

Optimal combination of treatment modality to increase survival in patients with anaplastic thyroid carcinoma

A STROBE compliant retrospective study

Joon-Hyop Lee, MD^a, Hee Kyung Ahn, MD^b, Jae Yeon Seok, MD, PhD^c, Kyu-Chan Lee, MD, PhD^d, Yong Soon Chun, MD, PhD^e, Yoo Seung Chung, MD, PhD^{a,*}, Young Don Lee, MD, PhD^a

Abstract

There is little consensus on the optimal treatment approach for newly diagnosed patients. The present study aims to provide additional evidence by evaluating a series of patients diagnosed with anaplastic thyroid carcinoma (ATC) and analyzing factors related to increased survival. This was a retrospective cohort report structured according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guideline. Demographics, chief complaint, history of prior thyroid cancer, stage at presentation, management modalities (surgery, chemotherapy, radiotherapy, or observation), completeness or resection, and survival period since initial diagnosis were reviewed for patients with documentation of histologic ATC diagnosis between 2003 and 2016. The median survival period for 34 patients (11 males, 23 females) was 93.5 days. Patients aged 70 or younger (111 days) tended to survive longer than those older 70 (88 days) ($P=.081$). Observation, surgery only, radiotherapy only, and chemo-radiotherapy after surgery group showed median survival of 88 days, 49 days (range 14–528), 61.5 days, and 225 days, respectively. There was also no significant difference in survival between the 10 (29.4%) stage IVb (225 days) and 23 (67.7%) IVc (88 days) patients ($P=.242$). The median survival of the R1 resection group was 514 days while that of the R2 group was 102 days ($P=.338$). There were no significant difference between patients with the de novo ATC (112 days) and patients with papillary thyroid carcinoma origin ATC (99 days) ($P=.297$). Results from our series of 34 patients with ATC show that more intense combination of surgery and chemo-radiotherapy tends to secure a longer survival period. Therefore we recommend a multi-modality approach after a comprehensive consultation with the patient.

Abbreviations: ATC = anaplastic thyroid carcinoma, CRDW = Clinical Research Database Warehouse, PTC = papillary thyroid carcinoma, SEER = Surveillance, Epidemiology, and End Results, STROBE = STrengthening the Reporting of OBservational studies in Epidemiology.

Keywords: anaplastic thyroid carcinoma, combination, STROBE, survival, treatment

1. Introduction

Anaplastic thyroid carcinoma (ATC) is a rare type of malignancy which accounts for <5% of all thyroid neoplasms.^[1,2] However,

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All authors contributed equally to this work.

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^a Thyroid and Endocrine Surgery Section, Department of Surgery, ^b Division of Hematology and Oncology, Department of Internal Medicine, ^c Department of Pathology, ^d Department of Radiation Oncology, ^e Department of Surgery, Gachon University College of Medicine, Gil Medical Center, Incheon, Republic of Korea.

* Correspondence: Yoo Seung Chung, Thyroid and Endocrine Surgery Section, Department of Surgery, Gachon University College of Medicine, Gil Medical Center, 1198 Guwol-dong, Namdong-gu, Incheon 405-760, Republic of Korea (e-mail: dryooseung@gilhospital.com).

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it shows dismal prognosis which accounts up to more than 50% of all thyroid cancer deaths.^[3] Survival time is generally short with 1-year survival rate reported between 10% and 20%.^[4] Long-term survival is rarely reported and usually leads to doubts on proper diagnosis rather than hope of cure.

Because of the small number of patients diagnosed with ATC and the rapid progression of the disease, there is little consensus on the optimal treatment approach for newly diagnosed patients or in which combination the treatment modalities should be offered. In this light, the present study aims to provide additional evidence to the existing literature by evaluating a series of patients diagnosed with ATC and analyzing factors related to increased survival at a tertiary referral center.

