0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(1):215–218

doi: 10.1210/jc.2006-1443

BRIEF REPORT

Prognostic Value of the Sixth Edition AJCC/UICC TNM Classification for Differentiated Thyroid Carcinoma with Extrathyroid Extension

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Context: The prognostic value of the sixth edition AJCC/UICC TNM classification is currently unclear.

Objective: The aim was to evaluate the prognostic value of the sixth edition.

Design and Patients: We retrospectively assessed 354 primary differentiated thyroid carcinomas (77 men and 277 women; age, 51.2 yr; follow-up, 107.6 months) between 1964 and 2003. Sixty percent of patients underwent lobectomy, 40% underwent subtotal/total thyroidectomy, and only 2% were given radioiodine. There were 153, 104, 86, and 11 patients in fifth stages I, II, III, and IV, and 175, 76, 14, 68, 10, and 11 patients in sixth stages I, II, III, IVA, IVB, and IVC, respectively.

Results: New T1–3 had no significant influence. In Cox proportional hazard analysis, T4a and T4b were significantly related to disease-specific survival (DSS). We separately analyzed 68 patients (age 45 yr or older) with extrathyroid extension. These T4 (fifth) tumors were reclassified as 6 T3, 52 T4a, and 10 T4b tumors. The 10-yr DSS rates were 100, 69.3, and 10.0% for T3, T4a, and T4b, respectively. T4b exhibited worse prognoses compared with T4a ($P < 0.0001$; hazard ratio, 10.1; 95% confidence interval, 4.1–25.3). Stages I and II in both editions achieved favorable prognoses. The 10-yr DSS rates were 67.0 and 27.3% in fifth stages III and IV, and 100, 74.5, 10.0, and 27.3% in sixth stages III, IVA, IVB, and IVC, respectively. DSS curves differed significantly between all sixth TNM stages ($P < 0.0001$).

Conclusion: The sixth edition more accurately predicts different outcomes according to the revised criteria for the degree of extrathyroid extension. **(*J Clin Endocrinol Metab* 92: 215–218, 2007)**

VARIOUS RISK DEFINITIONS for thyroid carcinoma have been evaluated (1–9). The American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) tumor-node-metastasis (TNM) classification has been used in clinical practice for differentiated thyroid carcinoma (DTC). This classification has also been evaluated to determine its utility in discriminating patients who have distinct outcomes (5–9). The fifth edition AJCC/UICC TNM classification (1997) was revised as the sixth edition in 2002 (10). A major alteration was the reclassification of tumor staging (T). Fifth edition T1 (≤1 cm) and T2 (between 1 and 4 cm) were redefined as sixth edition T1 (≤2 cm) and T2 (between 2 and 4 cm). However, there are controversial reports that the new definition of T1 or T2 had only a minor impact on survival or was impractical for papillary thyroid carcinoma (11, 12). In the sixth edition, T3 includes not only large tumors (4 cm or more) but also tumors with minimal extension, and T4 consists of T4a and T4b. Thus, the sixth edition divides fifth edition T4 tumors into T3 (minimal invasion), T4a (extended invasion), and T4b (more extensive unresectable invasion) tumors according to the degree of extrathyroid extension. The degree of extension has been closely related to adverse prognoses (6, 13–18). Therefore, the sixth edition is expected to predict more accurately different outcomes in patients with extrathyroid extension compared with the fifth edition.

The aim of the present study was to evaluate the prognostic value of the sixth edition AJCC/UICC TNM classification for DTCs, especially in those with extrathyroid extension.

Patients and Methods

Patients

A total of 498 primary DTCs were treated surgically at our institution between 1964 and 2003. For the present analysis, adequate medical information was not available in 144 (28.9%) patients because the information for the extent of invasion, nodal status, or outcomes was incomplete. Therefore, 354 (71.1%) patients (77 men and 277 women; mean age, 51.2 yr; mean follow-up, 107.6 months) were assessed retrospectively. This study was approved by the Human Research Committee of Yokohama City University.

There were 322 (91.0%) papillary and 32 (9.0%) follicular carcinomas, which were confirmed pathologically. Specific variants such as Tall cell or insular carcinoma were excluded. The mean tumor size was 2.7 ± 1.5 cm. There were 153, 104, 86, and 11 patients in fifth edition stages I, II, III, and IV, and 175, 76, 14, 68, 10, and 11 patients in sixth edition stages I, II, III, IVA, IVB, and IVC, respectively. Thyroid resection was lobectomy for 211 (59.6%)

First Published Online October 31, 2006

Abbreviations: CI, Confidence interval; DFS, disease-free survival; DSS, disease-specific survival; DTC, differentiated thyroid carcinoma; EBRT, extra beam radiotherapy; HR, hazard ratio; RI, radioactive iodine.

