ORIGINAL

Optimal surgical procedure for locally curative surgery in patients with anaplastic thyroid carcinoma: importance of preoperative ultrasonography

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Abstract. Anaplastic thyroid carcinoma (ATC) is a very aggressive disease showing a high mortality. However, long-term survival is expected when patients do not show distant metastasis at diagnosis and undergo locally curative surgery. In this study, we investigated the optimal surgical procedure for locally curative surgery for ATC in a series of 34 patients. Twenty patients underwent total thyroidectomy but there were no detectable skip lesions of ATC in the contralateral lobe on pathological examination. Cause-specific survival (CSS) of Stage IVA or IVB patients who underwent limited thyroidectomy did not differ from that of those who underwent total thyroidectomy. Clinical node metastasis on ultrasonography was not detected in 15 patients but 11 of these patients underwent lymph node dissection. Three of these were node-positive on pathological examination but only one showed metastatic node of ATC that was involved in the primary lesion. Of 19 patients having clinical node metastasis, 10 were ATC node positive on pathological examination. Taken together, for locally curative surgery in ATC patients, 1) total thyroidectomy may not be mandatory unless patients have clinical lesions in the contralateral lobe; 2) prophylactic modified radical neck dissection may not be mandatory for patients who do not demonstrate clinical signs of lymph node metastasis; and 3) extensive and careful therapeutic node dissection may be required for patients demonstrating clinical signs of node metastasis.

Key words: Anaplastic carcinoma, Thyroid, Prognosis, Surgery

ANAPLASTIC THYROID CARCINOMA (ATC) is thought to arise from differentiated carcinoma. Although differentiated carcinoma generally shows an indolent nature, ATC is one of the most aggressive human neoplasms and shows a high disease-specific mortality [1]. To date, some prognostic factors such as tumor size, patient age, leukocytosis, distant metastasis and rapid enlargement have been identified [2-5] and an evaluation system based on scoring these prognostic factors has been proposed [5]. Due to extremely aggressive character, combined modality therapy such as surgery in combination with chemotherapy and external beam radiotherapy (EBRT)

has been adopted for ATC. Fundamentally, however, long-term survival can be expected only when patients do not have distant metastasis at surgery and undergo locally curative surgery [6, 7]. Recently, we demonstrated that induction chemotherapy by weekly paclitaxel markedly contributes to the long-term survival of responders, especially those with Stage IVB on UICC TNM classification [8], because tumor shrinkage induced by this regimen facilitates locally curative surgery and may also be effective for micrometastases to distant organs [9].

Currently, however, whether extensive surgery such as routine total thyroidectomy with a wide range of lymph node dissection is necessary or limited surgery is adequate for locally curative surgery for ATC patients remains an open question. In this study, therefore, we focused on this issue and investigated the optimal surgical procedure for ATC in a series of 34 patients who

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underwent preoperative evaluation of primary lesions and lymph node metastases on ultrasonography and then received surgical treatment for local control.

Patients and Methods

Patients

Between 1992 and 2009, 34 patients with ATC underwent initial surgery for local curativity. All these patients underwent evaluation of primary lesions and lymph node metastasis on preoperative imaging studies including ultrasonography. All patients were diagnosed as having ATC on postoperative pathological examination.

One or two days before surgery, we evaluated the primary lesions and lymph node metastasis on ultrasonography. Lymph node metastasis was diagnosed on ultrasonography based on the criteria by Antonelli *et al.* [10]. Distant metastasis was evaluated at the time of diagnosis as ATC on CT scan.

Eight patients underwent induction chemotherapy with weekly paclitaxel [9] and clinical response was assessed according to Response Evaluation Criteria in Solid Tumors [11]. Four patients were responders (one complete response [CR] and 3 partial response [PR]) and the remaining 4 were non-responders (2 stable disease [SD] and 2 progressive disease [PD]) to paclitaxel. Continuous weekly paclitaxel was performed for 6 patients who were classified as CR, PR or SD after surgery. The other 17 patients underwent chemotherapy with various agents after surgery. Twenty-four patients underwent postoperative EBRT.

