



Anaplastic Thyroid Cancer: a Retrospective analysis of 120 cases

M. Aldehaim, R. Mahmood, F. Hussain, A. Memon, A. Al-Hebshi,
N. Al-rajhi, M. El-sebaie, E. Khalil, M. Ahmad

Research Centre, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia

Abstract

Introduction:

Anaplastic Thyroid Cancer (ATC) is one of the most lethal malignancies with very short survival and extremely poor treatment outcome. ATC accounts for 2-5% of all thyroid cancers worldwide with an annual incidence of about 2/million.

Objective:

To review the natural history and treatment outcome of ATC patients treated at King Faisal Specialist Hospital and Research Centre (KFSH and RC) located at Riyadh, Saudi Arabia.

Material and Methods:

Retrospective review of 120 Saudi cancer patients collected from registry data at KFSH & RC from 1976-2008. Search key words included: thyroid cancer, anaplastic, undifferentiated and not otherwise specified. Search was not restricted to particular age, gender, treatment or tumor size. Demographic information, baseline patient characteristics including date of diagnosis, type of treatment

and date of death were obtained from KFSH & RC registry data and Saudi death registry.

Results:

A total of 120 cases were identified at our cancer centre from 1976 to 2008. Of these total, 73 were females (60.8%) and 47 were males (39.2%). The average age at diagnosis was 63.34 +/- 12.8 years. Thirty-four patients underwent surgery (28.3%), 52 had a palliative radiation treatment (43.3%) and only 5 had chemotherapy (4.2%). The median survival was 53 days (0-457).

Conclusion:

Our review proves that ATC is rapidly fatal cancer and is unresponsive to currently available therapeutic options. More research is needed to understand the tumor biology and novel treatment options.

Keywords:

thyroid cancer, anaplastic, undifferentiated, radiation treatment, chemotherapy, median survival, Riyadh and Saudi Arabia.

Introduction

Thyroid cancer accounts for only 1% of all malignancies and 0.2% of cancer deaths in United States. ⁽¹⁾ Approximately 37,340 persons were diagnosed with thyroid cancer in 2008⁽¹⁾ Thyroid cancers are the 4th most common malignancy in Saudi Arabia; in 2008, 606 cases were diagnosed and it accounts for 6.6% of all cancers. In King Faisal Specialist Hospital & Research Center

(KFSH & RC) between 1975 and 2010, 4,652 cases were identified and 85-90% of them had papillary and follicular types.⁽²⁾

Anaplastic Thyroid Cancer (ATC) is extremely aggressive, with rapid course of disease progression, very short survival and extremely poor treatment outcomes.⁽³⁾ ATC accounts for 2-5% of all thyroid cancers and annual incidence is about 2/million. It accounts for 14-50% of the annual mortality from thyroid cancer.^(4,5,6)

Currently, there is poor understanding of this tumor's biology and there are no novel or biological therapeutics in large clinical research

Corresponding author: Mohammed Aldehaim, M.D., Research Centre, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia. Tel. No 00966114647272 Ext 24969. Mobile 00966506288013/001416-822-5559. Email: dr.alduhaim@gmail.com

trials for this rare type of cancer. Lack of this interest may be attributable to not only rarity of this cancer but also to unresponsiveness to previously tested treatments.

Reported literature is limited to few retrospective and prospective studies, with no standard consensus on therapeutic approach.⁽⁷⁾

It is hard to find a sufficient number of cases to study the natural history of the disease and its response to treatment. A number of treatment approaches have been tried aiming to improve outcome of ATC and among them are surgery, chemotherapy, radiotherapy or a combination of these modalities⁽⁸⁾.

The purpose of this retrospective study was to assess the natural history and treatment outcome at our institution and to compare that with internationally published data.

Material and Methods

Appropriate Institutional Review Board (IRB) approval was obtained to conduct this study. Data was obtained from King Faisal Specialist Hospital & Research Centre (KFSH & RC) tumor registry and it includes: patients' demographic information (age, sex), modalities of treatment, residence or address and date of diagnosis. Date of death was extracted from national information center.

We conducted a retrospective study of all cases with ATC between 1976 and 2008 at KFSH & RC, Riyadh, Saudi Arabia. SPSS version 16 was used to analyze the demographic and survival data.

Survival was calculated from the date of diagnosis, which is the date on which the biopsy was performed until the date of death. Estimates of the survival distribution of patients were constructed using the method of Kaplan– Meier.

All patients were involved in the demographic analysis but 110 patients with available data regarding exact date of death were involved in Kaplan Meir survival analysis.

Most of the patients were planned using 2-D planning system and treated with external beam radiotherapy (EBRT) using 6 MV linear

accelerator with parallel opposed pair of beams after fixation in a 5-point posifix shell. Selected cases which underwent surgical excision followed by adjuvant EBRT were planned using 3-D TPS and treated by 3-DCRT aiming to deliver high dose (66Gy in 61/2 weeks) respecting normal tissue tolerance doses.

