathyroidal extension, site of distant metastases at initial diagnosis and radioiodine refractory-DTC status were associated with OS[10]. Another prognosis of patients with DTC with distant metastases was related to age, metastatic site, histology and iodine affinity[11]. Therefore, this study aimed to investigate the prognostic factors of DTC in the elderly, especially in patients with distant metastasis, and the impact of different treatments on OS and CSS in the elderly.

SEER database is a large public database, accounting for about 28% of the American population, providing clinical information about patient demographics, tumor morphology, diagnosis, treatment, and prognosis. Its huge patient population may be helpful to predict the prognosis of elderly DTC patients.

Materials and methods

This study is based on the SEER database (https://seer.cancer.gov/) (data are obtained from Incidence-SEER 18 Regs in SEER database, November 2019 (2000 to 2017 varying). Participants in the study are identified through the SEER database, so this study was determined to not constitute human subjects research on review by the Committee on Clinical Investigations at our institution, thus Institutional Review Board approval was not required. All procedures carried out in the study of human subjects are carried out by the Helsinki Declaration of 1964 and its subsequent amendments or similar ethical standards.

The inclusion criteria of this study: (1) primary DTC; (2) diagnosed between 2010 and 2015; 3, the age is not less than 60 years old, exclusion criteria: (1) patients with other tumors; (2) patients with unknown race, marital status, survival time, metastatic sites, and surgical methods. A total of 19,208 DTC patients were included in this study according to the inclusion and exclusion criteria. Clinical features in the analysis included age, sex, race, marital status, histological type, TNM stage, operation status, radiotherapy status, chemotherapy status, tumor size, and survival time. Variables were classified variables to redefine them: age (60-79years, 80+), gender (Male, Female), race (White, Black, Asian or Pacific Islander, American Indian/Alaska Native), marital status (Married, Others), histological type (FTC and PTC), T stage (T0, T1, T2, T3, T4, TX). N stage (N0, N1, NX), M stage (M0, M1, MX), primary site surgery (No surgery, Thyroidectomy surgery, Subtotal or near-total thyroidectomy, Total thyroidectomy), radiotherapy (None/Unknown, Radioisotopes, Other radiation) and chemotherapy (None/Unknown, Yes) (Table 1).

Clinical results

The main outcomes of the current study are OS and CSS of elderly patients with DTC, and the OS is defined as the time from diagnosis of DTC to death of any cause (including DTC). CSS is defined as the time from the date of DTC diagnosis to DTC death (SEER specific cause death classification). All the included patients were staged by the seventh edition AJCC TNM staging system.

Statistical analysis

The prognostic factors of OS and CSS in elderly DTC patients with metastasis or non-metastasis were determined by univariate and multivariate analysis. Kaplan-Meier(K-M) method is used to estimate OS and CSS, and the significance of the difference is evaluated by Log-rank test. R version 4.4.2 was used as the statistical analysis tool. P value < 0.05 means statistical significance.

Results

There were 14,603 elderly DTC patients in the study, including 13,446 patients under 80 years old and 1157 patients over 80 years old. The sample consisted of 4263 males and 10,340 females (Table 1). Among them, 447 cases (3.1%) suffered from distant metastasis, among which 98 cases (21.9%) had bone metastasis, 6 cases (1.3%) had brain metastasis, 6 cases (1.3%) had liver metastasis, 207 cases (46.3%) had lung metastasis s, 43 cases (9.6%) had other site metastasis, and 87 cases (19.5%) had multiple site metastasis.

Cox regression analysis showed that age, N stage, M stage, primary site operation, operation at other sites, radiotherapy, chemotherapy, tumor size, and marital status were independent risk factors for OS and CSS in elderly DTC patients (all $P < 0.05$) (Table 2). Age, primary site surgery, radiotherapy, race, and tumor size are independent risk factors for OS and CSS in elderly DTC patients with distant metastasis (Table 3).

