ORIGINAL ARTICLE

Anaplastic Thyroid Carcinoma: A 20-year Institutional Review

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Received on: 25 January 2024; *Accepted on:* 20 February 2024; *Published on:* xxxx

Abstract

Background: Anaplastic thyroid cancers (ATC) are highly aggressive and lethal. Despite their low incidence, they account for a significant portion of thyroid cancer-related deaths. In this review, we will examine the clinical characteristics of ATC patients at our center over the past 20 years and their prognosis.

Materials and methods: We retrospectively reviewed all ATCs diagnosed at Hospital Raja Perempuan Zainab II, Kota Bharu, Malaysia, from 2004 to 2023. Patients were identified from our lab database, and their clinical details were obtained from their medical records.

Results: There were 42 patients, with a female-to-male ratio of 1.6:1 and a median age of 62 years. The majority (92.6%) presented with goiter larger than 4 cm and were female (61.9%). Only one patient had a history of differentiated thyroid cancer (DTC). Most patients (76.2%) presented with goiters lasting <10 years, while only 10 patients had a history lasting for >10 years. Hyperthyroidism was observed in only nine cases, while the rest were euthyroid. Common presenting complaints included dysphagia (59.5%), dyspnea (59.5%), and hoarseness of voice (57%). A large portion of the patients presented with advanced disease, with 26 patients showing distant metastasis, 28 patients exhibiting extrathyroidal extension, and 23 patients having lymph node involvement. The majority (66.7%) survive <3 months from the time of diagnosis.

Conclusion: The management of ATC has evolved from palliative care to personalized therapies. However, the prognosis still remains grim. Further research and clinical trials are needed to optimize treatment strategies to improve quality of life and overall survival (OS).

Keywords: Anaplastic thyroid cancer, Cancer, Endocrine, Surgery, Thyroid, Thyroid cancer.

World Journal of Endocrine Surgery (2023): 10.5005/jp-journals-10002-1463

Introduction

Anaplastic thyroid cancer (ATC) is an extremely aggressive, undifferentiated tumor originating from the thyroid follicular epithelium, boasting a disease-specific mortality rate approaching 100%. Although they account for only 1–2% of all thyroid cancers, they contribute to over half of thyroid cancer-related deaths, with a median survival of 5 months and 1-year survival rates ranging from 20 to 50%.[1–3] Early recognition is crucial for timely intervention, with discussions of end-of-life and comfort care being integral to initial disease management planning. Here, we will examine the clinical features and survival outcomes of ATC patients within our unit over the past 2 decades.

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How to cite this article: Teoh KH, AH Imisairi. Anaplastic Thyroid Carcinoma: A 20-year Institutional Review. World J Endoc Surg 2023;https://doi.org/10.5005/jp-journals-10002-1463.

Source of support: Nil

Conflict of interest: None

Institutional Review

A retrospective review was conducted for all ATC patients at our hospital from 2004 to 2023. Our lab database identified 42 patients with a median age of 62 years, ranging from 36 to 81 years. The majority (92.6%) presented with goiter larger than 4 cm, and most of the patients (61.9%) were female. Of the 42 cases, one patient had a history of papillary thyroid carcinoma (PTC). Most patient (76.2%) presented with goiters lasting <10 years, while only 10 had a history of goiters lasting for >10 years. Hyperthyroidism was observed in only nine cases, while the rest were euthyroid. The most common presenting complaints were dysphagia in 25 (59.5%), dyspnea in 25 (59.5%), and hoarseness of voice in 24 patients (57%). Unfortunately, a large portion of the patients presented with advanced disease, with 26 (61.9%) patients showing distant metastasis, 28 (66.7%) patients exhibiting extrathyroidal extension, and 23 (54.8%) patients having lymph node involvement (Table 1). In view of all patients presenting late, none of the patients received curative treatment. Only one patient underwent a single fraction hemostatic radiotherapy for her bleeding fungating tumor. The prognosis was poor, with the majority (66.7%) surviving <3 months from the time of diagnosis (Fig. 1).

Discussion

Incidence

ATC is uncommon but remains the leading cause of thyroid cancer-related deaths. According to the Surveillance, Epidemiology, and End Results (SEER) data in the United States, the incidence per 1,000,000 population is 0.9–1.2 cases with a median survival rate of 3–4 months.[4,5] Similarly, the incidence of ATC only accounts for only 1.2% of all thyroid cancer cases at our center.[6] Typically, patients diagnosed with ATC are older than those with differentiated thyroid cancer (DTC), with the majority being over 50 years of age and a mean age of 65–70.5 years.[2,4,7] The female-to-male ratio varies from 3.1:1 to 1.2:1, indicating a higher prevalence of female ATC patients in comparison to males.[2,8] These trends are also apparent in our

