

## ORIGINAL ARTICLE

# Analysis of patients with anaplastic thyroid cancer expected to have curative surgery

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**Purpose:** Anaplastic thyroid cancer (ATC) is rare and has a poor prognosis. The aim of this study was to analyze the clinicopathologic characteristics of patients diagnosed with ATC expected to undergo curative thyroidectomy, with the goal of finding differences between patients surviving  $\geq 6$  months and  $< 6$  months. **Methods:** From 1981 to 2010, 24 patients underwent thyroidectomy due to ATC. Among those patients, 12 suspected of distant metastasis preoperatively were excluded. The remaining 12 patients were analyzed by retrospective review of electronic medical records. **Results:** Median age was 55 years, and the male to female ratio was 1:5. All patients presented with neck mass at initial diagnosis. Five patients lived  $< 6$  months and seven patients lived  $\geq 6$  months after operation. In patients surviving  $\geq 6$  months, all lesions were  $< 5$  cm and all patients underwent total thyroidectomy. In patients surviving  $< 6$  months, two of the four lesions were  $> 5$  cm, and two of the five patients underwent less than total thyroidectomy ( $P = 0.287$  and  $0.152$ , respectively). All patients with lesion size  $< 5$  cm underwent total thyroidectomy and showed a shorter median operation time ( $P = 0.182$  and  $0.033$ , respectively). **Conclusion:** ATC showed female predominance. Patients initially presented with neck mass, and median age was 55 years. In patients with ATC who are expected to undergo curative thyroidectomy, surgery should actively be considered as primary therapy for patient survival when the size is  $< 5$  cm.

**Key Words:** Anaplastic thyroid cancer, Thyroidectomy

## INTRODUCTION

Anaplastic thyroid cancer (ATC) is a very rare disease with a poor prognosis [1-7]. The incidence of ATC is 1.6% according to the Surveillance, Epidemiology, and End Results (SEER) database, but it accounts for 14 to 39% of thyroid cancer deaths [7,8]. Although results concerning

survival have been variable, the mean survival time after initial diagnosis is generally considered to be 6 months [1,9]. At initial diagnosis, cervical lymph node metastasis is commonly present, and distant metastasis is found in  $> 50\%$  of patients [10-12].

Even with the rarity of ATC, many prognostic factors have been reported. Reporting their clinical experiences in

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a single institution, Venkatesh et al. [1] found that young age at initial diagnosis and locally confined disease were associated with better prognosis. A review article found that better prognosis was associated with female sex, lesion size < 6 cm, patient age < 60 years, less extensive disease, and no distant metastases at initial presentation [10]. Multidisciplinary treatment and presence of intrathyroidal disease were also associated with better prognosis [7,13]. Because of the rarity of the disease, the treatment modalities applied in these reports were varied. Thyroid malignancy is typically detected by health screening; thus, in the future, increased early detection of ATC cases is expected.

The aim of this study was to analyze the clinicopathologic characteristics of patients who were diagnosed with ATC and expected to have curative thyroidectomy preoperatively. The overall goal was to identify differences between patients surviving  $\geq 6$  months and those surviving < 6 months.

## METHODS

Between 1981 and 2010, 24 patients with ATC underwent thyroidectomy at Seoul National University Hospital. Cases of well-differentiated thyroid carcinoma with focal anaplastic transformation were excluded initially. Twelve patients were excluded because the existence of distant metastasis was unknown based on preoperative work-up (n = 7), distant metastasis in lung was found by positron emission tomography (n = 1), distant metastasis was found on computed tomography (CT) preoperatively (n = 3), or distant metastasis was suspected preoperatively because multiple bone metastases were found within 1 month after thyroidectomy (n = 1). Clinicopathologic data of the remaining 12 patients were analyzed retrospectively through review of electronic medical records. All patients underwent evaluation of their thyroid lesions and status of cervical lymph node metastasis on preoperative images, including neck ultrasonography and chest CT from bilateral middle lung field to the brain. The median follow-up period was 294.5 days.

Data processing and statistical analyses were per-

formed by a statistician with the SPSS ver. 19.0 (SPSS Inc., Chicago, IL, USA). To evaluate clinicopathologic characteristics between patients surviving < 6 months and  $\geq 6$  months, Fisher's exact test was used for the analysis of categorical data (such as lymph node metastasis) and Mann-Whitney U test was used for continuous variables. A P-value of < 0.05 was considered statistically significant.