For the elderly DTC patients with distant metastasis, we found that those aged 60–79 years showed better OS ($P < 0.001$, HR 1.78, 95% CI [1.28–2.46]) and CSS ($P = 0.03$, HR 1.50, 95% CI [1.04–2.19]) compared with those older than 80 years old. In terms of primary surgery, patients with total thyroidectomy ($P < 0.001$, HR 0.54, 95%CI [0.38–0.77]; $P = 0.01$, HR 0.57, 95%CI [0.38–0.86]) showed significantly better OS and CSS than those without surgery. It revealed that radioisotopes was associated with better OS and CSS ($P < 0.01$, HR 0.44, 95%CI [0.30–0.64]; $P < 0.001$, HR 0.43, 95%CI [0.28–0.67]). There was no significant difference in the effect of pathological classification on prognosis ($P = 0.84$, HR 1.03, 95%CI [0.75–1.42]; $P = 0.50$, HR 0.88, 95%CI [0.61–1.27]) (Table 2). The results of KM survival analysis suggested that the prognosis is better with total thyroidectomy than without surgery, patients treated with radiotherapy have better prognosis than those treated without radiotherapy, and chemotherapy was unfavorable for prognosis (Fig. 1).

The results of the survival comparison showed that compared with lung metastasis alone, lung-bone metastasis, lung-brain metastasis, and lung-multiple organ metastasis were statistically significant in OS and CSS. Compared with bone metastasis alone, bone-lung metastasis and bone-multi-site metastasis were statistically significant in OS and CSS. Compared with multi-site metastasis, Bone metastasis, brain metastasis,

Variable	Metastasis from thyroid cancer		
	Yes(*n*) (*n* = 447),n(%)	No (*n* = 14156),n(%)	All (*n* = 14603),n(%)
Age			
60–79 years	364 (81.4%)	13,082 (92.4%)	13,446 (92.1%)
≥ 80 years	83 (18.6%)	1074 (7.6%)	1157 (7.9%)
Classification			
PTC	307 (68.7%)	12,908 (91.2%)	13,215 (90.5%)
FTC	140 (31.3%)	1248 (8.8%)	1388 (9.5%)
Sex			
Male	191 (42.7%)	4072 (28.8%)	4263 (29.2%)
Female	256 (57.3%)	10,084 (71.2%)	10,340 (70.8%)
T stage			
T0	9 (2.0%)	17 (0.1%)	26 (0.2%)
T1	45 (10.1%)	8277 (58.5%)	8322 (57.0%)
T2	47 (10.5%)	1936 (13.7%)	1983 (13.6%)
T3	119 (26.6%)	2998 (21.2%)	3117 (21.3%)
T4	154 (34.5%)	623 (4.4%)	777 (5.3%)
TX	73 (16.3%)	305 (2.2%)	378 (2.6%)
N stage			
N0	201 (45.0%)	11,766 (83.1%)	11,967 (81.9%)
N1	192 (43.0%)	2230 (15.8%)	2422 (16.6%)
NX	54 (12.1%)	160 (1.1%)	214 (1.5%)
M stage			
M0	0	14,156(100.0%)	9373 (64.2%)
M1	447(100.0%)	0	5230 (35.8%)
Surgery of the primary			
No	135 (30.2%)	359 (2.5%)	494 (3.4%)
Thyroidectomy	30 (6.7%)	2281 (16.1%)	2311 (15.8%)
Subtotal or near total thyroidectomy	15 (3.4%)	339 (2.4%)	354 (2.4%)
Total thyroidectomy	267 (59.7%)	11,177 (79.0%)	11,444 (78.4%)
Surgery of other regional disease			
No/unknown	354 (79.2%)	13,957 (98.6%)	14,311 (98.0%)
Yes	93 (20.8%)	199 (1.4%)	292 (2.0%)
Radiation			
None/Unknown	143 (32.0%)	8250 (58.3%)	8393 (57.5%)
Radioisotopes	175 (39.1%)	5618 (39.7%)	5793 (39.7%)
Other radiation	129 (28.9%)	288 (2.0%)	417 (2.9%)
Chemotherapy			
None/Unknown	402 (89.9%)	14,100 (99.6%)	14,502 (99.3%)
Yes	45 (10.1%)	56 (0.4%)	101 (0.7%)
Tumor size			
≤ 1 cm	37 (8.3%)	5866 (41.4%)	5903 (40.4%)
> 1 and ≤ 2 cm	58 (13.0%)	3487 (24.6%)	3545 (24.3%)
> 2 and ≤ 4 cm	114 (25.5%)	2845 (20.1%)	2959 (20.3%)
> 4 cm	152 (34.0%)	1539 (10.9%)	1691 (11.6%)
Unknown	86 (19.2%)	419 (3.0%)	505 (3.5%)
Marital status			
Married	238 (53.2%)	9135 (64.5%)	9373 (64.2%)
Others	209 (46.8%)	5021 (35.5%)	5230 (35.8%)
Race			
White	325 (72.7%)	11,649 (82.3%)	11,974 (82.0%)
Black	43 (9.6%)	1008 (7.1%)	1051 (7.2%)
Asian or Pacific Islander	75 (16.8%)	1418 (10.0%)	1493 (10.2%)
American Indian/Alaska Native	4 (0.9%)	81 (0.6%)	85 (0.6%)