TABLE 1. Clinical outcomes by different T category, N category, and TNM stage in the fifth and sixth TNM classifications

			No. of patients	Disease death, no. (%)	DFS rates 10 yr (%)	DSS rates 10 yr (%)	HR	95% CI	*P* value
Fifth edition (n = 354)	T category	T1: ≤1 cm	54	0 (0)	88.7	100	NA	NA	
		T2: 1 cm <, ≤4 cm	195	6 (3.1)	82.1	98.0	1.0	Reference	
		T3: 4 cm <	19	1 (5.3)	70.6	94.1	2.9	0.3–23.9	0.3303
		T4: extrathyroid extension	86	27 (31.4)	45.5	66.2	11.5	4.8–28.0	0.0001
	N category	N0: negative	270	11 (4.1)	81.3	95.7	1.0	Reference	
		N1a: ipsilateral[a]	40	8 (20.0)	68.2	86.2	3.9	1.6–9.7	0.0034
		N1b: contralateral[b]	44	15 (34.1)	22.2	49.4	11.0	5.0–24.3	0.0001
	TNM stage	I: M0 (<45), T1N0 (≥45)	153	1 (0.65)	89.8	99.3	1.0	Reference	
		II: M1 (<45), T2-3N0 (≥45)	104	1 (0.96)	81.4	100	1.4	0.1–22.1	0.8218
		III: T1-3N1 or T4N0-1 (≥45)	86	23 (26.7)	41.9	67.0	45.3	6.0–340.1	0.0002
		IV: AnyTAnyNM1 (≥45)	11	9 (81.8)	0	27.3	242.4	29.5–1992.1	0.0001
Sixth edition (n = 354)	T category	T1: ≤2 cm	109	0 (0)	94.4	100	NA	NA	
		T2: 2 cm <, ≤4 cm	140	6 (4.3)	75.9	97.1	1.0	Reference	
		T3: 4 cm <, minimal extension	31	2 (6.5)	62.1	96.8	1.6	0.3–7.8	0.5874
		T4a: extended invasion[c]	61	13 (21.3)	50.0	73.4	5.4	2.0–14.3	0.0007
		T4b: unresectable invasion[d]	13	13 (100)	7.7	7.7	54.2	19.7–149.2	0.0001
	N category	N0: negative	270	11 (4.1)	81.3	95.7	1.0	Reference	
		N1a: central[e]	5	1 (20.0)	53.3	80.0	6.0	0.8–47.1	0.0856
		N1b: lateral[f]	79	22 (27.8)	46.9	69.3	7.2	3.5–14.8	0.0001
	TNM stage	I: M0 (<45), T1N0 (≥45)	175	1 (0.57)	90.9	99.4	1.0	Reference	
		II: M1 (<45), T2N0 (≥45)	76	1 (1.3)	77.3	100	2.3	0.1–36.8	0.5572
		III: T3N0 or T1-3N1a (≥45)	14	1 (7.1)	66.7	100	13.8	0.8–225.1	0.0660
		IVA: T1-3N1b or T4aN0-1 (≥45)	68	12 (17.6)	44.4	74.5	34.7	4.5–270.5	0.0007
		IVB: T4bAnyN (≥45)	10	10 (100)	10.0	10.0	433.5	52.6–3572.5	0.0001
		IVC: AnyTAnyNM1 (≥45)	11	9 (81.8)	0	27.3	339.6	40.5–2847.2	0.0001
68 patients (≥45 yr of age) with extrathyroid extension and no distant metastasis									
Fifth edition		T4 (stage III)	68	20 (29.4)	37.3	61.1			
Sixth edition		T3 (stage III)	6	0 (0)	66.7	100	NA	NA	
		T4a (stage IVA)	52	10 (19.2)	39.8	69.3	1.0	Reference	
		T4b (stage IVB)	10	10 (100)	10.0	10.0	10.1	4.1–25.3	0.0001

NA, Not available.
[a] Metastasis in ipsilateral cervical lymph nodes.
[b] Metastasis in bilateral, midline, or contralateral cervical or mediastinal lymph nodes.
[c] Tumor extends beyond the thyroid capsule and invades sc soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve.
[d] Tumor invades prevertebral fascia, mediastinal vessels, or encases carotid artery.
[e] Metastasis to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes).
[f] Metastasis to unilateral, bilateral, or contralateral cervical or superior mediastinal lymph nodes.

