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Interaction between tumor stage and age on survival outcomes of patients with anaplastic thyroid cancer

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Abstract

BACKGROUND

Anaplastic Thyroid Cancer (ATC) is an aggressive, rare malignancy associated with rapid growth and metastasis, and a very poor prognosis. We investigated the clinical characteristics, survival outcomes and independent prognostic factors associated with anaplastic thyroid cancer.

AIM

The aim of this study is to assess to what extent the interaction between age and tumor stage affects mortality.

METHODS

A total of 622 patients diagnosed with anaplastic thyroid cancer, between 2010 and 2017 were enrolled in our study by retrieving data from the Surveillance, Epidemiology and End Results (SEER) database. We analyzed demographics, clinical characteristics, overall mortality (OM) and cancer specific mortality (CSM) of ATC. Variables with a *P* value < 0.1 were incorporated into the multivariate cox model to determine the independent prognostic factors. Furthermore, we analyzed the interaction between age and tumor stage on mortality.

RESULTS

In the multivariate analyses, the divorced/separated population had a lower OM (HR = 0.63,95%CI: 0.42-0.94,p < 0.05) and CSM(HR = 0.61,95%CI 0.40-0.92,p < 0.05).OM was higher in tumors with direct extension only(HR = 6.26,95%CI: 1.29-30.42,p < 0.05) and tumors with distant spread(HR = 5.73,95%CI: 1.34-24.51,P < 0.05).CSM was also higher in tumors with direct extension(HR = 5.05,95%CI: 1.05-24.19,p < 0.05) and tumors with distant spread(HR = 4.57,95%CI: 1.08-19.29,p < 0.05).Mortality was not adversely affected by lymph node involvement.OM was lower in patients who received radiation (HR = 0.66,95%CI: 0.53-0.83,p < 0.01), chemotherapy(HR = 0.63,95%CI: 0.50-0.79,p < 0.01) or surgery(HR = 0.53,95%CI: 0.43-0.66,p < 0.01).CSM was also lower in patient who received radiation(HR = 0.64,95%CI: 0.51-0.81,p < 0.01),chemotherapy(HR = 0.62,95%CI: 0.50-0.78,p < 0.01) or surgery(HR = 0.51,95%CI: 0.41-0.63,p < 0.01). There was no significant interaction between age and tumor stage that affected mortality.

CONCLUSION

In this large US SEER database retrospective study, we found the mortality to be higher in advanced stage tumors with direct extension and distant metastasis. However, patients who received aggressive therapy showed a better overall survival. The aim of our study is to emphasize the importance of detecting ATC at an early stage and provide aggressive therapy to these patients. Since advanced stage ATC is associated

with a dismal prognosis, we emphasize the need for randomized control trials (RCTs) and development of novel therapies that will be used to treat ATC.

INTRODUCTION

Anaplastic thyroid cancer (ATC) is an aggressive and rare malignancy of the thyroid gland, accounting for approximately 1-2% of all thyroid cancers[1]. It is characterized by rapid growth, early metastasis, and a dismal prognosis, with a median survival time of less than six months[2]. Over the past decade, significant advancements in our understanding of ATC's pathogenesis and treatment have emerged, shedding light on the critical factors influencing patient outcomes. The interaction between tumor stage and patient age are among these factors that have increased the attention of the medical community. This introduction aims to provide a comprehensive overview of the dynamic interplay between tumor stage and age and its impact on the survival outcomes of patients with ATC.

Thyroid cancer, in general, has been on the rise in recent years, with ATC representing the most aggressive form. Age has long been recognized as a crucial determinant in cancer development and progression, with distinct patterns observed across various cancer types. For ATC, it is imperative to explore how age influences the disease's presentation, progression, and survival outcomes, as it may offer invaluable insights into personalized treatment strategies. Several studies have highlighted age as an independent prognostic factor for ATC patients, with older individuals often experiencing poorer survival rates[3]. Age-related disparities in tumor biology, immune response, and treatment tolerance contribute to these findings. Recent research suggests that age-related molecular alterations within ATC tumors may influence disease aggressiveness. These age-related genomic differences can affect tumor growth, response to therapy, and overall survival, further emphasizing the importance of considering age in the management of ATC[4].

Tumor stage at diagnosis remains a critical predictor of survival in ATC patients. The Tumor, Node, Metastasis (TNM) staging system provides valuable insights into disease severity[5]. However, it is essential to investigate how age modifies the prognostic significance of tumor stage in ATC. Age-related variations in clinical presentation and diagnostic delays are well-documented in ATC[6]. Older patients often present with more advanced disease due to less aggressive diagnostic workup, potentially confounding the association between tumor stage and age.

