Acta Oncologica Turcica 2009; 42: 1-7

Anaplastic Thyroid Carcinoma: Clinical Features, Prognostic Factors and Treatment Outcome

Anaplastik Tiroid Kanseri: Klinik Özellikler, Prognostik Faktörler ve Tedavi Sonuçları

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SUMMARY

The objective of this study is to analyse the clinical features, prognostic factors and treatment outcomes of the patients with the diagnosis of anaplastic thyroid carcinoma treated at Ankara Oncology Teaching and Research Hospital between 2001 and 2005. The records of 29 patients with the diagnosis of anaplastic thyroid carcinoma reviewed retrospectively. The association between survival and age, tumor size, pattern of development, and type of the resection was analyzed. The median survival of the patients with 5-8 cm tumors and with tumors larger than 8 cm was 2.8 and 4.5 months respectively. The difference was not statistically significant (p= 0.18). The median survival of the patients under and over 60 years of age was 3.5 and 3.8 months respectively. The difference was not statistically significant (p= 0.65). While the median survival of the patients with transformation from well differentiated thyroid carcinoma was 3.7 months, it was 3.6 months for the patients without any type of well differentiated thyroid carcinoma. The difference was not statistically significant (p= 0.95). The overall survival of the patients with R0, R1 and R2 resections were 3.3, 1 and 3.1 months respectively. The statistical difference was not significant (p= 0.318). Anaplastic thyroid carcinoma still carries a dismal prognosis and there is a strong need for innovative treatments.

Key Words: *Anaplastic thyroid carcinoma, prognostic factors, treatment outcome.*

ÖZET

Bu çalışmada 2001-2005 yılları arasında tedavi edilen 29 tiroid anaplastik karsinom tanılı hastanın klinik özellikleri, prognostik faktörleri ve tedavi sonuçları retrospektif olarak incelenmiştir. Sağkalım ile ilişkisi bakımından; yaş, tümör boyutu, gelişim özellikleri ve rezeksiyon tipleri analiz edilmiştir. Tümör boyutu 5-8 cm olan hastaların sağkalımı 2.8 ay iken, tümörü 8 cm den büyük olan hastaların sağkalımı 4.5 ay olarak bulunmuştur. Aradaki fark istatistiksel olarak anlamlı bulunmamıştır (p= 0.18). Altmış yaş altı ve üstü hastaların ortalama sağkalımları sırasıyla 3.5 ve 3.8 ay olarak bulunmuştur. Aradaki fark istatistiksel olarak anlamlı bulunmamıştır (p= 0.65). İyi diferansiye tiroid karsinomu zemininde gelişen ve tiroid karsinomu hikayesi olmayan hastaların ortalama sağkalımları sırasıyla 3.7 ay ve 3.6 ay olarak bulunmuştur. Aradaki fark istatistiksel olarak anlamlı bulunmamıştır (p= 0.95). R0, R1 ve R2 rezeksiyon uygulanan hastaların ortalama sağkalımları sırasıyla 3.3, 1 ve 3.1 ay olarak bulunmuştur. Aradaki fark istatistiksel olarak anlamlı bulunmamıştır (p= 0.31). Anaplastik tiroid kanserinde lokal kontrol oranlarını artırmaya ve uzak metastaz oranlarını azaltmaya yönelik yeni teknolojilere ve ilaçlara olan ihtiyaç halen devam etmektedir.