2. Materials and methods

This research was designed as a retrospective cohort study and was written in accordance to the Strengthening the Reporting of Observation studies in Epidemiology (STROBE) guideline.^[5] It has also been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. After gaining approval of the relevant institutional review board (GCIRB2016-332), all patients with documentation of histologic ATC diagnosis between 2003 and 2016 at our institution were identified. Our Clinical Research Database Warehouse (CRDW) system allows word search of the whole

electronic medical record database between 2003 and 2016. Pathologic records of all the patients with records of any positive search containing the word “anaplastic” were checked for confirmation of histologic ATC diagnosis. Demographics, chief complaint, history of prior thyroid cancer, stage at presentation, management modalities (surgery, chemotherapy, radiotherapy, or observation), completeness or resection, and survival period since initial diagnosis were reviewed.

Our protocol for treatment of ATC complies to the 2012 American Thyroid Association on ATC treatment,^[6] which recommends surgery and curative chemo-radiotherapy for stage IVA and resectable stage IVB and palliative treatment for unresectable or metastatic disease. The exact definition of tumor resectability in ATC is not well defined^[6] in the guideline; therefore, surgery was done at the discretion of the surgeon after carefully scrutinizing ultrasonography and computed tomography results along with patient performance status.

In our institution, patients who underwent surgery under fully informed consent of the likely outcome received total thyroidectomy and lymph node dissection whenever possible. Patients who refused or whose tumor was too extensive to receive surgery underwent palliative treatment without surgical intervention; histologic proofs of these patients were obtained through fine needle aspiration cytology results. Chemotherapy consisted of cisplatin 40 mg/m² per week and radiation therapy dose was set to 200 cGy per fraction at the neck area. The full protocol, however, varied case by case according to the clinical situations.

Patients were divided into 2 groups according to whether they received all treatment modalities (surgery and chemo-radiation) or not. The survival was calculated by the Kaplan–Meier curve after which they were compared through log-rank tests. *P*-values below .05 were deemed statistically significant. All data were analyzed by the SPSS 20.0 statistic software (IBM Co, Armonk, NY).

3. Result

Thirty-four patients, including 11 (32.4%) males and 23 (67.6%) females with histologic proof of ATC, were identified through our institution’s CRDW system and subsequent confirmation of histologic proof. The median age at diagnosis was 72 years (range: 37–90) among which 13 patients (38.2%) were 70 years old or younger (Table 1). The patients were followed-up for a median period of 115 days (range 7–1378). Initial chief complaints included 16 (47.1%) cases of neck mass, 7 (20.6%) dyspnea and voice change each, 3 (8.8%) neck pain, and 2 (5.9%) incidental findings.

At initial presentation 4 (11.8%) patients showed no evidence of metastasis, 5 (14.7%) had evidence of central compartment, 2 (5.9%) of lateral compartment metastasis, and 23 (67.7%) showed distant metastatic findings. Five (14.7%) patients did not undergo further workup to determine the presence of distant metastases either due to early death or patient’s refusal. Everyone with distant metastases had lung metastasis along with 3 patients who had additional metastasis to the bone, brain, and liver each. Six patients (17.6%) had a history of thyroidectomy due to previously diagnosed papillary thyroid carcinoma (PTC).

Regarding management, 17 (50%) underwent observation or symptomatic management, 7 (20.6%) received surgery only, 4 (11.8%) received radiotherapy only (median 3300 cGy, range: 1200–7100 cGy), 1 (2.9%) received chemo-radiotherapy (6 cisplatin cycles + 2250 cGy), and 5 (14.7%) received chemo-radiotherapy after surgery (mean 3 cisplatin cycles + median

Table 1

Clinical characteristics of the 34 patients.

