ORIGINAL RESEARCH

Survival and Prognosis of Anaplastic Thyroid Cancer: A 15-year Observation at a Single Asian Institute

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Abstract

Aim: Limited literature from Southeast Asia (SEA) exists on anaplastic thyroid cancer (ATC). The aim of this study was to ascertain factors associated with the survival of ATC at Putrajaya Hospital which is the main referral center for endocrine cases in West Malaysia.

Materials and methods: This is a retrospective analysis of all patients with ATC between January 2002 and December 2016. Data concerning comorbidities, stage of disease, and clinical course were collected *via* electronic medical records and analyzed with Kaplan-Meier survival and log-rank tests for univariate and Cox proportional hazards model for multivariate analysis. This study was approved by the Malaysian Medical Research Ethics Committee (MREC).

Results: A total of 76 patients were treated for ATC at our center, however, 11 had missing data and were excluded from the analysis. Of the remaining 65 patients, the majority were women (44 cases), and the mean age at presentation was 62 years. Majority of patients presented with stage IV C (50.8%) whilst others presented with IV A (3.1%) and IV B (46.2%). Most patients were treated palliatively (36.9%) whilst 29.2% underwent surgery only, 16.9% radiotherapy only, and 16.9% had multimodal therapies. Median survival was 2 months (range 1–14 months) with survival rates of 7.7–1.5% at 6 months and 1-year, respectively. Univariate analysis demonstrated that stage of disease and combination therapy improved survival. When correction was made for sex, age, and stage of disease, the only type of treatment received significantly affected outcomes. Multimodal therapy, either surgery and radiotherapy (hazard ratio 0.29, confidence interval 0.091–0.939, $p = 0.03$) or surgery followed by radiotherapy and chemotherapy (hazard ratio 0.09, confidence interval 0.01–1.0, $p = 0.05$) conferred better outcomes.

Conclusion: The findings in this study that multimodal therapy conferred improved outcomes were comparable to that of numerous other studies, however, more research is needed in assessing the best treatment for this deadly disease.

Keywords: Anaplastic thyroid cancer, Multidisciplinary approach, Outcomes, Treatments.

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Introduction

Literature on anaplastic thyroid cancer in Southeast Asia is limited. Malaysian studies reported that ATC comprises approximately 0.2% of all thyroid lesions and 2.7% of all thyroid cancers in Malaysia.[1,2] Due to its aggressive nature, all ATC are classified as stage IV with IVA being an intrathyroidal disease, IVB disease with extrathyroidal infiltration or cervical node metastases, and IVC for patients with distant metastases.[3] The American Thyroid Association (ATA) first published guidelines in 2012 on the management of this deadly disease which recommended a multidisciplinary approach when treating such patients.[4] Updates in the ATA guidelines published in 2021 outlined suggested treatment algorithms for each of the stages of ATC with an added emphasis on the importance of immunohistochemistry (IHC) and newer targeted therapies.[5] Due to the scarcity and lethal nature of ATC, randomized control trials are extremely challenging to be carried out.[6] This means that a large portion of our evidence supporting these guidelines comes from retrospective studies. Unlike treatment for differentiated thyroid cancers (DTC), to date, there is no uniformly agreed-upon and established treatment protocol with various trials still underway. The authors conducted this study to determine the characteristics and outcomes of patients in our local population which has never been reported previously with the intent to highlight the importance of rethinking how we treat ATC.

Materials and Methods

This study was conducted at Putrajaya Hospital which is the main referral center for endocrine cases in West Malaysia. The main objective of this study was to ascertain factors associated with the prognosis and survival of patients with ATC treated at our center. Data were collected retrospectively on all patients who sought treatment for ATC at Putrajaya Hospital between January 2002 and December 2016. Data collection was done retrospectively *via* the electronic medical records (EMR) system of the hospital. There was a reported total of 76 patients who were treated for ATC at our center. These patients were diagnosed with ATC either *via* fine-needle aspiration (FNA), core biopsy, or *via* postoperative histopathology. Reviewing these patients' medical records, we extracted data concerning patients' comorbidities, stage of disease, clinical course, and treatments received. Of the 76 patients treated for ATC, 11 patients were excluded from analysis due to significant missing information. Analysis of the remaining 65 patients was done using the IBM SPSS statistical software (version 21.0) and was reported as means, standard deviations, medians, ranges, or numbers