Anahtar Kelimeler: *Anaplastik tiroid kanseri, prognostik faktörler, tedavi sonuçları.*

INTRODUCTION

Anaplastic thyroid carcinoma (ATC) is a rare but one of the most aggressive and lethal human malignancies. ATC accounts for less than 2% of all thyroid cancers, nonetheless 14-39% of deaths related with thyroid malignancy occurs due to ATC (1,2). Median survival time is 3-9 months from time of diagnosis. Cervical lymph node metastasis (40-84%) is common, and more than 50% of the patients have metastatic disease at presentation and another 25% develop metastasis at some stage of disease. The most frequent sites of metastasis are lung (80%), bone (6%-15%), brain (5%-13%), adrenal glands (33%), and intraabdominal nodes (17%) (3-6). According to "The American Joint Committee on Cancer (AJCC)" ATC is regarded as stage 4, without taking into consideration the tumor size and the presence of lymph node or distant metastasis (7). Because of systemic nature of the disease at presentation, combination chemotheraphy is frequently used during the last few decades. Although ATC is radiation resistant, Radiotheraphy (RT) is given to relieve the local symptoms.

The peak incidence of ATC is in the 6^{th} to 7^{th} decade of life (3,4,6,8). There is a preponderance of the disease in women by a ratio of 3.1/1 and 1.2/1 (3,4,8).

ATC presents with rapidly enlarging bulky thyroid mass that is firm and frequently invades adjacent structures. The symptoms of mechanical compression like dysphagia, dysphonia, vocal cord paralysis and local tenderness are the other clinical symptoms (3,4,6,9). Thyroid function tests are usually normal and scintiscan shows a classical cold areas at the site of tumor.

PATIENTS and METHODS

The records of 29 patients with the diagnosis of ATC treated in Ankara Oncology Teaching and Research Hospital between 2001 and 2005 reviewed retrospectively.

The age, gender, tumor size, signs and symptoms, thyroid disease history, previous treatments, the type of the surgery and resection, adjacent organ involvement, and survival were the parameters analyzed. The reports of thyroid scintigraphy, computed tomography of the neck and thorax, ultrasonography of the neck, thyroid function tests were also used for analysis.

The patients were put into 2 groups with respect to their tumor size. The patients with 5 to 8 cm tumors constituted group 1 (n= 9) and the ones with greater than 8 cm tumors constituted group 2 (n= 20).

The patients were also put into 2 groups with respect to their ages. The patients aged under 60 years constituted group 1 (n= 14) and the ones over 60 years constituted group 2 (n= 15).

Another parameter for grouping was the pattern of development. Four patients with ATCs transformed from well differentiated thyroid carcinoma (WDTC) and 10 from benign thyroid disease with papillary transformation constituted group 1 (n= 14) and de novo developed ones (9 patients with known benign thyroid disease and 6 patients without any thyroid disease history) constituted group 2 (n= 15).

The patients were put in 4 groups with respect to the type of resection. Seven patients not amenable to surgery or operated with biopsy only, 9 patients operated with R0 (complete) resection, 1 patient with R1 (microscobic residuel disease) resection and 12 patients with R2 (macroscopic residuel disease) resection constituted groups 1, 2, 3, and 4 respectively.

Another parameter for grouping was the type of treatment. The patients without any surgical intervention other than biopsy and debulking constituted palliative treatment group (n= 7) and the ones operated with curative intent constituted the curative treatment group (n= 22).

Statistical analysis was performed using SPSS software (Statistical Software, Chicago, USA). Univariate analysis of continuous variables was performed using a t-test, and categorical values were determined using the Chi-square test. Equality of means and variances were analyzed with Shapiro and Levene's tests. Significance was determined for $p \leq 05$.

RESULTS

The clinical features of the patients are summerized in Table 1. Twenty-three (79.3%) of the patients were female and 6 (20.6%) were male. The most frequent symptoms were rapidly enlarging neck mass (100%), dyspnea (55%), hoarseness (48%), neck pain (45%) and dysphagia (24%). Fourteen patients presented with vocal cord paralysis and 13 patients with skin involvement. Twenty-three patients presented with bilateral involvement of thyroid glands. Fine

Table 1. Clinical features of the study population.