Factors	Cases (%)
Gender	
Male	11 (32.4)
Female	23 (67.6)
Age (y)	
≤70	13 (38.2)
>70	21 (61.8)
History of thyroid cancer	
No	28 (82.4)
Yes	6 (17.6)
Lymph node metastasis	
No	4 (11.8)
Yes	30 (88.2)
Distant metastasis	
No	17 (50)
Yes	17 (50)
Stage	
IVa	1 (2.9)
IVb	10 (29.4)
IVc	23 (77.7)
Resection	
R0	0 (0)
R1	2 (5.9)
R2	10 (29.4)
No operation	22 (74.7)
Radiotherapy	
No	24 (70.6)
Yes	10 (29.4)
Chemotherapy	
No	29 (85.3)
Yes	5 (14.7)

5760 cGy, range: 0–6600 cGy). There are 5 (14.7%) current survivors, among which 3 patients had been followed-up for less than a month since diagnosis. One patient survived 954 days and the other 261 days both after diagnosis and receiving chemo-radiotherapy postsurgery.

The median survival period for all patients was 93.5 days (range 3–954) (Fig. 1). Patients aged 70 or younger (median survival: 111 days, range: 5–954) tended to survive longer than

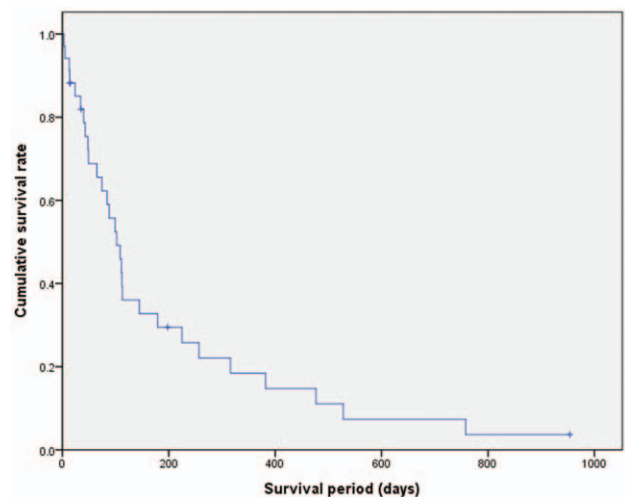


Figure 1. Survival analysis of all 34 patients.

Table 2
Number and survival status of patients receiving each treatment modality.

Treatment	Number of patients (%)	Median survival, days	Range, days
None	17 (50)	88	3–758
Surgery	7 (20.6)	49	14–528
Radiotherapy	4 (11.8)	61.5	14–179
Chemo-radiotherapy	1 (2.9)	111	(–)
Surgery + Chemo-radiotherapy	5 (14.7)	225	74–954
All	34 (100)	93.5	3–945

those older 70 (median survival: 88 days, range: 3–758) but this trend was slightly shy of statistical significance ($P=.081$). Likewise, there was no significant difference in survival between male (median survival: 111 days, range: 14–954) and female (median survival: 84 days, range: 3–758) patients ($P=.261$).

The observation group, surgery only group, radiotherapy only group, and chemo-radiotherapy after surgery group (in terms of management) displayed a median survival of 88 days (range 3–758), 49 days (range 14–528), 61.5 days (range 14–179), and 225 days (range 74–954), respectively ($P=.047$; Table 2 and Fig. 2). The 1 patient who received chemo-radiotherapy only survived for 111 days.

Five patients (14.7%) survived for more than 1 year and one of them still survives at the moment. His pathology result indicated 80% anaplastic thyroid cancer and 20% well-differentiated cancer and lived 954 days after initial diagnosis. Another patient died 758 days after diagnosis without receiving additional treatment apart from palliative tracheostomy.

There was no significant difference in median survival between patients with the de novo ATC (median survival: 112 days, range: 3–758) and patients with ATC with PTC origin (median survival: 99 days, range 65–954) ($P=.297$). Three patients demonstrated a PTC-free interval of 30, 10, and 1 year until diagnosis of ATC; the other 3 were under suspicion of remnant tumor (2 at lung and 1 at op bed) after the first iodine ablation scan. Only 2 patients who were under suspicion of remnant disease received laryngectomy and tumorectomy for ATC 12 and 9 months, respectively, after the prior operation on PTC; 2 presenting with large neck mass (30 years disease-free interval, remnant tumor)

