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Prognostic value of the 8th tumor-node-metastasis classification for follicular carcinoma and poorly differentiated carcinoma of the thyroid in Japan

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Abstract. Follicular thyroid carcinoma (FTC), a form of differentiated thyroid carcinoma, is the second most common malignancy arising from thyroid follicular cells. Recently, the tumor-node-metastasis (TNM) classification for differentiated thyroid carcinoma was revised from the 7th to the 8th edition. The diagnostic criteria for poorly differentiated carcinoma (PDC) were also updated in the latest World Health Organization (WHO) classification. In this study, we investigated whether these changes are appropriate for accurately predicting prognosis. Three hundred and twenty-nine patients diagnosed with postoperative pathologically confirmed FTC, who underwent initial surgery at our hospital between 1984 and 2004, were enrolled. For this study, patients were re-evaluated and diagnosed with FTC (N = 285) or PDC (N = 44) without typical nuclear findings of papillary thyroid carcinoma. For FTC, the 8th TNM classification was a more accurate predictor of prognosis than the 7th TNM classification. In the 8th TNM classification, cause-specific survival became significantly poorer from Stage I to IVB. The cause-specific survival of PDC based on the latest WHO classification was worse than, but did not significantly differ from, that of PDC based only on the former WHO classification. For PDC, neither of the TNM classifications could accurately predict prognosis. Taken together, we conclude that (1) the 8th TNM classification more accurately reflects the prognosis of FTC than the 7th TNM classification; (2) PDC based on the former WHO classification should be retained, at least in Japan; and (3) the TNM classification may not be suitable for predicting the prognosis of PDC.

Key words: Diagnostic criteria, Follicular carcinoma, Poorly differentiated carcinoma, Prognosis, Thyroid

FOLLICULAR THYROID CARCINOMA (FTC) is the second most common malignancy arising from thyroid follicular cells. Although regional lymph node metastasis is rare, FTC often metastasizes or recurs in distant organs, such as the lung and bone. FTC is difficult to diagnose on imaging studies and cytology. The majority of FTC cases are diagnosed based on postoperative pathological examination of specimens resected under a preoperative diagnosis of follicular neoplasm.

To date, several prognostic factors for FTC have been identified in Japan, including age, the extent of invasion, distant metastasis at diagnosis, and large tumor size [1-8]. Unlike in Western countries, Hürthle cell carcinoma does not have a poorer prognosis than FTC [1, 7]. Since FTC is a form of differentiated thyroid carcinoma, the tumor-node-metastasis (TNM) classification is applied to evaluate patient prognosis [9, 10]. Recently, the 8th TNM classification [9] was published, which contained some significant changes, including a cutoff age and staging of clinical node metastasis and extrathyroidal extension based on intraoperative findings (in the 7th TNM classification [10], extrathyroidal extension was strictly evaluated based on preoperative findings). Fur-

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Appendix: CSS, cause-specific survival; FTC, follicular thyroid carcinoma; PDC, poorly differentiated carcinoma; PTC, papillary thyroid carcinoma; RAI, radioactive iodine; TNM, tumor-node-metastasis; WHO, World Health Organization

thermore, the diagnostic criteria for poorly differentiated carcinoma (PDC) have been updated in the latest World Health Organization (WHO) classification [11]. In the former version [12], the diagnostic criteria were as follows: (1) a solid, trabecular, or insular growth pattern occupying the majority of the carcinoma lesions and (2) the absence of conventional nuclear features of papillary thyroid carcinoma (PTC). These criteria have also been adopted by the Japanese Society of Thyroid Surgery General Rules for the Description of Thyroid Cancer (7th edition) [13]. However, to diagnose PDC according to the latest version of the WHO classification [11], at least one of the following three features become mandatory: (1) convoluted nuclei, (2) ≥3 mitoses per 10 high-power fields, and (3) tumor necrosis. We previously showed that PDC based on the former version of the WHO classification [12] significantly predicted disease-free survival and cause-specific survival (CSS) [1]. In this study, we investigate whether the 8th TNM classification [9] and revised diagnostic criteria of the WHO classification [11] are appropriate for predicting the prognosis of FTC and PDC in Japan.