The management of ATC poses unique challenges in older patients, who may have comorbidities and reduced functional status. These factors can impact treatment choices and overall survival[7]. Over the past decade, novel treatment approaches, such as targeted therapies and immunotherapies, have shown promise in ATC[8]. However, the efficacy and safety of these treatments may vary with age, necessitating a nuanced assessment of their impact on survival outcomes. Combining surgery, radiation, and systemic therapies is often the cornerstone of ATC treatment. Understanding how age influences treatment response and tolerance is crucial in optimizing therapeutic strategies[9,10]. While age is typically considered a prognostic factor for various malignancies, thyroid cancer stands out due to its unique incorporation of age as a staging variable in the assessment of prognosis. Age can significantly impact treatment decision-making, with older patients often prioritizing quality of life over aggressive interventions. Shared decision-making between patients, families, and healthcare providers is paramount[11].

With the rapid evolution of precision medicine, ongoing research aims to identify age-specific biomarkers and therapeutic targets for ATC. Tailored treatment approaches may offer improved survival outcomes for both younger and older patients. International collaborations and data-sharing initiatives have facilitated the pooling of data from various centers, enabling the examination of large cohorts of ATC patients across different age groups[12].

MATERIALS AND METHODS

Study design

A retrospective cohort study was carried out on patients with ATC using data from the SEER research database. This database, managed by the United States National Cancer Institute (US NCI), is renowned for its comprehensive cancer-related dataset. It encompasses 18 population-based cancer registries, collectively known as SEER 18, which compile data on cancer incidence, clinicopathological characteristics of patients, and survival rates. Covering approximately 28% of the U.S. population, the SEER 18 database is a significant and authoritative resource for cancer research[13].

Data selection

Inclusion criteria:

We included all patients diagnosed with HSTCL between 2010 and 2017 in our cohort, identified from the SEER database using criteria related to primary site and histological type. Data for these patients were extracted from the SEER database using the specified ICD-9, ICD-10, and/or ICD-O-3 codes.

Exclusion criteria:

Patients with unknown age at diagnosis, race, or stage of ATC were excluded from the study.

Study variables

Main exposure

With the exception of the year of diagnosis, all variables within this cohort were utilized as primary predictors of prognosis.

Outcomes

Overall mortality was defined as patients who died from any cause by the end of the study being categorized as "yes," while those who did not were categorized as "no."

Cancer-specific mortality referred to patients who died from ATC at the end of the study being categorized as "yes," while those who died from other causes were classified as "no."

Survival months

Regarding overall mortality, survival time was computed from the date of diagnosis to either the date of death or the last follow-up date (December 31, 2017), as documented in the SEER registry.

Regarding cancer-specific mortality, survival time was determined from the date of diagnosis to either the date of death due to ATC or the last follow-up date, as documented in the SEER registry.

Sociodemographic and tumor characteristics

The following variables were extracted: Age at diagnosis, gender, race (White, Black, and others), ethnicity (Non-Hispanic and Hispanic), stage at diagnosis (localized, regional, and distant), geographic residential area, annual income, marital status, year of diagnosis, surgery, radiation and chemotherapy.

Statistical analysis

The Cox proportional hazards regression model relies on the assumption that hazard rates remain proportional over time. Variables with a significance level of < 0.1 in the univariate Cox regression model were included in the multivariate Cox proportional analysis to identify independent prognostic factors associated with overall mortality (OM) and cancer-specific mortality (CSM), where a hazard ratio (HR) > 1 indicates adverse prognostic factors. All tests were two-sided, with a confidence interval set at 95%, and a p-value < 0.05 considered statistically significant. Statistical analyses were conducted using STATA 18.0 software.

RESULTS

We conducted our study with a cohort of Anaplastic Thyroid Cancer (ATC) patients, comprising a total of 622 individuals. Table 1 provides a comprehensive overview of the baseline characteristics of our study population. In our cohort, 58.84% were female, and 41.16% were male. Age distribution at diagnosis revealed that 20.58% fell within the 00-59 age group, 54.98% within the 60-79 age group, and 24.44% were aged 80 and above. Marital status varied, with 55.31% being married, 16.40% single, 6.75% divorced/separated, and 21.54% widowed. Tumor stage distribution indicated that a significant proportion (74.44%) of patients presented with distant metastasis, while 5.47% had localized tumors. In terms of race, the majority were non-Hispanic white (61.09%), followed by Hispanic (18.01%), Other (13.34%), and non-Hispanic black (7.56%). Living area analysis showed 58.68% in counties with a population of 1 million persons, 24.28% in areas with 250,000 to 1 million persons, 5.14% in areas with 250,000 persons, 6.59% in nonmetropolitan counties adjacent to a metropolitan area, and 5.31% in nonmetropolitan counties not adjacent to a metropolitan area. Income per year exhibited a diverse distribution, with 4.66% earning less than $45,000, 35.85% earning $75,000 and above, and varying percentages in the income brackets between. Treatment modalities varied, with 42.93% not receiving radiation, 55.14% not receiving chemotherapy, and 56.43% not undergoing surgery. The study spanned across different years of diagnosis, ranging from 12.06% in 2010 to 15.92% in 2017. These baseline characteristics provide a detailed snapshot of the demographic and clinicopathologic profile of our ATC patient cohort.