Table 1: Patients' clinical presentations and survival rate

Patients' clinical presentations		
	Number	*Percentage (%)*
Sex		
Male	16	38.0
Female	26	61.9
Duration of goiter		
>10 years	10	23.8
<10 years	32	76.1
Toxic symptoms		
Yes	9	21.4
No	33	78.6
Presenting symptoms		
Dysphagia	25	59.5
Dyspnea	25	59.5
Hoarseness of voice	24	57
Neck pain	6	14
Tumor size		
>4 cm	39	92.9
<4 cm	3	7.1
Lymph node involvement		
Yes	23	54.8
No	19	
Extrathyroidal extension		
Yes	28	66.7
No	14	
Distant metastasis		
Yes	26	61.9
No	16	

series, as most of our patients were females (61.9%), over the age of 50 and had a median age of 62 years.

Presentation

Being an aggressive tumor, patients usually present with rapidly enlarging unresectable neck mass or metastasis.[9,10] The tumor volume can double within 1 week.[11] leading to symptoms, such as neck pain. Additionally, the swift growth may compress or invade the upper airway or digestive tract, causing dyspnea (35%), difficulty in swallowing (30%), hoarseness of voice (25%), and cough with occasional hemoptysis (25%). The sudden growth spurt can also sometimes be due to bleeding within the tumor.[2] Most of our patients presented late with goiters larger than 4 cm (92.6%). The largest goiter measured 29 × 13 cm. As a result, their main complaints were related to obstructive and invasive symptoms such as dysphagia (59.5%), dyspnea (59.5%), and hoarseness of voice (57%). The delayed presentation also translated to a higher incidence of metastatic disease diagnosed at presentation itself (61.9%). These rates are notably higher compared to other studies,[7–9,12] and we attribute their late presentation to the poor education level among our patients, who mostly come from a low socioeconomic group. The association between low education level and ATC risk was highlighted in the American Thyroid Association's (ATA) 2021 Guidelines for ATC.[3] They suspect it may be due to limited healthcare access and lower health consciousness contributing to neglected thyroid conditions, increasing the likelihood of ATC pathogenesis.[3] Lin et al.,[5] in their SEER database analysis, also identified socioeconomic status as an independent prognostic factor, where

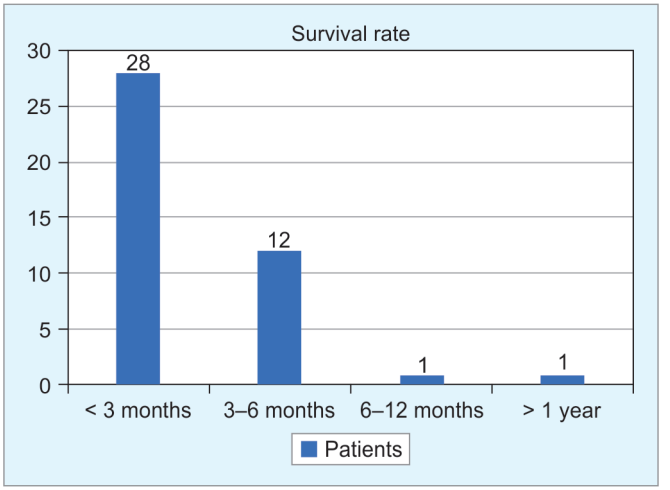

Fig. 1: Survival rate of ATC patients

those with higher income levels had longer survival times [hazard ratio (HR) = 0.79, 95% confidence interval (CI) = 0.66–0.86, and $p < 0.001$]. They postulated that this phenomenon could be attributed to higher-income patients being more proactive about their health and the widespread adoption of regular health checkups. This also leads to a higher proportion of high-income patients presenting with nonmetastatic disease (55.94%).[5]

A prior history or concurrent DTC was reported in approximately 23–58% of ATC patients.[7,8] PTC are the most prevalent, but follicular cancers and Hürtle cell cancer can also coexist.[2,7,8] These findings support the hypothesis that ATC tumorigenesis maybe a multistep dedifferentiating event of a DTC.[1,2] In our series, only one patient had a prior history of DTC. She initially had PTC and underwent total thyroidectomy followed by radioiodine ablation, but 1 year later, she was diagnosed with ATC. The reason the incidence of prior/concurrent DTC in our series (2.4%) is lower than that quoted in the literature is that all our patients presented late with advanced disease. If they had presented earlier and surgery had been done, allowing further histopathological examination of the whole thyroid gland, we suspect the incidence may have been higher. However, from a clinical standpoint, there were no differences in terms of patient characteristics, presentation and prognosis between ATC that occurred *de novo* or mutated from DTC.[1]

