Age increased the cancer-specific mortality risk of thyroid cancer with lung metastasis

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

Patients and Methods: A total of 1418 patients with initial distant metastases from Surveillance, Epidemiology, and End Results databases were investigated. Patients with a median follow-up time of 8 months (interquartile range [IQR]: 2–27) and a 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 analysed.

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) in patients aged ≤55 years, >55 but ≤65 years, >65 but ≤75 years, >75 but ≤85 years and >85 years. Kaplan–Meier curves showed that TC-specific mortality rate was associated with increased age (p < .001). Compared with patients ≤55 years, patients aged >55 but ≤65 years, >65 but ≤75 years, >75 but ≤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 sex, tumour size and radiation therapy (all p < .001). In TC with initial lung-metastasis, compared with patients ≤55 years, patients aged >55 but ≤65 years, >65 but ≤75 years, >75 but ≤85 years and >85 years had significantly higher adjusted HRs of 1.68 (1.20–2.36; p = .003), 2.18 (1.57–3.02), 2.16 (1.51–3.08) and 2.91 (1.79–4.75; p < .001). Similar results were obtained in papillary TC.

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

Keywords
age, cancer-specific mortality, lung-metastasis, risk stratification, thyroid cancer
INTRODUCTION

Thyroid cancer (TC) is one of the most common endocrine tumours, and its incidence has been increasing over the past four decades. At present, TC has become the sixth most common malignancy for women in the United States. TC is divided into two categories according to the cell origin: endoderm-derived follicular cells and neural crest-derived C-cells. The former includes differentiated TC (DTC) (papillary TC [PTC], follicular TC [FTC] and poorly differentiated TC), and anaplastic TC (ATC). Meanwhile, the latter category is also known as medullary TC (MTC). DTC accounts for approximately 90% of all TC types.

In terms of clinical characteristics, DTC is usually indolent, while ATC is the most aggressive variant, accounting for approximately 40% of all deaths from TC. The most common metastatic site of TC is the lung, followed by the bone, and occasionally the brain and liver. DTC is a unique malignancy because the age at diagnosis can be an independent risk factor for prognosis. In 2016, the American Joint Committee on Cancer (AJCC) released the eighth edition of the AJCC/TNM cancer staging system. According to this edition, the age cut-off used for DTC staging was increased from 45 to 55 years at diagnosis. Indeed, several studies had shown that age over 55 years was an important risk factor for metastasis and prognosis of DTC, as well as for the effect of radioactive iodine (RAI) therapy.

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

PATIENTS AND METHODS

2.1 Data source and study subjects

This retrospective study utilized data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER). A total of 1418 TC patients with distant metastases at diagnosis from 2010 to 2017 were investigated. Demographic data included race (White, Black, other, and unknown), sex, SEER cause-specific death classification, survival months, and age at diagnosis. The cancer characteristics included histology (defined by International Classification of Disease for Oncology-3), TNM stage (classified according to the 7th AJCC staging system), tumour 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. Patients were divided into five groups based on age: ≤55 years, >55 but ≤65 years, >65 but ≤75 years, >75 but ≤85 years and >85 years.

RESULTS

3.1 Demographic and clinical characteristics

The demographic and clinical characteristics of 1418 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), respectively. Patients were divided into five groups based on age: ≤55 years (25.39%, 360/1418), >55 but ≤65 years (23.55%, 334/1418), >65 but ≤75 years (26.02%, 369/1418), >75 but ≤85 years (18.90%, 268/1418), >85 years (6.14%, 87/1418). In addition, the 1034 (72.92% [1034/1418]) patients with initial lung metastasis were further analysed (Table 1). The overall TC-specific mortality rate was 49.58% (703/1418). Patients aged >85 years had the highest TC-specific mortality rate (82.76%, 72/87), followed by those aged >75 but ≤85 years (58.96%, 158/268), >65 but ≤75 years (53.93%, 199/369), >55 but ≤65 years (46.71%, 156/334) and ≤55 years (32.78%, 118/360).

