Anaplastic Thyroid Cancer: Recent Trend Toward Improved Survival

Chi Huang

Affiliated Hospital of Integrated Chinese and Western Medicine

Jiuying Ji

Affiliated Hospital of Integrated Chinese and Western Medicine

Tao Qian

Affiliated Hospital of Integrated Chinese and Western Medicine

Zongqi Fei

Affiliated Hospital of Integrated Chinese and Western Medicine

Binge Ma

Affiliated Hospital of Integrated Chinese and Western Medicine

Xiangtai Zeng

First Affiliated Hospital of Gannan Medical University

Jianhua wang (✉ 311w@163.com)

Affiliated Hospital of Integrated Chinese and Western Medicine

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Abstract

Background: Anaplastic thyroid carcinoma is a rare malignant tumor of the thyroid. In this study, we summarize the survival changes of Anaplastic thyroid carcinoma in recent years.

Methods: Patients with Anaplastic thyroid carcinoma were selected from The Surveillance, Epidemiology, and End Results database (1973-2015). Survival rates were calculated and survival trends were compared among different stage, different years, under surgery and under radiotherapy or not.

Results: A total of 1293 patients were enrolled in the study. The 5-year overall survival (OS) for Stage IVA, B and C were 26.6%, 11.7% and 2.5%, respectively. The 5-year cancer-specific survival (CSS) for the same respective stage were 43.5%, 22.3% and 4.9%. After year 1995, the CSS was further improvement ($\chi^2=13.608$, $P=0.003$ for log-rank test) and there was obvious improvement in survival for patients at stage IVB and stage IVC (stage IVB: $\chi^2=12.987$, $P=0.005$, stage IVC: $\chi^2=21.992$, $P<0.001$ for log-rank test). The surgery survival benefit was only observed in Stage IVB (OS: $\chi^2=43.887$, $P<0.001$, CSS: $\chi^2=27.301$, $P<0.001$ for log-rank test) and C (OS: $\chi^2=16.399$, $P<0.001$, CSS: $\chi^2=12.521$, $P<0.001$ for log-rank test). The radiotherapy OS benefit was observed in all different stage(stage IVA: $\chi^2=7.346$, $P=0.007$ for log-rank test, stage IVB: $\chi^2=37.491$, $P<0.001$ for log-rank test, stage IVC: $\chi^2=23.208$, $P<0.001$ for log-rank test) and the CSS benefit was observed in Stage IVB ($\chi^2=18.717$, $P<0.001$ for log-rank test) and C ($\chi^2=12.615$, $P<0.001$ for log-rank test). The median OS of patients with stage IV A receiving surgery, radiotherapy alone and the combination of the two is 4, 5 and 33 months (95% CI: 0.411-7.589, 0.000-10.500, 16.290-49.710, respectively). For Stage IVA patients, compared with the patients received surgery alone, the survival benefit was observed in patients who received surgery and radiotherapy combined (OS: $\chi^2=6.454$, $P=0.011$ for log-rank test).

Conclusion: The 5-year cancer-specific survival for Anaplastic thyroid carcinoma was improved in recent years since 1990s. Patients with local metastasis or distant metastasis could benefit from surgery and radiotherapy. For Stage IVA patients, surgery or radiotherapy alone did not improve the cancer-specific survival. Combination of surgery and radiotherapy should get survival benefit.

Introduction

Anaplastic thyroid carcinoma (ATC) is a rare malignancy and accounts for only a small fraction of all histological types of thyroid cancer. [1]. However, the median survival time of ATC is 5 months. It is the rarest but most deadly form of thyroid cancer. The 1-year survival rate was reported between 10% and 20%[2]. All patients with ATC were considered to have more advanced disease regardless of tumor size and lymph node involvement. Because of the aggressive behavior, ATC is classified as T4 and Stage IV cancer (IVA/B/C) by the latest American Joint Committee on Cancer Staging Manual. The Stage IVA is intrathyroid tumors(localized)and Stage IVB is primary tumor with gross extra thyroidal extension(regional).The Stage IVC indicates the presence of distant metastasis(distant)[3].

