ORIGINAL ARTICLE

PROGNOSTIC FACTORS FOR KOREAN PATIENTS WITH ANAPLASTIC THYROID CARCINOMA

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Abstract: *Background.* Anaplastic thyroid carcinoma (ATC), although rare, is one of the most aggressive human cancers, and patients with ATC have extremely poor prognoses despite various therapeutic measures. We wished to determine the prognostic factors of survival and effect of treatment on survival rate in patients with ATC.

Methods. We retrospectively reviewed the medical records of the 121 patients (41 men and 80 women) diagnosed with ATC from January 1995 to June 2004 at 5 major referral centers in Korea.

Results. Mean patient age at diagnosis was 64 ± 11 years (range, 17–84 years). Of the 121 patients, 11 (9%) had intrathyroidal tumors, 69 (57%) had extrathyroidal tumors or lymph node involvement, 29 (24%) had distant metastases, and 12 had no data about staging (9%). The mean tumor diameter was 5.5 ± 2.5 cm (range, 0.5–17.0 cm). At a median follow-up of 41 months (range, 26–122 months), 8 patients were alive. Median survival time was 5.1 months. The disease-specific survival rates were 42% at 6 months, 16% at 12 months, and 9% at 24 months. Sixteen patients (13%) received only supportive care, 25 (21%) received surgery alone, 20 (16%) received radiation treatment or chemotherapy without surgery, and 60 (50%) received surgery plus radiation treatment or chemotherapy. Multivariate analysis showed that age less than 60 years, tumor size less than 7 cm, and lesser extent of disease were independent predictors of lower disease-specific mortality.

Conclusions. Long-term survival is possible for ATC patients less than 60 years old and with small localized tumors. Although aggressive multimodal therapy, including surgery, radiation treatment, and chemotherapy, was not significantly associated

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with improved survival, we advocate aggressive multimodal therapy in selected ATC patients with good prognostic factors.
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Keywords: thyroid disease; anaplastic carcinoma; impact of therapy; prognostic factor; survival analysis

Anaplastic thyroid carcinoma (ATC), which accounts for about 2% of thyroid carcinoma, is one of the most virulent human malignancies.[1–4] Mean survival time after diagnosis is about 6 months regardless of treatment.[5–13] The disease is more common in women than in men, and occurs mostly in people over 60 years of age. ATC presents with pain, dysphagia, hoarseness, and occasional dyspnea due to extensive local invasion of surrounding tissues. This cancer is particularly difficult to manage because patients usually present with locally advanced disease, distant metastases, or both. At the time of diagnosis, 90% of patients were seen with direct invasion of adjacent structures, including the perithyroid fat, trachea, esophagus, vasculature, and muscles, and distant tumor foci are observed in 20% to 50% of patients. In some cases, ATC arises from the a pre-existing differentiated thyroid carcinoma.[14,15] About 50% of ATC patients succumb from upper airway obstruction and suffocation with the remaining patients dying from a combination of locally advanced or systemic disease.[16]

The most important prognostic factor for survival is the amount of disease present at the time of diagnosis.[9,17] Since ATC occurs infrequently, it is difficult to find a sufficient number of patients to study the natural history of the tumor and its response to treatment. Several treatment approaches have been used to improve the prognosis, including surgery, radiation treatment, chemotherapy, and combinations of these modalities.[18,19] We wished to determine the prognostic factors of survival and the effect of treatment on survival rate in patients with ATC. We therefore retrospectively reviewed the impact of treatment and its outcome in a group of patients ATC as identified from the medical records of 5 major referral centers in Korea.

MATERIALS AND METHODS

Subjects. Medical records of patients diagnosed with ATC from January 1995 to June 2004 were retrospectively reviewed. These patients were diagnosed at 5 major referral centers located around Seoul, Korea: Asan Medical Center, Korea Cancer Center Hospital, Seoul National University Hospital, Samsung Medical Center, and the National Cancer Center. The histopathological or cytopathological diagnosis of ATC was re-confirmed independently by 3 experienced pathologists (Y.L.O., G.G., and S.Y.C.). Following approval by the Institutional Research Ethics Board at each center, information from the patients was reviewed, with missing and additional follow-up data that were added after a retrospective review of patient medical record.