3.2 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). For patients aged >85 years, >75 but ≤85 years, >65 but ≤75 years, >55 but ≤65 years and ≤55 years, their TC-specific mortality rates were 82.76% (72/87), 58.96% (158/268), 53.93% (199/369), 46.71% (156/334) and 32.78% (118/360), respectively. Compared with patients ≤55 years, the crude HRs for
| Characteristics | Overall | ≤55 years | >55 but ≤65 years | >65 but ≤75 years | >75 but ≤85 years | >85 years |
|-----------------|---------|-----------|-------------------|-------------------|------------------|-----------|
| Number          | 1418    | 360       | 334               | 369               | 268              | 87        |
| Gender          |         |           |                   |                   |                  |           |
| Male            | 645     | 45.49     | 173               | 48.06             | 177              | 52.99     |
| Female          | 773     | 54.51     | 187               | 51.94             | 157              | 47.01     |
| Race            |         |           |                   |                   |                  |           |
| White           | 1043    | 73.55     | 283               | 78.61             | 237              | 70.96     |
| Black           | 155     | 10.93     | 32                | 8.89              | 45               | 13.47     |
| Others          | 5       | 0.35      | 43                | 11.94             | 51               | 15.27     |
| Unknown         | 215     | 15.16     | 2                 | 0.56              | 1                | 0.30      |
| Lymph node stage|         |           |                   |                   |                  |           |
| N0              | 396     | 27.93     | 72                | 20.00             | 93               | 27.84     |
| N1a             | 116     | 8.18      | 33                | 9.17              | 24               | 7.19      |
| N1b             | 432     | 30.47     | 142               | 39.44             | 114              | 34.13     |
| N1NOS           | 83      | 5.85      | 28                | 7.78              | 19               | 5.69      |
| NX              | 141     | 9.94      | 13                | 3.61              | 28               | 8.38      |
| Unknown         | 250     | 17.63     | 72                | 20.00             | 56               | 16.77     |
| Distant metastatic site |     |           |                   |                   |                  |           |
| Lung            | 1034    | 72.92     | 253               | 70.28             | 222              | 66.47     |
| Bone            | 543     | 38.29     | 134               | 37.22             | 156              | 46.71     |
| Brain           | 88      | 6.21      | 26                | 7.22              | 25               | 7.49      |
| Liver           | 160     | 11.28     | 40                | 11.11             | 38               | 11.38     |
| Thyroid cancer-specific mortality |       |           |                   |                   |                  |           |
| Alive           | 715     | 50.42     | 242               | 67.22             | 178              | 53.29     |
| Death           | 703     | 49.58     | 118               | 32.78             | 156              | 46.71     |
| Histology subtype |       |           |                   |                   |                  |           |
| PTC             | 617     | 43.51     | 208               | 57.78             | 145              | 43.41     |
| FTC             | 223     | 15.73     | 36                | 10.00             | 53               | 15.87     |
| MTC             | 102     | 7.19      | 36                | 10.00             | 40               | 11.98     |
| ATC             | 273     | 19.25     | 51                | 14.17             | 61               | 18.26     |
| Others          | 203     | 14.32     | 29                | 8.06              | 35               | 10.48     |
| Thyroid cancer-specific mortality |       |           |                   |                   |                  |           |
| TC              | 703     | 49.58     | 118               | 32.78             | 156              | 46.71     |
| PTC             | 184     | 12.98     | 31                | 8.61              | 45               | 13.47     |
| FTC             | 74      | 5.22      | 10                | 2.78              | 13               | 3.89      |
| MTC             | 50      | 3.53      | 15                | 4.17              | 22               | 6.59      |
| ATC             | 246     | 17.35     | 46                | 12.78             | 52               | 15.57     |
| Others          | 149     | 10.51     | 16                | 4.44              | 24               | 7.19      |
TABLE 1  (Continued)

| Characteristics                      | Overall     | ≤55 years  | >55 but ≤65 years | >65 but ≤75 years | >75 but ≤85 years | >85 years |
|--------------------------------------|-------------|------------|-------------------|-------------------|-------------------|---------|
| Radiation therapy                    |             |            |                   |                   |                   |         |
| Radiation beam or radioactive implants| 425         | 29.97      | 105               | 29.17             | 113               | 33.83   |
|                                      |             |            |                   |                   |                   |         |
| Radioisotopes or radiation beam plus isotopes or implants | 405         | 28.56      | 149               | 41.39             | 96                | 28.74   |
|                                      |             |            |                   |                   |                   |         |
| None or refused                      | 552         | 38.93      | 97                | 26.94             | 118               | 35.33   |
| Unknown                              | 36          | 2.54       | 9                 | 2.50              | 7                 | 2.10    |

