Validity of 6th edition of UICC TNM classification system for medullary thyroid carcinoma: A proposal for intraoperative evaluation of T category

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Abstract. Medullary thyroid carcinoma (MTC) accounts for 1.4% of all thyroid malignancies in Japan. Here, we studied the validity of a staging system evaluated preoperatively (Stage), intraoperatively (intra-Stage), and pathologically (pStage) based on the 6th and 7th UICC TNM classifications. One hundred and nineteen MTC patients who did not show distant metastasis at diagnosis and underwent locally curative surgery were enrolled in this study (average follow-up period: 173.4 months). Twenty-year clinical (not biochemical) disease-free survival (DFS) rates of Stage I, II, III, and IV A patients based on the 6th edition were 100, 88.2, 66.8, and 38.9%, respectively. DFS of Stage IVA patients was significantly poorer than that of Stage III patients (p = 0.03137). However, using the 7th edition, only 1 patient was classified with Stage I. Intra-Stage III patients based on the 6th edition showed a significantly poorer DFS (20-year DFS 50.0%) than intra-Stage II patients (92.9%) (p = 0.02668), and DFS of intra-Stage IVA patients (38.9%) tended to be poorer than that of intra-Stage III patients (p = 0.05439). Only one patient was classified with intra-Stage III using the 7th edition. In pStage, as many as 56 patients (47.1%) were classified with pStage IVA employing both editions. Taken together, Stage and intra-Stage were more useful to accurately discriminate high-risk patients than pStage, and their 6th editions were better than 7th editions. Although the number of patients was small, our data showed the possibility that intra-Stage in the 6th edition was the best staging system for MTC patients.

Key words: Medullary thyroid carcinoma, Prognosis, TNM classification, Stage
MTC, and local curative surgery is much more important for MTC than DTC. In such circumstances, 10- and 20-year disease-free survival rates of our MTC series were 89 and 82.5%, respectively, and cause-specific survival rates were 96.6 and 91.7%, respectively [18]. These survival rates were better than those reported in Western countries [3, 4, 10-14, 19-23]. In our series, extrathyroid extension, lymph node metastasis, and a large tumor size were regarded as prognostic factors, while gender, age, and \( \text{RET} \) gene mutations (except for MEN 2B) did not affect patients’ prognoses [18].

The UICC TNM classification has been the most widely adopted system to predict patients’ prognoses with thyroid carcinoma, and a few studies of MTC covering this topic have been published [24, 25]. This classification system, however, was revised from the 6th to 7th edition in 2010 [26, 27]. In the 7th edition, T3N0M0 patients were downstaged from Stage III to Stage II (Table 1). There are two kinds of Stage according to the time of evaluation: Stage is evaluated preoperatively and \( \text{pStage} \) is evaluated pathologically. However, we previously showed that evaluation of the prognosis of papillary carcinoma (PTC) patients based on intraoperative findings is very useful [28]. This is because extrathyroid extension, which is an important prognostic factor of thyroid carcinoma including MTC, can be most accurately evaluated during surgery. In this study, therefore, we investigated whether the 7th TNM classification system is superior to the 6th TNM classification system, and whether the intraoperative staging system can contribute to evaluate the prognosis of MTC patients.

**Patients and Methods**

**Patients**

Between 1975 and 2006, 119 patients, who were preoperatively diagnosed as having MTC without distant metastasis at surgery, underwent locally curative surgery, and we enrolled these patients in this study. All patients were also pathologically diagnosed with MTC. \( \text{RET} \) gene mutation analysis was performed for all patients; patients treated after November 1995 underwent the analysis preoperatively, and the analysis was performed postoperatively for patients who underwent surgery before that date. Seventy-three patients had sporadic non-hereditary disease, and the remaining 46 were diagnosed with hereditary MTC because germline \( \text{RET} \) gene mutations were detected. Six of these patients with \( \text{RET} \) gene mutations underwent prophylactic total thyroidectomy, although carcinoma in the thyroid could not be detected on imaging studies. Of 46 patients with hereditary MTC, 23, 2, and 21 patients were diagnosed with MEN 2A, MEN 2B, and FMTC, respectively.