Definition of Variables. Disease extent was defined as local (confined to the thyroid gland), regional (extension into adjacent tissue or lymph node involvement), or systemic (distant metastasis), or as unstaged. To simplify our analysis, weekly treatments with doxorubicin, as a radiosensitizer during concomitant radiation treatment, was not considered as chemotherapy, but was considered part of radiotherapy. Bilateral curative surgery was defined as thyroid surgery of equal or greater extent than subtotal thyroidectomy, whereas unilateral palliative surgery, performed to relieve obstructive symptoms, was defined as thyroid surgery of equal or lesser extent than unilateral lobectomy with isthmectomy. Previous goiter was defined as thyroid enlargement recognized by patient or physician at least 1 year before the diagnosis of ATC.

Analysis of Survival. Overall survival rates relative to prognostic factors and treatment modalities were analyzed. We performed subgroup analysis after excluding 16 patients who received only supportive treatment. We also performed subgroup analysis for patients treated with bilateral curative surgery.

Statistics. All data were reported as mean $\pm$ standard deviation and were analyzed using SPSS for Windows (version 13.0; SPSS, Chicago, IL). For univariate analysis, the log-rank test was used to compare Kaplan–Meier events. For multivariate analysis, a Cox proportional hazards model was developed by forward, stepwise regression for all independent variables that were significant in the univariate analysis. The independent variables used in the analysis were age (per decade), sex, tumor size (in 1-cm increments from 2 to 10 cm), extent of disease (local, regional, or systemic), treatment modality (surgery, radiation treatment, or chemotherapy), the presence of concomitant well-differentiated carcinoma, and the

Table 1. Disease-specific survival relative to treatment modality in 121 patients with anaplastic thyroid carcinoma.

Treatment modality	No. of patients (%) who survived for designated duration				Total
	≤6 mo	6–12 mo	12–24 mo	>24 mo	
Supportive care only	14 (88)	2 (13)			16
No surgical resection					
Radiation treatment only*	11 (85)	2 (15)			13
chemotherapy only	1 (50)	1 (50)			2
Combined radiation and chemotherapy	2 (40)	2 (40)	1 (20)		5
Unilateral palliative surgery†					
Radiation treatment*	3 (50)	3 (50)			6
Chemotherapy	1 (100)				1
Combined radiation and chemotherapy			2 (100)		2
No additional treatment	2 (40)	3 (60)			5
Bilateral curative surgery‡					
Radiation treatment*	18 (50)	8 (22)	2 (6)	8 (22)	36
Chemotherapy	4 (67)	1 (17)		1 (17)	6
Combined radiation and chemotherapy	2 (22)	4 (44)	2 (22)	1 (11)	9
No additional treatment	12 (60)	5 (25)	2 (10)	1 (5)	20
Total	70 (58)	31 (26)	9 (7)	11 (9)	121

**Weekly administration of doxorubicin as a radiosensitizer during concomitant radiation treatment was considered as part of radiation treatment.*
†Thyroid surgery of an extent equal to or less than unilateral lobectomy with isthmectomy and performed to relieve obstructive symptom.
‡Thyroid surgery of an extent equal to or greater than subtotal thyroidectomy and performed for curative resection.

presence of previous goiter. A p value $<.05$ was considered significant.

RESULTS

Patients' Characteristics and Treatment Modalities. Of the 121 pateints (41 men, 80 women) diagnosed with ATC, 49 were from Asan Medical Center, 28 from the Korea Cancer Center Hospital, 21 from Seoul National University Hospital, 17 from Samsung Medical Center, and 6 from the National Cancer Center. Their mean age at diagnosis was 64 ± 11 years (range, 17–84 years). Diagnosis of ATC was confirmed by histopathologically in 98 patients and cytopathologically in 23 patients. The mean tumor diameter was 5.5 ± 2.5 cm (range, 0.5–17.0 cm). Eleven (9%) patients had intrathyroidal tumors, 69 (57%) had extrathyroidal tumors or lymph node involvement, 29 (24%) had distant metastases, and the record of 12 patients (9%) contained no data about their disease stage.

Treatment modalities in these 121 ATC patients are shown in Table 1. Sixteen patients (13%) received only supportive care. Twenty patients (17%) received radiation or chemotherapy without surgery, 13 with radiation alone, 2 with chemotherapy alone, and 5 with both. Unilateral palliative surgery was performed in 14 patients (12%); of these, 6 received additional radiation treatment, 1 received additional chemotherapy, 2 received a combination of radiation and chemotherapy, and 5 had no additional treatment. Bilateral curative surgery was performed in 71 patients (59%); 36 later received radiation treatment, 6 received additional chemotherapy, 9 received a combination of radiation and chemotherapy, and 20 received no additional treatment.

