Age Increased Cancer-specific Mortality Risk of Thyroid Cancer With Lung Metastasis

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Research

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Abstract

Background: To investigate the relationship between age and cancer-specific mortality in thyroid cancer (TC) with lung-metastasis.

Methods: 1,418 patients with initial distant metastases from Surveillance, Epidemiology and End Results databases were investigated. Patients with median follow-up time of 8 months [interquartile range (IQR), 2–27] and median age of 66 years (IQR, 55-76) were divided into five groups by age and the association between age and TC-specific mortality was analyzed.

Results: The TC-specific mortality rates were 32.78% (118/360), 46.71% (156/334), 53.93% (199/369), 58.96% (158/268) and 82.76% (72/87) for patients with age of ≤55 years,56-65 years, 66-75 years, 76-85 years and >85 years. Kaplan-Meier curves showed that TC-specific mortality rate was associated with increased age ($p < 0.001$). Compared with patients ≤55 years, patients of 56-65 years, 66-75 years, 76-85 years and >85 years had significantly higher hazard ratios (HRs) of 1.69(1.26-2.26), 1.97 (1.47-2.64), 2.18(1.59-2.99) and 3.24(2.08-5.06) after adjustments for gender, tumor size and radiation therapy (all $p < 0.001$).

In TC with initial lung-metastasis, compared with patients ≤55 years, patients of 56-65 years, 66-75 years, 76-85 years and >85 years had significantly higher adjusted HRs of 1.68(1.20-2.36, p=0.003), 2.18(1.57-3.02), 2.16(1.51-3.08) and 2.91(1.79-4.75) ($p < 0.001$). Similar results could be obtained in papillary thyroid cancer.

Conclusions: The TC-specific mortality increased with age in TC patients with initial lung-metastasis, which suggested that further risk stratification based on age was necessary for TC over 55 years with lung-metastasis. Individual treatment strategy maybe recommended for patients over 85 years.

Background

Thyroid cancer (TC) is one of the most common endocrine tumors, and its incidence has been increasing in the past four decades(1). At present, its incidence is rising the second fasted among solid tumors and it has become the sixth most common malignancy in female population in the United States(2, 3). TC is divided into two categories according to the cell origin, one arising from endoderm-derived follicular cells, and the other arising from the neural crest-derived C-cells(4). The former category includes differentiated thyroid cancer (DTC) [papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), and poorly differentiated TC], and anaplastic thyroid cancer (ATC), while the latter category is known as medullary thyroid cancer (MTC)(4). DTC accounts for approximately 90% of all thyroid cancer types.(4, 5)

Clinical character of DTC is usually indolent, while ATC is the most aggressive variant, accounting for about 40% of all deaths from TC(5, 6). The most common metastatic site of TC is lung(7), followed by bone, and occasionally brain and liver(8, 9). DTC is a unique malignancy in which age at diagnosis can be an independent risk factor for prognosis(10, 11). In 2016, the American Joint Committee on Cancer (AJCC) released eighth edition of the AJCC/TNM cancer staging manual, and changed the age cutoff from 45 years to 55 years for the DTC prognostic staging system(12). Several studies have shown that age over 55 years is an important factor for metastasis and prognosis of DTC(13), also for the effect of radioactive iodine (RAI) therapy(14).

However, in TC patients with distant metastases who were over 55 years, there is no further risk stratification of age to clarify its impact on TC-specific mortality. The purpose of our research was to investigate the relationship between age and prognosis in TC patients who were over 55 years with lung metastasis at diagnosis, and to identify more precise risk stratification for this term of patients, offering personalized treatment therapy for optimal response.

Methods

Data source and study subjects

We retrieved data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database for a retrospective study(15). A total of 1,418 TC patients from year of 2010–2017 with distant metastases at diagnosis were investigated. Demographic data included race (white, black, other, and unknown), sex, SEER cause-specific death classification, survival months, age at diagnosis. The cancer characteristics included histology [defined by International Classification of Disease for Oncology-3 (ICD-O-3)], TNM stage (classified according to the 7th AJCC staging system), tumor size and distant metastases. Radiotherapy information was categorized as radiation beam or radioactive implants, radioisotopes or radiation beam plus isotopes or implants, none or refused, and unknown(16). Patients were divided into 5 groups based on age: ≤55 years, 56–65 years, 66–75 years, 76–85 years and over 85 years. The relationship between age and TC-specific mortality was analyzed.

All data were obtained from the SEER public database. We had received official permission for accessing these data for non-commercial use. Therefore, this study was exempted from review by the ethics committee of Shanghai Tenth People's Hospital.

Statistical analysis

Patient characteristics were statistically described. Differences in TC-specific survival time were compared among patients of different groups using Kaplan-Meier analysis and the log-rank test. The impacts of age on TC-specific survival were assessed by Cox proportional hazards regression and presented as hazard ratios (HRs) with 95% confidence intervals (CIs). A two-tailed p value < 0.05 was considered to be statistically significant. All data were analyzed using the Statistical Package for Social Science version 25 (SPSS, Inc., New York, NY, USA).

Results

Demographic and clinical characteristics

The demographic and clinical characteristics of 1,418 TC patients (645 males and 773 females) with initial distant metastases were displayed in Table 1. The median follow-up time was 8 months [interquartile range (IQR), 2–27]. PTC, FTC, MTC and ATC accounted for 43.51% (617/1418), 15.73% (223/1418), 7.19% (102/1418) and 19.25% (273/1418). Patients were divided into 5 groups: ≤55 years (25.39%, 360/1418), 56–65 years (23.55%, 334/1418), 66–75 years (26.02%, 369/1418), 76–85 years (18.90%, 268/1418), > 85 years (6.14%, 87/1418). In addition, 1,034 patients with initial lung metastasis accounted for 72.92% (1,034/ 1,418) and were further analyzed alone (Table 1). The overall TC-specific mortality rate was 49.58% (703/1418). Patients over 85 years had highest TC-specific mortality rate of (72/87), followed by patients of 76–85 years (58.96%, 158/268), 66–75 years (53.93%, 199/369), 56–65 years (46.71%, 156/334) and ≤ 55 years (32.78%, 118/360).