patients and subtotal/total thyroidectomy for 143 (40.4%) patients. Subtotal/total thyroidectomy was performed in 46 (30.1%), 42 (40.4%), 47 (54.7%), and 8 (72.7%) patients in fifth stages I, II, III, and IV, and in 52 (29.7%), 33 (43.4%), 7 (50.0%), 40 (58.8%), 3 (30.0%), and 8 (72.7%) patients in sixth stages I, II, III, IVA, IVB, and IVC, respectively. Six patients with minimal extension in sixth stage III underwent subtotal or total thyroidectomy. Thirty-nine of 52 patients with T4a tumor in stage IVA exhibited laryngotracheal invasion (eight laryngectomies and 31 tracheal resections). Node dissection was performed in 129 (84.3%), 96 (92.3%), 77 (89.5%), and 8 (72.7%) patients in fifth stages I, II, III, and IV, and in 148 (84.6%), 71 (93.4%), 11 (78.6%), 64 (94.1%), 5 (50.0%), and 11 (100%) patients in sixth stages I, II, III, IVA, IVB, and IVC, respectively. A total of 271 (76.6%) patients underwent TSH suppression. Radioactive iodine (RI) therapy was only performed in selected patients due to the fact that in Japan the use of RI is strictly controlled, and the number of centers performing RI therapy is extremely limited. RI therapy was performed in two stage IVA and five stage IVC patients. Extra beam radiotherapy (EBRT) was performed in three stage IVA and four stage IVB patients.

Tumor stage conversion in patients with extrathyroid extension

We also separately evaluated outcomes in 68 patients (age 45 yr or older) who had tumor with extrathyroid extension and no distant metastasis at diagnosis. In the fifth edition, these tumors were classified equivalently as T4. These 68 were divided into six T3, 52 T4a, and 10 T4b tumors according to the revised criteria for extrathyroid extension. Additionally, in the new definition 55 tumors changed from T2 (fifth) to T1 (sixth).

Evaluation of clinical outcomes

Disease-free survival (DFS) and disease-specific survival (DSS) were evaluated. Recurrence was defined as local disease arising from remnant thyroid tissue or regional nodes, or as distant disease metastasizing to other organs and was found in clinical and radiological examinations, thyroglobulin monitoring, ultrasound, x-ray, and/or computed tomography.

Statistical analysis

DFS and DSS were assessed with Kaplan-Meier analysis and compared using the log-rank test. The effects of T category, N category, and TNM stage on DSS were evaluated by univariate analysis using the Cox proportional hazards models [hazard ratio (HR), 95% confidence interval (CI)]. Differences were considered significant when *P* values were less than 0.05. Statistical analyses were performed with StatView version 5.0 (SAS Institute Inc., Cary, NC).

Results

Overall, recurrence and disease death occurred in 77 (21.8%) and 34 (9.6%) patients. Local recurrence, distant metastasis, and both occurred in 43, 16, and 18 patients.

Table 1 summarizes the outcomes by T category, N category, and TNM stage.

DSS rates for T1–3 in both editions ranged from 94.1 to 100%. In the fifth edition, T4 ($P < 0.0001$, HR 11.5, 95% CI

4.8–28.0) affected DSS. In the sixth edition, T4a ($P = 0.0007$, HR 5.4, 95% CI 2.0–14.3) and T4b ($P < 0.0001$, HR 54.2, 95% CI 19.7–149.2) affected DSS. As shown in Fig. 1, statistical significance was not calculated for the fifth and sixth edition T1 tumors because there was no disease death (Fig. 1, A and B). However, the DSS curves (Fig. 1B) apparently differed between T1–3, T4a, and T4b tumors.

Table 1 also presents the outcomes according to the sixth edition in 68 patients (age 45 yr or older) with extrathyroid extension. The 10-yr DFS and DSS rates were 66.7 and 100% for T3, 39.8 and 69.3% for T4a, and 10.0 and 10.0% for T4b, respectively. T4b was related more significantly to DSS than T4a ($P < 0.0001$, HR 10.1, 95% CI 4.1–25.3).

In the fifth edition, N1a ($P = 0.0034$, HR 3.9, 95% CI 1.6–9.7) and N1b ($P < 0.0001$, HR 11.0, 95% CI 5.0–24.3) affected DSS. In the sixth edition, N1b ($P < 0.0001$, HR 7.2, 95% CI 3.5–14.8) affected DSS.