Table 2 illustrates the crude analysis of factors associated with all-cause mortality (OM) and cancer-specific mortality (CSM) among US patients diagnosed with Anaplastic Thyroid Cancer between 2010 and 2017. Age at diagnosis demonstrated significant associations, with higher OM and CRM observed in older age groups: 60-79 years (OM HR = 1.38, 95%CI: 1.10-1.74; CRM HR = 1.29, 95%CI: 1.02-1.64) and 80 + years (OM HR = 1.64, 95%CI: 1.24-2.16; CSM HR = 1.16, 95%CI: 1.19-2.08). Tumor stage also showed significant associations, with higher HRs for more advanced stages, particularly in tumors with local spread (OM HR = 2.12,95%CI 1.22-3.66, $P < 0.01$; CSM

HR = 2.07, 95%CI: 1.16-3.66, $P < 0.01$) and tumors with distant spread (OM HR = 3.24, 95%CI: 2.05-5.12; CSM HR = 3.25, 95%CI: 2.01-5.24). Furthermore, treatment modalities like radiation, chemotherapy, and surgery demonstrated significant associations with lower OM and CRM. Radiation (OM HR = 0.61, 95%CI: 0.50-0.74; CRM HR = 0.59, 95%CI: 0.49-0.72), chemotherapy (OM HR = 0.61, 95%CI: 0.50-0.73; CRM HR = 0.60, 95%CI: 0.49-0.72), and surgery (OM HR = 0.50, 95%CI: 0.41-0.59; CRM HR = 0.47, 95%CI: 0.39-0.58) were all significantly associated with lower OM and CRM. Associations marked with $^{a}p < 0.05$ and $^{b}p < 0.01$ indicate statistical significance at the respective levels. Confidence intervals are reported at the 95% level.

In Table 3, multivariate analyses, age did not demonstrate an adverse effect on mortality outcomes. However, the divorced/separated population exhibited a significantly lower risk of overall mortality (HR = 0.63, 95%CI: 0.42-0.94, $P < 0.05$) and cancer-specific mortality (HR = 0.61, 95%CI: 0.40-0.92, $P < 0.05$). Conversely, overall mortality was higher in tumors with direct extension only (HR = 6.26, 95%CI: 1.29-30.42, $P < 0.05$) and those with distant spread (HR = 5.73, 95%CI: 1.34-24.51, $P < 0.05$). Similarly, cancer-specific mortality was elevated in tumors with direct extension (HR = 5.05, 95%CI: 1.05-24.19, $P < 0.05$) and distant spread (HR = 4.57, 95%CI: 1.08-19.29, $P < 0.05$). However, mortality was not adversely affected by lymph node involvement. Moreover, patients who received radiation (HR = 0.66, 95%CI: 0.53-0.83, $P < 0.01$), chemotherapy (HR = 0.63, 95%CI: 0.50-0.79, $P < 0.01$), or surgery (HR = 0.53, 95%CI: 0.43-0.66, $P < 0.01$) had significantly lower risks of overall mortality. Similarly, cancer-specific mortality was reduced in patients who received radiation (HR = 0.64, 95%CI: 0.51-0.81, $P < 0.01$), chemotherapy (HR = 0.62, 95%CI: 0.50-0.78, $P < 0.01$), or surgery (HR = 0.51, 95%CI: 0.41-0.63, $P < 0.01$).

In Table 4's multivariate Cox proportional hazard regression analyses considering the interaction between tumor stage and age, several notable findings emerge regarding all-cause mortality (OM) and Anaplastic Thyroid Cancer-related mortality (CSM). In terms of specific interactions, there is no interaction between tumor stage and age significantly influencing mortality outcomes. However, it's important to note that the confidence

intervals for many of these estimates are wide, indicating uncertainty in the estimates due to small sample sizes within some subgroups. Therefore, further investigation with larger datasets may be warranted to better understand the potential interactions between tumor stage and age on mortality outcomes in Anaplastic Thyroid Cancer patients.

DISCUSSION

In this large retrospective study using the SEER database, we found a female and non-Hispanic white predominance, most patients were diagnosed between 60 and 79 and at an advanced stage. There was almost an equal distribution between patients that received therapy and those that did not. Advanced age and advanced stage were associated with increased OM and CSM and all treatment modalities were associated with a lower OM and CSM, in the univariate analysis. In the univariate analysis however, age did not affect mortality and interestingly, distant metastasis and local involvement of the thyroid cancer were associated with higher OM and CSM. All treatment modalities were again associated with lower OM and CSM. Furthermore, age and tumor stage did not interact with each other to affect mortality.