Table 1
The clinical characteristics of thyroid cancer with distant metastases (SEER database years of 2010–2017)

Characteristics		Overall		≤ 55 years		56–65 years		66–75 years		76–85 years		> 85 years	
Number		1418		360		334		369		268		87	
		N	%	N	%	N	%	N	%	N	%	N	%
Gender	Male	645	45.49	173	48.06	177	52.99	158	42.82	116	43.28	21	24.14
	Female	773	54.51	187	51.94	157	47.01	211	57.18	152	56.72	66	75.86
Race	White	1043	73.55	283	78.61	237	70.96	262	71.00	197	73.51	64	73.56
	Black	155	10.93	32	8.89	45	13.47	42	11.38	24	8.96	12	13.79
	Others	5	0.35	43	11.94	51	15.27	65	17.62	45	16.79	11	12.64
	Unknown	215	15.16	2	0.56	1	0.30	0	0	2	0.75	0	0
Lymph node stage	N0	396	27.93	72	20.00	93	27.84	113	30.62	97	36.19	21	24.14
	N1a	116	8.18	33	9.17	24	7.19	27	7.32	20	7.46	12	13.79
	N1b	432	30.47	142	39.44	114	34.13	104	28.18	51	19.03	21	24.14
	N1NOS	83	5.85	28	7.78	19	5.69	11	2.98	19	7.09	6	6.90
	NX	141	9.94	13	3.61	28	8.38	51	13.82	36	13.43	13	14.94
	Unknown	250	17.63	72	20.00	56	16.77	63	17.07	45	16.79	14	16.09
Extrathyroidal extension	Lung	1034	72.92	253	70.28	222	66.47	283	76.69	207	77.24	69	79.31
	Bone	543	38.29	134	37.22	156	46.71	143	38.75	85	31.72	25	28.74
	Brain	88	6.21	26	7.22	25	7.49	16	4.34	18	6.72	3	3.45
	Liver	160	11.28	40	11.11	38	11.38	40	10.84	36	13.43	6	6.90
Thyroid cancer specific mortality	Alive	715	50.42	242	67.22	178	53.29	170	46.07	110	41.04	15	17.24
	Death	703	49.58	118	32.78	156	46.71	199	53.93	158	58.96	72	82.76
Histology subtype	PTC	617	43.51	208	57.78	145	43.41	152	41.19	95	35.45	17	19.54
	FTC	223	15.73	36	10.00	53	15.87	73	19.78	48	17.91	13	14.94
	MTC	102	7.19	36	10.00	40	11.98	11	2.98	13	4.85	2	2.30
	ATC	273	19.25	51	14.17	61	18.26	82	22.22	56	20.90	23	26.44
	Others	203	14.32	29	8.06	35	10.48	51	13.82	56	20.90	32	36.78

PTC, papillary thyroid cancer; FTC, follicular thyroid cancer; MTC, medullary thyroid cancer; ATC, anaplastic thyroid cancer; Others, other variants of thyroid cancer. According to the American Joint Committee on Cancer (AJCC) Staging Manual 7th Edition, lymph node category was classified into 5 groups as follows: no regional lymph node metastasis (N0); metastases to level VI [pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes] (N1a); metastasis to unilateral, bilateral, or contralateral cervical [Levels[illegible] or [illegible]] or retropharyngeal or superior mediastinal lymph nodes [Level [illegible]] (N1b); metastasis to regional lymph nodes but not otherwise specified (N1NOS); and regional lymph nodes cannot be assessed (NX).

Characteristics		Overall		≤ 55 years		56–65 years		66–75 years		76–85 years		> 85 years	
Thyroid cancer specific mortality	TC	703	49.58	118	32.78	156	46.71	199	53.93	158	58.96	72	82.76
	PTC	184	12.98	31	8.61	45	13.47	61	16.53	35	13.06	12	13.79
	FTC	74	5.22	10	2.78	13	3.89	25	6.78	16	5.97	10	11.49
	MTC	50	3.53	15	4.17	22	6.59	2	0.54	9	3.36	2	2.30
	ATC	246	17.35	46	12.78	52	15.57	75	20.33	51	19.03	22	25.29
	Others	149	10.51	16	4.44	24	7.19	36	9.76	47	17.54	26	28.89
Radiation therapy													
Radiation Beam or Radioactive implants		425	29.97	105	29.17	113	33.83	121	32.79	64	23.88	22	25.29
Radioisotopes or Radiation beam plus isotopes or implants		405	28.56	149	41.39	96	28.74	98	26.56	58	21.64	4	4.60
None or refused		552	38.93	97	26.94	118	35.33	136	36.86	140	52.24	61	70.11
Unknown		36	2.54	9	2.50	7	2.10	14	3.79	6	2.24	0	0.00

PTC, papillary thyroid cancer; FTC, follicular thyroid cancer; MTC, medullary thyroid cancer; ATC, anaplastic thyroid cancer; Others, other variants of thyroid cancer. According to the American Joint Committee on Cancer (AJCC) Staging Manual 7th Edition, lymph node category was classified into 5 groups as follows: no regional lymph node metastasis (N0); metastases to level VI [pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes] (N1a); metastasis to unilateral, bilateral, or contralateral cervical [Levels□□□ □ or □] or retropharyngeal or superior mediastinal lymph nodes [Level □] (N1b); metastasis to regional lymph nodes but not otherwise specified (N1NOS); and regional lymph nodes cannot be assessed (NX).

