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Anaplastic Thyroid Carcinomas Incidentally Found on Postoperative Pathological Examination

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Abstract
Background Anaplastic thyroid carcinoma (ATC) is occasionally found on postoperative pathological examination of patients with differentiated thyroid carcinoma (DTC). There is no general consensus on how we should treat these incidentally diagnosed ATC (incidental ATC).
Materials and methods A total of 675 patients with ATC were registered with the ATC Research Consortium of Japan. These patients were treated between 1995 and 2008 in 38 registered institutions. About 81 % of the ATC patients had common-type ATC and about 14 % had ATC co-existing with a metastatic DTC lesion. The remaining 5 % had incidental ATC. Among the patients with incidental ATC, we investigated 25 patients whose clinical data were fully available. We examined the clinical profile of incidental ATC, and the relationships between treatment and outcome in patients with incidental ATC.
Results The tumor size was clearly smaller, and patients with extrathyroid invasion or distant metastasis were significantly fewer in incidental ATC than in common-type ATC. Most incidental ATC coexisted with papillary carcinoma. While the clinical course of incidental ATC was favorable compared with common-type ATC, half of the patients had disease-related deaths. The prognostic factors of incidental ATC were nearly the same as those of common-type ATC, but the tumor size alone was an independent factor on multivariate analysis. Regarding treatments, the outcome was more favorable in those who underwent curative resection, and the clinical course showed a slight improvement by the addition of external beam radiotherapy and/or chemotherapy after curative resection, but it did not reach statistical significance.
Conclusion Incidental ATC is the only curable type of ATC, and further studies are needed to establish the effectiveness of additional postoperative radiotherapy and/or chemotherapy in incidental ATC.

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Introduction

Differentiated thyroid carcinoma (DTC) is a slow-growing tumor with a favorable prognosis and high frequency.

In contrast, anaplastic thyroid carcinoma (ATC), which is also considered to arise from follicular cells, is rare but highly malignant and associated with a poor prognosis. Most of the studies on ATC have been conducted at single facilities with limited numbers of patients. Therefore, to obtain more information on ATC, we established the ATC Research Consortium of Japan (ATCCJ) in 2009 as a multicenter registry for ATC, and retrospectively analyzed the registered patients [1].

In surgery for elderly patients with DTC, ATC is occasionally detected incidentally on postoperative pathological examination [1–4]. There is no consensus on how we should treat such incidentally diagnosed ATC (incidental ATC). The

prognosis has been reported to be favorable if small ATC remaining in the thyroid is completely resected [5, 6], but whether or not adjuvant therapy should be performed after the complete resection of incidental ATC is still unclear [7]. Also, clinicopathological characteristics of incidental ATC have not been sufficiently documented [1–4].

In this study, therefore, we evaluated the relationships among the clinicopathological characteristics of incidental ATC, treatments, and clinical courses in patients with incidental ATC registered with the ATCCJ.

Subjects and methods

As of December 2010, a total of 719 patients with ATC were registered with the ATCCJ from 38 Japanese institutions during the 14 years from 1995 to 2008. Since 11 of these patients were doubly registered from different institutions, the duplications were deleted. A further 33 patients were excluded because the diagnosis of ATC was not made by pathological or cytological examination. Finally, 675 patients with ATC were evaluated in this study. Of these patients, 546 (81 %) were registered with common-type ATC, 95 (14 %) with ATC occurring in the metastatic foci of DTC, and the remaining 34 (5 %) with incidental ATC. Concerning those registered with incidental ATC, a questionnaire was sent to the institution that reported them, requiring about the circumstances of the detection of lesions, their locations, sizes, coexisting lesions, and presence or absence and contents of additional treatments. From this questionnaire, detailed information was obtained on 25 patients, and they were analyzed in this study as patients with incidental ATC. The period from the day of surgery to that of death or the last confirmation of survival was regarded as the survival time.

Data analysis was performed using the statistical Package for Social sciences version 11 for Windows (IBM, Armonk, NY, USA). Differences between incidental and common-type ATC were analyzed using independent t (continuous variables) and Pearson's Chi squared test (categorical variables). Survival curves were determined using the Kaplan–Meier method, and the statistical significance of differences was evaluated using the Log–rank test. For multivariate survival analysis, the Cox proportional hazards model was used. Values of $p < 0.05$ were considered statistically significant.