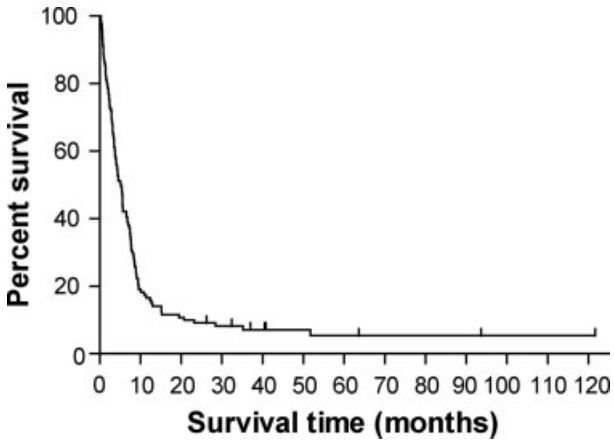

FIGURE 1. Overall disease-specific mortality in patients with anaplastic thyroid carcinoma. At a median follow-up of 41 months (range, 26–122 months), 8 patients were alive. Median survival time was 5.1 months. The disease-specific survival rates were 42% at 6 months, 16% at 12 months, and 9% at 24 months.

Disease-Specific Mortality. At a median follow-up of 41 months (range, 26–122 months), 8 patients were alive. The median disease-specific survival was 5.1 months (Figure 1). The overall disease-specific survival rates were 41% at 6 months, 16% at 12 months, and 8% at 24 months. The clinical char-

Table 2. Clinical characteristics of 11 patients who survived more than 24 months after diagnosis of anaplastic thyroid carcinoma.

No.	Age, y/sex	Primary tumor size, cm	Peri-thyroidal extension	Lymph node metastasis	Distant metastasis	Surgical extent	Additional treatment other that surgery	Survival, mo
1	68/F	3.5	Absent	Absent	Absent	Subtotal	Rradiation	122; Alive
2	41/F	4	Absent	Absent	Absent	Total	Radiation	94; Alive
3	17/F	1	Absent	Absent	Absent	Total	None	64; Alive
4	57/F	5	Present	Absent	Absent	Total	Radiation and chemotherapy	52
5	55/F	3.3	Absent	Absent	Absent	Total	Radiation	41; Alive
6	55/F	4	Present	Absent	Absent	Total	Radiation	41; Alive
7	56/F	4	Absent	Absent	Absent	Total	Radiation	37; Alive
8	52/M	3.5	Absent	Absent	Absent	Subtotal	Chemotherapy	35
9	54/F	1.7	Absent	Present	Absent	Total	Radiation	33; Alive
10	58/M	4	Absent	Present	Absent	Total	Radiation and chemotherapy	28
11	81/M	5	Absent	Present	Absent	Total	Radiation	26 Alive

acteristics of the 11 patients who survived more than 24 months were shown in Table 2.

Univariate and Multivariate Analyses of Prognostic Factors. Univariate analysis showed that patient age <60 years, tumor size <7 cm, lesser extent of disease, surgical resection (both palliative and curative), radiation treatment, and concomitant well-differentiated carcinoma were associated with lower disease-specific mortality (Table 3, Figure 2). On multivariate analysis, patient age, tumor size, and lesser extent of disease were identified as independent predictors of lower disease-specific mortality (Table 3).

Prognostic Factors for Patients Excluding Those who Received Only Supportive Treatment. Of 121 pateints with ATC, 16 received only supportive treatment after diagnosis. After excluding these patients, univariate analysis showed that age <60 years, tumor size <7 cm, lesser extent of disease, and concomitant well-differentiated carcinoma were significantly associated with lower disease-specific mortality (Table 4). On multivariate analysis, patient age, tumor size, and the presence of intrathyroidal disease were identified as independent predictors of lower disease-specific mortality (Table 4).

Prognostic Factors for Patients who Received Bilateral Curative Surgery. We observed that all 11 patients who survived longer than 24 months had received bilateral curative surgery (Table 1). We therefore performed subgroup analysis for the 71 patients who received bilateral curative surgery. Univariate analysis showed that patient age <60 years, female, tumor size <7 cm, and lesser

Table 3. Univariate and multivariate analyses of prognostic factors in 121 patients with anaplastic thyroid carcinoma.