The association between age and TC-specific mortality in patients with distant metastases at diagnosis

In TC patients with distant metastases, the overall TC-specific mortality rate was 49.58% (703/1418), specifically, with number of 82.76% (72/87), 58.96% (158/268), 53.93% (199/369), 46.71% (156/334) and 32.78% (118/360) for patients aged > 85 years, 76–85 years, 66–75 years, 56–65 years and ≤ 55 years, respectively. Compared with patients ≤ 55 years, the crude HRs for patients with age of 56–65 years, 66–75 years, 76–85 years and > 85 years were 1.61(1.27–2.05, $p < 0.001$), 1.96 (1.56–2.46, $p < 0.001$), 2.43(1.91–3.09, $p < 0.001$) and 4.99(3.69–6.76, $p < 0.001$) (Table 2). After adjustments for tumor size, gender and radioactive therapy, the HRs were 1.69 (1.26–2.26, $p < 0.001$), 1.97 (1.47–2.64, $p < 0.001$), 2.18 (1.59–2.99, $p < 0.001$) and 3.24 (2.08–5.06, $p < 0.001$) for patients with age of 56–65 years, 66–75 years, 76–85 years and > 85 years. Compared with patients of 56–65 years, 66–75 years and 76–85 years, patients of > 85 years had crude HRs of 3.17(2.38–4.22, $p < 0.001$), 2.42(1.84–3.19, $p < 0.001$) and 1.99(1.50–2.64, $p < 0.001$), respectively. However, after adjustments for tumor size, gender and radioactive therapy, the HR remained significant only compared with patients of 56–65 years [1.83(1.20–2.78), $p = 0.005$] (Table 3).

Table 2
The association between age and thyroid cancer-specific mortality in patients with distant metastases

Variants		Mortality	Unadjusted		Adjusted[a]	
		n/N (%)	HR (95%CI)	p	HR (95%CI)	p
TC		703/1418(49.58)				
Age	≤ 55 years	118/360(32.78)	Ref.			
	56–65 years	156/334(46.71)	1.61(1.27–2.05)	< 0.001	1.69(1.26–2.26)	< 0.001
	66–75 years	199/369(53.93)	1.96(1.56–2.46)	< 0.001	1.97(1.47–2.64)	< 0.001
	76–85 years	158/268(58.96)	2.43(1.91–3.09)	< 0.001	2.18(1.59–2.99)	< 0.001
	> 85 years	72/87(82.76)	4.99(3.69–6.76)	< 0.001	3.24(2.08–5.06)	< 0.001
PTC		184/617(29.82)				
Age	≤ 55 years	31/208(14.90)	Ref.			
	56–65 years	45/145(31.03)	2.22(1.41–3.51)	< 0.001	2.36(1.38–4.05)	< 0.001
	66–75 years	61/152(40.13)	2.97(1.93–4.58)	< 0.001	3.00(1.76–5.10)	< 0.001
	76–85 years	35/95(36.84)	3.28(2.00-5.37)	< 0.001	2.97(1.56–5.66)	0.001
	> 85 years	12/17(70.59)	6.72(3.42–13.19)	< 0.001	1.68(0.48–5.85)	0.416
FTC		74/223(33.18)				
Age	≤ 55 years	10/36(27.78)	Ref.			
	56–65 years	13/53(24.53)	1.15(0.50–2.65)	0.746	2.21(0.73–6.69)	0.159
	66–75 years	25/73(34.25)	1.43(0.68–2.08)	0.346	2.79(1.08–7.18)	0.034
	76–85 years	16/48(33.33)	1.49(0.67–3.30)	0.328	3.29(1.05–10.32)	0.041
	> 85 years	10/13(76.92)	6.55(2.46–17.44)	< 0.001	22.80(3.95-131.78)	< 0.001

TC, thyroid cancer; PTC, papillary thyroid cancer; FTC, follicular thyroid cancer; HRs, hazard ratios; CI, confidence interval; [a] Adjusted for gender, tumor size, and radiation therapy; SEER database years of 2010–2017.

Table 3
The association between age (> 55 years) and thyroid cancer-specific mortality in patients with distant metastases

Variants		Mortality	Unadjusted		Adjusted[a]	
		n/N (%)	HR (95%CI)	p	HR (95%CI)	p
TC		703/1418(49.58)				
Age	56–65 years	118/360(32.78)	Ref.			
	> 85 years	72/87(82.76)	3.17(2.38–4.22)	< 0.001	1.83(1.20–2.78)	0.005
	66–75 years	199/369(53.93)	Ref.			
	> 85 years	72/87(82.76)	2.42(1.84–3.19)	< 0.001	1.40(0.93–2.09)	0.104
	76–85 years	158/268(58.96)	Ref.			
	> 85 years	72/87(82.76)	1.99(1.50–2.64)	< 0.001	1.48(0.99–2.21)	0.058
PTC		184/617(29.82)				
Age	56–65 years	45/145(31.03)	Ref.			
	> 85 years	12/17(70.59)	3.11(1.63–5.90)	0.001	0.94(0.28–3.16)	0.913
	66–75 years	61/152(40.13)	Ref.			
	> 85 years	12/17(70.59)	2.11(1.13–3.93)	0.019	0.43(0.13–1.43)	0.168
	76–85 years	35/95(36.84)	Ref.			
	> 85 years	12/17(70.59)	2.16(1.12–4.17)	0.022	0.95(0.27–3.31)	0.933
FTC		74/223(33.18)				
Age	56–65 years	13/53(24.53)	Ref.			
	> 85 years	10/13(76.92)	5.16(2.21–12.08)	< 0.001	9.76(2.29–41.56)	0.002
	66–75 years	25/73(34.25)	Ref.			
	> 85 years	10/13(76.92)	4.91(2.28–10.55)	< 0.001	13.52(3.28–55.70)	< 0.001
	76–85 years	16/48(33.33)	Ref.			
	> 85 years	10/13(76.92)	4.21(1.85–9.59)	0.001	10.33(2.57–41.48)	0.001

TC, thyroid cancer; PTC, papillary thyroid cancer; FTC, follicular thyroid cancer; HRs, hazard ratios; CI, confidence interval; [a] Adjusted for gender, tumor size, and radiation therapy; SEER database years of 2010–2017.