No	Age	Gender	Thyroid disease history	Previous treatments	Tumor size	Surgery type	Resection type	Adjacent organ involvement	Death	Survial (months)
1	78	F	Papillary carcinoma (transformed)	BST, RAI	> 8 cm	Biopsy only	No	T, O, S, V, M	Local problems	2
2	53	M	No	No	5-8 cm	TT + ND + AOR	R0	M	Lung metastasis	1
3	42	F	Goiter	BST	> 8 cm	TT	R2	T, M	Unknown	5
4	54	F	Goiter	No	> 8 cm	TT + ND + AOR	R0	T, M, V	Local problems	7
5	59	F	Medullary carcinoma (transformed)	TT + ND	> 8 cm	CT + ND	R0	T, M	Local problems	9
6	54	M	No	No	> 8 cm	Biopsy only	No	T, O, M, V, S	Local problems	1
7	64	F	Goiter (transformed)	No	5-8 cm	TT + ND + AOR	R2	T, O	Local problems	1
8	68	F	Papillary carcinoma (transformed)	BST	> 8 cm	Biopsy only	No	T	Lung metastasis	3
9	43	F	Goiter (transformed)	No	5-8 cm	TT	R1	T	Lung metastasis	1
10	64	F	Goiter	RAI	> 8 cm	TT + ND + AOR	R0	T, O	Suicide	5
11	71	F	Papillary carcinoma (transformed)	TT + ND	> 8 cm	TL + ND + AOR	R0	T, O, L, M	Osefagus fistule	3
12	58	F	No	No	> 8 cm	TT + ND	R2	T, S	Operation complication	1
13	63	F	Goiter (transformed)	BST	> 8 cm	TT + TL + ND	R0	T, L, S	Local problems	4
14	65	F	Goiter (transformed)	BST	5-8 cm	Biopsy only	No	T, L, M, S	Local problems	4
15	54	F	Goiter (transformed)	BST	> 8 cm	Debulking	R2	T, L, M, S	Lung metastasis	4
16	72	F	Goiter (transformed)	No	> 8 cm	BST	R2	T, O, L, M, S	Local problems	6
17	53	F	Goiter	No	> 8 cm	No	No	T, O, L, M, S	Local problems	4
18	71	M	Goiter (transformed)	No	5-8 cm	TT + ND + AOR	R0	T, O, L, M, S	Local problems	2
19	48	F	Goiter	No	> 8 cm	TT + debulking	R2	T, O, L, M, S	Lung metastasis	6
20	14	F	Goiter (transformed)	No	> 8 cm	TT + ND + AOR	R0	-	Local problems	5
21	61	F	Goiter	No	5-8 cm	TT + debulking	R2	T	Lung, liver metastasis	2
22	54	M	Goiter (transformed)	No	> 8 cm	Debulking	R2	T, M, S	Local problems	6
23	44	M	No	No	> 8 cm	TT + TL + ND + AOR	R0	T, O, L, M, S	Local problems	4
24	75	F	Goiter (transformed)	No	> 8 cm	No	No	T, O, L, M, S	Local problems, lung metastasis	2
25	63	M	No	No	5-8 cm	TT + ND	R2	L, M	Local problems	6
26	61	F	Goiter	No	5-8 cm	Biopsy + debulking	R2	T, O, L, M	Local problems	6
27	59	F	Goiter	No	5-8 cm	No	No	T, L, M	Local problems	3
28	66	F	No	No	> 8 cm	Debulking	R2	T, M	Local problems	1
29	30	F	Goiter	No	> 8 cm	TT	R2	T, M	Lung metastasis	3

M: Male, F: Female, BST: Bilateral subtotal thyroidectomy, TT: Total thyroidectomy, ND: Neck dissection, RAI: Radioactive Iodine treatment, AOR: Adjacent organ resection, TL: Total laryngectomy, R0: Complete resection, R1: Resection with microscopic residuel disease, R2: Resection with macroscopic residuel disease, T: Trachea, O: Osefagus, L: Larynx, M: Muscle, V: Vessel, S: Skin, N: Normal, I: Increased.

needle aspiration biopsy (FNAB) was used as a diagnostic tool for 18 patients.