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and percentages. Univariate survival analysis was performed using Kaplan-Meier survival curves and log-rank tests whilst multivariate survival analysis was done using Cox proportional hazards model. A *p*-value of <0.05 was considered significant. This study is registered with the Malaysian National Medical Research Registry (NMRR) and the review of patients' medical records was approved by the Malaysian Medical Research Ethics Committee (NMRR-17-2080-37102).

Results

Patient Characteristics

Of the 65 patients, 44 (68%) were women and 21 (32%) were male. The mean age at presentation was 62 years (SD ± 11.5 years, range 33–81). The clinical characteristics of patients are shown in Table 1. The median tumor size at diagnosis was 7.35 cm (range 2–25 cm). 44.6% (29 patients) had a background of thyroid enlargement, either goiter or a differentiated thyroid carcinoma (DTC). All the patients with DTC backgrounds were papillary thyroid carcinoma (PTC). Our patients tend to present with the more extensive disease with only two patients (3%) presenting at stage IVA. Of the 33 patients who were diagnosed with stage IVC disease, 17 patients (51.5%) had lung metastasis, three patients (9.1%) had spine metastasis while the remaining 13 patients (39.4%) had multiple sites of metastases.

Table 1: Clinical characteristics of 65 patients with anaplastic thyroid cancer

Characteristics	*Subgroups*	*No of patients (%) N = 65*
Sex	Male	21 (32)
	Female	44 (68)
Ethnicity	Malay	46 (70.8)
	Indian	8 (12.3)
	Chinese	8 (12.3)
	Others	3 (4.6)
Tumor size	≤5 cm	11 (16.9)
	>5 cm	54 (83.1)
Pre-existing thyroid disease	Goiter	21 (32.3)
	Differentiated thyroid cancer	8 (12.3)
	None	36 (55.4)
Acute airway obstruction	Yes	11 (16.9)
	No	54 (83.1)
Leukocytosis (WCC ≥ 10,000/mm^3)	Yes	40 (61.5)
	No	25 (38.5)
Stage	IVA	2 (3)
	IVB	30 (46.2)
	IVC	33 (50.8)
Treatment received	Surgery only	19 (29.2)
	Radiotherapy only	11 (16.9)
	Surgery + radiotherapy	10 (15.4)
	Surgery + radiotherapy + chemotherapy	1 (1.5)
	Palliation	24 (36.9)

Treatment Characteristics

No patients underwent primary chemotherapy or radiotherapy, that is, chemotherapy and radiotherapy were only given to patients who have undergone surgery. Of the 30 patients who underwent surgery, 18 patients (60%) had R2 resection or debulking while 12 patients (40%) had R0 and R1 resection. Radical neck lymph node dissection was performed in 11 patients (36.7%) who underwent surgery. Only one patient (1.5%) underwent surgery followed by chemotherapy and radiotherapy with the majority of patients going for either surgery alone (n = 19, 29.2%) or palliation therapy (n = 24, 36.9%). During the clinical course of treatment, 13 patients (20%) required tracheostomy either primarily from acute airway obstruction or as part of debulking surgery. Table 2 shows the treatment received by our patients by stage of disease and it demonstrates that the stage of the patient did not result in patients receiving more aggressive treatment as there were other issues that challenged such aggressive treatments such as frailty and patients' choice.