In this cohort, lung was the most common site of metastasis, accounting for 72.92% (1,034/1,418). In these patients with lung metastasis, the overall TC-specific mortality rate was 55.03% (569/1034), with number of 85.51% (59/69), 62.32% (129/207), 60.78% (172/283), 54.05% (120/222) and 35.18% (89/253) for patients of > 85 years, 76–85 years, 66–75 years, 56–65 years and ≤ 55 years, respectively (Table 4). Compared with patients ≤ 55 years, the crude HRs for patients with age of 56–65 years, 66–75 years, 76–85 years and > 85 years were 1.75 (1.33–2.31, p < 0.001), 2.16 (1.67–2.80, p < 0.001), 2.45 (1.87–3.23, p < 0.001) and 4.96 (3.52–6.98, p < 0.001). After adjustments for tumor size, gender and radioactive therapy, the HRs were 1.68(1.20–2.36, p = 0.003), 2.18(1.57–3.02, p < 0.001), 2.16(1.51–3.08, p < 0.001) and 2.91(1.79–4.75, p < 0.001) for patients with age of 56–65 years, 66–75 years, 76–85 years and > 85 years. When compared with patients of 56–65 years, 66–75 years, and 76–85 years, patients of > 85 years had crude HRs of 2.94 (2.14–4.04, p < 0.001), 2.32 (1.72–3.14, p < 0.001) and 2.01(1.47–2.75, p < 0.001), respectively. After adjustments for tumor size, gender and radioactive therapy, the HR remained significant only compared with patients of 56–65 years [1.84(1.18–2.88), p = 0.007] (Table 5).

Table 4
The association between age and thyroid cancer-specific mortality in patients with lung metastasis

Variants		**Mortality**	**Unadjusted**		**Adjusted**[a]	
		n/N (%)	HR (95%CI)	p	HR (95%CI)	p
TC		569/1034(55.03)				
Age	≤ 55 years	89/253(35.18)	Ref.			
	56–65 years	120/222(54.05)	1.75(1.33–2.31)	< 0.001	1.68(1.20–2.36)	0.003
	66–75 years	172/283(60.78)	2.16(1.67–2.80)	< 0.001	2.18(1.57–3.02)	< 0.001
	76–85 years	129/207(62.32)	2.45(1.87–3.23)	< 0.001	2.16(1.51–3.08)	< 0.001
	> 85 years	59/69(85.51)	4.96(3.52–6.98)	< 0.001	2.91(1.79–4.75)	< 0.001
PTC		155/475(32.63)				
Age	≤ 55 years	25/161(15.53)	Ref.			
	56–65 years	36/104 (34.62)	2.35(1.41–3.92)	0.001	2.54(1.38–4.66)	0.003
	66–75 years	54/119(45.38)	3.34(2.08–5.38)	< 0.001	3.31(1.82–6.01)	< 0.001
	76–85 years	31/79(39.24)	3.37(1.96–5.79)	< 0.001	3.32(1.61–6.88)	0.001
	> 85 years	9/12(75.00)	6.81(3.15–14.70)	< 0.001	2.39(0.66–8.65)	0.183
FTC		52/117(44.44)				
Age	≤ 55 years	8/17(47.06)	Ref.			
	56–65 years	7/21(33.33)	0.86(0.31–2.38)	0.857	2.17(0.47–9.98)	0.321
	66–75 years	19/44(43.18)	1.08(0.47–2.50)	0.861	3.95(1.15–13.63)	0.030
	76–85 years	11/27(40.74)	1.18(0.45–3.12)	0.736	4.88(1.02–23.29)	0.047
	> 85 years	7/8(87.50)	3.46(1.20–9.96)	0.022	*	0.938

TC, thyroid cancer; PTC, papillary thyroid cancer; FTC, follicular thyroid cancer; HRs, hazard ratios; CI, confidence interval; [a] Adjusted for gender, tumor size, and radiation therapy; * due to the small sample size and relative high mortality in FTC patients of > 85 years, the HRs cannot be calculated; SEER database years of 2010–2017.

Table 5
The association between age (> 55 years) and thyroid cancer-specific mortality in patients with lung metastasis

Variants		Mortality	Unadjusted		Adjusted[a]	
		n/N (%)	HR (95%CI)	p	HR (95%CI)	p
TC		480/781(61.46)				
Age	56–65 years	120/222(54.05)	Ref.			
	> 85 years	59/69(85.51)	2.94(2.14–4.04)	< 0.001	1.84(1.18–2.88)	0.007
	66–75 years	172/283(60.78)	Ref.			
	> 85 years	59/69(85.51)	2.32(1.72–3.14)	< 0.001	1.22(0.79–1.88)	0.381
	76–85 years	129/207(62.32)	Ref.			
	> 85 years	59/69(85.51)	2.01(1.47–2.75)	< 0.001	1.44(0.92–2.24)	0.107
PTC		130/314(41.40)				
Age	56–65 years	36/104(34.62)	Ref.			
	> 85 years	9/12(75.00)	2.84(1.36–5.90)	0.005	1.03(0.30–3.51)	0.958
	66–75 years	54/119(45.38)	Ref.			
	> 85 years	9/12(75.00)	1.95(0.96–3.96)	0.064	0.68(0.20–2.29)	0.532
	76–85 years	31/79(39.24)	Ref.			
	> 85 years	9/12(75.00)	2.13(1.01–4.51)	0.047	1.18(0.33–4.24)	0.797
FTC		44/100(44.00)				
Age	56–65 years	7/21(33.33)	Ref.			
	> 85 years	7/8(87.50)	3.89(1.36–11.13)	0.011	23.14(2.18-245.47)	0.009
	66–75 years	19/44(43.18)	Ref.			
	> 85 years	7/8(87.50)	4.76(1.91–11.85)	0.001	2.72(0.38–19.77)	0.322
	76–85 years	11/27(40.74)	Ref.			
	> 85 years	7/8(87.50)	3.78(1.43–10.02)	0.007	8.71(1.76–43.22)	0.008

TC, thyroid cancer; PTC, papillary thyroid cancer; FTC, follicular thyroid cancer; HRs, hazard ratios; CI, confidence interval; [a] Adjusted for gender, tumor size, and radiation therapy; SEER database years of 2010–2017.