Materials and Methods

Patients

Three hundred and twenty-nine patients diagnosed with postoperative pathological diagnoses as "FTC", who underwent initial surgery at Kuma Hospital (Kobe, Japan) between 1984 and 2004, were enrolled. For this study, patients were re-evaluated and diagnosed with FTC (N = 285) or PDC (N = 44) without typical nuclear findings of PTC by M. H. Patients with other malignancies, such as anaplastic or medullary carcinoma, malignant lymphoma, and PTC were excluded. Patients who underwent locally non-curative surgery were also excluded. The background and clinicopathological features of the enrolled patients are summarized in Table 1. The median age of the patients was 50 (range, 13–87) years.

Surgical treatment

The extent of surgery in all 329 patients is summarized in Table 1. Hemithyroidectomy was primarily performed in patients with a follicular neoplasm. Distant metastases were detected on preoperative imaging studies in 15 (17.2%) of the 87 patients who underwent total thyroidectomy. The remaining 72 patients (82.8%) had other diseases, such as multinodular goiter and Graves' disease, or had tumors that were suspected of being

Table 1 Patient background and clinicopathological features

Characteristic	Patients (N = 329)[a]
Age (years), N (%)	
<45	135 (41.0)
45–54	65 (19.8)
≥55	129 (39.2)
Sex, N (%)	
Male	58 (17.6)
Female	271 (82.4)
Tumor size (cm), N (%)	
≤2.0	28 (8.5)
2.1–4.0	110 (33.4)
>4.0	191 (58.1)
pN stage, N (%)	
N0	322 (97.9)
N1	7 (2.1)
Extrathyroidal extension, N (%)	
No	322 (97.9)
Yes	
Preoperative findings	4 (1.2)[b]
Intraoperative findings	3 (0.9)[b]
Extent of thyroidectomy at initial surgery, N (%)	
Hemithyroidectomy	235 (71.5)
Subtotal thyroidectomy	7 (2.1)
Total thyroidectomy	87 (26.4)
Extent of lymph node dissection at initial surgery, N (%)	
Not performed	285 (86.6)
Central only	21 (6.4)
Central + MRND	23 (7.0)
pM stage, N (%)	
M0	311 (94.5)
M1[c]	18 (5.5)
Differentiation, N (%)[d]	
Well	285 (86.6)
PDC-1	13 (4.0)
PDC-2	31 (9.4)
Extent of invasion (FTC only)	
Minimal	225 (78.9)
Wide	60 (21.1)

[a] FTC (N = 285; 86.6%), PDC (N = 44; 13.4%).
[b] PDC only.
[c] Distant metastasis detected by postoperative RAI scintigraphy in 1 patient.
[d] PDC-1/2 based on the former/current diagnostic criteria of the WHO classification, respectively.
Abbreviations: FTC, follicular thyroid carcinoma; MRND, modified radial neck dissection; p, pathological; PDC, poorly differentiated carcinoma; RAI, radioactive iodine; WHO, World Health Organization.

highly malignant by the attending physician. Prophylactic lymph node dissection is not usually performed for follicular neoplasms. In our series, only 44 patients, including 7 N-positive patients, underwent lymph node dissection, due to suspicious PTC cytology and/or at the discretion of the attending physician.

Pathological diagnosis

As indicated previously, pathological diagnoses were re-evaluated by M. H., a thyroid pathologist. A diagnosis of PDC was made according to the former version of the WHO classification (also the Japanese Society of Thyroid Surgery General Rules for the Description of Thyroid Cancer [7th edition]) [12, 13] and according to the latest version of the WHO classification [11].

Postoperative follow-up

Unlike today, we did not perform a complete total thyroidectomy immediately following the diagnosis of aggressive histology (*e.g.*, widely invasive FTC or PDC) in the era of the enrolled patients. Radioactive iodine (RAI) ablation was not comprehensively performed, because of the limited use of RAI. Instead, scintigraphy was performed using a small quantity of RAI (3.0–13.0 mCi) to detect distant metastases in 36 patients who underwent total thyroidectomy. Postoperative scintigraphy detected distant metastases in a single patient who was classified as M1 in this study. Thirteen (72.2%) of the 18 M1 patients underwent RAI therapy (≥100.0 mCi). However, the remaining 5 patients (27.8%) did not, due to a poor-risk status and patient refusal. All patients were followed-up at least once or twice a year by laboratory examinations (*e.g.*, thyroglobulin and thyroid stimulating hormone levels and imaging studies, such as computed tomography, chest roentgenography, and ultrasound) to screen for recurrence in lymph nodes and distant organs.