Survival and Outcomes

Median survival was 2 months (range 1–14 months) from diagnosis. Six months and 1-year survival rates are 7.7% and 1.5%, respectively. Sixty-one patients (93.8%) died from disease progression while the remaining four patients (6.2%) died from either sepsis, cardiac causes, or perforated peptic ulcer. Univariate analyses of baseline characteristics and treatment modalities are shown in Table 3. Univariate analysis showed that the stage of disease at presentation significantly affected outcomes as shown in Table 3 and Figure 1. Furthermore, the univariate analysis demonstrated that patients who received combination therapy such as a combination of surgery with radiotherapy and chemotherapy had significantly longer median survival duration (p = 0.01). However, Cox-regression model analysis differed when treatment modalities were individually compared with palliative-intent treatment. Surgery with radiotherapy conferred better survival over surgery with radiotherapy and chemotherapy and surgery alone when individually compared with palliative-intent treatment as shown in the multivariate analysis in Table 4. No other factors such as sex, stage, and extent of disease significantly affected survival Cox proportional hazard models. When correction for sex, age, ethnicity, stage, and tumor size was made, combination therapy either surgery with radiotherapy or surgery with radiotherapy and chemotherapy remains statistically significant in improving survival as shown in Figure 2.

Discussion

Literature generally cites a median survival of 4–12 months which demonstrates the aggressive nature of this disease.[4,6] Our study showed a similarly bleak outlook with a median survival of 2 months. Interestingly, median survival was not shown to have improved in the last 30 years in a surveillance, epidemiology and end results (SEER) database of patients diagnosed between 1986 and 2015.[7] The unchanged survival of ATC is indeed a reflection of the difficulty to achieve a standardized efficient treatment strategy and the need to re-evaluate current treatment strategies.[8] Our study generally

Table 2: Treatment type received based on the stage of disease at diagnosis. The *p*-value for this cross-tabulation was 0.054

	Stage (% within stage group)			
Treatment type	*IV A*	*IV B*	*IV C*	*Total*
Surgery only	0 (0)	4 (13.3)	15 (45.5)	19
Radiotherapy only	0 (0)	5 (16.7)	6 (18.2)	11
Surgery + radiotherapy	1 (50.0)	8 (26.7)	1 (3.0)	10
Surgery + radiotherapy + chemotherapy	0 (0)	1 (3.3)	0 (0)	1
Palliative	1 (50.0)	12 (40.0)	11 (33.3)	24
Total	2 (100)	30 (100)	33 (100)	65

Table 3: Clinical characteristics and treatment modality impact on survival

Characteristics	*Subgroups*	*Median survival (months)*	*p-value*
Sex	Male	2	0.36
	Female	2	
Ethnicity	Malay	2	0.82
	Chinese	2	
	Indian	2	
	Others	2	
Stage	IVA	6	0.027
	IVB	2	
	IVC	2	
Treatment received	Surgery only	2	0.01
	Radiotherapy only	2	
	Surgery + radiotherapy	3	
	Surgery + radiotherapy + chemotherapy	7	
	Palliative	1	

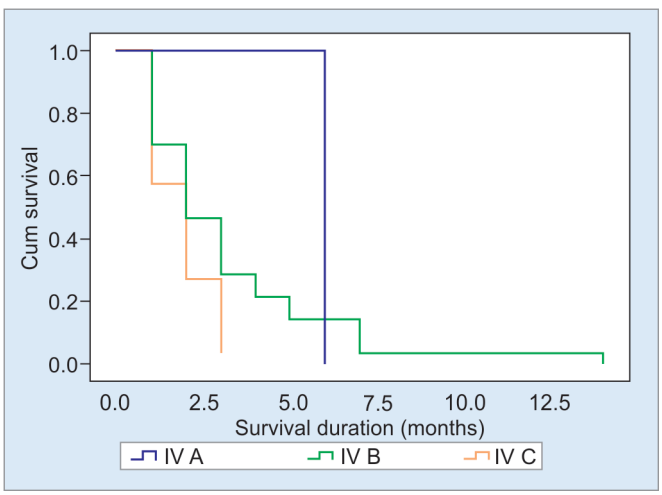

Fig. 1: Overall survival in anaplastic thyroid carcinoma by stage of disease. Overall median survival was 2 months. *p*-value was 0.027. (IV A. N = 2, median = 6 months;IV B. N = 30, median = 2 months;IV C. N = 33, median = 2 months)

Table 4: Multivariate analysis of clinical characteristics and treatment modalities on survival

