Impact of gross extrathyroidal extension into major neck structures on the prognosis of papillary thyroid carcinoma according to the American Joint Committee on Cancer eighth edition

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Abstract. This study investigated the impact of gross extrathyroidal extension into major neck structures on the prognosis of papillary thyroid carcinoma according to changes in the American Joint Committee on Cancer (AJCC)/Tumor-Node-Metastasis staging system. Overall, 183 patients with gross extrathyroidal extension into major neck structures were enrolled. The 10-year disease-specific survival (DSS) of patients in each stage showed appropriate correlation and stratification with the AJCC eighth edition. However, the 10-year DSS rate in stage III was better than the expected 10-year DSS rate, according to the AJCC eighth edition. Patients in stage III were subcategorized into three new groups: stage IIIA, patients with only recurrent laryngeal nerve invasion; stage IIIB, patients with superficial invasion of the aerodigestive tract; and stage IIIC, patients with intraluminal invasion of the aerodigestive tract. The prognostic differences among these three groups and stage IV A were examined. Although the DSS rate of patients in stage IIIA was excellent, that of patients with T4a disease was worse due to the progression of aerodigestive tract infiltration. Of the four groups, the time to locoregional recurrence was the shortest for patients in stage IVA. The distant recurrent-free survival for patients in stages IIIC and IVA tended to be worse than those for patients in stages IIIA and IIIB. These results indicate that the progression of aerodigestive tract infiltration has an impact on the incidence of distant recurrence, and the presence of T4b disease has an impact on the incidence of distant and locoregional recurrences.

Key words: Papillary carcinoma, Thyroid, Gross extrathyroidal extension, Prognosis, Tumor-node-metastasis staging system

Materials and Methods

Ethical statement

The institutional review board approved our study.
nosis, was performed for all PTC patients with extension into major neck structures. The following variables were extracted from the medical charts for analysis: prognosis, rate of locoregional or distant recurrence, and invasion site.

Evaluations
Cervical ultrasonography was routinely performed for all patients with thyroid carcinoma. For patients with suspected PTC extension into major neck structures, enhanced computed tomography or magnetic resonance imaging was further performed for preoperative evaluation. Patients with an intraluminal invasion of the aerodigestive tract were evaluated by endoscopic examination. The extent of invasion into major neck structures evaluated by preoperative imaging was confirmed by intraoperative findings. Curative resection, which was confirmed based on the intraoperative pathological diagnosis, was performed for all PTC patients with extension into major neck structures, and aerodigestive function was preserved or reconstructed when possible.

Definitions
Extension into major neck structures was defined as tumor invasion of the larynx, trachea, esophagus, recurrent laryngeal nerve (RLN), mediastinal vessels, carotid artery or prevertebral fascia from the thyroid primary tumor site (excluding invasion into the sternothyroid or sternohyoid muscle), or metastatic lymph node with surrounding organ invasion. Tumor extension (TNM) was classified into surgical stages. Patients in stage III (with tumor extension: T4a) by the AJCC-8 classification were subcategorized into three new groups: stage IIIA, patients with only RLN invasion; stage IIIB, patients with superficial invasion of the aerodigestive tract; and stage IIIC, patients with intraluminal invasion of the aerodigestive tract. The 10-year DSS rates of patients in each stage by the AJCC-8 classification were 95.6%, 87.5%, 80.6%, 48.5%, and 40.2% in stages I, II, III, IVA, and IVB, respectively (Fig. 1). The 10-year disease-free survival (DFS) rates of patients in stages I, III, and IVA by the AJCC-8 classification were 88.2%, 70.8%, and 0%, respectively (p = 0.0039, log-rank test; Fig. 2). All nine patients down-staged to stage II by the AJCC-8 classification were removed from the DFS analysis because of having distant metastasis at the initial treatment. Although there was a 19% increase in the number of patients with gross extrathyroidal extension into major neck structures in stages I and II by changing the age cutoff, no significant difference was found in the DSS of patients in stages I and II by the AJCC-7 and AJCC-8 classifications (p = 0.315, log-rank test). The DSS rate in older patients with gross extrathyroidal extension showed an appropriate correlation and stratification with AJCC-8. Moreover, the DFS rate showed an appropriate stratification with AJCC-8, similar to the DSS rate. AJCC-8 had better predictability for DSS than did AJCC-7. However, the 10-year DSS rate in stage III was better than the expected 10-year DSS rate (60%–70%) by surgically resectable, additional surgery was performed.