**Table 1** 6th and 7th TNM classification for MTC patients

<table>
<thead>
<tr>
<th>Stage</th>
<th>6th</th>
<th>7th</th>
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<tbody>
<tr>
<td>Stage I</td>
<td>T1N0M0</td>
<td>T1(T1a, T1b)N0M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2N0M0</td>
<td>T2, T3 N0M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T1, T2, T3 N1aM0</td>
<td>T1, T2, T3 N1aM0</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>T1, T2, T3 N1bM0</td>
<td>T1, T2, T3 N1aM0</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>T4a any N M0</td>
<td>T4a any N M0</td>
</tr>
<tr>
<td>Stage IV/C</td>
<td>Any T Any N M1</td>
<td>Any T Any N M1</td>
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**Therapeutic strategy for MTC in our department**

Before 1996, we routinely performed total thyroidectomy for MTC patients. However, after 1996, when preoperative \( \text{RET} \) gene mutation analysis could be performed, we changed the strategy and performed hemithyroidectomy for MTC patients without germline \( \text{RET} \) mutations, if the primary lesion was limited to one lobe. Regarding lymph node dissection, we routinely performed central node dissection and also MND at least on the side ipsilateral to the primary lesion regardless of whether or not clinically apparent lymph node metastasis was preoperatively detected. For prophylactic total thyroidectomy in patients who had germline \( \text{RET} \) mutations but did not demonstrate apparent carcinoma lesions in the thyroid on imaging studies, we generally dissected only the central compartment.

According to our policy as indicated above, total thyroidectomy was performed in 75 patients, and the remaining 44 underwent hemithyroidectomy. All except one patient underwent central node dissection (CND). One hundred and twelve patients underwent uni- or bilateral modified radical neck dissection (MND). Four patients also underwent therapeutic dissection of the upper mediastinal compartment.

**Evaluation of Stage of MTC patients**

We evaluated three kinds of stage for each patient: preoperative stage (Stage), intraoperative stage (\( \text{pStage} \)), and pathological stage (\( \text{pStage} \)). Stage consists of T and N. Since we enrolled patients without distant metastasis at diagnosis, all patients were classified as M0. The tumor size for evaluating the T factor was based...
Prognosis of medullary carcinoma

To date, 5 patients have died of MTC. Four of these had sporadic MTC and the remaining one had MEN 2B. One patient with MEN 2A who refused surgery for pheochromocytoma died of a heart attack and another MEN 2A patient died of acute adrenal failure.

Statistical analyses

The Kaplan-Meier method and log rank test were adopted to analyze time-dependent variables. A $p$-value less than 0.05 was regarded as significant, and a $p$-value ranging from 0.05 to 0.1 was considered marginal.

Results

Preoperative, intraoperative, and pathological Staging of 119 MTC patients in our series

Of the 119 patients, 19, 30, 54, 15, and 1 were classified with T1a, T1b, T2, T3, and T4a, respectively. One female patient had vocal cord paralysis because of tumor extension, and was classified with T4a. Twenty-one and one patient were diagnosed with N1b and N1a, respectively. Based on the 6th UICC TNM classification, 46 (38.6%), 42 (35.3%), 8 (6.7%), and 23 (19.3%) were classified as Stage I, II, III, and IV A, respectively. Eight T3N0M0 patients classified with Stage III in the 6th edition were re-staged to Stage II in the 7th edition, and, therefore, only 1 patient (0.8%) was classified with Stage III. The number of Stage II patients using the 7th edition increased to 49 (41.2%).

We then proposed an intraoperative staging system based on TNM classification. In this system, N category was the same as the preoperative classification, as indicated above. Twenty-one, 26, 49, 18, and 5 patients were classified with intra-T1a, intra-T1b, intra-T2, intra-T3, and intra-T4a, respectively. To date, 5 patients have died of MTC. Four of these had sporadic MTC and the remaining one had MEN 2B. One patient with MEN 2A who refused surgery for pheochromocytoma died of a heart attack and another MEN 2A patient died of acute adrenal failure.