As summarized in Table 1, stages I and II in both editions achieved favorable DSS. In the fifth edition, stages III and IV were significantly related to reduced DSS. The 10-yr DFS and DSS rates were 41.9 and 67.0% in stage III and 0 and 27.3% in stage IV, respectively. In the sixth edition, stages IVA, IVB, and IVC were significantly related to reduced DSS. The 10-yr DFS and DSS rates were 66.7 and 100% in stage III, 44.4 and 74.5% in stage IVA, 10.0 and 10.0% in stage IVB, and 0 and 27.3% in stage IVC, respectively. As shown in Fig. 1, DSS curves (Fig. 1C) differed significantly between all four fifth TNM stages ($P < 0.0001$). Furthermore, those (Fig. 1D) differed significantly between all six sixth TNM stages ($P < 0.0001$).

Discussion

There are two major differences between the fifth and sixth editions of the AJCC/UICC TNM classification. The first is the revised definition for T1 tumors. The sixth edition T1 tumors comprise all tumors up to 2 cm. In our series, 55 tumors had a change from T2 (fifth) to T1 (sixth). However, such tumor stage conversion did not influence DSS.

Another major alteration is the new classification for extrathyroid extension. Various risk definitions include tumor

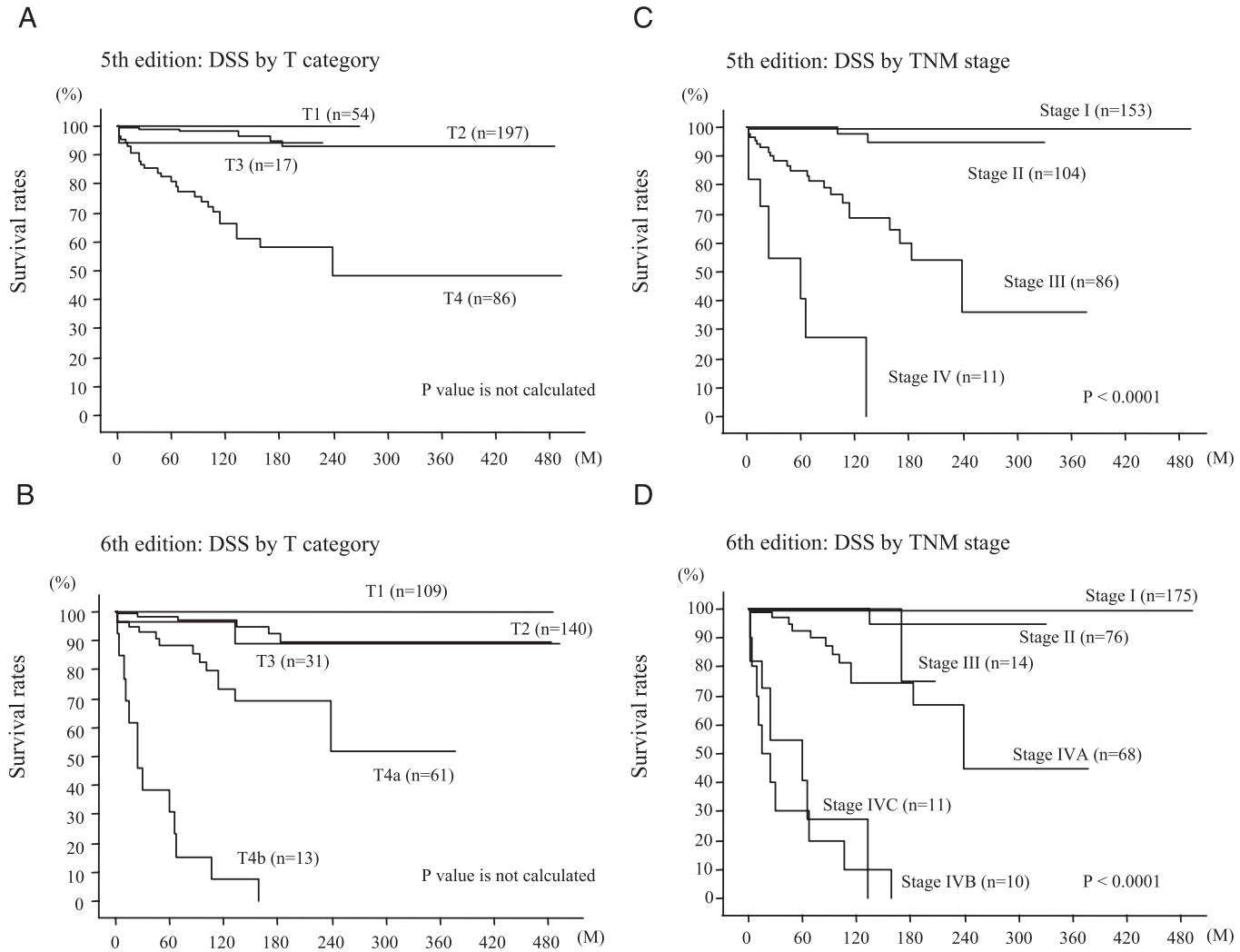

FIG. 1. The DSS curves by T category and TNM stage in the fifth and sixth editions. Statistical significance was not calculated for the fifth and sixth edition T1 tumors because there were no patients who died of disease (A and B). However, the DSS curves (B) by T category were apparently different between T1–3, T4a, and T4b tumors. The DSS curves (C) differed significantly between all four fifth TNM stages ($P < 0.0001$). Furthermore, those (D) differed significantly between all six sixth TNM stages ($P < 0.0001$).

extension as an adverse indicator (1–9). However, the degree of extension was not thoroughly assessed because only the presence or absence of extension was described in many risk definitions. In the fifth edition, extrathyroid extensions were classified equivalently as T4 regardless of the various degrees of extension. In the sixth edition, these were divided into T3, T4a, and T4b according to the degree of extension. This new classification for extrathyroid extension is considered most important, and we therefore evaluated whether this alteration is valuable to predict different outcomes. Our overall results revealed that T4b tumors (HR 54.2) had worse DSS than T4a tumors (HR 5.4). In addition, our series included seven younger patients (<45 yr of age) with T4a tumor, and they achieved favorable prognosis. Older age is generally associated with an adverse prognosis (5, 17, 18).