	Univariate analysis		Multivariate analysis	
Variable	Log-rank statistics	*p* value	Hazard ratio (95% CI)	*p* value
Age (<60 yr)	10.88, df = 1	.001	0.47 (0.30–0.74)	.001
Gender (female)	1.17, df = 1	.280	NA	
Tumor size (< 7 cm)	26.95, df = 1	<.001	0.37 (0.23–0.60)	<.001
Disease extent*	28.44, df = 2	<.001		<.001
Local			0.14 (0.06–0.37)†	<.001
Regional			0.54 (0.34–0.85)†	.008
Systemic			NA	
Surgical resection	19.52, df = 1	<.001	NA	
Radiation treatment	8.05, df = 1	.005	NA	
Chemotherapy‡	2.31, df = 1	.128	NA	
Concomitant well-differentiated carcinoma	5.58, df = 1	.018	NA	
Previous goiter	0.076, df = 1	.783	NA	

Abbreviations: 95% CI, 95 percent confidence interval; df, degrees of freedom; NA, not associated.
**Local, confined to the thyroid gland; regional, extension into adjacent tissue or lymph node involvement; systemic (distant metastases); and unstaged.*
†Versus systemic disease.
‡Weekly administration of doxorubicin as a radiosensitizer during concomitant radiation treatment was not included.

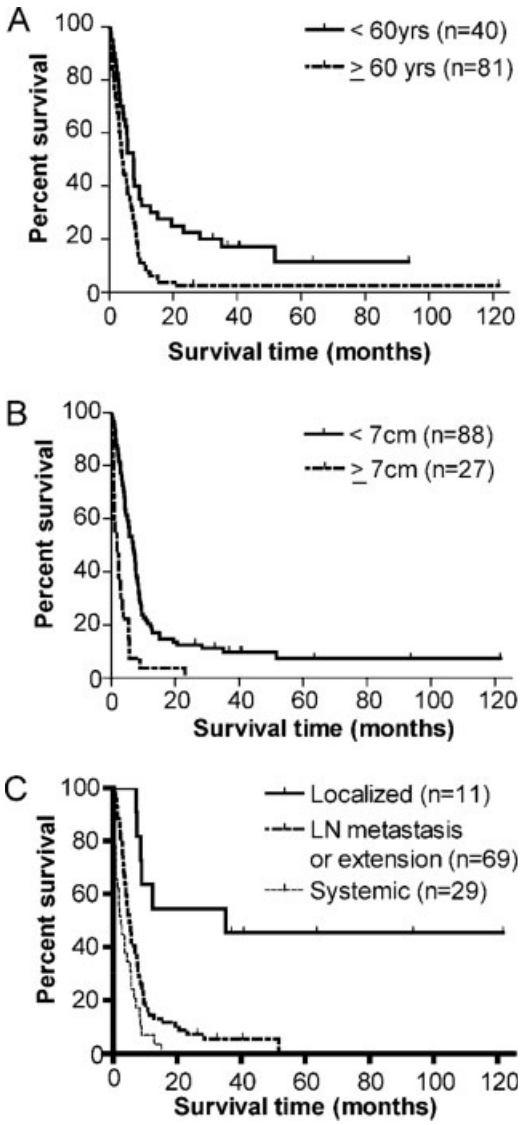

FIGURE 2. Disease-specific mortality in patients with anaplastic thyroid carcinoma by univariate analysis: (**A**) age at diagnosis, (**B**) maximal diameter of tumor, and (**C**) extent of disease defined as local (confined to the thyroid gland), regional (extension into adjacent tissue or lymph node involvement), systemic (distant metastasis), and unstaged.

extent of disease were significantly associated with lower disease-specific mortality (Table 5). Additional radiation treatment adjuvant to surgery had only a marginal effect ($p = .057$). Multivariate analysis showed that patient age and sex, tumor size, and intrathyroidal disease were independent predictors of lower disease-specific mortality (Table 5).

DISCUSSION

Most reports on ATC have come from specialized centers, which may be prone to referral bias. We attempted to overcome this possibility by enrolling patients from 5 independent cancer referral centers around Seoul, Korea. The demographic and clinical characteristics of our patients were similar to those in other series.[5,7,8,10–14,20,21] Intrathyroidal ATC was uncommon, and most patients were seen with regional disease or distant metastases. In addition, our patients had a median survival time of 5.1 months, similar to that in other series.[14,20,22] Thirty-six of the 121 patients were considered only for supportive care, palliative radiation treatment, or palliative chemotherapy, and these patients showed a 12-month survival rate of 3% with a median survival time of 2.9 months. However, the outcome for the 11 patients with intrathyroidal disease, which is amenable to bilateral curative resection, was not as poor: the 12-month survival rate in this subgroup was 64%, and the median survival time of 12.3 months.