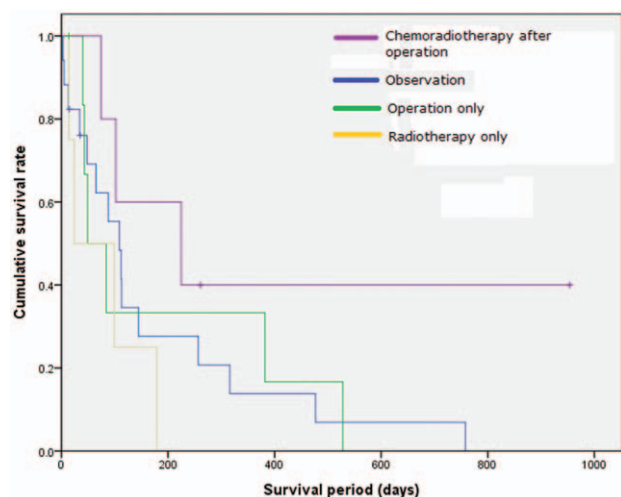


Figure 2. Survival analysis according to management type.

and dyspnea (10 years disease-free interval, remnant tumor) each did not receive further treatment. The age at surgery did not affect the outcome as the survival periods of the groups younger and older age 70 did not differ ($P=.219$).

There was only 1 patient with stage IVa who died 109 days later after receiving operation. There was also no significant difference in median survival between the 10 (29.4%) stage IVb (median survival 225 days, range: 14–758) and 23 (67.7%) IVc (median survival 88 days, range: 3–954) patients ($P=.242$). There were 3 stage IVb and 4 stage IVc patients in the surgery only group and 1 stage IVb and 4 stage IVc cases in the surgery with chemo-radiotherapy group.

Twelve patients (35.3%) received surgery, among which 2 (16.7%) had microscopic residual tumor (R1 resection) and the other 10 (83.3%) had macroscopic residual tumor (R2 resection). One of the R1 group patients was the long-term survivor with 8 to 2 anaplastic to follicular well-differentiated component proportion in the final pathology report; the other R1 patient presented with a recurred mass after receiving total thyroidectomy for PTC a year before. All R2 patients had tumors involving the whole lobe and extending to adjacent tissues. Among the 10 patients who received R2 resection, only one received excisional biopsy due to inoperable extensive tumor invasion to the nerve, trachea, and internal jugular vein; the others received total thyroidectomy with lymph node dissection (or tumorectomy in recurred cases). One patient had minimal remnant papillary component, another had minimal follicular component with the predominantly anaplastic histologic component, and the others were of pure anaplastic nature by pathologic review. The median survival period of the R1 group was 514 days (range: 74–954) while that of the R2 group was 102 days (range: 14–528) ($P=.338$).

Of note, there were 2 (5.9%) cases in which the lesion was found incidentally without prior symptoms. One died 225 days after diagnosis with R2 resection and chemo-radiotherapy, and the other 88 days after confirmation with R2 resection only.

4. Discussion

Randomized control trials or treatment protocols on ATC are lacking due to the extremely low incidence combined with the aggressive nature and the dismal outcome. The present study analyzed the long-term institutional experience of the rare but fatal disease despite the given circumstances. It evaluated the effects that age, symptom at presentation, preoperative stage, completeness of resection, history of prior thyroid cancer, and type of treatment modalities have on their survival. Our result demonstrated that multi-modality treatment, including surgery and concurrent chemo-radiation gained patients statistically longer survival period, while age 70 or younger over older 70 at diagnosis, stage IVb over IVc at presentation or R1 resection over R2 at surgery did not.