We performed a comprehensive literature search on the PubMed database focusing on review of treatment and outcomes in ATC. Search key words included: thyroid cancer, anaplastic, undifferentiated and not otherwise specified. Search was not restricted to particular age, sex, treatment or size.

Results

A total of 120 cases were identified between 1976 and 2008. Of these total, 73 were females (60.8%) and 47 were males (39.2%). The average age at diagnosis was 63.34 +/- 12.8 years. The majority of our patients were from the central region (60 cases (50%)), the rest of cases were distributed equally between the main four geographical provinces and one case was from Yemen (Table 1).

At the time of presentation, 52.9% patients were found to have distant metastasis, 25.5% had locoregional extension, 5% had localized disease and the remaining 16.5% had unknown disease extension. Thirty-four patients underwent surgery (28.3%), 52 had palliative radiation treatment (20 Gy/ 5 fractions or 30 Gy/

Regions	City	Cases	Total	Percentage
Central	Riyadh	39	60	50%
	Alqassim	13		
	Other	8		
Western	Makkah	4	16	13.3%
	Taif	6		
	Jeddah	3		
	Other	3		
Northern	Hail	7	15	12.5%
	Arar	4		
	Other	4		
Southern	Abha	4	15	12.5%
	Najran	3		
	Other	4		
Eastern	Dammam	3	13	10.8%
	Qatif	3		
	Khobar	2		
	Other	5		

Table 1. Cases distribution based on regions

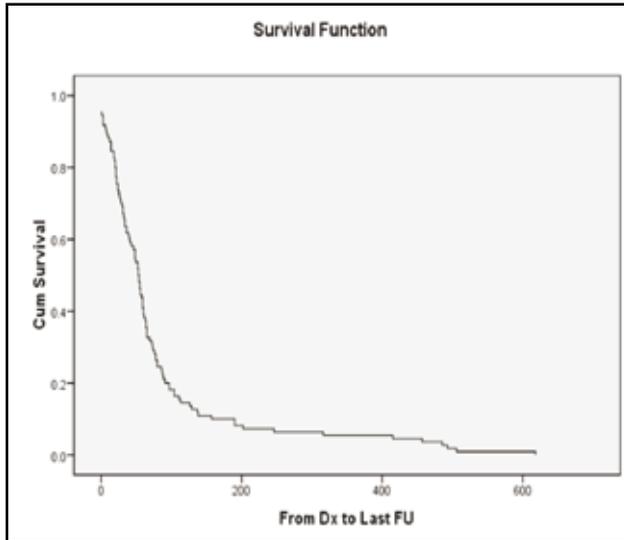


Fig. 1: Kaplan Meir Survival Curve for ATC cases

10 fractions) (43.3%) and only 5 had palliative chemotherapy (4.2%). The median survival was 53 days (0-457) (Figure 1). Distributions of cases referred in Figure 2 showed highest referral rate in 1988 with 7.4% incidence. On the other hand, the lowest rates were late 70s and early 90s.

Discussion

Most cases of ATC reported in literature were from specialized cancer centers. The characteristics of our patients (age and gender) are similar to other studies that showed ATC is a disease of the elderly (38% of our populations age ranged from 60-69 years). In one American - German prospective study of 5,583 cases of thyroid cancers, 67% of patients who had ATC were 70 years or above. In the same study, female constituted 70% and males 30% of ATC patients.⁽⁹⁾

A limited number of our patients were treated

with radical intent adopting a multimodality regimen aiming for cure.

In the present study, patients who presented with advanced stages and poor performance status have palliative treatment and they accounted for a poor median survival (53 days) in contrast to other published studies.^(10,11,12,13)

In this study, cases referred to our institution were unequally distributed from different provinces of Saudi Arabia. Most of the patients were found in central part and that may reflect the general population distribution and easy accessibility to our institution.

Our data seems to suggest that whereas referrals to KFSH & RC were rising in late 80s, it has normalized and in recent years may have even been declining. Similar trends have been reported in other countries such as incidence of ATC in Italy, India^(14, 15, 16) and Sri Lanka.⁽¹⁷⁾ The incidence of ATC did not change significantly in a study from Scotland.⁽¹⁸⁾ It is difficult to speculate the reasons but this may have been due to improved diagnostic ability and applied Immunohistochemical (IHC) stains to suggest different diagnosis other than ATC.

There is no standardized treatment for ATC. It is important to select the right treatment approach to increase locoregional and distant disease control, increase median survival and most importantly improve patient’s quality of life. Surgery, chemotherapy and radiotherapy alone will not control this disease but a combination of these treatments may increase local control as is shown in other studies.^(19, 20, 21, 22)