Patients who underwent only debulking surgery and those without dissection of carcinoma lesion were deleted from the series. Follow-up periods averaged 23.2 ± 31.3 months (4-143 months).

Statistical analysis

Fisher's exact test was adopted for comparing variables. The Kaplan-Meier method with log-rank test was adopted to analyze patient's prognosis. A *p* value < 0.05 was considered significant.

Results

Background and clinicopathological features of 34 patients

Table 1 summarizes the backgrounds and clinicopathological features of these 34 patients. They con-

Table 1 Backgrounds and clinicopathological features of 34 patients

Gender (male/female)	7/27
Age (years)	62.6 ± 10.6
Primary lesions limited in one lobe	18
*Not limited in one lobe	16
Clinical node metastasis (yes/no)	19/15
Stage (IVA/IVB/IVC)	8/21/5
Thyroidectomy (total/subtotal/lobectomy)	20/5/9
Lymph node dissection (Not done/central only/central and ^MND)	4/4/26
Pathological node metastasis (yes/no)	20/14
Pathological node metastasis of ATC (yes/no)	11/23

*Primary lesions exceeded the isthmus or other pathological lesions were present in the contralateral lobe.

^Modified radical neck dissection

sisted of 7 males and 27 females with an average patient age of 62.6 ± 10.6 years (35-84 years). Eighteen patients (53%) had primary lesions limited to one lobe and no other pathological lesions were detected in the contralateral lobe. The remaining 16 had large primary lesions exceeding the isthmus or other pathological lesions such as papillary carcinoma and follicular tumor were detected in the contralateral lobes. Lymph node metastasis was preoperatively detected in 19 patients (56%); 13 in central compartment, 18 in lateral compartment and 12 in both compartments. Five patients showed distant metastases at surgery and were classified as having Stage IVC.

According to the surgical notes, 24 patients, including one with lung metastasis at surgery, underwent locally curative surgery. Minimal residual carcinoma lesion was suspected in the remaining 10 patients and 6 of these did not have distant metastasis at surgery.

Extent of thyroidectomy

Total thyroidectomy, subtotal thyroidectomy and lobectomy (with or without isthmectomy) were performed for 20 patients, 5 patients and 9 patients, respectively. Seven patients who underwent total thyroidectomy and 3 who underwent subtotal thyroidectomy did not have apparent pathological lesions in the contralateral lobe on preoperative ultrasonography. Of 4 responders to weekly paclitaxel, 2 underwent limited thyroidectomy because carcinoma lesions did not exceed the isthmus. One underwent total thyroidectomy because of the largeness of primary lesion. The remaining one who underwent lobectomy demonstrated small papillary carcinoma lesions in the contralateral lobe but these were not dissected because of multiple

lung metastases. Of 4 non-responders to weekly paclitaxel, one underwent limited thyroidectomy because primary tumor was limited in one lobe. Of the remaining 3 who underwent total thyroidectomy, 2 had large primary lesions exceeding the isthmus. On pathological examination, there were no detectable skip lesions of ATC in the contralateral lobe of 25 patients who underwent total or subtotal thyroidectomy.

Extent of lymph node dissection and pathological findings of metastasis

Of 15 patients diagnosed as negative for lymph node metastasis on preoperative ultrasonography, 4 did not undergo lymph node dissection and other 4 underwent central node dissection only. The remaining 7 patients and 19 diagnosed as positive for node metastasis (26 in total) underwent central node dissection and unilateral or bilateral modified radical neck dissection (MND). Eight of these underwent prophylactic MND (one patient was only central node-positive and the remaining 7 were node-negative on ultrasonography) and the remaining 18 underwent therapeutic MND, because they were diagnosed as lateral node-positive on ultrasonography. One of these patients also underwent mediastinal node dissection.