The onset of ATC is sudden and rapid, and only 10% of patients have tumors confined to the thyroid gland. Forty percent of patients have extra thyroidal extension and lymph node metastasis, and the remaining patients have distant metastasis. The common metastatic sites are lung (25%), mediastinum (25%), liver (10%), bone (6%), kidney/adrenals (5%), heart (5%), and brain 3%[4].

The treatment of ATC depends on the tumor stage at the time of diagnosis. According to the recommendations of American Thyroid Association, surgical resection should be provided for patients with stage IVA or IVB resectable disease if an R0(no residual tumor) or R1 (microscopic residual tumor) surgical resection is possible. Chemotherapy and radiation therapy should be performed within 1 to 2 weeks after surgery. Several prognostic factors with low disease-specific mortality have been identified, the most consistently: younger age (< 60 years), female sex, intrathyroidal neoplasm, and multimodal therapy [5].

However, most studies were conducted based on small numbers of patients from single institutions. And there have been no reports on the survival changes of ATC for decades. Hence, in this study, we summarize the survival changes of ATC in recent years using the Surveillance, Epidemiology, and End Results (SEER) database.

Materials And Methods

Data Collection.

Patients with anaplastic thyroid carcinoma were selected from the SEER database (1973–2015). The study included a total of 1293 patients. This study was approved by the Institutional Review Board of the Affiliated Hospital of Integrated Chinese and Western Medicine, Nanjing University of Chinese Medicine. The synopsis of Inclusion criteria were given as follows: the site code represented “thyroid (146),” patients with intrathyroid tumors(localized, Stage IVA), primary tumor with gross extra thyroidal extension(regional, Stage IVB), and distant metastasis(distant, Stage IVC), ATC was diagnosed by positive cytology or histology, ATC was the only primary cancer type, and information about overall survival (OS) and cancer-specific survival (CSS) months was clear.

The study data included gender, age at diagnosis, TNM staging, surgery, radiotherapy, survival, OS, and CSS. CSS refers to the time from the date of diagnosis to the date of death caused by ATC.

Statistical Analysis.

The differences between groups were analyzed by using the χ^2 test. The Kaplan-Meier method was utilized to analyze CSS and OS. The difference was determined with log-rank test. All statistical analyses were executed with SPSS 25.0.

Results

Baseline Features

Between 1973–2015, a total of 1642 patients were diagnosed with ATC in the SEER database. 349 patients were excluded from this study because of their survival months were less than 1 month or unknown. Finally, a total of 1293 patients were enrolled in the study, including 495 male (38.3%) and 798 female (61.7%) patients. The female to male ratio is 1.6/1. The median age at diagnosis was 70.0 years (range 15–99) with no significant differences between sexuality. The mean tumor size was 60.0 mm (Range; 0–996 mm), however, 31.0% patients (n = 401) had missing information on this variable. Patients' characteristics are shown in Table 1. The cohort was divided into four subgroups according to the year of diagnosis by every ten years.

Table 1
Patients' characteristics

Characteristics (patients eligible for analysis)	N (%)
Sex	798(61.7)
Female	495(38.3%)
Male	
Median age	70.0
Median tumour size (mm)	60.0
≤ 60	466
> 60	426
Stage	80
IVA	494
IVB	645
IVC	680
Surgery	597
performed	867
not performed	426
Radiation	73
performed	122
None/Unknown	389
Years of diagnosis	709
1976–1985	
1986–1995	
1996–2005	
2006–2015	

Atc Survival

Stage-related trends

Among the 1293 eligible patients, the median OS was 4 months (95% confidence interval [CI]: 3.718–4.282). The median CSS is 5 months (95% CI:4.507–5.493). The 5-year OS for Stage IVA, B and C were

26.6%, 11.7% and 2.5%, respectively. The 5-year CSS for the same respective stage were 43.5%, 22.3% and 4.9%. The median OS for stage IVA, B and C are 9, 6 and 3 months (95% CI: 4.275–13.725, 5.126–6.874, 2.777–3.223, respectively). The median CSS was 38, 8 and 4 months (95% CI: 4.086–71.914, 6.905–9.095, 3.609–4.391, respectively) for the same respective stage. ATC patients with distant metastasis (Stage IVC) had poor prognosis (CSS: ($\chi^2 = 150.088$, $P < 0.001$ for log-rank test) (Fig. 1a and 1b).