Statistical analysis
Descriptive statistics were computed for demographic and outcome variables. Survival curves were constructed using the Kaplan–Meier method, and between-group comparisons were performed using the log-rank test. A p-value < 0.05 was considered statistically significant. All statistical analyses were conducted using the BellCurve for Excel (SSRI Co., Ltd., Tokyo, Japan).

Results
During the study period, 1,122 patients with thyroid carcinoma underwent primary thyroid surgery. Overall, 233 patients had surrounding organ invasion by PTC, including 183 with gross extrathyroidal extension into major neck structures, 83 with gross extranodal extension, and 33 with both. Of these, 183 patients with gross extrathyroidal extension into major neck structures were enrolled. The study cohort included 46 males (25.1%) and 137 females (74.9%). The patients’ mean age at the initial treatment was 60 (range, 11–92) years. The mean follow-up period after surgery for surviving patients was 146 months. Thirty-five cases of stage IV by the AJCC-7 classification were down-staged to stages I and II by the AJCC-8 classification. Therefore, by changing the age cutoff, stages I and II patients by the AJCC-8 classification accounted for 36.1% of the total, as opposed to 16.9% by the AJCC-7 classification (Table 1).

The 10-year DSS rates of patients in each stage by the AJCC-8 classification were 95.6%, 87.5%, 80.6%, 48.5%, and 40.2% in stages I, II, III, IVA, and IVB, respectively (Fig. 1). The 10-year disease-free survival (DFS) rates of patients in stages I, III, and IVA by the AJCC-8 classification were 88.2%, 70.8%, and 0%, respectively (p = 0.0039, log-rank test; Fig. 2). All nine patients down-staged to stage II by the AJCC-8 classification were removed from the DFS analysis because of having distant metastasis at the initial treatment. Although there was a 19% increase in the number of patients with gross extrathyroidal extension into major neck structures in stages I and II by changing the age cutoff, no significant difference was found in the DSS of patients in stages I and II by the AJCC-7 and AJCC-8 classifications (p = 0.315, log-rank test). The DSS rate in older patients with gross extrathyroidal extension showed an appropriate correlation and stratification with AJCC-8. Moreover, the DFS rate showed an appropriate stratification with AJCC-8, similar to the DSS rate. AJCC-8 had better predictability for DSS than did AJCC-7. However, the 10-year DSS rate in stage III was better than the expected 10-year DSS rate (60%–70%) by
the AJCC-8 classification [3].

Overall, in the gross extrathyroidal extension group, there were 21 (11.5%) cases of locoregional recurrences, 27 (14.8%) cases of distant recurrences, and 30 (16.4%) cases of cancer-related deaths (Table 2). The number of deaths and locoregional or distant recurrence tended to increase with disease progression. During the follow-up period, 30 patients died, including 24 (80%) due to distant metastasis, 2 (6.7%) due to locoregional recurrence, and four (3.3%) due to other causes. The leading cause of death was distant metastasis, whereas deaths caused by locoregional recurrences were minimal.

### Table 1 Baseline characteristics of patients with extrathyroidal extension into major structures in the neck

| Characteristic                              | Patients (N= 183) |
|---------------------------------------------|-------------------|
| Age (years), N (%)                          |                   |
| <45                                         | 31 (16.9)         |
| 45–54                                       | 35 (19.1)         |
| ≥55                                         | 117 (64.0)        |
| Sex, N (%)                                  |                   |
| Male                                        | 46 (25.1)         |
| Female                                      | 137 (74.9)        |
| Differentiation, N (%)                      |                   |
| Well                                        | 164 (89.6)        |
| Poorly                                      | 19 (10.4)         |
| Gross extrathyroidal extension, N (%)       |                   |
| T4a                                         | 164 (89.6)        |
| T4b                                         | 19 (10.4)         |
| Distant metastasis at the initial treatment, N (%) |         |
| M0                                          | 23 (12.6)         |
| M1                                          | 160 (87.4)        |
| Stage (AJCC 7th edition), N (%)             |                   |
| I                                           | 26 (14.2)         |
| II                                          | 5 (2.7)           |
| IVA                                         | 119 (65.0)        |
| IVB                                         | 15 (8.2)          |
| IVC                                         | 18 (9.8)          |
| Stage (AJCC 8th edition), N (%)             |                   |
| I                                           | 57 (31.1)         |
| II                                          | 9 (4.9)           |
| III                                         | 90 (49.2)         |
| IVA                                         | 13 (7.1)          |
| IVB                                         | 14 (7.7)          |

Abbreviation: well, well differentiated; poorly, poorly differentiated.