Haymart et al concluded in a study of 2742 patients from the National Cancer Database between 1998 and 2008 that older age and omission of treatment were associated with higher mortality.^[7] Similarly, a multivariate analysis of 516 patients from the Surveillance, Epidemiology, and End Results (SEER) database identified age and combination of surgical resection and radiotherapy as independent predictors of survival.^[3] Furthermore, a recent multicenter registry study of 329 patients published by the Korean Society of Thyroid Head and Neck Surgery identified age older 70 years, symptoms or distant metastasis at presentation, and curative intent resection with

radiotherapy (or concurrent chemo-radiotherapy) as significant factors affecting survival.^[8]

Our results are by and large in accordance with the results of these large cohorts. We had initially dichotomized our patient group according to age 60, 65, 70, and 75 but age older than 70 group was the closest to retaining statistical significance favoring worse survival among them. A higher number of participants in our cohort may have secured statistical significance. At the moment, however, we can only assume that age 70 is a potentially useful parameter in stratifying the survival risks of patients with ATC.

Despite minimal improvements in outcomes, no treatment has demonstrated a significant improvement in outcome. Foscetabulin, one of the most recently trialed medications in 2014, did not have significant effect on progression-free survival.^[9] Other trials using sorafenib, efatutazone + paclitaxel, or pazopanib regimens did not prove otherwise.^[10–13] However, the ATA guideline for management of patients with ATC mentions that radiation therapy could achieve local control even in patients with un-resected disease^[6]; both R2 resection and no surgery at all. Likewise, our results demonstrate that the intensity of treatment modality, regardless of preoperative stage or completeness of resection, was the only factor resulting in increased survival.

A point that should be noted is that even though statistical significance was lacking the group which underwent observation only had a longer median survival than the surgery only group. This was the result of a small number of patients combined with one outlier patient in the observation group who lived for 758 days. She was admitted to our institution in tracheostomy state due to dyspnea after being diagnosed of ATC at another hospital. She underwent observation only due to patient's wish but interestingly survived for an additional 2 years, only visiting to replace the tracheostomy tube until her death. Without the outlier, the median survival of the observation group drops to 68 days, which is similar to the 49 days of the surgery only group. Moreover, the literature reports that 10% of ATCs are intra-thyroidal,^[6,14,15] but there was only one stage IVa patients in our cohort, which makes it difficult for our result to be applied to stage IVa patients in general.

All limitations of a retrospective study of limited size applied to this study. For example, in our study, only 2 patients received R1 resection and no one received R0 resection. In such situation, there was little point in comparing R0 (or R1) resection group survival to that of R2 and R3 group would not have much meaning. Furthermore, because of the rarity and fatal outcome of the disease, there was no set treatment protocol prior to the publication of the 2012 ATC guideline. Likewise, a proper preoperative evaluation of preoperative status was not possible in some cases either because patients did not receive surgery or because patients died too early. This made it difficult to assess the degree of influence that baseline pathologic characteristics had on survival period. Such limitations, which apply to most studies dealing with ATC, limit the generalizability of the results.

5. Conclusion

Results from our series of 34 patients with ATC are poor with median survival of 93.5 days and 1-year survival at only 14.7%. A more intense combination of surgery and chemo-radiotherapy tends to secure a longer survival period. Even amidst the lack of

guidelines due to the fatal and rare character of the disease, we recommend a multi-modality approach after a comprehensive consultation with the patient. Moreover, additional researches are needed to develop an optimal chemo-radiation protocol.

Author contributions

Conceptualization: Joon-Hyop Lee, Hee Kyung Ahn, Jae Yeon Seok, Kyu-Chan Lee, Yoo Seung Chung, Young Don Lee.

Data curation: Joon-Hyop Lee, Young Soon Chun.

Formal analysis: Joon-Hyop Lee, Hee Kyung Ahn, Jae Yeon Seok, Young Soon Chun, Yoo Seung Chung, Young Don Lee.

Investigation: Joon-Hyop Lee.

Methodology: Joon-Hyop Lee, Young Soon Chun.

Supervision: Hee Kyung Ahn, Kyu-Chan Lee, Yoo Seung Chung, Young Don Lee.

Validation: Kyu-Chan Lee.

Writing – original draft: Joon-Hyop Lee, Hee Kyung Ahn, Jae Yeon Seok, Yoo Seung Chung.

Writing – review & editing: Joon-Hyop Lee, Jae Yeon Seok, Young Soon Chun.

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