ATC is a rare cancer that tends to occur in older patients compared to differentiated thyroid cancers with a mean age of 65 years old at the time of diagnosis[14,15]. Our study mirrors the literature as most patients were diagnosed between 60 and 79. Previously available literature has highlighted a female predominance with up to 70% in the Kebebew series[14]. A similar trend was seen in the Nagaiah series[15]. Our study results are in adequacy with the current literature with a female involvement close to 60%. More than two thirds of our cohort had distant metastasis at the time of diagnosis. Distant metastasis at the time of diagnosis has been reported in up to 50% of patients in the available literature[16,17].

Most patients with ATC die within a few months, primarily because of local extension and airway obstruction[18]. Thus, tumor size plays an important role in the mortality of patients with ATC even without distant metastasis as shown in the

literature[19,20]. A similar trend was observed in our cohort, patients with local invasion had the highest OM and CSM. Distant metastasis has also been shown to be a single predictor of poor outcome in the literature[21,22] with similar results in our cohort. Age has been shown to be an important independent factor of poor prognosis in several rare cancers[23-25]. Although the univariate analysis revealed a poor prognosis associated with advanced age, those results did not hold true in the multivariate analysis while considering covariates. This could be explained by the fact that most patients are diagnosed at advanced age[14,15], an observation that was made in our cohort as well, with most patients diagnosed between 60-79 years old followed by patients 80 years or older.

Several studies addressing cancer mortality have focused on the interaction of two or more independent prognostic factors. Some studies revealed a notable interaction while others did not find any[24, 26]. In an effort to better understand factors associated with mortality of this malignancy with a very dismal prognosis, we conducted a study looking at the extent to which two independent prognostic factors would interact to affect mortality. We found that although age and advanced/Locally invasive disease individually affect prognosis, they do not interact to enhance mortality. This novel finding adds to the literature by unveiling an important area of this pathology that has not been studied yet. This finding suggests a novel area of study within ATC prognosis.

It has been demonstrated in the literature that married patients tend to have a lower mortality compared to their non married counterparts[23,26]. It was hypothesized that married patients may have stronger social support leading to a better outcome. However, a recent study on Primary cardiac sarcoma found a lower OM in widowed patients[27]. Interestingly, divorced patients had the best outcome in our cohort. A somehow similar trend was observed in anal canal squamous cell carcinoma where divorced patients had the second-best overall survival following married patients[28]. Our findings can be explained by a lower sample size of divorced patients in our cohort. Furthermore, most patients are diagnosed at an advanced stage and social support may not play a crucial role in mortality as seen in other cancers[23,27].

Although most patients are diagnosed at an advanced stage, all treatment modalities offered were associated with a lower OM and CSM. This finding is extremely important as early detection and management of this dismal cancer may significantly impact mortality. This data may assist treating oncologists in decision making for management of patients with this deadly malignancy. Patients with suspected locally invasive ATC should be promptly evaluated for resection as this may significantly impact their mortality. Historically, metastatic ATC is incurable with a median survival of 4.2 months. However, this data included a period from 1985 and 2009[29]. Our more recent and updated data offers a better prognostic picture. The study suggests a more favorable prognosis for ATC patients compared to historical data, likely due to advancements in targeted therapy and precision oncology. The findings may assist oncologists in decision-making regarding the management of ATC patients, emphasizing the importance of evaluating and managing based on cancer stage rather than age. Furthermore, available treatment modalities should be offered rather than end of life care given the improved mortality associated with our cohort. Overall, the study provides valuable insights into the demographic, clinical, and prognostic factors of ATC, highlighting the importance of early detection, prompt management, and the potential impact of treatment modalities on patient outcomes.

Certain limitations must be considered in the interpretation of the results of this study. The information available for chemotherapy did not specify if this treatment was given as neoadjuvant or adjuvant. Furthermore, the SEER database, the largest cancer database in the USA that is publicly available, does not provide information on comorbidities.

CONCLUSION

In conclusion, our ATC mortality study from 2010 to 2017 reveals notable trends: Heightened risk in the 80 + age group, with distant metastasis and residing in nonmetropolitan areas without adjacency to a metropolitan center. A distinctive finding is the protective effect among divorced/separated individuals. This aligns with existing

literature, emphasizing age and tumor stage as crucial influencers in ATC outcomes. From a clinical perspective, recognizing the vulnerability of the elderly and the impact of marital status informs targeted interventions. Regional disparities in nonmetropolitan areas highlight the need for focused healthcare strategies. Future research should probe mechanisms behind the protective effect among divorced/separated individuals and address healthcare disparities in nonmetropolitan areas. Our study provides a foundation for understanding ATC mortality factors, guiding the development of personalized healthcare strategies.

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