Variable	*Hazard ratio (95% CI)*	*p-value*
Sex (male vs female)	1.51 (0.47–2.38)	0.89
Stage: IVB vs IVA	0.29 (0.04–2.18)	0.29
Stage: IVC vs IVA	0.59 (0.34–1.04)	0.59
Treatment: surgery + chemo + radiotherapy (vs palliative)	0.23 (0.03–1.75)	0.15
Treatment: surgery + radiotherapy (vs palliative)	0.42 (0.19–0.92)	0.03
Treatment: surgery alone (vs palliative)	1.17 (0.61–2.24)	0.63
Treatment: radiotherapy alone (vs palliative)	0.81 (0.38–1.73)	0.58

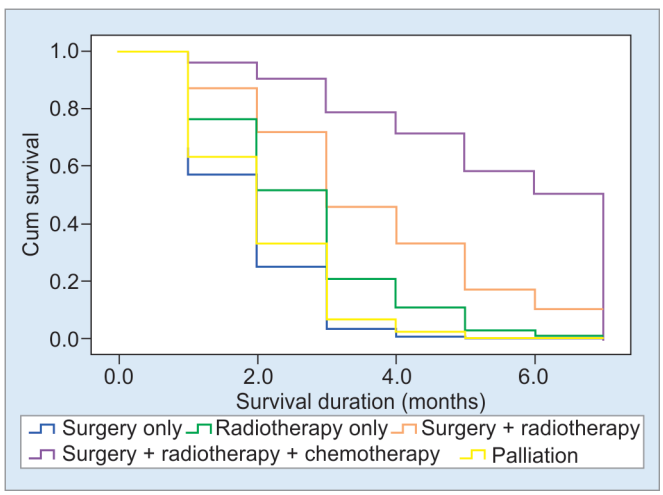

Fig. 2: Survival function plot by treatment modalities after correcting for sex, age, ethnicity, stage of disease, tumor size and NYHA functional classification. The hazard ratios for each modality were derived in reference to palliation. [Surgery only = HR 1.23 (CI 0.52–2.88, p = 0.638). Radiotherapy only = HR 0.59 (0.25–1.35, p = 0.209). Surgery & radiotherapy = HR 0.29 (0.091–0.939, p = 0.03). Surgery, radiotherapy & chemotherapy = HR 0.09 (0.01–1.0, p = 0.05)]

conforms with various other retrospective and prospective studies as well as the latest ATA guidelines published in 2021 which stress the importance of a multidisciplinary approach and multimodal therapy when treating ATC patients.[5]

Studies are still taking place to not only determine which combination of therapy works best for ATC but also the timing

of these treatment options. Various studies generally propose surgery followed by adjuvant chemotherapy and radiotherapy. In fact, one study suggested that maximal debulking surgery should be performed before adjuvant treatment even in stage IVC patients.[9] This was supported by a retrospective Japanese study which demonstrated that debulking surgery achieved better outcomes as compared to no attempts for resection.[10] Of course, the importance of complete resection should not be understated with some studies showing lower local recurrence rates in R0/R1 resections.[11] Several studies, both retrospective and prospective show that surgery followed by adjuvant chemotherapy and radiotherapy conferred better outcomes although the type of radiotherapy, that is, intensity-modulated radiotherapy (IMRT) versus external beam radiotherapy (EBRT) as well as the type of radiosensitizing chemotherapy can be argued.[11,12] These studies also cautioned the potential adverse event associated with such aggressive trimodal treatments. Furthermore, a large cohort of 516 patients demonstrated that stage and a combination of surgery with EBRT improved cause-specific survival.[13] These findings that surgery followed by adjuvant treatment were supported by a study of 50 patients reviewed retrospectively as well a prospective study involving 30 patients who achieved high long-term survival and complete remission when they underwent surgery followed by radiotherapy and chemotherapy.[14,15]