Sixty-one patients exhibited recurrence in various organs, including the lungs, bone, liver, brain, and regional lymph nodes. Mailed questionnaires were used to survey patients who were referred to other hospitals near their residence to obtain CSS data. To date, 30 patients have died of thyroid carcinoma. The median follow-up period for CSS was 167 (range, 6–382) months. Two hundred and forty-six (74.8%), 142 (43.2%), and 49 (14.9%) patients were followed-up for 10, 15, and 20 years, respectively.

Results

Pathological diagnosis of FTC and PDC

Two hundred and eighty-five patients (86.6%) were diagnosed with FTC. Of these, 225 and 60 patients were diagnosed with minimally and widely invasive FTC, respectively, according to the former version of the WHO classification (also the Japanese Society of Thyroid Surgery General Rules for the Description of Thyroid Cancer [7th edition]) [12, 13]. Forty-four patients were diagnosed with PDC according to the former version of the WHO classification [12]. Thirty-one patients were also diagnosed with PDC according to the latest version of the WHO classification [11]. Thirteen patients were assigned to PDC-1 (PDC based on the former version of the WHO classification only [12]) and 31 patients were assigned to PDC-2 (PDC based on the latest WHO classification [11]) to compare their prognosis.

CSS of patients with FTC

The CSS of patients with FTC was analyzed according to the 7th and 8th TNM classifications [9, 10]. Kaplan-Meier curves of CSS for patients with FTC based on the 7th TNM classification [10] are shown in Fig. 1a. Although Stage II patients had a significantly poorer CSS than Stage I patients, the CSS of Stage II and III patients did not differ. The CSS of Stage II patients was also significantly poorer than that of Stage I patients according to the 8th TNM classification [9] (Fig. 1b).

As shown in Fig. 1c, the CSS was significantly poorer in patients with widely invasive FTC than in those with minimally invasive FTC. Next, we analyzed the CSS of minimally and widely invasive FTC in Stage I and II patients according to the 8th TNM classification [9]. Although the CSS was poorer in the following order of Stage II widely invasive, Stage II minimally invasive, Stage I widely invasive, and Stage I minimally invasive (Fig. 1d), statistical significance was not reached.

Differences in the prognosis of FTC and PDC

CSS was compared between patients with FTC, PDC-1, and PDC-2. The CSS of PDC-1 patients was significantly poorer than that of FTC patients ($p = 0.003$). The CSS of PDC-2 patients was also poorer than that of PDC-1 patients, although the difference was not significant (Fig. 2).