Table 1. Basic characteristics of all included patients. Note: Others: Divorced, Separated, Single (never married), Unknown, Unmarried or Domestic Partner, Widowed.

Variable	Differentiated thyroid carcinoma			
	Overall survival		Thyroid cancer-specific survival	
	Hazard ratio(95%CI)	*p*	Hazard ratio (95%CI)	*p*
Age				
60–79 years	1(Reference)	N/A	1(Reference)	N/A
≥ 80 years	3.23 (2.87, 3.65)	< 0.001	2.33 (1.90, 2.87)	< 0.001
Classification				
PTC	1(Reference)	N/A	1(Reference)	N/A
FTC	0.96 (0.82, 1.13)	0.62	1.08 (0.84, 1.39)	0.554
Sex				
Male	1(Reference)	N/A	1(Reference)	N/A
Female	0.63 (0.57, 0.71)	< 0.001	0.83 (0.69, 1.01)	0.06
T stage				
T0	1(Reference)	N/A	1(Reference)	N/A
T1	0.98 (0.40, 2.40)	0.96	0.50 (0.07, 3.67)	0.49
T2	0.96 (0.38, 2.45)	0.93	1.17 (0.15, 9.10)	0.88
T3	1.09 (0.44, 2.71)	0.86	1.89 (0.25, 14.23)	0.54
T4	2.65 (1.06, 6.60)	0.04	6.20 (0.82, 46.58)	0.08
TX	0.84 (0.33, 2.15)	0.71	1.27 (0.16, 9.85)	0.82
N stage				
N0	1(Reference)	N/A	1(Reference)	N/A
N1	1.57 (1.37, 1.79)	< 0.001	2.29 (1.86, 2.83)	< 0.001
NX	1.65 (1.27, 2.14)	< 0.001	1.83 (1.24, 2.69)	0.00
M stage				
M0	1(Reference)	N/A	1(Reference)	N/A
M1	2.41 (2.01, 2.88)	< 0.001	3.60 (2.85, 4.54)	< 0.001
Surgery of the primary				
No	1(Reference)	N/A	1(Reference)	N/A
Thyroidectomy	0.41 (0.33, 0.51)	< 0.001	0.45 (0.31, 0.65)	< 0.001
Subtotal or near total thyroidectomy	0.49 (0.35, 0.68)	< 0.001	0.84 (0.52, 1.36)	0.48
Total thyroidectomy	0.37 (0.30, 0.44)	< 0.001	0.39 (0.30, 0.51)	< 0.001
Surgery of other regional disease				
No/unknown	1(Reference)	N/A	1(Reference)	N/A
Yes	1.32 (1.04, 1.67)	0.02	1.58 (1.17, 2.14)	0.00
Race				
White	1(Reference)	N/A	1(Reference)	N/A
Black	1.23 (1.02, 1.48)	0.03	0.76 (0.51, 1.13)	0.17
Asian or Pacific Islander	0.78 (0.65, 0.92)	0.00	1.01 (0.78, 1.31)	0.93
American Indian/ Alaska Native	1.53 (0.88, 2.65)	0.13	2.00 (0.82, 4.86)	0.13
Radiation				
None/Unknown	1(Reference)	N/A	1(Reference)	N/A
Radioisotopes	0.58 (0.51, 0.65)	< 0.001	0.58 (0.46, 0.73)	< 0.001
Other radiation	1.03 (0.84, 1.26)	0.76	1.21 (0.93, 1.56)	0.16
Chemotherapy				
None/Unknown	1(Reference)	N/A	1(Reference)	N/A
Yes	1.83 (1.39, 2.40)	< 0.001	1.97 (1.43, 2.71)	< 0.001
Tumor size				
≤ 1 cm	1(Reference)	N/A	1(Reference)	N/A
> 1 and ≤ 2 cm	1.22 (1.03, 1.44)	0.02	1.23 (0.79, 1.91)	0.37
> 2 and ≤ 4 cm	1.59 (1.23, 2.06)	< 0.001	1.62 (0.99, 2.63)	0.05
> 4 cm	2.06 (1.62, 2.61)	< 0.001	2.27 (1.43, 3.59)	< 0.001
Unknown	2.26 (1.67, 3.07)	< 0.001	3.46 (2.04, 5.86)	< 0.001
Marital status				
Married	1(Reference)	N/A	1(Reference)	N/A
Others	1.31 (1.17, 1.45)	< 0.001	1.33 (1.10, 1.60)	0.00