**Table 1.** Clinicopathologic and demographic characteristic of 12 patients with anaplastic thyroid cancer

Variable	Value
Age (yr)	55 (23-86)
Sex (M:F)	1:5
Initial clinical symptom	
Neck mass	11 (91.7)
Multiple clinical symptom <sup>a)</sup>	1 (8.3)
Duration of neck mass (mo) (n = 11)	107.5 $\pm$ 198.7 (1-600)
Operation method	
Total thyroidectomy	10 (83.3)
Near total thyroidectomy	1 (8.3)
Subtotal thyroidectomy	1 (8.3)
Extent of LND	
CLND (done : not done)	8:4 (66.7:33.3)
LLND (done : not done)	2:10 (16.7:83.3)
Pathologic characteristics	
Size of the lesion (cm) (n = 11) <sup>b)</sup>	4 (1.7-6)
Size of the lesion (< 5 cm : $\geq 5$ cm) (n = 11)	9:2 (81.8:18.2)
LN metastasis (yes : no) (n = 8)	6:2 (75:25)
ETE (microscopic : grossly : no) (n = 11)	4:4:3 (36.3:36.3:27.4)
Vascular invasion (yes : no) (n = 10)	2:8 (20:80)
Lymphatic invasion (yes : no) (n = 11)	1:10 (9.1:90.9)
Encapsulation (yes : no) (n = 10)	2:8 (20:80)
Multicentricity (yes : unknown)	10:2 (83.3:16.7)
Postop adjuvant therapy (n = 8)	
RTx only	7 (87.5)
RTx + CTx	1 (12.5)
RTx dosage (cGy) (n = 8)	6,030 (2,000-8,900)
Postoperative metastasis (found : not found)	2:10 (16.7:83.3)
Status at last follow-up (alive : dead) (n = 6)	2:4 (33.3:66.7)
Alive (< 6 mo : $\geq 6$ mo)	5:7 (41.6:58.3)

Values are presented as median (range), number (%) or mean  $\pm$  SD (range).

LND, lymph node dissection; CLND, central lymph node dissection; LLND, lateral lymph node dissection; LN, lymph node; ETE, extrathyroidal extension; RTx, radiotherapy; CTx, chemotherapy.

<sup>a)</sup>One patient presented with a palpable neck mass, voice change, and mild dyspnea. <sup>b)</sup>In one patient, the size of the lesion was not assessable due to the removal in several pieces.

Institutional Review Board approval was obtained for this retrospective study, and informed consent was also obtained for all studies and procedures.

## RESULTS

### Clinicopathologic characteristics and demographic findings

Table 1 summarizes the clinicopathologic features of the 12 patients. Median age was 55 years (range, 23 to 86 years), and the male to female ratio was 1:5. All patients presented with a growing neck mass at initial diagnosis. The mean duration of the neck mass was  $107.54 \pm 198.78$  months (range, 1 to 600 months). Four patients experienced an acutely increased neck mass before visiting the clinic, with durations ranging 1 to 84 months. Ten patients (83.3%) underwent total thyroidectomy, one patient underwent near-total thyroidectomy, and one patient underwent subtotal thyroidectomy. Central lymph node and lateral lymph node dissections were performed in 66.7% and 16.7% of patients, respectively. Lesions ranged 1.7 to 6 cm in size (median, 4 cm). Lesions were  $< 5$  cm in nine pa-

tients and  $\geq 5$  cm in two patients.

Cervical lymph node metastasis records were available for eight patients. Metastasis occurred in six of the eight patients (75%). External beam radiotherapy (median dosage, 6,030 cGy; range, 2,000 to 8,900 cGy) was performed postoperatively in 87.6% of patients (7 of 8). One patient who underwent subtotal thyroidectomy received the vincristine, adriamycin, and prednisolone chemotherapeutic regimen twice, with radiotherapy as adjuvant therapy.

Of the 12 patients, five survived  $< 6$  months and seven survived  $\geq 6$  months. Postoperative Seoul National University distant metastases were found in 16.7% of patients (2 of 12).