Note: According to the American Joint Committee on Cancer (AJCC) Staging Manual 7th edition, lymph node category was classified into five 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 I, II, III, IV or V) or retropharyngeal or superior mediastinal lymph nodes (Level VII) (N1b); metastasis to regional lymph nodes but not otherwise specified (N1NOS); and regional lymph nodes cannot be assessed (NX).

Abbreviations: ATC, anaplastic thyroid cancer; FTC, follicular thyroid cancer; MTC, medullary thyroid cancer; others, other variants of thyroid cancer; PTC, papillary thyroid cancer; SEER, Surveillance, Epidemiology, and End Results; TC, thyroid cancer.

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

| Variants | Mortality n/N (%) | Unadjusted HR (95% CI) | p Value | Adjusted a HR (95% CI) | p Value |
|----------|-------------------|------------------------|---------|------------------------|---------|
| TC       | 703/1418 (49.58)  |                        |         |                        |         |
| Age (years) |          |                    |         |                        |         |
| ≤55      | 118/360 (32.78)   |                        | Ref.    |                        |         |
| >55 but ≤65 | 156/334 (46.71)  | 1.61 (1.27–2.05)       | <.001   | 1.69 (1.26–2.26)       | <.001   |
| >65 but ≤75 | 199/369 (53.93)  | 1.96 (1.56–2.46)       | <.001   | 1.97 (1.47–2.64)       | <.001   |
| >75 but ≤85 | 158/268 (58.96)  | 2.43 (1.91–3.09)       | <.001   | 2.18 (1.59–2.99)       | <.001   |
| >85      | 72/87 (82.76)     | 4.99 (3.69–6.76)       | <.001   | 3.24 (2.08–5.06)       | <.001   |
| PTC      | 184/617 (29.82)   |                        |         |                        |         |
| Age (years) |          |                    |         |                        |         |
| ≤55      | 31/208 (14.90)    |                        | Ref.    |                        |         |
| >55 but ≤65 | 45/145 (31.03)   | 2.22 (1.41–3.51)       | <.001   | 2.36 (1.38–4.05)       | <.001   |
| >65 but ≤75 | 61/152 (40.13)   | 2.97 (1.93–4.58)       | <.001   | 3.00 (1.76–5.10)       | <.001   |
| >75 but ≤85 | 35/95 (36.84)    | 3.28 (2.00–5.37)       | <.001   | 2.97 (1.56–5.66)       | .001    |
| >85      | 12/17 (70.59)     | 6.72 (3.42–13.19)      | <.001   | 1.68 (0.48–5.85)       | .416    |
| FTC      | 74/223 (33.18)    |                        |         |                        |         |
| Age (years) |          |                    |         |                        |         |
| ≤55      | 10/36 (27.78)     |                        | Ref.    |                        |         |
| >55 but ≤65 | 13/53 (24.53)    | 1.15 (0.50–2.65)       | .746    | 2.21 (0.73–6.69)       | .159    |
| >65 but ≤75 | 25/73 (34.25)    | 1.43 (0.68–2.08)       | .346    | 2.79 (1.08–7.18)       | .034    |
| >75 but ≤85 | 16/48 (33.33)    | 1.49 (0.67–3.30)       | .328    | 3.29 (1.05–10.32)      | .041    |
| >85      | 10/13 (76.92)     | 6.55 (2.46–17.44)      | <.001   | 22.80 (3.95–131.78)    | <.001   |

Abbreviations: CI, confidence interval; FTC, follicular thyroid cancer; HRs, hazard ratios; PTC, papillary thyroid cancer; TC, thyroid cancer.

aAdjusted for sex, tumour size and radiation therapy; Surveillance, Epidemiology, and End Results database years of 2010–2017.
patients with age of >55 but ≤65 years, >65 but ≤75 years, >75 but ≤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; \(p<0.001\)), respectively (Table 2). After adjustments for tumour size, sex and radioiodine 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 aged >55 but ≤65 years, >65 but ≤75 years, >75 but ≤85 years and >85 years. Compared with patients aged >55 but ≤65 years, >65 but ≤75 years and >75 but ≤85 years, patients >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 adjusting for tumour size, sex and radioiodine therapy, the HR remained significant only when compared with patients aged >55 but ≤65 years (1.83 [1.20–2.78]; \(p=0.005\); Table S1).