Table 2. Multivariate analysis for overall survival and cancer–specific survival for total elderly differentiated thyroid cancer. Note: NA: not available; Others: Divorced, Separated, Single (never married), Unknown, Unmarried or Domestic Partner, Widowed.

liver metastasis and other site metastasis had statistical significance in OS and CSS (Fig. 2; Tables 1, 2, 3, 4, 5 and 6 in the supplement).

Discussion

TC is the most common endocrine malignant tumor, and DTC is the most common thyroid cancer. DTC originates from thyroid follicular epithelial cells, accounting for the majority of thyroid malignant tumors (> 90%), DTC has a relatively good prognosis and a high 5-year disease-specific survival rate. Only a small number of patients shows invasion and have distant metastasis, while the 5-year CSS of DTC patients with distant metastasis was lower[12–14]. DTC patients with metastasis progress rapidly, and it is easy to cause death in the absence of effective treatment[15]. Many studies have shown that age is a risk factor related to prognosis. Correlation meta-analysis showed that the OS of thyroid cancer patients over 60 years old was lower than that of young patients[2]. Although distant metastasis is not common in DTC patients, the elderly are prone to distant metastasis and a higher incidence of large tumors, which hurts the survival rate[2,4,12]. The survival rate of DTC patients with metastasis varies greatly. Age, treatment and tumor size, and so on can affect the prognosis of patients[3].

Elderly DTC patients with distant metastasis are classified as IVB stage. These patients show more aggressive behavior and their 5-year survival rate decreases. About 10% of DTC patients have distant metastasis, mainly lung and bone metastasis, and less than 5% of them are involved in other organs, such as liver, brain and skin[15–19]. Due to the limited knowledge of diseases, fear of treatment and pessimism about unknown life span, some elderly people have not taken active treatment measures. Nowadays, the elderly population is gradually increasing, and many countries have entered an aging society. More attention should be paid to the treatment of the elderly DTC population[20]. Elderly DTC patients should further consider the influence of patients' age and life expectancy when making disease diagnosis and treatment decisions, to determine a more suitable treatment plan for elderly patients[21].

For papillary thyroid carcinoma, active monitoring, surgical treatment or thermal ablation can be performed. Surgery is still the first choice for patients with DTC, if it can be cured by surgery. While elderly DTC patients with distant metastasis need to consider surgery, radiotherapy and other options[18,22]. Population-based research suggests that for elderly DTC patients, the risk of death without surgical treatment is higher than those with surgical treatment[2]. For patients with DTC, postoperative thyrotropin suppression therapy is currently recommended. Inhibitor doses of levothyroxine can be used to inhibit the progression of metastatic thyroid cancer as well as to reduce the recurrence rate in patients treated with surgery or radioiodine[23]. High-risk group of patients with TC are more suitable for total thyroidectomy, supplemented by RAI after surgery[2]. For DTC patients with bone metastasis, such as cervical metastasis, surgical intervention is related to a good prognosis[24]. For patients with brain metastases, surgery is also the first choice of treatment[3].