The association between age and PTC-specific mortality in patients with distant metastases at diagnosis

In PTC patients with initial distant metastases, the overall mortality rate was 29.82% (184/617), with number of 70.59% (12/17), 36.84% (35/95), 40.13% (61/152), 31.03% (45/145) and 14.90% (31/208) for patients of > 85 years, 76–85 years, 66–75 years, 56–65 years and ≤ 55 years, respectively (Table 2). Compared with patients ≤ 55 years, the crude HRs for patients of 56–65 years, 66–75 years, 76–85 years and > 85 years were 2.22(1.41–3.51, p < 0.001), 2.97(1.93–4.58, p < 0.001), 3.28(2.00-5.37, p < 0.001) and 6.72(3.42–13.19, p < 0.001) (Table 2). After adjustments for tumor size, gender and radioactive therapy, the HRs remained significant in patients aged 56–65 years [2.36(1.38–4.05), p < 0.001], 66–75 years [3.00 (1.76–5.10), p < 0.001] and 76–85 years [2.97(1.56–5.66), p = 0.001], but the HR of > 85 years group didn't reach significancy because small number of patients.

In PTC patients, lung was also the most common site of metastasis, accounting for 76.99% (475/617). In these patients with lung metastasis, the overall PTC-specific mortality rate was 32.63%(155/475), with number of 75.00% (9/12), 39.24% (31/79), 45.38%

(54/119), 34.62% (36/104), and 15.53% (15/161) for patients of > 85 years, 76–85 years, 66–75 years, 56–65 years and ≤ 55 years, respectively (Table 4). Compared with patients ≤ 55 years, the crude HRs for patients of 56–65 years, 66–75 years, 76–85 years, and > 85 years were 2.35(1.41–3.92, $p = 0.001$), 3.34(2.08–5.38, $p < 0.001$), 3.37(1.96–5.79, $p < 0.001$) and 6.81(3.15–14.70, $p < 0.001$) (Table 4). After adjustments for tumor size, gender and radioactive therapy, the HRs remained significant for patients of 56–65 years [2.54(1.38–4.66), $p = 0.003$], 66–75 years [3.31(1.82–6.01), $p < 0.001$] and 76–85 years [3.32(1.61–6.88), $p = 0.001$], but the HR of > 85 years group didn't reach significancy because small number of patients.

Kaplan-Meier analyses of TC-specific survival of TC patients with lung metastasis

In TC patients with distant metastases, TC-specific survival curves decreased significantly with the increase of age (Log Rank $p < 0.001$) (Fig. 1A), and the survival curve of patients over 85 years has an obvious decline with the worst prognosis. Similar results were observed in PTC (Fig. 1B) and FTC (Fig. 1C). There was no significant survival difference among all age groups in ATC patients (Fig. 1D).

In TC patients with lung metastasis, the TC-specific survival curves also decreased significantly as age of patients increased (Log Rank $p < 0.001$) (Fig. 2A). Similar results could be observed in PTC (Fig. 2B) and FTC (Fig. 2C), and the increased age had no significant impact on the survival of ATC patients (Fig. 2D). The survival curve of patients over 85 years showed a sharp decrease and similar trends could also be observed when we further divided patients in to 4 groups (71–75 years, 76–80 years, 81–85 years and > 85 years) **(Supplemental Fig. 1A, 1B and 1C)**. Still, increased age had no significant impact on survival of ATC patients **(Supplemental Fig. 1D).**

Discussion

In our study, we demonstrated that the TC-specific mortality rate was increased with age in patients with lung metastasis, especially for patients over 85 years. However, since ATC was the most aggressive subtype with the worst prognosis, age has no significant impact on ATC-specific mortality(17).TC was one of the most common endocrine tumors, and its variants had different prognosis due to various reasons(1, 17, 18). It was a special type of malignancy as age could be an important risk factor for prognosis(19). As early as 2009, previous study had pointed out that advanced age was related to poor prognosis(10). The eighth edition of the AJCC/TNM cancer staging manual changed the age cutoff from 45 years to 55 years for the DTC prognostic staging system(12). DTC patients who were over 55 years and developed distant metastases at diagnosis were considered to be in stage ⅣB(12), and had the worst prognosis.

Ito Y et al found that age over 55 years was an independent risk factor for lung recurrence in a group of PTC without initial distant metastasis and was also the strongest predictor for cancer-related death by a 10 years follow-up.(13). Another study also found that in DTC patients with lung metastasis, age over 45 years was an independent risk factor for disease progression(20). Sabra MM et al. conducted a retrospective study on 199 consecutive patients with follicular cell–derived TC and confirmed that cancer-related progression-free survival was shorter in patients with age over > 45 years(21). In addition, a 5-year study including 54 patients with DTC-related pulmonary disease indicated that age over 45 years and tumor dedifferentiation was independent risk factor for shorter cancer-specific survival(22). However, nearly none of previous studies had stratified by age and investigated the prognostic value of age in TC patients with distant metastases.

Our study selected TC patients with distant metastases at diagnosis from SEER database, and further stratified the risk for patients over 55 years based on their age. Our results showed that even in patients with the worst prognosis in the TNM staging system (age over 55 years with distant metastases), age still had a great impact on the prognosis of such patients, especially for patients over 85 years.

The reason why TC patients with distant metastases at diagnosis had a strongly age-dependent survival rate may be explained as follows: firstly, TC patients with advanced age were more likely resistant to radioactive iodine (RAI) treatment(14, 23); Secondly, the thyroid-stimulating hormone (TSH) levels would increase with normal aging, which was an independent risk factor for malignancy in thyroid nodules(24); In female patients with menopause, elevated luteinizing hormone (LH)/follicle-stimulating hormone (FSH) could also affect the growth of TC because LH and FSH had the same α subunit as TSH(25); Moreover, due to aging, decline in immune system functions and increase in all-cause mortality may also contributed to poor prognosis of TC(26).

Besides age, BRAF V600E mutation was also an important risk factor for poor prognosis in TC patients(27, 28). Previous studies indicated that age was a continuous mortality risk factor in patients with BRAF V600E mutation, especially for patients who were ≥ 75 years or male patients ≥ 60 years(11, 29). Our conclusions were partly in line with them. In recent years, some scholars had further pointed out the influence of age on the prognosis of TC. They assumed that whether age and BRAF mutations both could be two independent poor prognostic indicators(30), and our study results may serve as a supporting evidence. However, due to the lack of information on BRAF mutations in our data, we cannot further clarify the impact of BRAF mutations and age on TC-specific prognosis.