Although the evidence is compelling that maximal debulking with the aims of achieving R0 or R1 resection followed by adjuvant chemotherapy and radiotherapy may be beneficial not only in local control but also in distant metastatic control, some studies have concluded noteworthy findings that perhaps the timing of chemotherapy in relation to surgery mattered just as much as the combination of treatment per se. A study published in 2001 of 79 ATC patients suggested that primary chemotherapy and radiotherapy followed by surgery conferred a longer survival over patients who underwent primary surgery followed by radiotherapy and chemotherapy except in cases of small focal intrathyroidal ATC lesions.[16] In addition, a trial comparing three protocols demonstrated weekly doxorubicin with concurrent radiotherapy followed by surgery at 4 weeks post-chemotherapy initiation had favorable outcomes in local control, however, overall median survival remained bleak with a median survival of 2–4.5 months in all three protocols tested.[17] The importance of timing of treatment such as chemotherapy was shown in a small retrospective series of 13 patients who received weekly induction of paclitaxel which reported promising responses with one patient achieving a complete response.[18] This study was then expanded to a multicenter nationwide prospective single-arm study which illustrated that weekly paclitaxel is not only feasible but confers a clinical benefit rate of 73% in terms of response to treatment and stability of disease with acceptable adverse events.[19]

In the past two decades or so, attention has extended beyond the traditional combination therapy of surgery, chemotherapy, and radiotherapy into identifying genetic mutations leading to ATC and the development of targeted therapies. It is well understood that ATC can arise either de novo or from dedifferentiation of a preexisting DTC with the p53 mutation playing an important role.[20] Almost half of the ATC cases we report had a background of thyroid disease. Hence, the incidence of ATC may reduce when incidences of DTCs are reduced, as a study showed with population-based iodination of salt in Slovenia.[21] Other identified genes include the RAS and BRAF mutations with numerous other mutations identified to smaller proportions.[22] A study looking into the effects of these mutations on survival of ATC showed that p53 mutations were associated with a shorter duration of treatment failure.[23] This study also characterized that the BRAF mutation was more commonly seen in ATC arising from DTC. The comprehension of these mutations may hold the key to treating ATC more effectively as knowing the exact mutation may assist physicians in selecting more suitable targeted therapies. A study looking into the potential benefits of Vemurafenib in treating nonmelanoma cancers with BRAF V600 mutations showed potential benefits in ATC patients carrying such mutations.[24] Furthermore, such targeted agents may be considered as a salvage therapy especially when other treatment options have either failed patients or become unsuitable. A retrospective analysis looking into using Lenvatinib as salvage therapy in ATC suggested that there may be some disease-modifying effects, although this is not without prominent toxicities.[25] Other studies show that these tyrosine kinase inhibitors such as imatinib may at least confer some stability of disease in advanced ATC.[26]

Our study was limited to two main aspects. Firstly, this was retrospective, hence certain biased observations are unavoidable. Secondly, our study spanned a 15-year period in which several evolving regimes of radiotherapy and chemotherapy were given, hence we could not appraise the efficacy of each type of radiotherapy or chemotherapy given. It is possible that the patients who were selected to undergo aggressive therapy had better performance status, hence they fared better. However, when we corrected for disease extent and age, we still found that patients who received a combination of surgery with radiotherapy or surgery with chemotherapy and radiotherapy had significantly better survival. This is the first study in this region looking into ATC survival and treatment options and this study generally observes the same findings as numerous other papers which emphasizes the importance of combination therapy. Although future trials are riddled with issues of scarcity of disease, time-sensitive decision making, and cost of newer targeted therapies, the authors believe that not only does this study add weightage to current evidence supporting combination therapy, but it also stresses the urgency in the re-examination of current paradigms used to treat ATC.

Conclusion

ATC, a rapidly lethal disease, is still confounded with no standardized protocol of treatment. The ATA revised its guidelines on managing ATC in 2021 with emphasis on multimodal, individualized treatment however, the exact dose and timing of treatment modalities remain a closed book. With the scarcity and deadly course of ATC, many of the guideline recommendations are drawn from retrospective studies. In this retrospective analysis, the authors report that our overall survival is comparable to other literature. Furthermore, our findings were in line with various other studies which note that multimodal combination therapy of surgery, chemotherapy, and radiotherapy had a significant effect on improving survival in ATC. Although exciting prospects await physicians in developing newer targeted therapies, more research is needed in assessing not only which combination of treatments is best suited adopted as protocol but also the timing of each modality of treatment.

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