Years-related Trends

We used the SEER18 cohort to compare the improvement in survival over the past 40 years. The cohort was divided into four subgroups according to the year of diagnosis by every ten years.

Using diagnosis year 1976–1985 as reference, the OS of the next 3 decades were not significant improved ($\chi^2 = 0.077, 0.890, 0.212$; $P = 0.782, 0.345, 0.645$) (Fig. 2a). The 5-year OS for patients diagnosed in 1976–1985, 1986–1995, 1996–2005 and 2006–2015 was 6.3%, 5.7%, 10.0% and 7.4%, respectively. The median OS was 4, 3, 4 and 4 months (95% CI: 2.931–5.069, 2.228–3.772, 3.460–4.540, 3.566–4.434, respectively) for the same respective time periods. The difference in OS for patients with stage IVB and stage IVC in recent decades were not statistical significance. ($\chi^2 = 0.458, 2.917, 1.589$; $P = 0.498, 0.088, 0.207$ for Stage IVB; $\chi^2 = 2.454, 0.277, 0.421$; $P = 0.117, 0.598, 0.517$ for Stage IVC) (Fig. 2b and 2c).

However, the CSS were improved in the recent decades and the difference reached statistical significance. ($\chi^2 = 13.608$, $P = 0.003$ for log-rank test) (Fig. 2d). The 5-year CSS was 10.0%, 9.5%, 18.4%, 16.5% for patients diagnosed among 1976–1985, 1986–1995, 1996–2005, 2006–2015. The Median CSS was 4, 4, 6 and 6 months (95% CI: 2.947–5.053, 3.151–4.849, 5.024–6.976, 5.261–6.739, respectively) for the same respective time periods. There was obvious improvement in survival for patients at stage IVB and stage IVC, and the differences were statistically significant. (stage IVB: $\chi^2 = 12.987$, $P = 0.005$, stage IVC: $\chi^2 = 21.992$, $P < 0.001$ for log-rank test) (Fig. 2e and 2f). The median CSS for patients diagnosed with stage IVB in 1976–1985, 1986–1995, 1996–2005 and 2006–2015 was 5, 7, 10 and 8 months (95% CI: 2.985–7.015, 3.461–10.539, 5.602–14.398, 6.619–9.381, respectively). The median CSS for patients diagnosed with Stage IVC for the same respective time periods was 3, 2, 3 and 4 months. (95% CI: 1.853–4.147, 1.222–2.778, 2.294–3.706, 3.336–4.664, respectively).

Surgery-related Trends

Surgery was related to an improved survival. The patients who received surgery had better OS and CSS than those who did not receive surgery (OS: $\chi^2 = 105.303$, $P < 0.001$, CSS: $\chi^2 = 84.033$, $P < 0.001$ for log-rank test) (Fig. 3a and 3b). The survival benefit was only observed in Stage IVB (OS: $\chi^2 = 43.887$, $P < 0.001$, CSS: $\chi^2 = 27.301$, $P < 0.001$ for log-rank test) (Fig. 4a and 4b) and C (OS: $\chi^2 = 16.399$, $P < 0.001$,

CSS: $\chi^2 = 12.521$, $P < 0.001$ for log-rank test) (Fig. 4c and 4d) instead of Stage IVA (OS: $\chi^2 = 3.651$, $P = 0.056$) (Fig. 4e). The 5-year OS for patients with and without surgery is 12.3% and 3.2%. The median OS of patients with or without surgery is 6 months and 3 months (95% CI: 5.299–6.701, 2.754–3.246, respectively). The 5-year CSS of patients with or without surgery is 22.5% and 8.1% respectively. The median CSS of patients with surgery is 8 months and that of patients without surgery is 4 months (95% CI: 7.064–8.936, 3.591–4.409, respectively).