The atypical survival time of the 11 "long-term" survivors, more than 24 months after diagnosis of ATC as shown in Table 2, may raise a question regarding the accurate histologic/cytologic diagnosis of ATC in these individuals. Other thyroid neoplasm, including lymphoma, de-differentiated medullary thyroid carcinoma, and high-grade follicular thyroid carcinomas can occasionally be misdiagnosed as ATC. We made every effort to confirm the pathological diagnosis of each recruited patients. This included a new review of all pathology slides by an experienced pathologist and immunostaining of samples with various antibodies, Furthermore, all patients with cytologically diagnosed as ATC had extensive disease, could not be treated surgery, and died within 6 months of diagnosis.

Patient age, sex, tumor size, extent of disease, presence of acute local symptoms, coexistence of multinodular goiter or well-differentiated thyroid carcinoma, surgical resection, and multimodal therapy have all been reported to influence upon the survival of patients with ATC.[8,9,14,23–28] In this study, we found that patient age, tumor size, and extent of disease were independent predictors of survival. ATCs can arise from preexisting, well-differentiated thyroid cancers or may be accompanied by other thyroid diseases, including differentiated thyroid carcinoma and multinodular goiter, all of which may influence the clinical course of ATC.[8,13,14,24,25] We found that concomitant differentiated thyroid carcinoma was associated with a lower disease-specific mortality in univariate analysis, but was not an independent prognostic factor in multivariate analysis.

Table 4. Subgroup analysis after excluding 16 patients who received only supportive treatment.

	Univariate analysis		Multivariate analysis	
Variable	Log-rank statistics	*p* value	Hazard ratio (95% CI)	*p* value
Age (<60 yr)	9.46, df = 1	.002	0.56 (0.35–0.91)	.018
Sex (female)	1.54, df = 1	.214	NA	
Tumor size (<7 cm)	30.10, df = 1	<.001	0.34 (0.19–0.61)	<.001
Disease extent*	20.11, df = 2	<.001		.001
Local			0.16 (0.06–0.41)†	<.001
Regional			0.61 (0.37–1.01)†	.054
Systemic			NA	
Radiation treatment	2.24, df = 1	.134	NA	
Chemotherapy‡	2.27, df = 1	.132	NA	
Concomitant well-differentiated carcinoma	4.10, df = 1	.043	NA	
Previous goiter	0.12, df = 1	.725	NA	

Abbreviations: 95% CI, 95 percent confidence interval; df, degrees of freedom; NA, not associated.
**Local, confined to the thyroid gland; regional, extension into adjacent tissue or lymph node involvement; systemic (distant metastases); and unstaged.*
†Versus systemic disease.
‡Weekly administration of doxorubicin as a radiosensitizer during concomitant radiation treatment was not included.

No standardized treatment is available for patients with ATC. It is important to select an appropriate approach for each patients, to control the disease locally, to increase survival time, and to improve the patient's quality of life. Although some studies have shown no survival benefit from surgical resection, radiation treatment, or chemotherapy, other studies have suggested that multimodal therapy may be beneficial in some patients with ATC.[7,11,12,18,19,23,26,27,29–33] We found that those patients who underwent bilateral curative surgery had better survival compared with patients who had unilateral palliative surgery, but this may be just another reflection of differences in tumor burden. A major confounding factor in analyzing the effect of treatment on outcome has been selection bias, because patients who underwent bilateral curative surgery often had less extensive disease than patients who underwent palliative surgery or radiation alone.[1] Although it is impossible to control for such factors in a retrospective study, our subgroup comparison of patients who received bilateral curative surgery also demonstrated no survival advantage from additional radiation treatment. Given the small number of patients who had intrathyroidal ATC, it was not surprising to find that the disease-specific mortality rate was not significantly lower in patients treated with a combination of surgical resection and radiation treatment. Nevertheless, aggressive surgical resection plus radiation treatment might be warranted in patients with localized disease.

In most studies of chemotherapeutic agents in patients with ATC, patients have received weekly

Table 5. Subgroup analysis of 71 patients who received bilateral curative surgery.