In this cohort, lung was the most common site of metastasis, accounting for 72.92% (1034/1418). In these patients with lung metastases, the overall TC-specific mortality rate was 55.03% (569/1034). For patients aged >85 years, >75 but ≤85 years, >65 but ≤75 years, >55 but ≤65 years and ≤55 years, their TC-specific mortality rates were 85.51% (59/69), 62.32% (129/207), 60.78% (172/283), 54.05% (120/222) and 35.18% (89/253), respectively (Table 3). Compared with patients aged ≤55 years, the crude HRs for patients aged >55 but ≤65 years, >65 but ≤75 years, >75 but ≤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 tumour size, sex and radioiodine 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 aged >55 but ≤65 years, >65 but ≤75 years, >75 but ≤85 years and >85 years, respectively. When compared with patients aged >55 but ≤65 years, >65 but ≤75 years, and >75 but ≤85 years, patients aged >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 tumour size, sex and radioiodine therapy, the HR remained significant only compared when with patients aged >55 but ≤65 years (1.84 [1.18–2.88]; \(p=0.007\); Table S2).

### Table 3: The association between age and thyroid cancer-specific mortality in patients with lung metastasis

| Variants | Mortality n/N (%) | Unadjusted HR (95% CI) | \(p\) Value | Adjusted\(^a\) HR (95% CI) | \(p\) Value |
|----------|------------------|------------------------|-------------|------------------------|-------------|
| **TC**   |                  |                        |             |                        |             |
| Age (years) |                  |                        |             |                        |             |
| ≤55      | 89/253 (35.18)   | Ref.                   |             |                        |             |
| >55 but ≤65 | 120/222 (54.05) | 1.75 (1.33–2.31)       | <.001       | 1.68 (1.20–2.36)       | .003        |
| >65 but ≤75 | 172/283 (60.78) | 2.16 (1.67–2.80)       | <.001       | 2.18 (1.57–3.02)       | .001        |
| >75 but ≤85 | 129/207 (62.32) | 2.45 (1.87–3.23)       | <.001       | 2.16 (1.51–3.08)       | <.001       |
| >85      | 59/69 (85.51)    | 4.96 (3.52–6.98)       | <.001       | 2.91 (1.79–4.75)       | <.001       |
| **PTC**  |                  |                        |             |                        |             |
| Age (years) |                  |                        |             |                        |             |
| ≤55      | 25/161 (15.53)   | Ref.                   |             |                        |             |
| >55 but ≤65 | 36/104 (34.62)  | 2.35 (1.41–3.92)       | .001        | 2.54 (1.38–4.66)       | .003        |
| >65 but ≤75 | 54/119 (45.38)  | 3.34 (2.08–5.38)       | <.001       | 3.31 (1.82–6.01)       | <.001       |
| >75 but ≤85 | 31/79 (39.24)   | 3.37 (1.96–5.79)       | <.001       | 3.32 (1.61–6.88)       | .001        |
| >85      | 9/12 (75.00)     | 6.81 (3.15–14.70)      | <.001       | 2.39 (0.66–8.65)       | .183        |
| **FTC**  |                  |                        |             |                        |             |
| Age (years) |                  |                        |             |                        |             |
| ≤55      | 8/17 (47.06)    | Ref.                   |             |                        |             |
| >55 but ≤65 | 7/21 (33.33)   | 0.86 (0.31–2.38)       | .857        | 2.17 (0.47–9.98)       | .321        |
| >65 but ≤75 | 19/44 (43.18)  | 1.08 (0.47–2.50)       | .611        | 3.95 (1.15–13.63)      | .030        |
| >75 but ≤85 | 11/27 (40.74)  | 1.18 (0.45–3.12)       | .736        | 4.88 (1.02–23.29)      | .047        |
| >85      | 7/8 (87.50)     | 3.46 (1.20–9.96)       | .022        |                        | b           |

Abbreviations: CI, confidence interval; FTC, follicular thyroid cancer; HRs, hazard ratios; PTC, papillary thyroid cancer; TC, thyroid cancer.