CSS of patients with PDC

We subsequently analyzed the relationship between

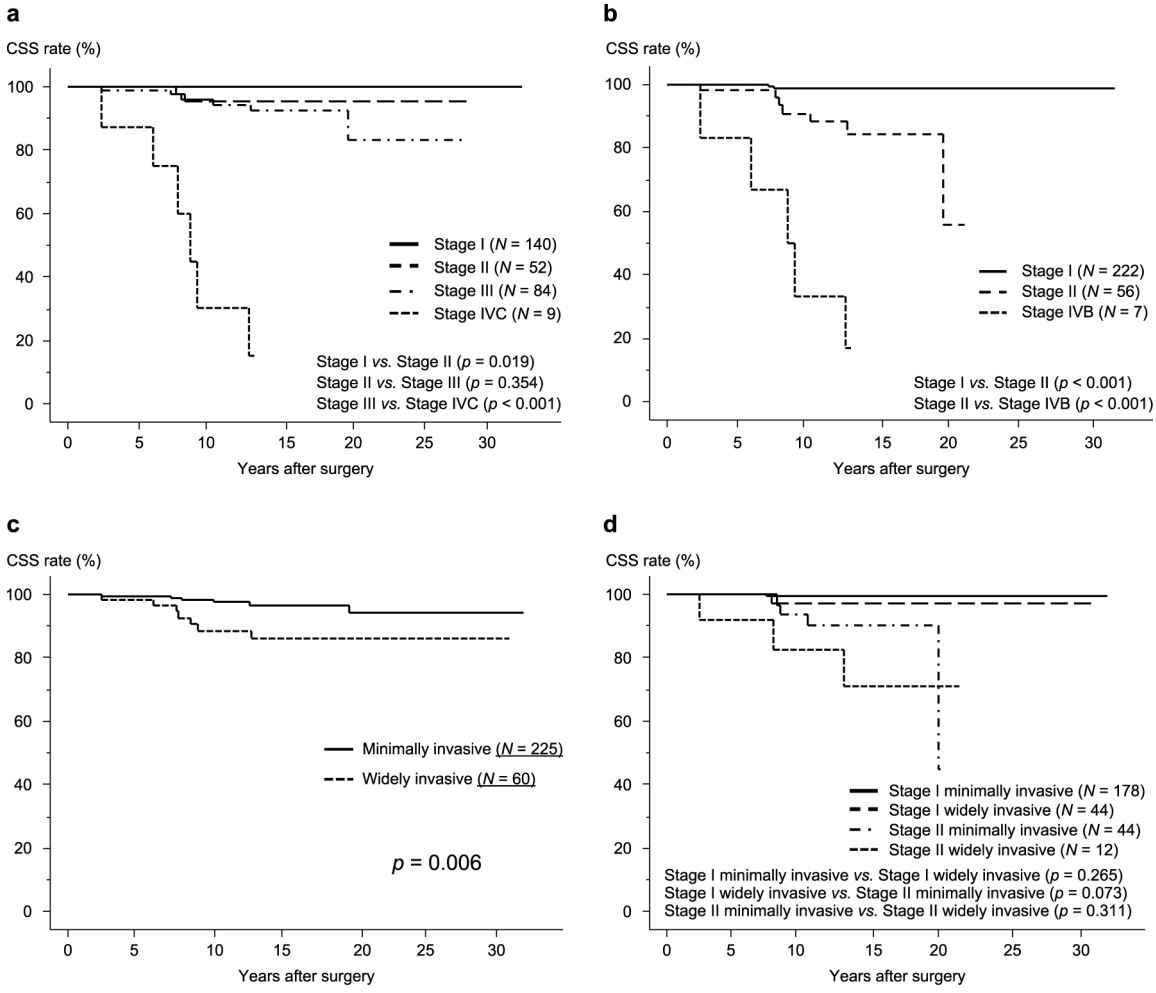

Fig. 1 Kaplan-Meier curves of cause-specific survival (CSS) for follicular thyroid carcinoma (FTC) patients with Stage I–IV disease (N = 285) based on (a) the 7th or (b) the 8th tumor-node-metastasis classification. (c) Kaplan-Meier curves of CSS for FTC patients with minimally (N = 60) or widely (N = 125) invasive disease. (d) Kaplan-Meier curves showing the relationship between CSS and Stage I/II and minimally or widely invasive disease in patients with FTC.

PDC and disease stage in relation to CSS. We further analyzed PDC-1 and PDC-2 as a single PDC group. Because only 1 patient had Stage IVA disease according to the 7th TNM classification [10], this patient was excluded from the analysis. The 8th TNM classification [9] adopted extrathyroidal extension based on intraoperative findings. Therefore, 3 patients, including 1 Stage IVA patient based on the 7th TNM classification [10], were classified as Stage III according to the 8th TNM classification [9]. As shown in Fig. 3a–b, the CSS of patients with PDC did not differ significantly among Stage I, II, and III (1 Stage IVA patient was excluded) in the 7th TNM classification [10] and among Stage I–IVB (only 3 Stage III patients were enrolled) in the 8th TNM classification [9].

Discussion

In this study, we show that (1) the 8th TNM classification [9] more accurately predicts the CSS of patients with FTC than the 7th TNM classification [10], (2) PDC based on the latest and former WHO classification [11, 12] exhibited a significantly poorer CSS than FTC, and (3) the prognosis of patients with PDC cannot be accurately predicted using either the 7th or the 8th TNM classification [9, 10], except for older M1 patients.