Table 2 demonstrates the relationship between clinical and pathological lymph node metastasis. Of 11 patients without preoperatively detected node metastasis who underwent prophylactic node dissection, 3 (27%) were diagnosed as node-positive on pathological examination. However, node metastasis of ATC was detected in only one patient and in this case, the node was involved in the primary lesion and dissected en bloc together with the primary lesion. Metastases of differentiated carcinoma only were detected in the remaining 2 patients. Of 19 patients who were diagnosed as node-positive on preoperative ultrasonography, 17 (89%) were pathologically confirmed as having node metastasis and 10 (53%) were ATC node-positive. The specificity and sensitivity of ATC node metastasis on ultrasonography were 91% and 53%, respectively.

We then analyzed the relationships between clinical node metastasis and pathological node metastasis of ATC separately in the central and lateral compartments. As shown in Table 3, of 17 patients who were regarded as negative for clinical central node metastasis, 1 (6%) was diagnosed as node-positive for ATC on pathological examination. This patient was later-

Table 2 Relationships between N and pN in 30 patients with ATC who underwent lymph node dissection

		pN		
		0	1	Total
N	0	8	3(*^1)	11
	1	2	17(*10)	19
	Total	10	20(*11)	30

*Number of patients having metastasis of ATC

^One lymph node involved in the primary lesion was metastatic (See Table 3).

Specificity for ATC node metastasis; 91% (10/11)

Sensitivity for ATC node metastasis; 53% (10/19)

Table 3 Relationships between clinical central node metastasis and pathological metastasis of ATC in the central and lateral compartments in 30 patients with ATC who underwent lymph node dissection

		pN central *[lateral]		
		0	1	Total
N central	0	16[3]	1[1]	17[4]
	1	8[2]	5[3]	13[5]
	Total	24[5]	**6[4]	30[9]

*Number of patients having lateral node metastasis

**This indicates that 2 patients are central-positive but lateral-negative.

Table 4 Relationships between clinical lateral node metastasis and pathological metastasis of ATC in the lateral and central compartments in 26 patients with ATC who underwent lymph node dissection

		pN lateral **[central]		
		0	1	Total
N central	0	7[2]	*1	8[2]
	1	10	8[4]	18[4]
	Total	17[2]	^9[4]	26[6]

*One lymph node involved in the primary lesion was metastatic.

**Number of patients having central node metastasis

^This indicates that 5 patients are central-negative but lateral-positive.

al node-positive on ultrasonography and showed metastasis of ATC also in the lateral compartment. Of 8 patients diagnosed as lateral node-negative on ultrasonography, 1 (13%) was diagnosed as having ATC metastasis in the lateral compartment (Table 4), but as indicated above, the metastasis was involved in primary lesion and dissected en bloc. Five of 13 patients (38%) and 8 of 18 patients (44%) who were preoperatively diagnosed as node-positive in the central and

lateral compartments, respectively, were pathologically confirmed as ATC node-positive in these compartments (Tables 3, 4). Furthermore, in our series, 2 patients were central-positive but lateral-negative and 5 were central-negative but lateral-positive (Tables 3, 4).

Carcinoma recurrence

Recurrence to local lesions and distant organs were observed in 13 and 14 patients, respectively. Six of 24 patients (25%) who underwent locally curative surgery and 7 of 10 patients (70%) with suspicion of minimal carcinoma remnant in local lesions showed local recurrence to various sites. The recurrence rate showed a significant difference ($p = 0.0223$) between these two groups. Recurrence to regional lymph nodes was observed only in one patient. This patient was preoperatively diagnosed as central and lateral node-positive and pathologically confirmed as ATC node-positive in the central compartment. Although only metastasis of differentiated carcinoma was pathologically detected in the lateral compartment, recurrence of ATC occurred in the lateral compartment during follow-up and this patient died of its enlargement. Two patients showed recurrence to the axillary lymph nodes and retropharyngeal nodes, respectively.

None of 14 patients who underwent limited thyroidectomy showed a recurrence to the remnant thyroid, although 4 of these patients showed other local recurrences of ATC. As indicated above, small papillary carcinoma lesions in the contralateral lobe remained undissected in one Stage IVC patient. The lesion showed about 50% enlargement postoperatively but it was not confirmed whether that lesion showed anaplastic transformation. This patient died of lung metastasis six months after surgery.