Diagnosis

Fine needle aspiration (FNA) cytology is typically the initial biopsy of choice as it provides sufficient diagnosis without much morbidity. ATA's 2021 guidelines stated that although the diagnostic yield of FNA varies significantly, ATC can still be diagnosed in over 60% of cases.[3] Us-Krasovec et al.[13] even reported an FNA accuracy as high as 89.7%. They recognized that diagnostic accuracy is constrained by the sampling technique due to the presence of inflammation, necrosis, and hemorrhagic areas, which can be difficult to avoid. Furthermore, marked desmoplastic tumors can impede adequate sampling. They suggest that for large tumor, aspiration should be performed at two or three different sites to obtain a representative sample. This is crucial in differentiated tumors that are transforming into ATC, where maybe only a small area of anaplastic changes are present.[13] In cases where FNA results are indeterminate, a core biopsy is recommended, which also provides sufficient material for molecular testing and immunostaining.[3] In our series, FNA was

used to diagnose all but four patients where ultrasound-guided core biopsy was needed as the FNA came back unsatisfactory. All four were large goiters ranging from 8 × 8 to 29 × 13 cm.

Morphological patterns of ATC vary greatly on cytopathology, with sarcomatoid (26–53%), pleomorphic giant cell (25–50%), and squamoid (19–21%) types being frequently observed.[7,8,11] Mixed morphologies, the most common being that of spindle and giant cell patterns, often occur too.[3,10] Elevated mitotic rates (>1 mitosis per high power field) and raised Ki-67 proliferation indices (>30%) are typical, and their absence may suggest a different diagnosis.[3] Other common findings include atypical mitoses (85%), tumor necrosis (77%), and prominent neutrophil infiltrates (71%).[8] Due to its undifferentiated nature, ATC lacks thyroid-lineage markers, such as thyroid transcription factor 1 (TTF-1) and thyroid-specific proteins like thyroglobulin (TG). In a 34-year study at Memorial Sloan Kettering Cancer Center (MKKCC) involving 360 cases, nearly all cases were negative for TG (96%) and TTF-1 (70%) but positive for cytokeratins AE1/AE3 (76%) and Pax8 (70%).[8] Thus, the detection of Pax8 on immunohistochemistry can help diagnose ATC when an undifferentiated high-grade neoplasm is observed on cytology. However, Pax8 is not thyroid-specific and is also found in the kidney and Müllerian system, necessitating careful diagnosis differentiation from renal to ovarian carcinomas that do not typically metastasize to the thyroid.[3]

Other diagnostic procedures include laboratory evaluation, imaging studies, evaluation of the airway and vocal cords and testing for v-Raf murine sarcoma viral *oncogene homolog B (BRAF)* V600E mutation. Serum TG levels are assessed to identify coexisting metastatic DTC, which, when present, will be markedly elevated. *BRAF* V600E mutations are determined through immunohistochemical staining on biopsy samples to aid in the decision for targeted therapy.[3,10] Neck ultrasound is useful for quick assessment of tumor extension and lymph node involvement, while positron emission tomography/computed tomography (PET/CT) scan is increasingly being used to stage and follow-up patients as ATC avidly picks up 18-fluorodeoxyglucose (18FDG) due to its hypermetabolic state.[3,10,14] Contrasted CT scans of the neck and thorax are invaluable in detecting invasion of ATC to neighboring major vessels, upper respiratory and digestive tract and distant metastasis. ATCs are all categorized as stage IV, with IVA denoting surgically resectable cases, IVB indicating confinement of the disease to the neck but unresectable, and IVC having distant metastases.[3] Prognostic factors consistently linked with ATC outcomes include age, tumor extension, and the presence of distant metastasis.[2,3,5,12,15,16]

Treatment

Due to the low incidence of ATC, medical facilities typically do not encounter many cases. Studies published usually span several years, during which treatment regimens have evolved.[7,8,13] Therefore, even the proposed management approach by the National Comprehensive Cancer Network (NCCN) and the ATA draws upon case studies and clinical experience.[3,10]

Due to its aggressiveness and generally poor response to treatment, ATC management is tailored based on disease stage, prognosis, available treatments, comorbidities, and patient preferences.[3] Early comprehensive counseling covering palliative care, pain management, intensive care unit options, and end-of-life decisions is essential. Subsequent treatments are then guided by interval developments in tumor response to treatment, progression, and adverse events.[3]

Multimodal therapy, combining surgery, chemotherapy, radiotherapy and/or targeted therapy, has significantly improved overall survival (OS) rates.[1,3] Hu et al. observed a 6.6-month median OS in patients who underwent surgery, which extended to 9.6 months with the addition of adjuvant therapy.[17] In contrast, those who did not undergo surgery only had 2.1 months of median survival. Alternative treatment strategies, including primary chemotherapy, radiotherapy alone, palliative therapy or no treatment at all, yielded a median survival of about 3 months. In a separate study, Rao et al. noted that omission of surgery significantly reduces median OS (6.5 vs 22.1 months, p-value 0.0008, and HR = 0.2).[18] Similar outcomes were observed in our institute, where the majority presented late and survived <3 months (66.7%), primarily receiving palliative care.