### Clinicopathologic differences between patients surviving $< 6$ months and $\geq 6$ months

Table 2 summarizes the clinicopathologic differences between patients surviving more or less than 6 months. In patients surviving  $\geq 6$  months, females predominated ( $P = 0.152$ ) and the median age was younger (56 years vs. 54 years,  $P = 0.463$ ). All patients in this group underwent total thyroidectomy ( $P = 0.152$ ). The size of the lesion in patients surviving  $\geq 6$  months was always  $< 5$  cm ( $P = 0.109$ ), and

**Table 2.** Clinicopathologic differences between patients surviving  $< 6$  months and  $\geq 6$  months

Variable	$< 6$ mo survival (n = 5)	$\geq 6$ mo survival (n = 7)	P-value
Age (yr)	56 (53-76)	54 (23-86)	0.463
Sex			
M:F	2:3	0:7	0.152
Duration of neck mass (mo) (n = 11)	$124.2 \pm 266$	$93.6 \pm 148$	0.827
Operation method			0.152
Total thyroidectomy	3	7	
Less than thyroidectomy	2	0	
Extent of LND			
CLND (done : not done)	2:3	6:1	0.222
LLND (done : not done)	0:5	2:5	0.47
Pathologic characteristics			
Size of the lesion (cm) (n = 11)	5 (1.8-6)	4 (1.7-4.5)	0.287
Size of the lesion ( $< 5$ cm : $\geq 5$ cm) (n = 11)	2:2	7:0	0.109
Lymph node metastasis (yes : no) (n = 8)	2:0	4:2	1
ETE (microscopic : grossly) (n = 11)	2:1:2	2:3:1	0.535
Vascular invasion (yes : no) (n = 10)	2:3	0:5	0.444
Lymphatic invasion (yes : no) (n = 11)	1:4	0:6	0.455
RTx dosage (cGy) (n = 8)	5,420 (2,000-8,900)	6,030 (3,050-6,660)	1

Values are presented as median (range) or mean  $\pm$  SD.

LND, lymph node dissection; CLND, central lymph node dissection; LLND, lateral lymph node dissection; ETE, extrathyroidal extension; RTx, radiotherapy.

**Table 3.** Clinicopathologic differences between patients with lesions <5 cm and ≥5 cm

Variable	<5 cm (n = 9)	≥5 cm (n = 2)	P-value
Median age (yr)	54 (23-86)	61.5 (56-67)	0.478
Sex			
M:F	0:9	2:0	0.018
Duration of neck mass (mo) (n = 10)	72.5 ± 131	300.5 ± 432.5	0.585
Operation method			0.182
Total thyroidectomy	9	1	
Less than thyroidectomy	0	1	
Operation time (min)	140 (85-200)	247.5 (240-255)	0.033
Pathologic characteristics			
Lymph node metastasis (yes : no) (n = 8)	5:2	1:0	1
ETE (microscopic : grossly : no) (n = 10)	2:4:2	1:0:1	0.435
Vascular invasion (yes : no) (n = 9)	1:6	0:2	1
Lymphatic invasion (yes : no) (n = 10)	0:8	1:1	0.200
Median RTx dosage (cGy) (n = 8)	5,680 (2,000-6,660)	7,550 (6,200-8,900)	0.096
Estimated blood loss (mL) (n = 8)	100	550	0.098

Values are presented as median (range) or mean ± SD.

ETE, extrathyroidal extension; RTx, radiotherapy.

there were no cases of lymphatic invasion ( $P = 0.455$ ). However, these results were not statistically significant.

All patients with lesions of <5 cm in size underwent total thyroidectomy ( $P = 0.182$ ), and the operation time was significantly shorter than the operation time in patients with larger lesions (140 minutes vs. 247.5 minutes,  $P < 0.05$ ). All patients with lesions of <5 cm in size were female, whereas all patients with lesions of ≥5 cm in size were male ( $P = 0.018$ ). No patient with a lesion of <5 cm displayed lymphatic invasion ( $P = 0.200$ ) (Table 3). However, these findings were not statistically significant.

## DISCUSSION

The aim of this study was to analyze the clinicopathologic characteristics of patients diagnosed with ATC who were expected to undergo curative thyroidectomy preoperatively, with the aim of revealing differences between patients surviving <6 months and ≥6 months. The present retrospective analysis of 30 years of experience at a single institution contributes to the understanding of the demographic and clinicopathologic differences between these patient groups. Female predominance, initial pre-

sentation with neck mass, and a median age of 55 years were found, similar to the findings of other published reports [1,11,14,15]. The median age of this study was younger than that of a large-scale study among Western patients with a mean age of 71.3 years [7]. Although our analysis involved a very small sample size, the demographic findings are considered to be relatively reliable.

Treatment modalities for ATC include combination therapy with surgical resection for local control, external beam radiotherapy, and chemotherapy. The combination of surgery and radiotherapy is the most effective treatment modality in controlling local disease [16]. Radical resection of ATC is considered to be an important therapy in locally advanced disease [17]. One published report, based on a 30-year single-center experience, found that maximal debulking surgery combined with adjuvant chemotherapy was the best method in patients with ATC [18], while another study indicated that tumor debulking should be performed before adjuvant therapy. They reported a single center experience of eight patients who underwent potentially curative surgery, and estimated the 2- and 5-year survival rates as 75% and 50%, respectively [19]. The role of surgery as a treatment modality has been unclear; nevertheless, surgery should be considered in the

treatment of ATC, especially when treating its relatively less aggressive forms. Multimodal treatment including surgery is ideal for prolonged locoregional control and patient survival [20].