Cause-specific survival (CSS) of patients

To date, 22 patients, including all five Stage IVC patients, have died of carcinoma three to 82 months after surgery. Four died of local growth, 13 died of distant metastasis, and one died of complications of EBRT. Details of the cause of death were unknown for the 4 remaining patients, although they died of ATC. Four patients showed local and/or distant recurrence but survived during follow-up 9 to 50 months after surgery. Two patients died of other diseases unrelated to ATC 74 and 91 months after surgery, respectively, without recurrence of ATC. The other 6 patients, including 3 responders to weekly paclitaxel,

survived without signs of recurrence 11 to 143 months after surgery.

We investigated the prognostic value of the factors examined in this study in the subset of 29 patients with Stage IVA or IVB. CSS of patients with locally curative surgery was significantly better than that of those with suspicion of minimal carcinoma remnant ($p = 0.0010$) (Fig. 1-a). All 6 patients with suspicion of minimal carcinoma remnant died of carcinoma within 19 months after surgery. Extent of thyroidectomy, total thyroidectomy or limited thyroidectomy, did not affect patient prognosis (Fig. 1-b) (one-year CSS rate 60% vs 51%). Similar finding was obtained in the analysis of 23 patients who underwent locally curative surgery (data not shown). Patients having lymph node metastasis of ATC tended to show a worse CSS (one year CSS rate 42%) than those without ATC metastasis (one year CSS rate 64%), although the difference did not reach significance ($p = 0.1826$) (Fig. 1-c).

Five of 6 patients with suspicion of minimal carcinoma remnant underwent postoperative EBRT, but all these died of carcinoma within 19 months as indicated above. Of 23 patients who underwent locally curative surgery, 19 underwent EBRT. Fig. 1-d indicates the CSS of 19 patients with EBRT and 4 without EBRT. In this series, however, no difference of prognosis could be detected between the two groups.

Discussion

ATC is an aggressive disease showing a high mortality and in our series, 22 patients (64%) died of carcinoma. Although not only surgery but also chemotherapy and EBRT are popular modalities of therapy for ATC, previous studies showed that long-term survival is expected only when distant metastasis is not detected at surgery and locally curative surgery can be performed [6, 7]. Our results in the present study that patients with suspicion of minimal carcinoma remnant were more likely to show local recurrence and showed significantly worse CSS than those who underwent locally curative surgery are not discrepant to previous findings [6, 7]. However, the optimal surgical procedure for locally curative surgery in ATC remains unclear. After the 1990s, the resolution of ultrasonography significantly increased, which facilitated accurate evaluation of the primary lesion and lymph node metastasis in thyroid malignancies, including ATC. In this study, we investigated the records of 34 ATC pa-

Fig. 1-a Kaplan-Meier curves for Stage IVA or IVB patients who underwent locally curative surgery and those with suspicion of minimal carcinoma remnant.

Fig. 1-b Kaplan-Meier curves for Stage IVA or IVB patients who underwent total thyroidectomy and limited thyroidectomy.

Fig. 1-c Kaplan-Meier curves for Stage IVA or IVB patients who were ATC node-positive and negative.

Fig. 1-d Kaplan-Meier curves for Stage IVA or IVB patients who underwent locally curative surgery with and without EBRT.

tients who underwent surgery in the era of high resolution of ultrasonography in order to elucidate this issue and demonstrated some important findings.

The first important finding is that, on pathological examination, skip lesions of ATC in the contralateral lobe were not detected in any of the patients who underwent total thyroidectomy. Furthermore, none of the patients who underwent limited thyroidectomy showed recurrence of ATC in the remnant thyroid. One patient showed enlargement of papillary carcinoma lesions, that had been preoperatively detected but were not dissected because of multiple lung metastases. However, this lesion was not confirmed as showing anaplastic transformation and the patient died of

lung metastasis 6 months after surgery, indicating that the residual thyroid lesion was not directly life-threatening. Furthermore, in the subset of patients with Stage IVA or IVB, CSS of patients who underwent total thyroidectomy did not differ from that of those who underwent limited thyroidectomy. These findings suggest that total thyroidectomy may not be mandatory for ATC patients, if no lesions suspected of malignancy are present in the contralateral lobe on preoperative ultrasonography.