In 2015, the American Thyroid Association (ATA) released management guidelines for DTC patients, and only recommended computerized tomography (CT) imaging for DTC patients with high risk who had elevated serum thyroglobulin (Tg) (generally > 10 ng/mL) or rising Tg antibodies(31). On the other side, lung was the most common site of distant metastasis in TC patients(7–9), thus, based on the results of our study, for elder patients, especially those over 85 years, chest CT screening should be performed to detect lung metastatic disease. Moreover, more radical treatment strategies can be adopted for elder TC patients with distant metastases. In previous studies for DTC patients with advanced age, targeted therapy [such as Mitogen-activated protein kinase/Extracellular signal-regulated kinase inhibitors, etc.] followed by RAI treatment could significantly reverse the patients' resistance to RAI(5, 32, 33). Besides, immunotherapy could also be considered to improve their prognosis(34).

Conclusions

In conclusion, TC-specific mortality increases with age in patients with lung metastasis. For elder TC patients, chest CT screening was recommended for early detection of lung metastasis to evaluate the prognosis more precisely and to make personalized treatment strategy.

Abbreviations

TC
Thyroid cancer
IQR
Interquartile range
HRs
Hazard ratios
DTC
Differentiated thyroid cancer
PTC
Papillary thyroid cancer
FTC
Follicular thyroid cancer
ATC
Anaplastic thyroid cancer
MTC
Medullary thyroid cancer
AJCC
American Joint Committee on Cancer
RAI
Radioactive iodine
SEER
Surveillance, Epidemiology, and End Results

ICD-O-3
International Classification of Disease for Oncology-3
CIs
Confidence intervals
ATA
American Thyroid Association
CT
Computerized tomography
Tg
Thyroglobulin

Declarations

Ethics approval and consent to participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All the data investigated in this study was obtained from the SEER database, which was publicly available, and we received permission for using the data for non-commercial use. This study was exempt by the ethics committee of Shanghai Tenth People's Hospital.

Consent for publication

All authors have read and approved the final manuscript.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

AP and JY: conception and design. XH, SQ and QX: acquisition, statistical analysis or interpretation of the data. All authors: drafting of the manuscript, reviewing, and approving the final version of the manuscript.

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References

1. Pereira M, Williams VL, Hallanger Johnson J, Valderrabano P. Thyroid Cancer Incidence Trends in the United States: Association with Changes in Professional Guideline Recommendations. Thyroid. 2020;30(8):1132–40. .https://doi.org/10.1089/thy.2019.0415.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics. 2019. CA Cancer J Clin. 2019;69(1):7–34.https://doi.org/10.3322/caac.21551.
3. Force USPST, Bibbins-Domingo K, Grossman DC, Curry SJ, Barry MJ, Davidson KW, et al. Screening for Thyroid Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2017;317(18):1882–7.

.https://doi.org/10.1001/jama.2017.4011.

4. Fagin JA, Wells SA. Jr. Biologic and Clinical Perspectives on Thyroid Cancer. N Engl J Med. 2016;375(11):1054–67. https://doi.org/10.1056/NEJMra1501993.
5. Araque KA, Gubbi S, Klubo-Gwiezdzinska J. Updates on the Management of Thyroid Cancer. Horm Metab Res. 2020;52(8):562 – 77. https://doi.org/10.1055/a-1089-7870.
6. Lin Y-H, Jang C-S, Wu C-S, Hsu L. Unusual presentation of anaplastic thyroid carcinoma with diffuse neck and thoracic nodules and hyperthyroidism. Dermatologica Sinica. 2017;35(2):85 – 7. https://doi.org/10.1016/j.dsi.2017.01.003.
7. Lee YK, Kim D, Shin DY, Lee CR, Lee EJ, Kang SW, et al. The Prognosis of Papillary Thyroid Cancer with Initial Distant Metastasis is Strongly Associated with Extensive Extrathyroidal Extension: A Retrospective Cohort Study. Ann Surg Oncol. 2019;26(7):2200–9. .https://doi.org/10.1245/s10434-019-07314-x.
8. Hirsch D, Levy S, Tsvetov G, Gorshtein A, Slutzky-Shraga I, Akirov A, et al. Long-Term Outcomes and Prognostic Factors in Patients with Differentiated Thyroid Cancer and Distant Metastases. Endocr Pract. 2017;23(10):1193 – 200. https://doi.org/10.4158/EP171924.OR.
9. Rajabi S, Shakib H, Dastmalchi R, Danesh-Afrooz A, Karima S, Hedayati M. Metastatic propagation of thyroid cancer; organ tropism and major modulators. Future Oncol. 2020;16(18):1301–19. .https://doi.org/10.2217/fon-2019-0780.
10. Haymart MR. Understanding the relationship between age and thyroid cancer. Oncologist. 2009;14(3):216 – 21.https://doi.org/10.1634/theoncologist.2008-0194.
11. Shen X, Zhu G, Liu R, Viola D, Elisei R, Puxeddu E, et al. Patient Age-Associated Mortality Risk Is Differentiated by BRAF V600E Status in Papillary Thyroid Cancer. J Clin Oncol. 2018;36(5):438 – 45. https://doi.org/10.1200/JCO.2017.74.5497.
12. Perrier ND, Brierley JD, Tuttle RM. Differentiated and anaplastic thyroid carcinoma: Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2018;68(1):55–63. https://doi.org/10.3322/caac.21439.
13. Ito Y, Kudo T, Kobayashi K, Miya A, Ichihara K, Miyauchi A. Prognostic factors for recurrence of papillary thyroid carcinoma in the lymph nodes, lung, and bone: analysis of 5,768 patients with average 10-year follow-up. World J Surg. 2012;36(6):1274–8. .https://doi.org/10.1007/s00268-012-1423-5.
14. Li C, Wu Q, Sun S. Radioactive Iodine Therapy in Patients With Thyroid Carcinoma With Distant Metastases: A SEER-Based Study. Cancer Control. 2020;27(1):1073274820914661. https://doi.org/10.1177/1073274820914661.
15. Doll KM, Rademaker A, Sosa JA. Practical Guide to Surgical Data Sets: Surveillance, Epidemiology, and End Results (SEER) Database. JAMA Surg. 2018;153(6):588–9. .https://doi.org/10.1001/jamasurg.2018.0501.
16. Liu Z, Chen S, Huang Y, Hu D, Wang M, Wei W, et al. Patients Aged >/=55 Years With Stage T1-2N1M1 Differentiated Thyroid Cancer Should Be Downstaged in the Eighth Edition AJCC/TNM Cancer Staging System. Front Oncol. 2019;9:1093. https://doi.org/10.3389/fonc.2019.01093.
17. Subbiah V, Kreitman RJ, Wainberg ZA, Cho JY, Schellens JHM, Soria JC, et al. Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600-Mutant Anaplastic Thyroid Cancer. J Clin Oncol. 2018;36(1):7–13. https://doi.org/10.1200/JCO.2017.73.6785.
18. Chmielik E, Rusinek D, Oczko-Wojciechowska M, Jarzab M, Krajewska J, Czarniecka A, et al. Heterogeneity of Thyroid Cancer Pathobiology. 2018;85(1–2):117–29. https://doi.org/10.1159/000486422.
19. Shen X, Zhu G, Liu R, Viola D, Elisei R, Puxeddu E, et al. Patient Age-Associated Mortality Risk Is Differentiated by BRAF V600E Status in Papillary Thyroid Cancer. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2018;36(5):438 – 45. https://doi.org/10.1200/JCO.2017.74.5497.
20. Chen P, Feng HJ, Ouyang W, Wu JQ, Wang J, Sun YG, et al. Risk Factors for Nonremission and Progression-Free Survival after I-131 Therapy in Patients with Lung Metastasis from Differentiated Thyroid Cancer: A Single-Institute, Retrospective Analysis in Southern China. Endocr Pract. 2016;22(9):1048–56. .https://doi.org/10.4158/EP151139.OR.
21. Sabra MM, Ghossein R, Tuttle RM. Time Course and Predictors of Structural Disease Progression in Pulmonary Metastases Arising from Follicular Cell-Derived Thyroid Cancer. Thyroid. 2016;26(4):518 – 24. https://doi.org/10.1089/thy.2015.0395.