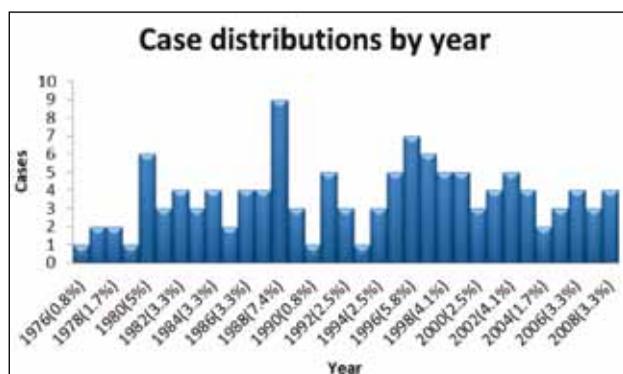


Fig. 2: Case distribution by year

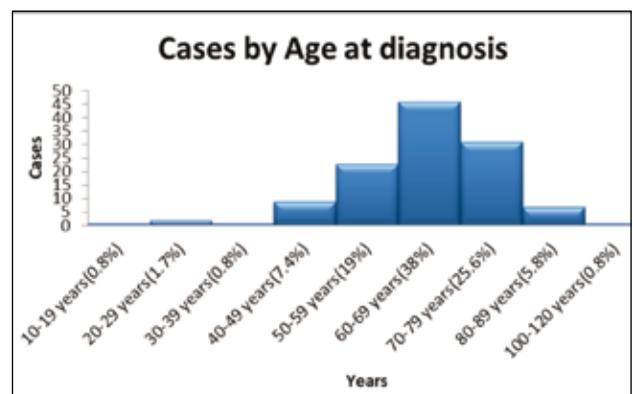


Fig. 3: Cases by age at diagnosis

Radiation alone does not alter the course of ATC in most patients. Nevertheless, most patients die of uncontrolled locoregional symptomatic disease and distant metastasis. Aggressive radiotherapy may control locoregional disease; however, toxicities can be a limiting factor. Complications such as pharyngoesophagitis, trachitis⁽²⁷⁾, skin changes and radiation myelopathy have been reported. Our patients were treated either in 1 or 2 weeks (20 Gy in 5 fractions / 1 week or 30 Gy in 10 fractions / 2 weeks) short course radiation therapy schedule with no reported severe undue complications. Daily doses of greater than 3Gy should be cautiously used as it can increase the incidence of myelopathy.⁽²⁸⁾ In the present study, no case while in radiation was reported to have myelopathy as a late toxicity but most presented with advanced disease and had short term survival. Recently, the use of Intensity Modulated Radiation Treatment (IMRT) versus 3D conformal Radiation Treatment (3DRT) did not influence toxicity.⁽²⁹⁾ ATC commonly presented as a bulky tumor and there is no uniform consensus for target volume delineation especially in post operative setting. Most of the radiation plans treated a very large volume of normal tissue, hence losing the potential benefit of IMRT.

ATC cells are inherently radio-resistant and together with very rapid proliferation rate pose a challenge for radiation therapy. Dose escalation and hyperfractionation have been proposed to offset the rapid proliferation and radio-resistance of anaplastic disease.^(19, 20, 29)

ATC is a relatively resistant disease to chemotherapy. Because of the rarity of disease, there are no phase III randomized clinical trials to draw any firm conclusion about the role of cytotoxic drugs and the information we have at this point is from phase II trials. Shimaoka reported the response of anaplastic thyroid cancer to chemotherapy in a randomized phase II trial conducted by Eastern Cooperative Oncology Group⁽³⁰⁾ of 39 patients with anaplastic thyroid cancer enrolled in the study, 21 were treated with doxorubicin alone, and 18 were treated with combination of doxorubicin and cisplatin. Only one patient (5%) achieved partial response

in doxorubicin alone group while there were six responses (34 %) in the combination group of the study (three complete response and three partial responses). However patients treated with combination chemotherapy did neither have statistically longer duration of response, nor time to relapse. Investigator concluded that combination chemotherapy is better in terms of response but without survival advantage.⁽³⁰⁾

The collaborative Anaplastic Thyroid Cancer Health Intervention Trials group reported a phase II study of paclitaxel. Twenty patients were treated on this study with the response rate of about 50%. However this high response rate has not been confirmed in any subsequent phase II or III trial.⁽³¹⁾

There has been poor understanding of the tumor biology of ATC highlighting the need for better tumor biology understanding and implementation of targeted molecular therapies bringing new hope for finding more effective treatment for such fatal disease. Recently, there has been increasing interest in ATC tumor biology and which led to the development of novel biological targeted therapies. Two of the most promising classes are tyrosine kinase angiogenesis inhibitors^(23, 24) and vascular disrupting agents.^(25,26) These agents need to be investigated in large randomized clinical trials before being implemented in the treatment of ATC.

Chemotherapy alone may not be sufficient to achieve durable response in this fatal disease and combination of cytotoxic chemotherapy along with targeted therapies will need to be tested in future clinical trials.

Conclusions

Our review proves that ATC a rapidly fatal cancer, and unresponsive to currently available therapeutic options. In the current study, patients who presented with far advanced disease have very poor survival as there are limited surgical resection and the inability to use higher radiation doses respecting normal tissue tolerance. More research is needed to understand the tumor biology and novel treatment options. All patients with ATC should be considered for treatment in

a clinical trial to get more useful information in terms of activity of specific agents, response rate and survival.

Acknowledgment

To Mr. Asif Mahmood from research center in KFSH & RC for his positive contribution to this project.

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