Although many studies have been performed with various treatment approaches, the survival benefits of these modalities remain unclear [21]. Reported prognostic factors include patient age, tumor size, extent of disease, and treatment modality. However, these factors have been found under heterogeneous combinations of treatment modalities or palliative therapy. Two published reports have concerned Korean patients diagnosed with ATC. Chang et al. [6] reported difficulties in the treatment of ATC due to its poor prognosis. Kim et al. [22] stated that curative surgery and adjuvant radiotherapy should be applied in selected patients with tumor size <5 cm, age <55 years, and no distant metastasis at initial presentation. However, these previous studies included some palliative cases that underwent debulking or incomplete surgery (e.g., biopsy only).

We assessed the usefulness of surgery in patients who were expected to undergo curative surgery preoperatively. Analysis of 12 patients indicated that surgery should be actively considered when the tumor size is <5 cm and there is no evidence of distant metastasis on preoperative work up. Even with the small sample size, the median operation time was appreciably shorter compared to that in patients with lesions of  $\geq 5$  cm. Moreover, all patients with lesions of <5 cm underwent total thyroidectomy. The findings indicate that, in patients with lesions of <5 cm in size, total thyroidectomy is a convenient and simple option for an experienced surgeon.

In this study, three of the seven patients who survived  $\geq 6$  months showed focal residual differentiated thyroid cancer cells by pathologic review. Although the proportion of focal differentiated thyroid cancer cells was very small, this finding may suggest a relationship between relatively good survival and ATC originated from differentiated thyroid cancer. However, two of three patients showing focal differentiated thyroid cancer cells survived <6 months from initial surgery, and only one patient survived  $\geq 6$  months. Therefore, it is difficult to say that relatively good survival has a relationship with ATC

derived from differentiated thyroid cancer.

The median survival from initial surgery of the seven patients who survived  $\geq 6$  months was 2,782 days (range, 865 to 3,153 days). Statistical data related to mortality were obtained from the National Statistics Office, and the last end point for mortality statistics was 31 December 2010. Six of the seven patients underwent surgery between 2002 and 2007; one patient underwent surgery in 1997 and died in 1999. Therefore, in spite of the dismal prognosis of ATC, good survival can be expected in patients with ATC who undergo curative surgery.

Three of the five patients surviving  $\geq 6$  months and five of the seven patients surviving <6 months underwent postoperative adjuvant radiotherapy treatment at median dosages of 5,420 and 6,030 cGy, respectively. The effectiveness of radiotherapy for local disease control cannot be discussed within the context of this study. Further large-scale, multicenter studies will be required to assess this topic among patients expected to undergo curative surgery. Even we couldn't find the role of radiotherapy as an adjuvant treatment modality, the remaining is the fact that prolonged survival was achieved in small group of patients underwent curative resection.

For unknown reasons, the incidence of well-differentiated thyroid cancer is increasing [10,23], while the incidence of ATC has decreased. Several possible explanations are offered for the decreasing incidence [10], such as aggressive resection of well-differentiated thyroid malignancy, which eliminates the potential of dedifferentiation [24], and improved iodine prophylaxis and socioeconomic status [25]. This trend leads to the expectation that future cases of ATC cancer should be detected at earlier stages than in past decades. The present attempt to find prognostic factors in patients with ATC with expected curative thyroidectomy preoperatively can offer one clue for the treatment of ATC.

This study had some limitations. Firstly, the sample size was very small. However, the demographic results echo those of other published studies, making it more likely that these data from a single center are valid. Secondly, there was a possibility of selection bias, because the authors limited the cases to patients who underwent thyroidectomy. To overcome these limitations, because of the

rarity of the disease, a multicenter approach utilizing strict inclusion criteria would be required.

In conclusion, the results of this study suggest that ATC cancer shows a female predominance, initially presents with neck mass, and involves patients with a median age of 55 years. For patients with ATC who expect to undergo curative thyroidectomy preoperatively, surgical treatment should be considered actively when the size of the lesion is < 5 cm. Total thyroidectomy can be performed easily by an experienced surgeon. Further multicenter clinical analyses are required to establish a standard protocol for the management of early-stage ATC to improve patients' survival.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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