The 10-year DSS rate in patients with gross extrathyroidal extension by the AJCC-8 classification

The 10-year DSS rates for patients in stages I, II, III, IVA, and IVB were 95.6%, 87.5%, 80.6%, 48.5%, and 40.2%, respectively (p < 0.001, log-rank test). The survival differences (calculated by log-rank test) between patients in stages I and II (p = 0.323), stages II and III (p = 0.455), stages III and IVA (p = 0.625), and stages IVA and IVB (p = 0.238) were not significant.

Abbreviations: AJCC-8, American Joint Committee on Cancer eighth edition; DSS, disease-specific survival.

Of the 90 patients in stage III by the AJCC-8 classification, 15, 34, and 37 patients were subcategorized into stages IIIA, IIIB, and IIIC as our new categories, respectively. The 10-year DSS rates in these three groups of stages III and stage IVA were 100%, 83.5%, 66.4%, and 48.5%, respectively (p < 0.001, log-rank test). The survival differences (calculated by log-rank test) between patients in stages I and II (p = 0.323), stages II and III (p = 0.455), stages III and IVA (p = 0.625), and stages IVA and IVB (p = 0.238) were not significant.
in stage IIIC, and 4 patients (30.8%) in stage IVA. Isolated locoregional recurrence around the aerodigestive tract, great vessel, or prevertebral fascia was detected in only 1 patient (2.9%) with IIIB disease in stage III. However, 3 patients (23.1%) in stage IVA had isolated locoregional recurrence around the aerodigestive tract or prevertebral fascia (Table 3). The 10-year distant recurrence-free survival (DRFS) rates in the three groups of stage III and stage IVA tended to be worse than those of patients in stages IIIA and IIIB.

Table 2  Locoregional recurrence and distant recurrence according to the AJCC-8

| Stage I (n = 57) | Stage II (n = 9) | Stage III (n = 90) | Stage IVA (n = 13) | Stage IVB (n = 14) | Total |
|------------------|------------------|-------------------|-------------------|-------------------|-------|
| Locoregional recurrence | 3 (5.3%) | 1 (11.1%) | 9 (10.0%) | 4 (30.8%) | 4 (28.6%) | 21 |
| Distant recurrence | 5 (8.8%) | 19 (21.1%) | 3 (33.3%) | 3 (23.1%) | 1 (7.1%) | 27 |
| No. of death | 3 (5.3%) | 1 (11.1%) | 16 (17.8%) | 3 (23.1%) | 3 (21.4%) | 30 |

Abbreviation: No., number

Fig. 2  The 10-year DFS rate in patients with gross extrathyroidal extension by the AJCC-8 classification

The 10-year DFS rates for patients in stages I, III, and IVA were 88.2%, 70.8%, and 0%, respectively (p = 0.004, log-rank test). The survival differences (calculated by log-rank test) between patients in stages I and III (p = 0.033) and stages I and IVA (p < 0.001) were significant, but that between patients in stages III and IVA (p = 0.054) was not significant.

Abbreviations: AJCC-8, American Joint Committee on Cancer eighth edition; DFS, disease-free survival.

Fig. 3  Comparison of the 10-year DSS rate among patients in the three groups of stage III and Stage IV by the AJCC-8 classification

The 10-year DSS rates for patients in stages IIIA, IIIB, IIC, and IVA were 100%, 83.5%, 66.4%, and 48.5%, respectively (p = 0.188, log-rank test). The survival differences (calculated by log-rank test) between stages IIIA and IIIB (p = 0.643), stages IIIA and IIC (p = 0.093), stage IIIA and IVA (p = 0.262), stages IIIB and IIC (p = 0.078), stages IIIB and IVA (p = 0.274), and stages IIC and IVA (p = 0.963) were not significant.

Abbreviations: AJCC-8, American Joint Committee on Cancer eighth edition; DSS, disease-specific survival; stage IIIA, patients with only recurrent laryngeal nerve invasion; stage IIIB, patients with superficial invasion of the aerodigestive tract; stage IIC, patients with intraluminal invasion of the aerodigestive tract.