22. Leite AK, Kulcsar MA, de Godoi Cavalheiro B, de Mello ES, Alves VA, Cernea CR, et al. Death Related to Pulmonary Metastasis in Patients with Differentiated Thyroid Cancer. Endocr Pract. 2017;23(1):72 – 8. https://doi.org/10.4158/EP161431.OR.
23. Liu X, Fan Y, Liu Y, He X, Zheng X, Tan J, et al. The impact of radioactive iodine treatment on survival among papillary thyroid cancer patients according to the 7th and 8th editions of the AJCC/TNM staging system: a SEER-based study. 2020;72(3):871 – 84.https://doi.org/10.1007/s13304-020-00773-y.
24. Nagayama Y. Thyroid Autoimmunity and Thyroid Cancer - The Pathogenic Connection: A 2018 Update. Horm Metab Res. 2018;50(12):922 – 31. https://doi.org/10.1055/a-0648-4593.
25. Liu J, Chen G, Meng XY, Liu ZH, Dong S. Serum levels of sex hormones and expression of their receptors in thyroid tissue in female patients with various types of thyroid neoplasms. Pathol Res Pract. 2014;210(12):830–5. .https://doi.org/10.1016/j.prp.2014.09.002.
26. Muller L, Di Benedetto S, Pawelec G. The Immune System and Its Dysregulation with Aging. Subcell Biochem. 2019;91:21–43. https://doi.org/10.1007/978-981-13-3681-2_2.
27. Abdullah MI, Junit SM, Ng KL, Jayapalan JJ, Karikalan B, Hashim OH. Papillary Thyroid Cancer: Genetic Alterations and Molecular Biomarker Investigations. Int J Med Sci. 2019;16(3):450 – 60. https://doi.org/10.7150/ijms.29935.
28. Ming J, Liu Z, Zeng W, Maimaiti Y, Guo Y, Nie X, et al. Association between BRAF and RAS mutations, and RET rearrangements and the clinical features of papillary thyroid cancer. Int J Clin Exp Pathol. 2015;8(11):15155–62.
29. Xing M, Alzahrani AS, Carson KA, Shong YK, Kim TY, Viola D, et al. Association between BRAF V600E mutation and recurrence of papillary thyroid cancer. J Clin Oncol. 2015;33(1):42–50. https://doi.org/10.1200/JCO.2014.56.8253.
30. Subash A, Sinha P, Singh A. BRAF mutation and age in differentiated thyroid cancer risk stratification: Two sides of the same coin. Oral Oncol. 2020;106:104732. https://doi.org/10.1016/j.oraloncology.2020.104732.
31. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, 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):1–133. https://doi.org/10.1089/thy.2015.0020.
32. Brown SR, Hall A, Buckley HL, Flanagan L, Gonzalez de Castro D, Farnell K, et al. Investigating the potential clinical benefit of Selumetinib in resensitising advanced iodine refractory differentiated thyroid cancer to radioiodine therapy (SEL-I-METRY): protocol for a multicentre UK single arm phase II trial. BMC Cancer. 2019;19(1):582. https://doi.org/10.1186/s12885-019-5541-4.
33. Wadsley J, Gregory R, Flux G, Newbold K, Du Y, Moss L, et al. SELIMETRY-a multicentre I-131 dosimetry trial: a clinical perspective. Br J Radiol. 2017;90(1073):20160637. https://doi.org/10.1259/bjr.20160637.
34. Mehnert JM, Varga A, Brose MS, Aggarwal RR, Lin CC, Prawira A, et al. Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with advanced, PD-L1-positive papillary or follicular thyroid cancer. BMC Cancer. 2019;19(1):196. https://doi.org/10.1186/s12885-019-5380-3.