Results

Clinical profile of incidental ATC patients

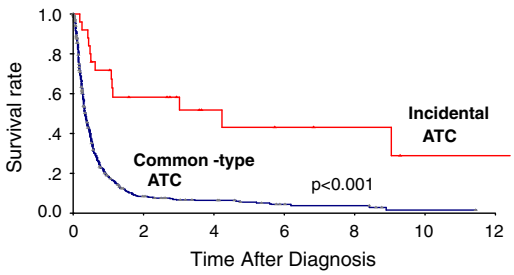
To clarify the clinical profile of incidental ATC patients, major clinicopathological factors were compared with those of common-type ATC patients (Table 1). There was no difference in the mean age between the two groups, but the percentage of females was significantly higher in those with incidental ATC. The tumor size was clearly smaller, and lesions that showed extrathyroid invasion and those that showed distant metastasis at the initial examination were significantly fewer, in incidental ATC patients. Coexisting lesions were predominantly papillary carcinoma in incidental ATC patients, and there was only one case of follicular tumor. Although papillary carcinoma was also frequently observed in those with common-type ATC, the difference was significant.

The overall survival (OS) was significantly longer in patients with incidental than in those with common-type ATC, and the 1- and 2-year survival rates were also clearly higher in those with incidental ATC. However, 12 (48 %) of the 25 patients with incidental ATC died due to ATC before the end of the follow-up period (Fig. 1). The median

Table 1 Clinicopathological factors in incidental and common-type anaplastic thyroid carcinoma

	Incidental ATC ($n = 25$)	Common-type ATC ($n = 546$)	p value
Age (years)	66.6 ± 11.3	68.7 ± 11.0	0.734
Male:female ratio	3:22 (1:7.3)	208:338 (1:1.6)	0.010
Tumor size, cm (mean ± SD)	2.1 ± 2.1	6.5 ± 2.6	0.000
Extrathyroid invasion	13/25 (52.0 %)	426/536 (79.5 %)	0.004
Distant metastasis	3/21 (12.5 %)	215/525 (41.0 %)	0.005
Coexisting papillary carcinoma	24/25 (96.0 %)	123/476 (24.9 %)	0.000

ATC anaplastic thyroid carcinoma, *SD* standard deviation



	Incidental ATC (n=25)	Common-type ATC (n=546)
Disease-related death	12 (48.0%)	478 (84.9%)
1-year survival rate	71.8%	18.6%
2-year survival rate	58.3%	8.5%

Fig. 1 Overall survival of patients with incidental and common anaplastic thyroid carcinoma (ATC)

Table 2 Clinicopathological factors and survival

Factors	*n*	1-year survival rate (%)	*p* value*
Age (years)			0.233
<65	13	76.9	
≥65	12	65.6	
Gender			0.022
Male	3	33.3	
Female	22	77.0	
Tumor size (cm)			0.042
<1.5	13	84.6	
≥1.6	8	37.5	
Extrathyroid invasion			0.031
−	12	90.9	
+	13	46.2	
Distant metastasis at diagnosis			0.050
−	21	75.9	
+	3	33.3	
WBC (/mm^3) at diagnosis			0.003
<10,000	21	76.2	
≥10,000	2	0	
Acute symptom			0.4931
−	16	81.3	
+	9	55.6	

WBC white blood cell

* Overall survival

Table 3 Treatments and outcome

Factor	*n*	1-year survival rate %	*p* value*
Curative resection			
−	6	33.3	0.001
+	19	83.9	
<40 Gy	8	50.0	
EBRT			0.4035
≧40 Gy	17	82.4	
−	16	62.5	
CT			0.7189
+	9	77.8	

CT chemotherapy, *EBRT* external beam radiotherapy

* Overall survival

survival time was 575 days in incidental ATC and 110 days in common-type ATC patients. In incidental ATC patients, the most frequent cause of death was distant metastasis (eight patients), followed by general debility (four patients); none died due to suffocation or bleeding caused by progression of the local lesion.

Prognostic factors of incidental ATC

Clinicopathological factors of incidental ATC related to the clinical course were evaluated (Table 2). Age did not affect survival, but women showed a 1-year survival rate that was clearly higher than that of men. When the tumor size was categorized into <1.6 and ≥1.6 cm (median tumor size 1.6 cm), the outcome was significantly poorer in the ≥1.6 cm group. The differences in OS of those factors were significant. The survival outcome was also significantly poorer in those with extrathyroid invasion.

Patients with leukocytosis at diagnosis showed significantly poor prognosis. While the clinical course was unfavorable in those with distant metastasis at diagnosis, the difference did not reach significance (it is uncertain whether these distant metastases originated from DCT or ATC). The survival outcome was also not particularly poor in those who developed acute symptoms within 1 month.