Common radiotherapy methods is RAI. In addition, External irradiation radiotherapy (EBRT) and stereotactic radiotherapy (SRT) are also treatments[24]. RAI is suitable for metastatic patients who absorb iodine but are not suitable for surgical resection, mostly for patients with lung metastasis and bone metastasis[25]. In RAI-compatible metastatic diseases, RAI is still the first choice, which is beneficial to the OS[26].RAI is the first-line treatment for metastatic DTC, although bone metastases are usually radioiodine-resistant[19]. For patients with refractory DTC who are not suitable for surgery, EBRT can be considered. EBRT and SRT are mostly used in patients with bone metastasis at present[24,27]. The local tumor control effect of SRT is similar to surgical resection, which can realize effective local disease control, especially for DTC patients with single metastasis[19]. A systematic review by Fussey et al. confirmed that EBRT improved local area control in elderly patients with high-risk characteristics[28]. Chemotherapy is to inject chemical components into the blood, and the chemical components move with the blood all over the body to find and destroy cancer cells. The results of this study suggest that the prognosis of patients with chemotherapy is worse than that without chemotherapy. The overall deterioration in general condition caused by applying chemotherapy to elderly patients may actually be harmful to patients with papillary thyroid cancer with distant metastases. Chemotherapy is rarely used to treat patients with metastatic DTC because of its toxicity and lack of efficacy, and the side effects caused by cytotoxicity are more pronounced, especially in the elderly[15,29,30]. Molecularly targeted drugs have attracted attention in the treatment of radioiodine-resistant differentiated thyroid cancer (RAIR-DTC). Multi-kinase inhibitors (MKI) may affect the quality of life, so the risk-benefit ratio should be fully evaluated[31]. Sorafenib and lenvatinib are MKIs approved for the treatment of patients with radioiodine-refractory differentiated thyroid cancer (RR-DTC)[25,26,32]. Sorafenib has been reported as a neoadjuvant therapy that may reduce tumor volume sufficiently for further thyroidectomy and RAI. In clinical trials, sorafenib was able to extend the median progression-free survival of patients by 5 months. And lenvatinib improved median progression-free survival by 14.7 months in a related study[17]. Sorafenib and lenvatinib significantly improved progression-free survival and overall remission rates in patients with progressive RR-DTC, respectively[33].

Gender is an important risk factor for poor prognosis in elderly patients with DTC. Thyroid cancer is more prevalent in women[34], but the disease is more aggressive in male patients. It has been shown that male patients have worse OS and CSS than female patients[35,36]. However, for elderly DTC patients with distant metastasis,