Thyroid function tests of 22 (76%) patients were within normal range, 2 (7%) patients were presented with hyperthyroidism and 5 (17%) patients with hypothroidism. Nine patients had hypoactive nodules and 3 patients had hyperactive nodules at thyroid scintigraphy.

Distant metastases at the time of diagnosis was present for 8 patients (7 patients with lung and 1 patient with lung and liver metastasis). Two additional lung metastasis developed during the follow-up of the patients.

Five (17%) patients were given preoperative doxorubicin containing chemotheraphy regimens and objective response was documented for only 2 patients. However, R0 resection was only possible for 1 patient in this group. Adjuvant RT and chemotheraphy were given to 14 and 16 patients respectively.

The tumor size of all patients was greater than 5 cm. While the median survival of the patients with 5 to 8 cm tumors was 2.8 months, it was 4.5 months for the patients with tumors larger than 8 cm. At statistical analysis, the difference was not significant (p= 0.18).

The median age of the patients at presentation was 58.8 years (range 14-78). While the median survival of the patients under 60 years of age was 3.5 months, it was 3.8 months for the patients over 60 years of age. At statistical analysis, the difference was not significant (p= 0.65).

While the median survival of the patients with disease transformed from WDTC was 3.7 months, it was 3.6 months for the patients with de novo ATC. At statistical analysis, the difference between the pattern of development and survival was not significant (p= 0.95).

The median survival of the patients with R0, R1 and R2 resections were 3.3, 1 and 3.1 months respectively. The statistical difference between different resection groups was not significant (p= 0.318).

Nine patients were operated with total thyroidectomy with neck dissection and adjacent organ resection, 3 patients with total thyroidectomy with neck dissection, 3 patients with total thyroidectomy and 1 patient with subtotal thyroidectomy. Biopsy was the only possible surgical intervention for 4 patients and 3 patients were not amenable to surgery. The mean survival for these patients was 2.7 months (1-4 months). Debulking surgery was used for 6 patients (Table 1).

Tracheostomy was needed for 15 patients during the course of disease. Post-operative complications were observed for 21 patients and most frequent ones were the surgical site infection (11 patients), dyspnea (4 patients) and hypocalcemia (3 patients).

While the median survival of 7 patients operated with palliative intent was 3.1 months, it was 3.8 months for the 22 patients operated with curative intent. At statistical analysis, the difference was not significant (p= 0.44).

The cumulative survival curve of the study population with Kaplan-Meier analysis is shown in Figure 1 (mean survival: 3.76 months). Eleven patients died during their stay at hospital. The cause of death was local problems for 17 patients, problems related with metastatic disease for 7 patients and other problems for 5 patients.

Pre-operative and post-operative carcinoembriyonic antigen (CEA) and CA19-9 levels were measured for 11 patients and the results were within normal range other than 1 patient with liver metastasis.

DISCUSSION

Age, sex, tumor size, resectability, and extent of the disease have been shown to affect the prognosis of the disease (6). Female sex and tumor size less than 6 cm and complete resection have been shown to be associated with better prognosis (5). In another study, age and extent of the disease were the most important prognostic factors (10). The evidence of metastatic disease at presentation is also associated with worse prognosis (8 months vs. 3 months) (4). In a series by Sugitani et al. the most important risk factors were the presence of acute symptoms, tumor size more than 5 cm, distant metastasis, and leukocytosis more than 10.000 (11). The favorable prognostic factors are younger age, female sex, smaller lesions, small foci of ATC, and no evidence of metastasis at distant sites (4,8). There seems to be no significant survival advantage in the transformed group over the de novo group (4). In a Japanese study, a prognostic index (PI) based on the presence of acute symptoms, large tumors (> 5 cm), distant metastasis, and leucocytosis was devised and no patients with PI index greater than 3 survived longer than 6 months (11). In this series, the association between survival and tumor size, age, pattern of development