Postoperative evaluation of recurrence

About one week after surgery, we routinely measured calcitonin levels before and after stimulation by calcium gluconate with or without tetragastrin (17-19). We classified patients as being biochemically cured when basal calcitonin was within the normal range and the peak calcitonin level was less than 3-fold greater than basal calcitonin, as described previously (17-19). Eighty-three of the 119 patients (69.7%) were diagnosed as biochemically cured.

Serum CEA and calcitonin levels were measured 2 to 4 times per year. Systematic imaging studies were not performed for patients who were diagnosed as biochemically cured and without postoperative elevation of serum CEA and calcitonin. In patients with elevated serum CEA and calcitonin levels, imaging studies such as ultrasonography, CT scan, and PET-CT were also performed. Postoperative follow-up periods averaged 173.4 months (13-391 months). In this study, we regarded patients as showing carcinoma recurrence when carcinoma recurrences were observed on imaging studies. We analyzed the clinical disease-free survival (DFS) of patients and did not regard patients as showing recurrence when serum calcitonin level elevated during follow-up. To date, 19 patients have shown carcinoma recurrence. The organs to which MTC recurred were the regional lymph node in 14 patients, distant organs such as the bone, lung, and liver were 11 patients, and both the regional nodes and distant organs in 6 patients.
intra-Stage II patients increased to 49.

Twenty-one, 26, 49, 21, and 2 patients were classified with pT1a, pT1b, pT2, pT3, and pT4a, respectively. Of 5 intra-T4a patients, 3 were pathologically classified with pT3 and the remaining 2 were classified with pT4a. However, all 5 patients were classified with pN1b and were staged in pStage IVA. Regarding the pN category, 53, 10, and 56 patients were graded as pN0, pN1a, and pN1b, respectively. Taken together, 28 (23.5%), 23 (19.3%), 12 (10.1%), and 56 (47.1%) patients were classified with pStage I, II, III, and IVA in the 6th edition, respectively. Two patients in pStage III in the 6th TNM classification transition to pStage II in the 7th edition and the numbers of patients with pStage II and pStage III in the 7th edition were 25 and 10, respectively.

Biochemical cure of MTC patients based on each staging system

Table 2 indicates the incidence of biochemical cure in patients based on each staging system. As indicated above, evaluation of biochemical cure was based on calcitonin levels before and after stimulation by calcium gluconate with or without tetragastrin about one week after surgery, but not based on the change in calcitonin levels during follow-up. As shown in Table 2, the incidence of biochemical cure significantly decreased in patients with Stage IVA in the 6th and 7th editions, and only 21.7% (5 of 23 patients) were biochemically cured. The incidences of biochemical cure of Stage I, II and III patients were high, ranging from 76.2% to 84.8% in the 6th edition. In the 7th edition, one patient classified as Stage III was biochemically cured. The incidence of biochemical cure in patients with intra-Stage IVA in the 6th edition was low at 21.7%, but that of in patients with intra-Stage I, II, and III was high, ranging from 77.8 to 84.8%. Similar to Stage, one patient with intra-Stage III in the 7th edition was biochemically cured. In contrast, the incidence of pStage IV both in the 6th and 7th editions was 42.9%, which was higher than that of Stage IVA and intra-Stage IVA patients in both editions.

Clinical DFS of MTC patients based on preoperative staging system

We analyzed the clinical DFS of MTC patients based on the findings of imaging studies. We did not analyze biochemical DFS based on the change in calcitonin levels during follow-up. Fig. 1-a shows Kaplan-Meier curves for DFS of patients in each T classification. T3 and T2 patients showed a significantly poorer DFS than T2 (p = 0.03740) and T1b (p = 0.04281) patients, respectively, although DFS of T1b patients did not differ from that of T1a patients. To date, in the 6th edition, 3 stage II patients, 1 Stage III patient, and 15 Stage IV A patients showed MTC recurrence, but no Stage I patients have exhibited recurrence. Stage IV A patients showed a significantly poorer DFS than Stage III patients (p = 0.03137), although DFS between Stage I and Stage II patients and between Stage II and Stage III patients did not significantly differ (Fig. 1-b). Twenty-year DFS rates of Stage I, II, III, and IVA patients were 100, 88.2, 66.8, and 38.9%, respectively.