	Metastases at diagnosis of differentiated thyroid carcinoma			
	Overall survival		Thyroid cancer-specific survival	
Variable	Hazard ratio(95%CI)	*p*	Hazard ratio (95%CI)	*p*
Age				
60–79 years	1(Reference)	N/A	1(Reference)	N/A
≥ 80 years	1.78 (1.28, 2.46)	< 0.001	1.50 (1.04, 2.19)	0.03
Classification				
PTC	1(Reference)	N/A	1(Reference)	N/A
FTC	1.03 (0.75, 1.42)	0.84	0.88 (0.61, 1.27)	0.50
Sex				
Male	1(Reference)	N/A	1(Reference)	N/A
Female	0.96 (0.71, 1.29)	0.79	1.01 (0.73, 1.41)	0.95
T stage				
T0	1(Reference)	N/A	1(Reference)	N/A
T1	1.56 (0.18, 13.41)	0.69	1.21 (0.14, 10.68)	0.87
T2	1.13 (0.12, 10.53)	0.92	1.05 (0.11, 10.29)	0.97
T3	1.73 (0.20, 14.98)	0.62	1.69 (0.19, 14.71)	0.63
T4	2.82 (0.33, 24.39)	0.35	2.36 (0.27, 20.63)	0.44
TX	1.40 (0.16, 12.62)	0.76	1.23 (0.13, 11.27)	0.85
N stage				
N0	1(Reference)	N/A	1(Reference)	N/A
N1	1.14 (0.83, 1.56)	0.41	1.11 (0.78, 1.57)	0.57
NX	1.13 (0.71, 1.80)	0.62	1.12 (0.66, 1.92)	0.67
Surgery of the primary				
No	1(Reference)	N/A	1(Reference)	N/A
Thyroidectomy	0.83 (0.48, 1.46)	0.52	1.10 (0.61, 1.98)	0.75
Subtotal or near total thyroidectomy	0.96 (0.44, 2.09)	0.92	1.22 (0.55, 2.71)	0.63
Total thyroidectomy	0.54 (0.38, 0.77)	< 0.001	0.57 (0.38, 0.86)	0.01
Surgery of other regional disease				
No/unknown	1(Reference)	N/A	1(Reference)	N/A
Yes	0.98 (0.69, 1.39)	0.89	0.94 (0.63, 1.41)	0.78
Race				
White	1(Reference)	N/A	1(Reference)	N/A
Black	0.55 (0.32, 0.93)	0.03	0.39 (0.21, 0.75)	0.00
Asian or Pacific Islander	0.64 (0.43, 0.94)	0.02	0.64 (0.41, 1.01)	0.06
American Indian/ Alaska Native	4.86 (1.46, 16.17)	0.01	3.56 (0.83, 15.35)	0.09
Radiation				
None/Unknown	1(Reference)	N/A	1(Reference)	N/A
Radioisotopes	0.44 (0.30, 0.64)	< 0.001	0.43 (0.28, 0.67)	< 0.001
Other radiation	1.00 (0.72, 1.40)	0.98	1.13 (0.78, 1.64)	0.51
Chemotherapy				
None/Unknown	1(Reference)	N/A	1(Reference)	N/A
Yes	1.22 (0.82, 1.82)	0.32	1.41 (0.92, 2.16)	0.12
Tumor size				
≤ 1 cm	1(Reference)	N/A	1(Reference)	N/A
> 1 and ≤ 2 cm	2.04 (0.87, 4.79)	0.10	1.65 (0.68, 4.02)	0.27
> 2 and ≤ 4 cm	1.91 (0.79, 4.61)	0.15	1.30 (0.52, 3.24)	0.57
> 4 cm	1.99 (0.85, 4.63)	0.11	1.66 (0.71, 3.92)	0.24
Unknown	2.97 (1.19, 7.42)	0.02	2.66 (1.04, 6.79)	0.04
Marital status				
Married	1(Reference)	N/A	1(Reference)	N/A
Others	1.06 (0.79, 1.42)	0.69	1.13 (0.82, 1.58)	0.45

Table 3. Multivariate analysis for overall survival and cancer–specific survival for elderly differentiated thyroid cancer with distant metastasis. Note: NA: not available; Others, Divorced, Separated, Single (never married), Unknown, Unmarried or Domestic Partner, Widowed.