Although the CSS of Stage II FTC was significantly poorer than that of Stage I FTC, the CSS of Stage III FTC did not differ significantly from that of Stage II FTC, according to the 7th TNM classification [10]. In contrast, CSS was more accurately predicted by the 8th

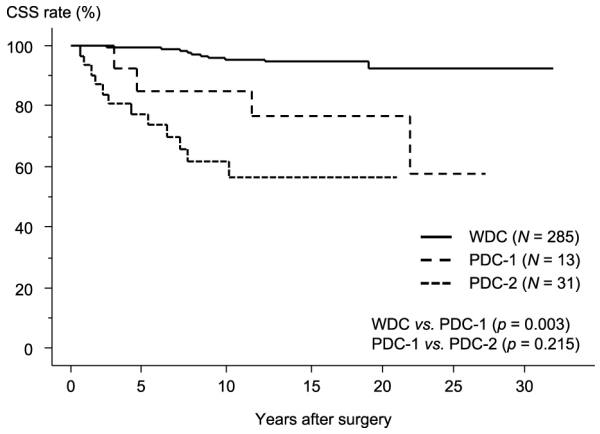

Fig. 2 Kaplan-Meier curves of cause-specific survival (CSS) stratified according to the extent of tumor differentiation. PDC-1/2 = poorly differentiated carcinoma based on the former/current diagnostic criteria of the World Health Organization classification, respectively; WDC = well differentiated carcinoma.

TNM classification [9]. Unlike PTC, N-positivity and significant extrathyroidal extension are not common in FTC, suggesting that FTC staging largely depends on age, tumor size, and M stage. In our series, the CSS of M0 (well differentiated) carcinomas of ≤2.0 cm and 2.1–4.0 cm were largely comparable ($p = 0.630$). Therefore, patients with the potential for a poorer prognosis of Stage II according to the 7th TNM classification [10] should be primarily M1 patients of <55 years. In contrast, the CSS of M0 FTCs of >4.0 cm was significantly poorer than that of M0 FTCs of ≤4.0 cm ($p = 0.049$). Stage II in the 8th TNM classification [9] included both patients aged ≥55 years with carcinomas of >4.0 cm and M1 patients aged <55 years, which may, at least partially, explain the superiority of the 8th TNM classification [9] over the 7th TNM classification [10].

The extent of invasion is another important prognostic factor for FTC [1, 5]. In our series, widely invasive FTC was associated with a significantly poorer CSS than minimally invasive FTC, which is similar to the findings of our previous study [1]. According to the 8th TNM classification [9], CSS was poorer in the order of Stage II widely invasive, Stage II minimally invasive, Stage I widely invasive, and Stage I minimally invasive. However, statistical significance was not established. This may be due to the limited number of patients enrolled in each category. The extent of invasion may influence CSS at each stage. However, further studies are needed to more accurately elucidate this point. In our series, the prognosis of widely invasive FTC was generally good. This may be because, in our series, the majority of patients who were diagnosed with widely invasive FTC exhibited gross capsular invasion in the absence of vascular invasion. If larger numbers of widely invasive FTCs with extensive vascular invasion were enrolled, then the outcomes of these patients may differ from those in this study.