We analyzed the DFS of patients based on the 7th UICC TNM classification. The number of those who showed MTC recurrence was 4 patients with Stage II and 15 with Stage IVA. Fig. 1-c indicates the DFS of MTC patients in each Stage employing the 7th ed-
Fig. 1-a  Kaplan-Meier curves for DFS of patients in each T category.

Fig. 1-b  Kaplan-Meier curves for DFS of patients in each Stage in the 6th UICC classification system.

Fig. 1-c  Kaplan-Meier curves for DFS of patients in each Stage in the 7th UICC classification system.
curves for DFS of patients in each Stage. The number of Stage III patients was too small to analyze. DFS of Stage IVA patients was significantly poorer ($p = 0.00000$) than that of Stage II patients, and DFS of Stage II patients did not differ from that of Stage I patients.

**Clinical DFS of MTC patients based on intraoperative staging system**

Fig. 2-a shows the DFS of patients in each intra-T category. Patients with intra-T3 showed a significantly poorer DFS than those with intra-T2 ($p = 0.00106$), respectively. DFS did not differ between patients with intra-T1a and intra-T1b, intra-T1b and intra-T2, and intra-T3 and intra-T4a. Fig. 2-b shows Kaplan-Meier curves for DFS of patients in each intra-Stage using the 6th edition. Two intra-Stage II, 2 intra-Stage III, and 15 intra-Stage IVA patients showed MTC recurrence. DFS of patients in intra-Stage I and II did not differ, but DFS of those in intra-Stage IVA and III was significantly or tended to be poorer than that of those in intra-Stage III ($p = 0.05439$) and intra-Stage II ($p = 0.02668$), respectively.

We analyzed the same issue based on the 7th TNM classification. The number of intra-Stage III patients decreased to 1, and that of intra-Stage II patients increased to 49. Accordingly, the Kaplan-Meier curves of patients in each Stage were the same as those in Stage using the 7th edition (data not shown).
Prognosis of medullary carcinoma

Clinical DFS of MTC patients based on pathological staging system

DFS of pT3 patients was significantly poorer than that of pT2 patients \((p = 0.00269)\), although no significant difference could be established between pT1a and pT1b, pT1b and pT2, and pT3 and pT4a (Fig. 3-a). None of the patients with pStage I and II have shown MTC recurrence and one pStage III and 18 pStage IVA patients have shown such recurrence to date. Fig. 3-b indicates the DFS of patients in each pStage in the 6th edition. The DFS rates of pStage IVA and pStage III patients were lower than pStage III and pStage II patients, respectively, but no significant difference could be established.

One patient who showed recurrence in pStage III using the 6th edition was graded as pStage II using the 7th edition. Fig. 3-c shows the Kaplan-Meier curves of patients in each pStage. DFS of pStage IVA patients tended to be poorer \((p = 0.09503)\) than that of pStage III patients.

Carcinoma death of MTC patients

To date, 5 patients have died of MTC. All 5 patients were graded in Stage IVA, intra-Stage IVA, and pStage IVA in the 6th and 7th classifications. Four of these patients were not biochemically cured.

Discussion

In this study, we investigated the validity of preoperative (Stage), intraoperative (intra-Stage), and pathological (pStage) staging systems for MTC based on the 6th and 7th UICC TNM classifications.

In our series, as many as 56 patients (47.1%) were classified in pStage IVA using both the 6th and 7th editions. Although only 2 patients were graded with pT4a, 56 (47.1%) were graded with pN1b, because lateral node metastasis that was undetectable on preoperative imaging studies was frequently detected on pathological examination. Accordingly, almost half of the patients in our series were classified in the highest stage and, definitely, pStage is not appropriate to discriminate high-risk patients with MTC from others. These findings were similar to those in PTC in our previous study [29]. We showed that the incidence of biochemical cure in Stage IVA patients was lower than that in Stage I, II, and III patients based of all kinds. However, the incidence of biochemical cure in pStage IVA patients was 42.9%, which was higher than that in Stage IVA and intra-Stage IVA patients, which can also support our conclusion indicated above.