	Univariate analysis		Multivariate analysis	
Variable	Log-rank statistics	*p* value	Hazard ratio (95% CI)	*p* value
Age (<60 yr)	11.26, df = 1	.001	0.38 (0.20–0.73)	.004
Sex (female)	4.65, df = 1	.031	0.50 (0.28–0.92)	.025
Tumor size (<7 cm)	25.61, df = 1	<.001	0.26 (0.13–0.53)	<.001
Disease extent*	14.18, df = 2	.001		.004
Local			0.15 (0.05–0.46)†	.001
Regional			0.56 (0.28–1.11)†	.098
Systemic			NA	
Radiation treatment	3.62, df = 1	.057	NA	
Chemotherapy‡	0.05, df = 1	.822	NA	
Concomitant well-differentiated carcinoma	2.88, df = 1	.090	NA	
Previous goiter	0.08, df = 1	.779	NA	

Abbreviations: 95% CI, 95 percent confidence interval; df, degrees of freedom; NA, not associated.
**Local, confined to the thyroid gland; regional, extension into adjacent tissue or lymph node involvement; systemic (distant metastases); and unstaged.*
†Versus systemic disease.
‡Weekly administration of doxorubicin as a radiosensitizer during concomitant radiation treatment was not included.

doses of doxorubicin as a radiosensitizing agent during radiation treatment, but doxorubicin has been found to confer no survival benefits.[23,33] We also found that none of the 12 patients who received weekly doxorubicin as a radiosensitizer showed improved survival (data not shown). To simplify our analyses, these treatments with doxorubicin were considered part of radiation treatment, not independent chemotherapy. Thus, a total of 25 patients received chemotherapy, 6 who received chemotherapy alone and 19 who received radiation treatment plus chemotherapy. Of these 25 patients, 22 received doxorubicin plus cisplatin regimens, 2 received gemcitabine, and 1 received doxorubicin, but chemotherapy was not an independent prognostic factor for patient survival. This result is in agreement with previous series, which found that doxorubicin monotherapy[34,35]; bleomycin, cyclophosphamide, and 5-fluorouracil[36] had little effect on clinical response.

ATC in pediatric/adolescent populations is exceedingly rare.[37] Interestingly, 1 of our patients was a 17-year-old female (patient number 3 in Table 2) who was diagnosed with ATC after coming to the hospital for treatment of an incidentally found 1-cm nodule on her neck. Ultrasound-guided fine-needle aspiration suggested this tumor was a poorly differentiated carcinoma. Following a total thyroidectomy and routine central neck dissection, she was diagnosed with an ATC 1.0 cm in diameter, but no microscopic perithyroidal extensions or lymph node metastases were detected. She did not receive any additional radiation treatment or therapy with radioactive iodine and was followed regularly on an outpatient basis. Annual neck ultrasonography has shown no evidence of recurrence, and she remains alive, 64 months after surgery.

This study had several limitations. First, we could not follow a schematic plan for staging and treatment,[18,19] since the management preference of the oncology team at each center was quite different. Second, the tumors may have been understaged, primarily because FDG-PET was not widely used in Korea during the study period (1995–2004). We routinely staged ATC from neck/chest spiral CTs, bone scans, and chest X-rays. Third, the definition of "bilateral curative surgery" is heterogeneous. Although it generally consists of total thyroidectomy with bilateral extensive neck dissection, preoperative staging procedures in Korea are limited, making intraoperative decision making on surgical extent quite commonplace. If a surgeon decided that extensive surgery was not feasible, an extensive radical dissection was not performed. Furthermore, some patients, who received a preoperative cytological diagnosis of poorly differentiated thyroid cancer, underwent surgery with an extent not appropriate for ATC.

Although 2 small series from Japan evaluated the factors influencing survival rate,[9,26] the number of patients was too small to identify significant factors influencing survival rate. Thus, to our knowledge, this report is the first on a sufficiently large number of Asian patients with ATC to enable analysis of prognostic factors and the impact of treatment on survival.

In conclusion, ATC patients younger than 60 years old, those with smaller primary tumors, or those with localized tumors may achieve relatively long-term survival. Although we found no significant associations between aggressive multimodal therapy, including surgery, radiation treatment, and chemotherapy, and improved survival, our results suggest that aggressive multimodal therapy should be used in selected patients with good prognostic factors.

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