Discussion

In this study, we demonstrated that the DSS of patients with gross extrathyroidal extension into major neck structures showed an appropriate correlation and stratification with AJCC-8, despite reclassification of 19% of patients with gross extrathyroidal extension into major neck structures into stages I and II when the age cutoff was changed. However, the DSS rate in stage III was better than the expected 10-year DSS rate in stage III by...
the AJCC-8 classification. A comparison among patients in the three new groups in stage III showed that the prognoses of patients with RLN invasion only were excellent. The prognoses of patients with T4a disease were worse due to the progression of aerodigestive tract infiltration. A comparison of the prognoses of patients in the three groups of stage III and stage IV A indicated that the progression of aerodigestive tract invasion or great vessel or prevertebral fascia invasion had an impact on the incidence of distant recurrence. In particular, the great vessel or prevertebral fascia invasion had an impact on the incidence of both distant recurrence and locoregional recurrence. Although the definition of the T3 category has changed substantially from AJCC-7, the definitions of T4a and T4b with gross extrathyroidal extension into major neck structures remain unchanged in both AJCC-7 and AJCC-8. Several authors reported that the number of relatively high-risk patients who would be down-staged to the lower stages with the change in age cutoff was expected to be small [4-6]. However, patients with lateral neck lymph metastasis (N1b) belong to stage IV A by the AJCC-7 classification, and it is unclear how T4 disease influenced prognosis based on AJCC-8 with the change in age cutoff. Although 19% of patients were reclassified into the lower stages, the prognoses of patients in stages I or II between AJCC-7 and AJCC-8 did not show a significant difference. Changing the age cutoff was appropriate for patients with gross extrathyroidal extension in major neck structures, except that the DSS rate in stage III was better than the expected 10-year DSS rate (60%–70%) by the AJCC-8 classification.

To examine the differences in the DSS rate between stage III and stage IV A, 90 patients in stage III were subcategorized into three groups. The survival rate of patients with aerodigestive tract invasion was worse due to the progression of aerodigestive tract infiltration and that of the patients with T4b disease tended to be further
worse with no significant difference in the 10-year DSS. However, the survival rate of patients with RLN invasion only was excellent and that of patients with superficial invasion of the aerodigestive tract was higher than the expected 10-year DSS rate (60%–70%) in stage III by the AJCC-8 classification. Our results suggest that extrathyroidal extension into the RLN without aerodigestive tract invasion is eligible for exclusion form the T4a category. Ito et al. demonstrated that PTC extending to the RLN only showed a better prognosis than that extending to other posterior organs, such as the trachea and esophagus; thus, RLN extension should be down-staged compared to deeper areas, such as extension into the trachea or esophageal mucosa [7]. Moreover, Ito et al. demonstrated that the cancer-specific survival of TNM-8 Stage III patients with tumor extension into the trachea adventitia and cartilage, esophageal muscle layer, and RLN was significantly better than that of those with tumor extension into the thyroid cartilage, larynx, tracheal mucosa, and esophageal mucosa [8]. Significant differences in the DSS rates of patients with superficial invasion and those with an intraluminal invasion of the trachea or larynx were reported in our previous studies [9, 10]. Considering the favorable survival, extrathyroidal extension into the RLN without aerodigestive tract invasion in eligible for down-staging.

Only a few studies have reported the prognosis of patients with T4b disease because this disease has a very low incidence and is difficult to treat. A comparative study of the AJCC-7 and AJCC-8 as regards predicting recurrence and survival in patients with papillary thyroid carcinoma from Korea demonstrated that only T4 disease (macroscopic massive invasion) was related to overall survival. However, the adjusted T classification by both AJCC editions did not reliably predict recurrence and survival. Although this study included 2,930 patients with PTC, the distribution of stage III or IV disease by the AJCC-8 classification was small (stage III, 58 [2%; stage IV, 8 [0.3%]) [11]. Furthermore, a study from the Memorial Sloan Kettering Cancer Center on stage migration with the new AJCC staging system for differentiating thyroid cancer demonstrated that the cancer-specific survival, overall survival, and recurrence-free survival showed a more appropriate correlation and stratification with AJCC-8. The data revealed that the new staging system more accurately reflected the biology of the disease with a better spread of survival curves, which lumped stages I, II, and III together, with a survival difference shown in only stage IV. However, the distribution of stage III or IV by the AJCC-8 classification was small (stage III, 68 [1.9%; stage IV, 38 [1%]) [12]. Although the sample size in our data was also small, a comparison of the prognoses of patients in the three groups of stage III and stage IVA showed that patients in