\(^a\)Adjusted for sex, tumour size and radiation therapy.

\(^b\)Due to the small sample size and relative high mortality in FTC patients of >85 years, the HRs cannot be calculated; Surveillance, Epidemiology, and End Results database years of 2010–2017.
3.3 The association between age and PTC-specific mortality in patients with distant metastases at diagnosis

In PTC patients with initial distant metastases, the overall PTC-specific mortality rate was 29.82% (184/617). For patients aged >85 years, >75 but ≤85 years, >65 but ≤75 years, >55 but ≤65 years and ≤55 years, their PTC-specific mortality rates were 70.59% (12/17), 36.84% (35/95), 40.13% (45/115), 31.03% (45/145) and 14.90% (31/208), respectively (Table 2). Compared with patients ≤55 years, the crude HRs for patients aged >55 but ≤65 years, >65 but ≤75 years, >75 but ≤85 years, and >85 years were 2.22 (1.41–3.51; \( p < .001 \)), 2.97 (1.93–4.58; \( p < .001 \)), 3.28 (2.00–5.37; \( p < .001 \)) and 6.72 (3.42–13.19; \( p < .001 \)), respectively (Table 2). After adjusting for tumour size, sex and radioiodine therapy, the HRs remained significant in patients aged >55 but ≤65 years (2.36 [1.38–4.05]; \( p < .001 \)), >65 but ≤75 years (3.00 [1.76–5.10]; \( p < .001 \)), >75 but ≤85 years (2.97 [1.56–5.66]; \( p = .001 \)), but the HR for patients aged >85 years group did not reach significance because of the small sample size.

In PTC patients, lung was also the most common site of metastasis, accounting for 76.99% (475/617). In these patients with lung metastases, the overall PTC-specific mortality rate was 32.63% (155/475). For patients aged >85 years, >75 but ≤85 years, >65 but ≤75 years, >55 but ≤65 years and ≤55 years, their PTC-specific mortality rates were 75.00% (9/12), 39.24% (31/79), 45.38% (54/119), 34.62% (36/104), and 15.53% (25/161), respectively (Table 3). Compared with patients ≤55 years, the crude HRs for patients aged >55 but ≤65 years, >65 but ≤75 years, >75 but ≤85 years, and >85 years were 2.35 (1.41–3.92; \( p = .001 \)), 3.34 (2.08–5.38; \( p < .001 \)), 3.37 (1.96–5.79; \( p < .001 \)) and 6.81 (3.15–14.70; \( p < .001 \)), respectively (Table 3). After adjustments for tumour size, sex and radioiodine therapy, the HRs remained significant for patients aged >55 but ≤65 years (2.54 [1.38–4.66]; \( p = .003 \)), >65 but ≤75 years (3.31 [1.82–6.01]; \( p < .001 \)) and >75 but ≤85 years (3.32 [1.61–6.88]; \( p = .001 \)), but the HR of the >85 years group did not reach significance because of the small sample size.

3.4 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 increased age (log-rank \( p < .001 \); Figure 1A), and the survival curve of patients over 85 years showed an obvious decline with the worst prognosis. Similar results were observed in PTC (Figure 1B) and FTC (Figure 1C). There were no significant survival differences among all age groups in ATC patients (Figure 1D).

![Figure 1](image.png)

**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 \( p < .001 \)).
In TC patients with lung metastasis, the TC-specific survival curves also decreased significantly with increased age (log-rank \( p < .001 \); Figure 2A). Similar results were observed in PTC (Figure 2B) and FTC (Figure 2C), but not in ATC patients (Figure 2D). The survival curve of patients over 85 years showed a sharp decrease and similar trends were also observed when we further divided patients into four groups (>70 but ≤75 years, >75 but ≤80 years, >80 but ≤85 years and >85 years; Figure S1A–C). Still, advanced age had no significant impact on the survival of ATC patients (Figure S1D).