In managing stage IVA and IVB ATC, surgery's role is crucial, but emphasis is placed on minimizing morbidity. A highly experienced thyroid cancer surgeon who is ready to halt the procedure if morbidity risks rise significantly is essential.[3] Resection of the larynx, pharynx, and esophagus are discouraged due to ATC's poor prognosis and the availability of targeted therapy.[1,3] Prophylactic central or lateral neck node dissection is not necessary, but removing clinically apparent disease is crucial.[3] Additionally, surgery may be considered for stage IVB patients whose disease has shown a positive response to initial medical or radiation treatments.[3,19] However, the extent of surgery in these patient groups remains a topic of debate, as studies have shown that neither the extent nor the margins of tumor resection significantly impact their survival.[7,17]

Given the aggressiveness of ATC, achieving local control is essential in managing the high local progression and recurrence rate. Surgery is recommended whenever feasible, but external beam radiation therapy (EBRT) is often utilized in advanced cases to achieve local control.[1] Retrospective studies and SEER database analysis have shown improved OS with EBRT.[20–22] The combination of radiochemotherapy (RCT) further enhances OS (adjusted HR = 0.69, 95% CI = 0.56–0.85, and $p < 0.001$), as indicated by Zhou et al.'s analysis of the SEER database. This improvement in survival was consistent across subgroups stratified by surgery and the presence of distant metastasis.[23] The ATA, in their 2021 guideline on ATC, recommends concurrent systemic therapy with standard fractionation intensity-modulated radiation therapy (IMRT) for nonmetastatic patients with good performance status after surgery. For patients with no *BRAF* V600E mutations, ATA recommends either dual chemotherapy drugs, such as a combination of paclitaxel/carboplatin, cisplatin/doxorubicin, and docetaxel/doxorubicin, or single-agent chemotherapy of paclitaxel or doxorubicin alone as the systemic component.[3] The timing of RCT in relation to other treatments requires further investigation, but initiating adjuvant therapy promptly after surgery is crucial due to ATC's short doubling time of only 3–12 days. Therefore, RCT should ideally commence within 2–3 weeks after surgery and no later than 6 weeks.[3] In our patients, only one underwent radiotherapy, receiving a single fraction for a bleeding fungating tumor.

For the 20–50% of patients with ATC harboring the *BRAF* V600E mutation, targeted therapy has emerged as a viable treatment option for advanced ATC.[24] The overall response rate (ORR) of this subgroup of patients treated with dabrafenib plus trametinib was 56% in a recent phase II basket trial, which also observed three complete responses.[24] The median progression-free survival (PFS) stood at 6.7 months, and the median OS was 14.5 months. It is noteworthy that in the trial, all 35 stage IVC patients had undergone at least one prior therapy, with surgery or radiotherapy

being the most common treatment choices for 83% of them.[24] This combination of targeted therapy can also be used neoadjuvant in stage IVB patients to enhance the chances of complete tumor resection.[25] After surgery, these patients follow a chemoradiation treatment approach similar to that described for stage IVA patients.

Unfortunately, there is no cure for stage IVC patients, and the prognosis is inevitably fatal. Dabrafenib plus trametinib is still recommended for stage IVC patients whose tumor has *BRAF* mutation, as it has shown promising results in inducing tumor regression.[3] For patients lacking access to targeted therapy or those without *BRAF* mutations, chemotherapy can be considered, and options include combining taxane-based chemotherapy with anthracycline, cisplatin or carboplatin, or single agent taxane or anthracycline. In cases of advanced disease where patients either do not wish for or are no longer fit for systemic therapy, prioritizing palliation of symptoms becomes crucial.

Conclusion

The ATC is an aggressive tumor with a poor prognosis. However, the treatment paradigm has shifted from palliative care to personalized therapies, underlining the significance of molecular-based approaches and surgery, regardless of disease stage. Although surgery, radiotherapy, chemotherapy, and targeted therapy used in multimodal approaches improved survival rates, long-term cure remains challenging. Continued research and clinical trials are essential to optimize treatment strategies and enhance quality of life and OS for ATC patients.

Clinical Significance

The results of my institutional review clearly support the evidence that low socioeconomic status results in poorer outcomes for ATC patients. It also sheds light on the difficulty of early detection of ATC in an area where the majority of the patients are from the lower income group and ATC's grim prognosis.

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