Our series include 8 patients who underwent induction chemotherapy with weekly paclitaxel. Two of 4 responders and one of 4 non-responders underwent limited thyroidectomy because their primary lesions

were limited in one lobe. The incidence of patients receiving limited thyroidectomy might increase in the future if induction chemotherapy is effective and size of primary lesion is reduced. The extent of thyroidectomy should be decided according to whether primary lesions exceed the isthmus and other pathological lesions are detected in contralateral lobe at the time of surgery even though patients underwent induction chemotherapy.

The second important issue is the extent of lymph node dissection. ATC can initially metastasize not only to central and but also to lateral compartments, because 2 patients were central-positive but lateral-negative and 5 were central-negative but lateral-positive (Tables 3, 4). However, all cases having lateral ATC metastasis were diagnosed as lateral node-positive on preoperative ultrasonography with the one exception indicated above (Table 4). This exception had lateral node metastasis involved in carcinoma lesion and dissected en bloc. Furthermore, outside of the one exception, all clinical lateral node-negative cases were also pathologically negative for ATC metastasis. In the central compartment, ATC metastasis was overlooked in one patient (Table 3), although this patient was diagnosed as clinically positive for lateral node metastasis. We previously showed that the negative predictive value and sensitivity of ultrasonography for node metastasis in central compartment was lower than those in the lateral compartment [12, 13]. Central node metastasis is generally difficult to detect because the presence of air-filled trachea and the thyroid disturbs the screening on ultrasonography. Furthermore, tumor size of ATC tended to be larger than that of differentiated carcinoma, which should make screening of the central compartment more difficult for ATC patients. In our series, none of the ATC patients without clinical node metastasis showed a recurrence to the regional lymph nodes. These findings suggest that, for locally curative surgery of ATC without clinical node metastasis, prophylactic MND may not be mandatory. However, routine central node dissection is recommended because of the possibility of overlooking ATC metastasis on ultrasonography.

In our series, 19 patients were diagnosed as having clinical node-positive and 10 of these patients showed ATC metastasis. One patient who was ATC node-positive showed recurrence to regional lymph nodes and died due to their growth. In this series, we failed

to establish a difference in CSS of ATC node-positive and negative patients, but one-year CSS rates significantly differed (64% vs 42%) between the two groups (Fig. 1-c), indicating that the lack a significant difference in the former analysis have been due to type II error induced by the small number of patients. It is therefore suggested that extensive and careful lymph node dissection, dissection of the central and lateral compartments at least ipsilateral to the primary lesion, should be performed for patients diagnosed as node-positive on ultrasonography. This is because a high incidence of ATC metastasis was included among clinical node metastases detected on ultrasonography and ATC metastasis cannot be discriminated from metastasis from differentiated carcinoma on imaging studies.

For most ATC patients, EBRT and chemotherapy are performed as adjuvant therapies. Especially, EBRT has been widely adopted for local control in combination with surgery. We performed postoperative EBRT for 5 of 6 patients with suspicion of minimal carcinoma remnant, but all patients died of carcinoma within 19 months after surgery. Of 23 patients with Stage IVA or IVB who underwent locally curative surgery, 19 underwent postoperative EBRT. However, no significant difference for CSS could be established between patients with and without EBRT. This may be due to the small number of patients who did not undergo EBRT, but at least in our series, the effectiveness of EBRT for local control of minimal carcinoma remnant and for prolonging survival of patients who underwent locally curative surgery could not be proven. Whether ATC patients without distant metastasis can survive for a long time depends predominantly on surgical curativity and studies for optimal surgery are important.

In summary, preoperative ultrasonography largely contributes to determining the extent of thyroidectomy and lymph node dissection for locally curative surgery in ATC patients. If the primary lesion is limited to one lobe on ultrasonography, total thyroidectomy may not be mandatory. For lymph node dissection, central node dissection should be routinely performed, but if node metastasis was not detected on ultrasonography, prophylactic MND may not be needed. However, extensive and careful lymph node dissection may be required for ATC patients demonstrating clinical node metastasis.

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