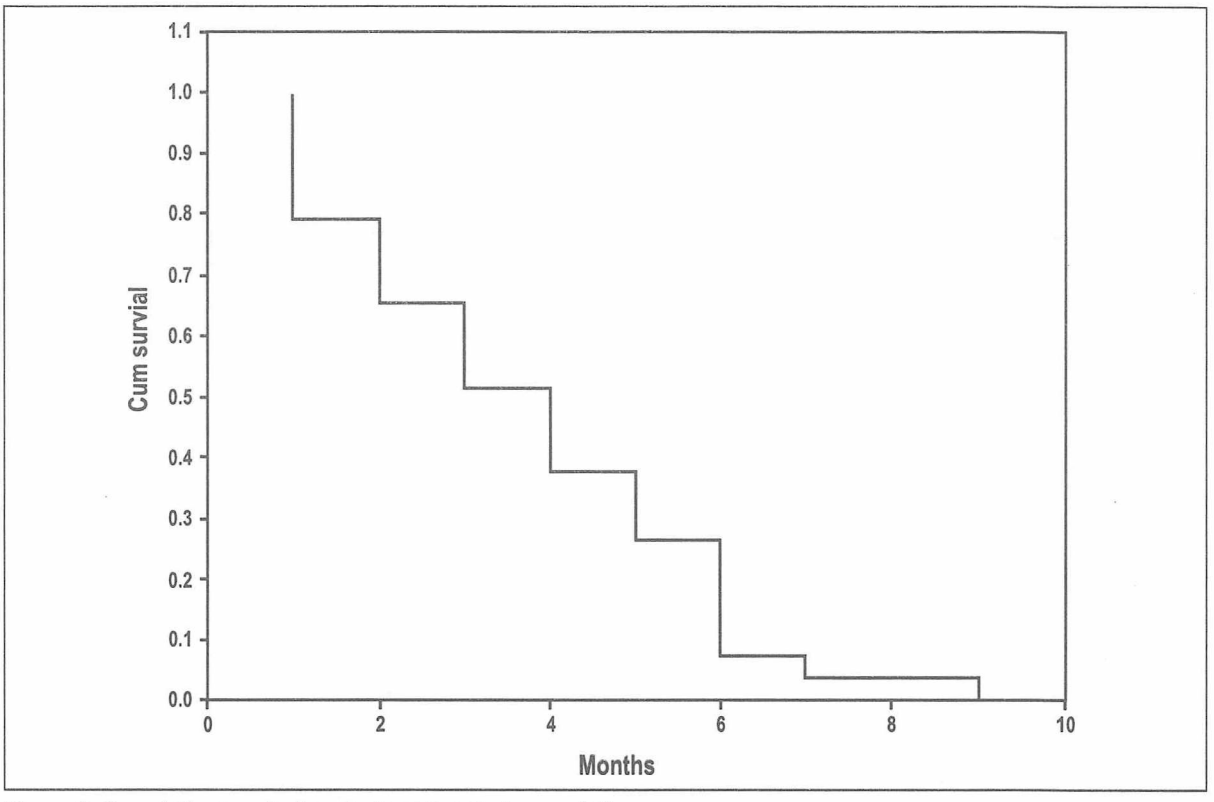

Figure 1. Cumulative survival analysis of the study population.

and resection type could not be demonstrated. This might be related to the small number of the study population.

FNAB was used as a diagnostic tool for 18 patients in this series. The diagnosis of ATC is usually made on clinical findings and FNAB. FNAB is shown to be accurate in 90% of the cases (12,13). In case of inability to obtain a diagnosis, open biopsy may be used. Insicional biopsy is associated with poor healing, delay of treatment and acceleration of tumor growth (12). The most frequent symptoms were rapidly enlarging neck mass (100%), dyspnea (55%), hoarseness (48%), neck pain (45%) and dysphagia (24%). Rapidly enlarging mass that is firm and fixed to surrounding structures in an elderly patient should raise the suspicion of ATC. Fourteen patients presented with vocal cord paralysis and 13 patients with skin involvement in this series. The mass is usually larger than 5 cm and is associated with pressure symptoms.