### Table 3 Locoregional recurrence and distant recurrence for patients among the three groups in Stage III and Stage IVA

| Stages     | Locoregional recurrence | Distant recurrence | No. of death |
|------------|-------------------------|-------------------|--------------|
| Stage IIIA (n = 15) | 2 (13.3%) | 3 (13.3%) | 2 (13.3%) |
| Stage IIIB (n = 34) | 3 (8.8%) | 6 (17.6%) | 5 (14.7%) |
| Stage IIIC (n = 37) | 4 (10.8%) | 11 (29.7%) | 9 (24.3%) |
| Stage IVA (n = 13) | 4 (30.8%) | 3 (23.1%) | 3 (23.1%) |

Abbreviation: No., number

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**Fig. 6** Comparison of the 10-year DRFS rate among patients in the three groups of stage III and stage IVA by the AJCC-8 classification

The 10-year DRFS rates for patients in stages IIIA, IIIB, IIIC and IVA were 79.6%, 82.6%, 52.3%, and 40.1%, respectively \((p = 0.116, \text{log-rank test})\). The survival difference (calculated by log-rank test) between stages IIIB and IIIC \((p = 0.047)\) was significant, but those between patients in stages IIIA and IIIB \((p = 0.733)\), stages IIIA and IIIC \((p = 0.082)\), stages IIIB and IVA \((p = 0.203)\), stages IIIB and IVA \((p = 0.307)\), and stages IIIC and IVA \((p = 0.633)\) were not significant.

Abbreviations: DRFS, distant recurrence-free survival; stage IIIA, patients with only recurrent laryngeal nerve invasion; stage IIIB, patients with superficial invasion of the aerodigestive tract; stage IIIC, patients with intraluminal invasion of the aerodigestive tract.
stage IVA had the shortest time to locoregional recurrence. Meanwhile, the DRFS rate tended to be worse for patients in stages IIIC and IVA than for those in stages IIIA and IIIB. These results indicate that massive extrathyroidal extension, including intraluminal invasion of the aerodigestive tract, or the presence of great vessel or prevertebral fascia invasion, has more aggressive biological malignancy. Patients with these massive extrathyroidal extensions need careful monitoring for locoregional and distant recurrence. Hotomi et al. demonstrated that extrathyroidal invasion was one of the most significant risk factors for patients with PTC, and the degree and site of invasion are important prognostic factors for PTC. They considered that the biological characteristics of PTC with massive invasion are not uniform, and the prognosis of patients with massive extrathyroidal invasion is determined by the biological malignancy of the tumor [13].

Our surgical strategy for locally advanced differentiated thyroid carcinoma is implemented with curative surgical intent for all patients and functional preservation or reconstruction, if possible. Shave excision is performed for patients with superficial invasion of the aerodigestive tract. For patients with intraluminal invasion of the aerodigestive tract, tumor resection including an intraluminal portion with a small surgical margin is performed and multiple margin samples are examined via frozen section analysis to pathologically confirm the presence of negative margins. Our surgical strategy is considered for patients in stage III because of the good LRFS. Stage IV disease has more aggressive features than stage III disease. Surgical treatment for patients in stage IVA is often discouraged because it is not expected to be beneficial. However, the LRFS for at least 5 years postoperatively was maintained in approximately 80% of cases. This result suggests the potential of our surgical strategy for patients in stage IVA and emphasizes the need for patient selection and careful postoperative monitoring.

Our study has several limitations that need acknowledging. First, the retrospective nature of our study and the evaluation of a limited number of PTC cases with gross extrathyroidal extension into major neck structures are apparent potential sources of bias. Second, the retrospective study design lacked external validation. Lastly, the numbers of patients in stages I and II were very small, which shows that our hospital chooses to operate on advanced cases mainly, in contrast to many other high-volume centers. Further research is needed to ascertain the validity of our study results.

In conclusion, the DSS rate in cases of gross extrathyroidal extension into surrounding major neck structures showed appropriate correlation and stratification with AJCC-8. Although the DSS rate of patients with T4a disease was worse due to the progression of aerodigestive tract infiltration, that of patients with RLN invasion only was excellent. Invasion into just the RLN may be downstaged. The progression of aerodigestive tract infiltration or the presence of great vessel or prevertebral fascia invasion has an impact on the incidence of distant recurrence. Specifically, the presence of great vessel or prevertebral fascia invasion has a huge impact on the incidence of distant and locoregional recurrences. These massive extrathyroidal extensions may worsen the biological characteristics and should be further evaluated.

Disclosure

No competing financial interests exist.

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