Figures

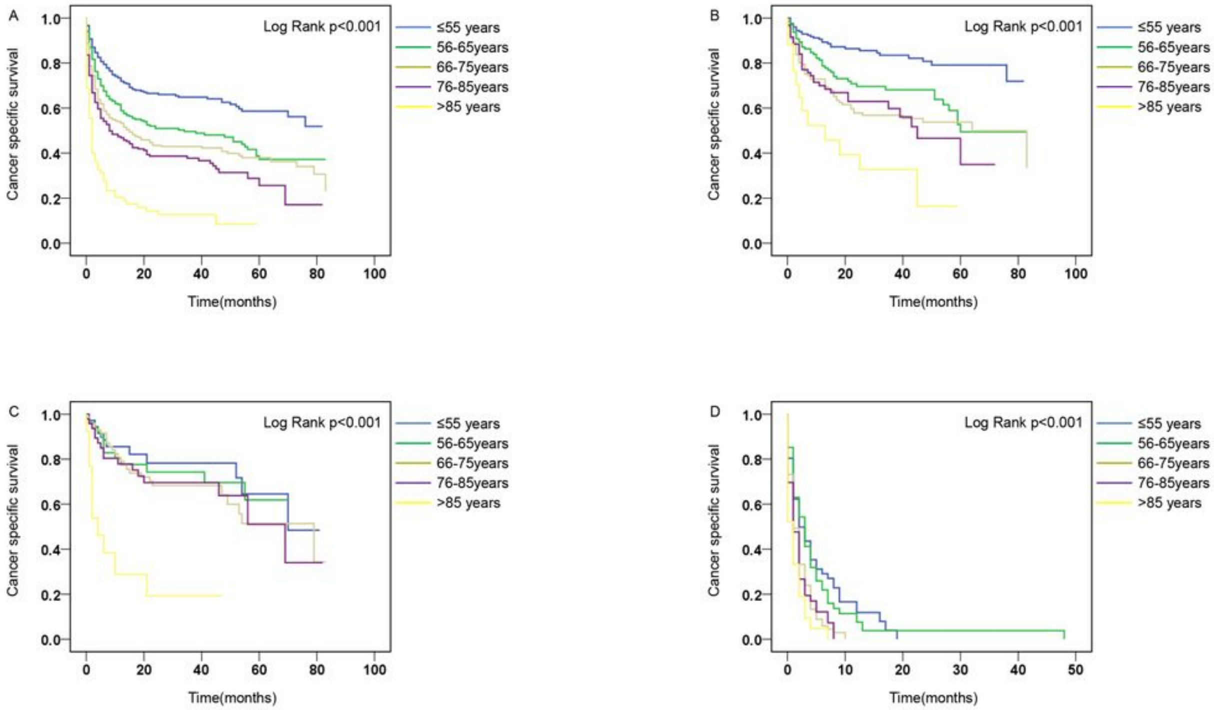

Figure 1

Disease-specific survival of thyroid cancer with distant metastases stratified by age using Kaplan–Meier analysis. (A) All thyroid cancer patients. (B) papillary thyroid cancer patients. (C) follicular thyroid cancer patients. (D) anaplastic thyroid cancer patients. (All Log Rank $p < 0.001$).

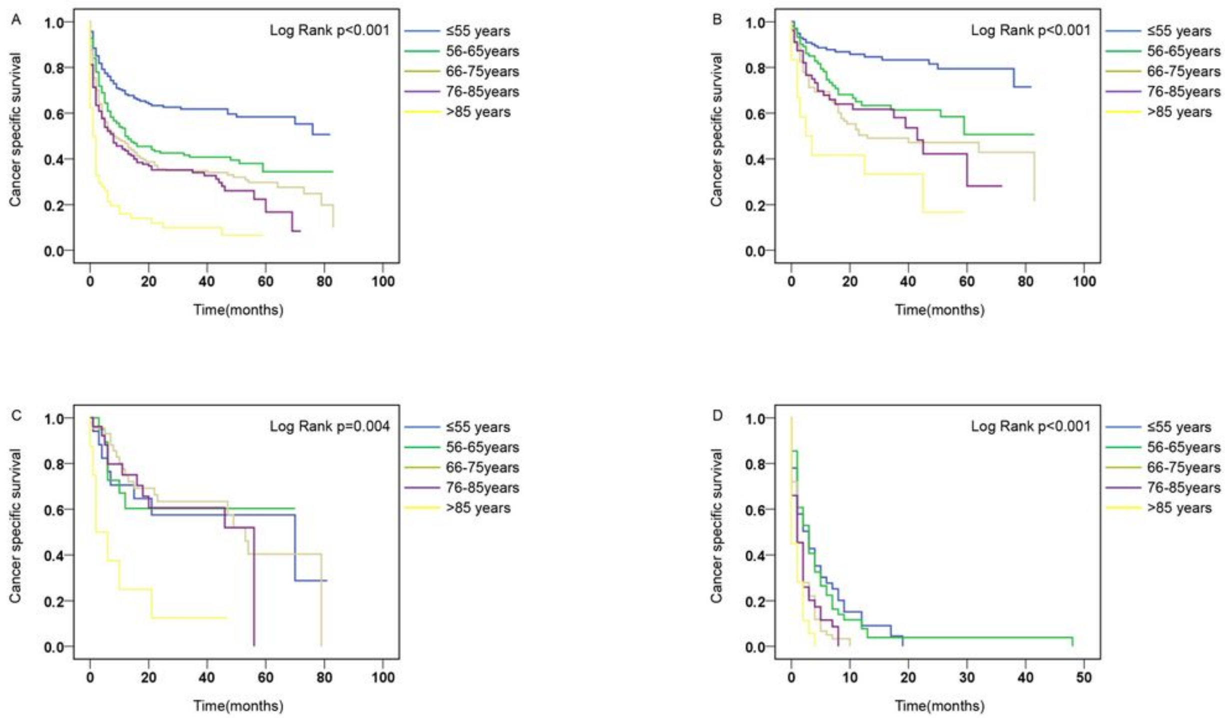

Figure 2

Disease-specific survival of thyroid cancer with lung metastasis stratified by age using Kaplan–Meier analysis. (A) All thyroid cancer patients. (B) papillary thyroid cancer patients. (C) follicular thyroid cancer patients. (D) anaplastic thyroid cancer patients. [(A.B.D) Log Rank p < 0.001, (C) Log Rank p = 0.004].

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