Treatments and outcome

The treatments performed for incidental ATC and outcomes were evaluated (Table 3). All patients underwent surgery. The 1-year survival rate was clearly higher, and the survival outcome was significantly more favorable, in those who underwent curative resection of ATC. The effect of external beam radiotherapy (EBRT) was evaluated by dividing the patients into those irradiated with ≥40 Gy and those receiving <40 Gy (including those who did not receive EBRT), but no difference in the outcome was found. The effect of chemotherapy was evaluated by dividing the patients into those who underwent one or more courses of any chemotherapy and the others, but there was no difference in the outcome. The drugs used for chemotherapy were doxorubicin + cisplatinum in three, taxane in three, and etoposide + cisplatinum in three, but no regimen was clearly effective.

Additional treatments and outcome

As observed above, the outcome was clearly more favorable in those who underwent curative resection. The outcome was compared according to whether or not additional postoperative EBRT or chemotherapy was performed. Of the six patients who did not undergo curative resection, five received EBRT, and two of them also received chemotherapy. No additional treatment was performed in the remaining one patient. The 1-year survival rate was 50 % or less in all these patients, and all of them died due to ATC. Of the 19 patients who underwent curative resection, no additional treatment was performed in six, but seven underwent EBRT, one underwent chemotherapy, and five

Table 4 Additional treatments and outcome

Treatments	*n*	1-year survival rate (%)	Disease-related death (%)
Non-curative resection only	1	0	1 (100)
Non-curative resection + RT	3	50.0	3 (100)
Non-curative resection + RT + CT	2	33.3	2 (100)
Curative resection only	6	50.0	4 (67)
Curative resection + RT	7	87.5	2 (25)
Curative resection + CT	1	100.0	0 (0)
Curative resection + RT + CT	5	100.0	0 (0)

CT chemotherapy, *RT* radiotherapy

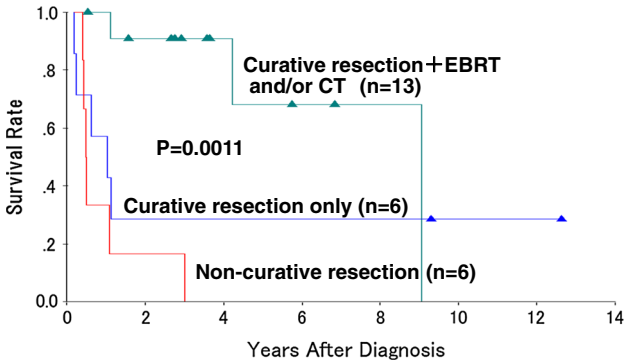


Fig. 2 Treatments and overall survival curves. *CT* chemotherapy, *EBRT* external beam radiotherapy

received both EBRT and chemotherapy. The 1-year survival rate was 50 % in those who underwent curative resection alone, and four of the six patients died due to ATC, but five of the seven patients who underwent curative resection plus EBRT survived, with a 1-year survival rate of 87 %. None of the one patient who underwent additional chemotherapy and five who underwent additional EBRT and chemotherapy died due to ATC (Table 4).

The OS was compared among those who did not undergo curative resection, those who underwent curative resection alone, and those who underwent curative resection plus EBRT and/or chemotherapy (Fig. 2). The clinical course was more favorable in those who underwent curative resection and additional radiotherapy and/or chemotherapy, and significant differences were observed among the three groups.

When multivariate analysis (Cox regression model) was performed using five factors, i.e. those factors shown to have affected the outcome on univariate analysis and the above treatment factor, only the tumor size was significantly correlated with OS, and the difference in the treatment groups did not reach significance, with $p = 0.055$ (Table 5).

Table 5 Multivariate analysis; Cox regression model

Factor	*p* value	Hazard ratio	95 % CI
Gender (male, female)	0.731	0.70	0.09–5.36
Tumor size (<1.5 cm, ≧1.5 cm)	0.035	5.65	1.13–28.37
Extrathyroid invasion (–, +)	0.393	0.42	0.06–3.15
WBC at diagnosis (<10,000/mm^3, ≧10,000/mm^3)	0.152	6.28	0.57–77.81
Treatments (non-curative surgery, curative surgery, curative surgery + RT and/or CT)	0.055	0.28	0.08–1.03

CI confidence interval, *CT* chemotherapy, *RT* radiotherapy, *WBC* white blood cell