Only 23 patients (19.3%) were classified in Stage IVA both in the 6th and 7th editions. In our series, T3 patients showed a significantly poorer DFS than T2 patients. This is not discrepant with our previous finding that a tumor size larger than 4 cm was a prognostic factor for MTC patients [18]. In Stage based on the 6th edition, 20-year DFS rates were successively poorer from Stage I to Stage IV A patients: 100% in Stage I, 88.2% in Stage II, 66.8% in Stage III, and 38.9% in Stage IVA, although a significant difference in DFS could be established only between Stage III and Stage IV A patients. This indicates that Stage in the 6th edition is useful to evaluate the prognosis of MTC patients. However, in the 7th edition, T3N0M0 patients are re-staged to Stage II, and in our series, only one patient was classified with Stage III. This is too few a number to analyze. Furthermore, we showed that T3 and T2 had different prognostic values because T3 patients showed a significantly poorer DFS than T2. It is therefore suggested that Stage in the 7th edition is less appropriate than that in the 6th edition.

It is difficult to accurately evaluate extrathyroid extension based on preoperative findings. We can classify patients with T4a only when a patient has recurrent laryngeal nerve paralysis because of tumor extension or a tumor shows a definite intratracheal extension on CT scan or MRI. This indicates that most extrathyroid extension can be overlooked. Indeed, in our series, only one of 5 patients classified with intra-T4a was graded with T4a. Furthermore, minimal extension corresponding to T3 cannot be evaluated on preoperative imaging studies but on intraoperative findings. In contrast to PTC [30], not only massive but also minimal extension affected patients’ prognosis and, therefore, evaluation of minimal extension is also important [19]. Since 5 of 6 MTC showing minimal extension on intraoperative findings were larger than 4 cm and all patients with intra-T4a were also classified as N1b, the number of patients with intra-Stage III based on 6th edition increased by only one and that of intra-Stage IVA patients did not change compared with Stage III and Stage IVA. However, the 20-year DFS rates of intra-Stage III patients decreased to 50.0% and that of intra-Stage II patients increased to 92.9%. Furthermore, DFS of intra-Stage III patients was significantly poorer than that of intra-Stage II patients and DFS of intra-Stage IVA patients tended to be poorer than that of intra-Stage III patients. Although the number of patients was
Fig. 3-a  Kaplan-Meier curves for DFS of patients in each pT category.

Fig. 3-b  Kaplan-Meier curves for DFS of patients in each pStage in the 6th UICC classification system.

Fig. 3-c  Kaplan-Meier curves for DFS of patients in each pStage in the 7th UICC classification system.
comparably small in our series, the intra-Staging system based on the 6th edition may be better than the preoperative staging system. In contrast, based on the 7th edition, the number of intra-Stage III patients decreased to only 1 and, accordingly, the staging of patients was the same as that of those of Stage in the 7th edition. Therefore, similar to Stage, intra-Stage based on the 7th edition is less useful than that based on the 6th edition.

Also in PTC, we proposed an intraoperative staging system [28]. In this system, we proposed a revision of the N grading system based on the size of node metastasis (3 cm or larger) and extranodal tumor extension. Indeed, Sugitani et al. also showed that DTC with lymph node metastasis 3 cm or larger led to a dire prognosis and was classified into high-risk [31]. However, in the series of MTC, we could not establish a difference in prognosis between patients with clinical node metastasis 3 cm or larger and/or extranodal tumor extension and patients with clinical node metastasis without these features (data not shown). This may because the number of N1 patients was small, at 22, but, in this study, we did not include the N grading based on the above criteria.

In our series, only 5 patients died of MTC and all patients were classified with Stage IVA in this study. It is therefore suggested that extrathyroid extension and/or clinical node metastasis in the lateral compartment can be predictors of carcinoma death. However, further studies are necessary to elucidate more sensitive prognostic factors affecting the cause-specific survival of patients.

In this study, we compared the prognostic significance of MTC among preoperative, intraoperative, and pathological staging systems based on the 6th and 7th UICC TNM classifications. In our series, intraoperative evaluation of the stage based on the 6th TNM classification might be the most useful to effectively discriminate MTC with a poor prognosis, at least for DFS. Studies using larger numbers of patients with longer follow-up periods are necessary to elucidate whether our findings can be applied to the cause-specific survival of MTC patients.

References