Surgical ablation is the standart form of treatment for ATC, but it is usually not feasable. It is documented that thyroidectomy, when feasable, should be performed (14). The role of the surgery depends on the extent of the disease at presentation. The surgery alone does not alter the course of the disease. Complete resection of the all gross disease without sacrificing vital structures can result with prolonged survival. However, it should be noted that less extensive disease undergoes more complete resections. Potentially curative resections did have a bearing on survival only if followed by post-operative RT and chemotheraphy (15). It should be remembered that only the surgery followed by chemoradiation prevents death from asphyxiation and may not have any effect on distant disease. In this series, 7 patients were not amenable to surgery or just operated with biopsy only, 9 patients operated with R0 resection, 1 patient with R1 resection and 12 patients with R2 resection. We believe in that complete surgical resections should be tried whenever possible in selected patients. The resection of vital structures should be attemped only if all gross cervical and mediastinal disease can be resected. Tracheostomy was needed for 15 patients during the course of disease. Tracheostomies are performed only in patients with impending airway obstruction that can not undergo local resection. Prophylactic tracheostomies are usually associated with lower survival (2 months). The number of patients requiring tracheostomy has declined dramatically over the last 40 years with proper application of RT.

Most patients with ATC die from uncontrolled local symptoms. Eleven patients in this series died during their stay at hospital. The cause of death was local problems for 17 patients, problems related with metastatic disease for 7 patients and other problems for 5 patients. Even in patients with metastatic disease, local control of the disease can improve short-term survival rates. RT can play an adjunctive role to surgery in local control of the disease. The timing, the dose and the pattern of delivery of the RT are the contravertial issues. Several studies show that preoperative RT may help to increase the resectability rate (16). RT is now increasingly applied before surgery with the hope of increasing resectability rates. No patients were given pre-operative RT in this series. Current protocols use doses between 30 to 60 Gy. Hyperfractionated and accelerated local RT combined with doxorubicin as a radiosensitizer improves survival in the management of select patients with ATC (16,17). Yet, the efficacy of RT must be balanced with its toxicity. Although RT does not alter the course of disease in most cases, in combination with surgery and chemotheraphy, it can prolong short-term survival in a select subset of patients.

Five (17%) patients were given pre-operative doxorubicin containing chemotheraphy regimens and objective response was documented for only 2 patients. However, R0 resection was only possible for 1 patient in this group. Because of the systemic nature of the disease, the importance of chemotheraphy can not be underestimated. Neither monotheraphy with doxorubicin nor combinations (cisplatin, bleomycin, melphalan, methotrexate etc.) and new agents such as paclitaxel has shown any promise (8,18,19). It has been shown that anaplastic cell lines express less mdr1 mRNA and P glycoprotein and more multidrug resistance-associated protein that expells chemotheraphy agents out of cells (20). Neverthless it was suggested that combination treatment is superior to single-agent theraphy (21).

Chemotheraphy combined with RT can increase the radiosensitivity of ATC and enhance surgical resectability (22). RT in the post-operative period is also associated with increased survival. In this series, adjuvant RT and chemotheraphy were given to 14 and 16 patients respectively. However, today postoperative external RT no longer has been used. Radioiodine and external thyroid hormone supplementation appeared to have no inhibiting influence on ATC. Regardless of the disagreement about the sequence of treatment, multimodality treatment holds the best hope for future treatment strategies.

In conclusion, the management of ATC has evolved over the decades with no improvement in outcome. Curative resections without sacrificing major structures and causing excessive morbidity should be tried whenever possible. Even the patients with small foci of ATC should undergo complete curative resection with lymph node dissection. RT can be administered pre-operatively, both pre and post-operatively, with higher, hyperfractioned and accelerated doses. Polychemotheraphy protocols even with newer agents like paclitaxel remain the weak link in the management of ATC. ATC still carries a dismal prognosis and there is a strong need for innovative treatment strategies.

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