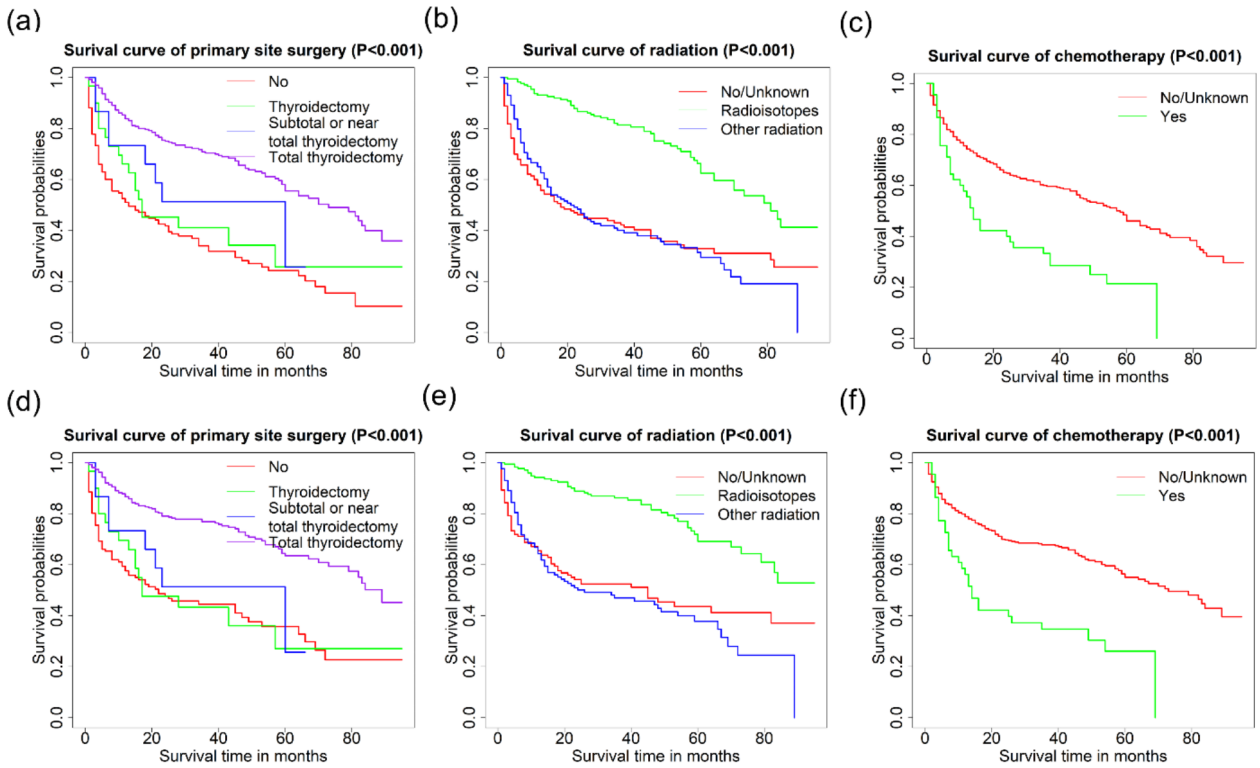

Fig. 1. Kaplan-Meier Survival Curves of Elderly Patients with DTC Metastases Treated with Surgery or Chemotherapy or Radiotherapy. Kaplan–Meier curves of overall survival (**a**) and thyroid cancer-specific survival (**d**) according to whether or not surgery of primary site; Overall survival (**b**) and thyroid cancer-specific survival (**e**) for elderly DTC patients with distant metastasis with or without radiotherapy; Kaplan–Meier curves of overall survival (**c**) and thyroid cancer-specific survival (**f**) according to whether or not chemotherapy.

the prognosis between men and women is not statistically significant. Sex is not an independent risk factor in the distant metastatic population, but there is no information about tumor molecular characteristics in SEER database, and more research is needed to verify this result in the future.

In all age groups, studies have shown that the overall prognosis of bone metastasis caused by DTC is worse than that of lung metastasis[24]. The results of our KM survival curve show that there is no significant difference in the prognosis of single-site metastasis (lung, bone, brain and liver) in elderly DTC patients, and the prognosis of single site metastasis is significantly different from that of multiple site metastasis. The low incidence and small sample of liver and brain metastasis may also be the reasons that lead to no significant difference in the prognosis with lung and bone metastasis. Early identification of distant metastatic sites is helpful to good prognosis.

There are some limitations in the current research. First of all, SEER database lacks factors that may affect the prognosis of elderly DTC patients, such as drinking, BMI and smoking. Secondly, this study is retrospective, and there may be selection bias. Finally, there are some inherent limitations in SEER database, including the lack of information about some key prognostic factors and complications, such as the scope of surgery, radioactive iodine dose, selective or multi-kinase inhibitors and thermal ablation, it may lead to biased results. Prospective research is needed in the future to further verify the conclusion.

The elderly are a vulnerable group, and elderly DTC patients with metastasis need our attention. In the elderly, surgery and radiation therapy correlate with a good prognosis, and there is insufficient evidence for chemotherapy in patients with DTC with metastases. Defining their risk factors and the influence of treatment measures on survival can provide the basis for clinical decision-making.