Because the criteria for PDC became significantly

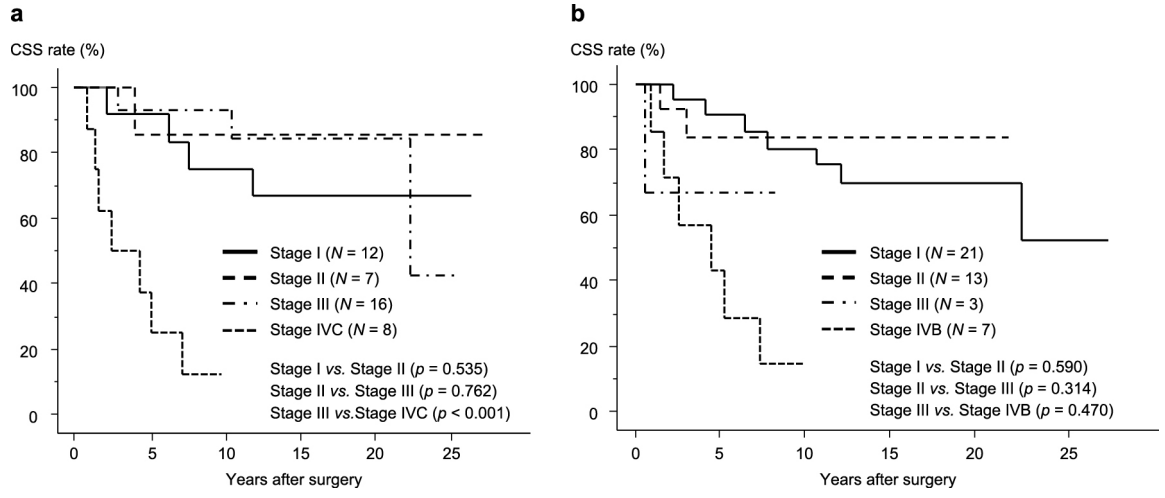

Fig. 3 Kaplan-Meier curves of cause-specific survival (CSS) for poorly differentiated carcinoma patients with Stage I–IV disease based on (a) the 7th ($N = 43$) or (b) the 8th ($N = 44$) tumor-node-metastasis (TNM) classification. One patient with Stage IVA disease based on the 7th TNM classification was excluded.

more strict in the latest WHO classification [11], the number of patients diagnosed with PDC decreased from 44 to 31. As shown in Fig. 2, the CSS of PDC based only on the former version of the WHO classification [12] was significantly poorer than that of FTC. The CSS of PDC based on the latest version of the WHO classification [11] was poorer than that of PDC based only on the former version of the WHO classification [12], although no significant difference was observed between them, which may be due to the limited sample size. However, since the CSS of PDC based only on the former version of the WHO classification [12] was significantly poorer than that of FTC, it may be better to retain the diagnostic criteria of PDC based on the former version, at least in Japan.

The CSS of PDC did not exhibit any significant change with stage according to the 7th or 8th TNM classification [9, 10]. We investigated the relationship between the prognosis of PDC patients and age. However, the CSS of PDC patients did not differ according to age (data not shown). Therefore, it is suggested that the TNM classification may be useful for FTC patients, but is not meaningful to predict the prognosis of PDC patients. Further studies are needed to investigate the prognostic factors for PDC in a larger cohort of patients.

Our study has several limitations. Firstly, this is a retrospective study. Secondly, since significant extrathyroidal extension is rare in FTC, we did not enroll patients who were classified as having Stage IVA or III disease according to the 7th or 8th TNM classification, respectively [9, 10]. In our PDC series, only 1 and 3 patients were classified as having Stage IVA and III disease according to the 7th or 8th TNM classification, respectively [9, 10]. Therefore, we could not sufficiently analyze the CSS of FTC and PDC among these stages. Thirdly, this study enrolled patients who were initially diagnosed as FTC. Therefore, PDC patients in this study were selected from a series of patients diagnosed with FTC. However, PDC can also be diagnosed from a series of patients with PTC. Thus, PDC in this study does not include all of the PDC patients who underwent surgery during this period. Lastly, at present, we perform complete total thyroidectomy for widely invasive FTC or PDC immediately after the initial surgery, which may contribute to the more rapid detection and treatment of distant metastasis and/or recurrence. However, in the era of the patients enrolled in this study, we very occasionally performed a second such surgery soon after the initial procedure. We now perform RAI ablation or adjuvant RAI therapy after total thyroidectomy for high-risk patients. However, at the time, most of the patients who were regarded as high-risk by physicians underwent RAI scintigraphy only. We are uncertain as to whether these differences affect the CSS of patients with FTC. However, they should be considered as limitations of this study.

In summary, we show that the 8th TNM classification [9] more accurately predicts the CSS of patients with FTC than the 7th TNM classification [10]. However, the prognosis of patients with PDC cannot be accurately determined using the TNM classification. For PDC, the current and former diagnostic criteria of the WHO classification [11, 12] significantly reflect patient prognosis. Therefore, we suggest that the former diagnostic criteria of the WHO classification [12] should be retained, at least in Japan.

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Disclosure

None of the authors have any potential conflicts of interest associated with this research.

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