Radiotherapy-related Trends

Adoption of radiotherapy was associated with an improved survival (Fig. 5a and 5b). The OS for patients who received radiotherapy were superior to those who did not receive radiotherapy ($\chi^2 = 51.402$, $P < 0.001$ for log-rank test). The OS benefit was observed in all different stage (stage IVA: $\chi^2 = 7.346$, $P = 0.007$ for log-rank test, stage IVB: $\chi^2 = 37.491$, $P < 0.001$ for log-rank test, stage IVC: $\chi^2 = 23.208$, $P < 0.001$ for log-rank test) (Fig. 6a, 6b and 6c). The 5-year OS for patients with and without radiotherapy is 9.6% and 4.7% respectively. The median OS for patients with radiotherapy is 5 months and that of patients without radiotherapy is 2 months (95% CI: 4.561–5.439, 1.631–2.369, respectively). The CSS for patients with radiotherapy were also better than patients without radiotherapy ($\chi^2 = 22.958$, $P < 0.001$ for log-rank test). However, for patients with Stage IVA, the benefit was not statistically significant ($\chi^2 = 2.067$, $P = 0.151$ for log-rank test) (Fig. 6d). The CSS benefit was observed in Stage IVB ($\chi^2 = 18.717$, $P < 0.001$ for log-rank test) and C ($\chi^2 = 12.615$, $P < 0.001$ for log-rank test) (Fig. 6e and 6f). The 5-year CSS of patients with and without radiotherapy is 17.1% and 13.7%. The Median CSS of patients with radiotherapy is 6 months and that of patients without radiotherapy is 4 months (95% CI: 5.367–6.633, 3.351–4.649, respectively).

Combined Surgery And Radiotherapy For Stage Iva

The above analysis data shows that patients with stage IVA have not obtained CSS improvement from surgery or radiotherapy alone. Therefore, we further analyzed the effect of combined surgery and radiotherapy on the survival of patients with stage IVA. The results showed that compared with patients with stage IVA who received surgery alone, the survival of patients who received surgery and radiotherapy combined treatment was significantly improved (OS: $\chi^2 = 6.454$, $P = 0.011$ for log-rank test) (Fig. 7). The median OS of patients with stage IV A receiving surgery, radiotherapy alone and the combination of the two is 4, 5 and 33 months (95% CI: 0.411–7.589, 0.000–10.500, 16.290–49.710, respectively).

Discussion

In the current study, we extracted a large amount of data from the SEER program to examine the largest series of ATC cases which were reported so far. Although the annual incidence of ATC has increased across the world in recent decades, data on the survival prognosis of ATC are deficiently described due to its rareness.

Our study reported that ATC patients with distant metastasis (Stage IVC) had poor prognosis, which were consistent with previous studies[6, 7]. About 15% of ATC patients present with extensive local invasion, half of which have distant metastases at the time of initial diagnosis[8]. In this analysis, 100 of the 261 patients (38.3%) presented with distant disease when diagnosed. Metastatic disease is a significant cause of death, even with adequate local control. De Crevoisier R reported that metastases and tracheal extension were significant prognostic factors for poor prognosis. Tumor death was related to metastatic progression in 68%[9]. Previous studies reported that the disease-related deaths for metastatic disease were range 47.5–90%[7, 9–12].

In the past few decades, due to the rapid progress of ATC, the prognosis has barely been improved. ATC is still a fatal disease. The difference in OS for patients with Stage IVB and Stage IVC in recent decades were not statistical significance. However, the CSS was further improvement. This phenomenon may be resulted from the fact that most ATC patients are older and may die from other diseases such as cardiovascular disease. For the ATC disease itself, its prognosis is improved. As a shortcoming of this research, we did not use competing risks analysis methods to assess the cancer-specific survival with consideration for competing risk events, we will do this work in future research. In this research, adoption of surgery and radiotherapy alone were associated with improved survival. Intriguingly, the benefit of surgery and radiotherapy was only observed in Stage IVB and C instead of Stage IVA. The application of surgery or radiotherapy alone did not have a significant impact on the survival of patients with stage IV A. Early diagnosis of ATCs are expected to have a better prognosis because complete removal of disease is more probable, the benefit of surgery was stable in intrathyroidal ATCs but more primarily seen in patients with local metastasis or distant metastasis. For stage IV A patients, radiotherapy alone did not yield survival benefits. The application of radiotherapy in patients with stage A needs further study. Compared with the patients received surgery alone, the survival benefit was observed in patients who received surgery and radiotherapy combined. This result is similar to other studies. With the gradual deepening research of ATC, optimal combination of treatment modality has played an increasingly important role. Joon-Hyop Lee analyzed thirty-four ATC patients and found that a more intense combination of surgery and chemo-radiotherapy tends to secure a longer survival period[13]. Additionally, there is another limitation in our study. Only 63 patients at Stage IVA in 1976–1985. Therefore, we did not analyze the OS and CSS of patients at Stage IVA in different years. Finally, the study was designed based on the condition of USA population, and the conclusions should thus be extended to other ethnic groups with caution.