4 | DISCUSSION

In the present study, we demonstrated that the TC-specific mortality rates were increased with age in patients with lung metastasis, especially in patients over 85 years of age. 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 tumours, and its variants had different prognoses due to various reasons.17,18 It was also a special type of malignancy because a patient’s age at diagnosis could be an important risk factor for prognosis.11 As early as 2009, a previous study pointed out that advanced age was related to poor prognosis.10 The eighth edition of the AJCC/TNM cancer staging manual changed the age cut-off from 45 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 et al.13 found that age over 55 years was an independent risk factor for lung recurrence in a group of PTC patients without initial distant metastasis. Furthermore, it was also the strongest predictor of cancer-related death by a 10 years follow-up. Another study also found that in DTC patients with lung metastasis, age over 45 years was an independent risk factor for disease progression.19 Sabra et al.20 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 >45 years old. In addition, a 5-year study including 54 patients with DTC-related pulmonary disease indicated that age over 45 years and tumour dedifferentiation were independent risk factors for shorter cancer-specific survival.21 However, nearly none of the previous studies were stratified by age and investigated the prognostic value of age in TC patients with initial distant metastases.

Our study investigated TC patients with distant metastases at diagnosis from the SEER database, and further stratified the risk for patients over 55 years based on their age. Our results showed that age still had a great impact on the prognosis of patients with

![Figure 2](image-url)
the worst prognosis in the TNM staging system (age over 55 years with distant metastases), especially for those over 85 years of age.

The reason why the survival rate of TC patients with distant metastases at diagnosis was strongly age-dependent may be explained as follows: First, TC patients with advanced age were more likely resistant to RAI treatment; second, due to ageing, a decline in immune system functions and an increase in in-cause mortality may also be contributed to the poor prognosis of TC.

In addition to age, BRAF V600E mutation was also an important risk factor for poor prognosis in TC patients. Previous studies have indicated that age was a continuous mortality risk factor in patients with BRAF V600E mutation, especially in patients aged ≥75 years or male patients ≥60 years. Our conclusions were partly in line with these findings. 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, and our study results may serve as 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 released management guidelines for DTC patients, recommending that serum thyroglobulin (Tg) and anti-Tg antibodies should be assessed longitudinally during follow-up of DTC. However, the increase of Tg was nonspecific as it only indicated the presence of distant metastases and the exact sites for metastases were usually unknown. Sometimes, it was difficult for clinicians to accurately determine the distant metastatic sites by high Tg levels and other atypical clinical symptoms. Therefore, based on our results, chest computerized tomography (CT) scanning especially of the lung, a common metastatic site, could often be helpful in detecting lung metastasis as early as possible. Moreover, for suspected distant metastases which were iodine-non-avid, fluorine-18-fluorodeoxyglucose positron emission tomography (FDG-PET) could be of particular use. The guidelines recommended CT or FDG-PET imaging for DTC patients with high risk who had elevated Tg (generally >10 ng/ml) or rising Tg antibodies. Herein, we thought that for elderly patients with elevated Tg or Tg antibodies levels, CT or FDG-PET screening could be used as a more common tool for early detection of lung metastasis. Moreover, more radical treatment strategies can be adopted for elderly patients with TC and distant metastases. Seminal studies assessing the role of targeted therapy such as mitogen-activated protein kinase/extracellular signal-regulated kinase inhibitors to enhance radiiodine uptake in RAI refractory TC patients had shown promising results. In vitro and in vivo studies had also identified new tyrosine kinase inhibitors which could enhance endogenous sodium iodide symporter expression and increase radiiodine uptake. In addition, immunotherapy could also be considered to improve their prognosis.

5 | CONCLUSIONS

In conclusion, TC-specific mortality was increased with age in patients with lung metastasis. For elderly TC patients, CT or FDG-PET screening may be of special use in the early detection of lung metastasis, leading to a more precise evaluation of the prognosis and development of more personalized treatment strategies.

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CONFICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Aimei Peng and Jie Yang: Conception and design. Xiu Huang, Yueye Huang and Qing Xia: Collection, assembly, statistical analysis or interpretation of the data. All authors: Drafting of the manuscript, reviewing, and approving the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data used and analysed during the current study are available from the corresponding author on reasonable request.

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