We separately evaluated 68 patients (age 45 yr or older) who had tumors with extrathyroid extension and no distant metastasis at diagnosis. These were the same T4 tumors (fifth). The outcomes in these 68 patients differed significantly between the new tumor stages, T3, T4a, and T4b. None of the six patients with minimal extension (T3) died of disease. Minimal extension had a minor impact on outcomes (11, 14), similar to our current investigation, while T4b ($P < 0.0001$, HR 10.1) had a worse DSS than T4a. Thus, the new definition for tumor extension is considered valuable to predict different outcomes according to the various degree of extension.

Regarding N category, this study found that the fifth edition N1a and N1b affected DSS, whereas the sixth edition N1a did not. These results may suggest that the new definition of N category has no advantage.

In the present analyses for TNM stage grouping, stages I and II in both editions exhibited favorable prognoses. The 10-yr DFS and DSS rates were 41.9 and 67.0% in fifth stage III, whereas they were 66.7 and 100% in sixth stage III. These results suggest that sixth stage III is considered a low to moderate risk group. Similarly, those rates were 44.4 and 74.5% in stage IVA, 10 and 10% in stage IVB, and 0 and 27.3% in stage IVC, respectively. Outcomes in fifth stage IV and sixth stage IVC were the same. Thus, stage IVA is an intermediate risk group, and stages IVB and IVC are critical risk groups.

TSH suppression, EBRT, and RI therapy are successful adjuvant therapies (7, 15, 16, 19, 20). EBRT is valuable for controlling local disease. RI therapy is effective for eradicating malignant tumor cells at local and distant sites. Only selected patients in our series received radiotherapies. We consider that increased use of radiotherapies may influence our results. Adjuvant radiotherapies could be important in our future practice.

Finally, lobectomy and node dissection were performed in about 65 and 90% of our patients in stages I and II, respectively. They achieved favorable prognoses. We therefore consider that such treatment differences may be allowed as regional practice for some lower stage patients when the use of RI is limited.

Conclusion

Sixth edition stages I and II achieved favorable prognoses. Stage III represents the low to moderate risk group. Stage IVA is an intermediate risk group. Stages IVB and IVC are critical high-risk groups. The sixth edition TNM classification more accurately predicts outcomes in patients with extrathyroid extension according to the revised criteria for the degree of extension, but we found no advantage in the new definitions of T1 and T2 or N category.

Acknowledgments

Received July 5, 2006. Accepted October 23, 2006.

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Disclosure Summary: The authors have nothing to disclose.

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