Conclusion

In conclusion, by analyzing 1293 ATCs patients treated during 1976–2015, the 5-year CSS for ATC was improved in recent years since 1990s. Patients with local metastasis or distant metastasis could benefit from surgery and radiotherapy. For Stage IVA patients, combined surgery and radiotherapy should get survival benefit than surgery alone.

Abbreviations

OS: overall survival; CSS: cancer-specific survival; ATC: Anaplastic thyroid carcinoma; SEER: Surveillance, Epidemiology, and End Results; CI: confidence interval;

Declarations

Ethics approval and consent to participate

This study used previously collected de-identified data, the need for informed consent had been waived due to the retrospective nature of the study, and was deemed exempt from review by the Ethics Committee of the Affiliated Hospital of Integrated Chinese and Western Medicine, Nanjing University of Chinese Medicine.

Consent for publication

Not applicable.

Availability of data and materials

The datasets are available in the SEER repository and can be obtained from <https://seer.cancer.gov>.

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contributions

JW and XZ designed the study, JJ and TQ collected the data, CH analyzed the data, ZF organized the manuscript, BM reviewed the paper and revised the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

The stage-related survival trends. (a) The ATC patients with Stage IVC had worse OS as compared to the other stages. (b) The ATC patients with Stage IVC had worse CSS as compared to the other stages.

Figure 2

The years-related survival trends. (a) The OS of the next 3 decades were not significant improved since 1976-1985. (b) The difference in OS for patients with stage IVB in recent decades were not statistical significance. (c) The difference in OS for patients with stage IVC in recent decades were not statistical significance. (d) The CSS were improved in the 4 decades and the difference reached statistical significance. (e) The CSS for patients at stage IVB were improved in the 4 decades and the difference reached statistical significance. (f) The CSS for patients at stage IVC were improved in the 4 decades and the difference reached statistical significance.

Figure 3

The surgery-related survival trends. (a) The patients who received surgery had better OS as compared to patients did not receive surgery. (b) The patients who received surgery had better CSS as compared to patients did not receive surgery.

Figure 4

The surgery-related survival trends in different stages. (a) The surgery resulted in improved OS was observed in Stage IVB. (b) The surgery resulted in improved CSS was observed in Stage IVB. (c) The surgery resulted in improved OS was observed in Stage IVC. (d) The surgery resulted in improved CSS was observed in Stage IVC. (e) Surgery was not associated with CSS in patients with Stage IVA.

Figure 5

The radiotherapy-related survival trends. (a) The patients who received radiotherapy had better OS as compared to patients did not receive radiotherapy. (b) The patients who received radiotherapy had better CSS as compared to patients did not receive radiotherapy.

Figure 6

The radiotherapy-related survival trends in different stages. (a) The radiotherapy resulted in improved OS was observed in Stage IVA. (b) The radiotherapy resulted in improved OS was observed in Stage IVB. (c) The radiotherapy resulted in improved OS was observed in Stage IVC. (d) Radiotherapy was not associated with CSS in patients with Stage IVA. (e) The radiotherapy resulted in improved CSS was observed in Stage IVB. (f) The radiotherapy resulted in improved CSS was observed in Stage IVC.

Figure 7

The survival trends in different treatment for Stage IVA. The combination of surgery and radiotherapy resulted in improved OS was observed in Stage IVA.