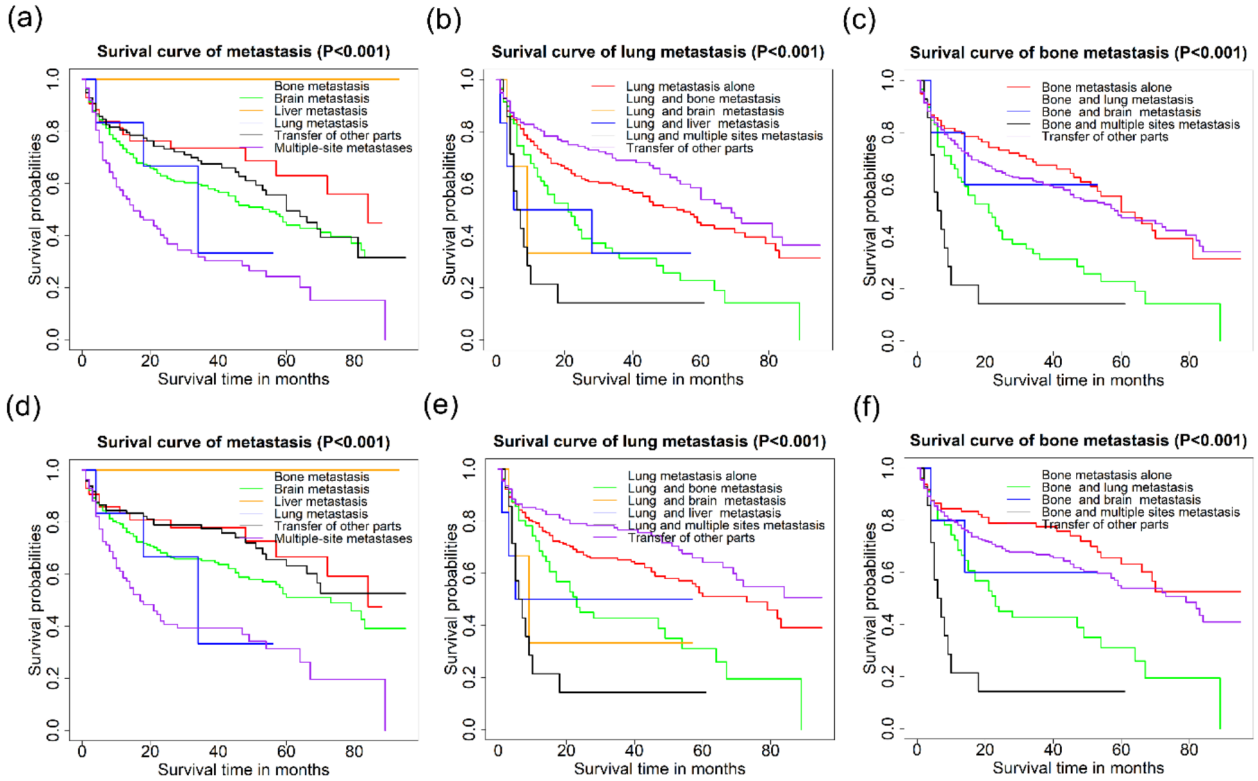

Fig. 2. Kaplan–Meier Curve of Elderly Patients with DTC Metastases according to The Site of Metastasis. Kaplan–Meier curve of overall survival (**a**, **b**, **c**) and thyroid cancer-specific survival (**d**, **e**, **f**) according to the site of metastasis (isolated metastasis versus multiple-site metastases; isolated lung metastasis versus metastasis of ≥ 2 sites (including lung); isolated bone metastasis versus metastasis of ≥ 2 sites (including bone)).

Data availability

The datasets generated and analysed during the current study are available in the SEER*Stat repository, at https://seer.cancer.gov/seerstat/.

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Author contributions

Shuqian Chen and Gang Chen designed the study; Shuqian Chen acquired data; Shuqian Chen wrote the manuscript; Shuqian Chen , Lizhen Xu and Shuyao Pan analyzed the clinical data; Gang Chen revised the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

Participants in the study are identified through the SEER database, so this study was determined to not constitute human subjects research on review by the Committee on Clinical Investigations at our institution, thus Institutional Review Board approval was not required. All procedures carried out in the study of human subjects are carried out by the Helsinki Declaration of 1964 and its subsequent amendments or similar ethical standards.

Additional information

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