Discussion

Incidental ATC was smaller than common-type ATC and less frequently showed extrathyroid invasion or distant metastasis at the initial examination, and is considered to be an early form of ATC. Also, coexisting lesions were predominantly papillary carcinoma, suggesting anaplastic transformation [8, 9] from papillary carcinoma. Incidental ATC was observed more frequently in females. Usually, DTC more frequently affects females, and the gender difference in incidence is considered to be narrower in ATC. If incidental ATC is an early form of ATC, the results of this study contradict this general concept and are difficult to explain. Further evaluation in a larger number of patients is considered necessary. While common-type ATC is a lethal tumor, the clinical course of incidental ATC is relatively favorable and it has been considered a curable carcinoma [10, 11]. Therefore, the analysis of prognostic factors of incidental ATC is considered to be important. On univariate analysis, small tumor size, a female gender, localization of the tumor within the thyroid capsule, and no leukocytosis at the initial examination were significantly correlated with a favorable survival outcome. The tumor size [1, 5, 12], gender [6, 12], extrathyroid invasion [1, 3, 5, 6], and leukocytosis [1, 10, 13] have often been reported as prognostic factors of ATC. While age [1, 3, 5, 6, 10] and presence or absence of acute symptoms [1, 13] have also been suggested as prognostic factors of ATC, no significant difference was noted in this study, and they are not considered to be prognostic factors of incidental ATC. In this study, also, the presence of distant metastasis did not significantly affect the outcome and was not a significant

prognostic factor, possibly because some of the distant metastasis were from the coexisting DTC.

Regarding the relationship between treatment and survival, the outcome was significantly more favorable only in the patients who underwent curative resection of incidental ATC, and no significant difference was noted according to whether or not EBRT or chemotherapy was performed. There have been a number of reports that the prognosis of ATC was favorable when the primary lesion could be completely resected [1, 5, 6, 9], and this is also considered to apply to incidental ATC. In the evaluation of common-type ATC using the ATCCJ database [1], EBRT, chemotherapy, and radical surgery were reported to significantly affect the outcome, unlike with incidental ATC. However, in incidental ATC, the 1-year survival rate tended to be higher in those who underwent EBRT or chemotherapy.

Whether or not the postoperative addition of radiotherapy or chemotherapy is significant in incidental ATC is a very interesting question. In this study, the survival outcome was compared among groups that underwent non-curative resection, curative resection alone, and curative resection plus EBRT and/or chemotherapy. Univariate analysis showed significant differences in OS among the three groups. Multivariate analysis also showed nearly significant differences, suggesting the usefulness of EBRT and/or chemotherapy as adjuvant therapies. Multimodal therapy consisting of surgery, radiotherapy, and chemotherapy has been reported to be effective for the treatment of ATC [14–17]. The analysis of common-type ATC suggested that the addition of radiotherapy and chemotherapy to surgical treatment is effective [1], and multivariate analysis indicated significant benefits of additional treatments in stage IVB ATC. Multimodal therapy is initially planned and implemented for relatively advanced cases, but the treatments are often changed or abandoned due to the rapid progression of ATC. Most of the patients who received surgery, radiotherapy, and chemotherapy had less extensive disease, so it is not surprising that the outcome is favorable in such a biased group. However, in incidental ATC, particularly patients with curative resection, there is no such bias. In this study, two-thirds of the patients with incidental ATC died due to the disease after curative resection without additional treatment, but none who received EBRT and chemotherapy as adjuvant therapies died due to the disease. This was surprising, and further evaluation with additional patients is considered necessary.

In this study, a multicenter retrospective database was used. Therefore, although the 25 patients with incidental ATC selected as subjects were re-checked, the reliability of the data was inevitably limited.

To summarize, incidental ATC mostly coexisted with papillary carcinoma and corresponded to an early stage of anaplastic transformation from papillary carcinoma. While the clinical course of incidental ATC was favorable compared with common-type ATC, nearly half of the patients had disease-related deaths. The prognostic factors of incidental ATC were nearly the same as those of common-type ATC, but the tumor size alone was an independent factor on multivariate analysis. Regarding treatments, the outcome was more favorable in those who underwent curative resection, and the clinical course showed a slight improvement with the addition of EBRT and/or chemotherapy after curative resection, but this did not reach statistical significance.

Incidental ATC is the only curable type of ATC, and postoperative adjuvant radiotherapy and/or chemotherapy is recommended to achieve long-term survival. Further studies are needed to establish the effectiveness of additional postoperative radiotherapy and/or chemotherapy in incidental ATC.

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