PROGNOSTIC IMPACT OF DIFFERENT TNM-BASED STAGE GROUPINGS FOR ORAL SQUAMOUS CELL CARCINOMA

Matthias Kreppel, MD,[1,4] Uta Drebber, MD, PhD,[2,4] Daniel Rothamel, MD, DMD, PhD,[1,4] Hans-Theodor Eich, MD, PhD,[3,4] Alexander Kübler, MD, DMD, PhD,[5] Martin Scheer, MD, DMD,[1,4] Joachim E. Zöller, MD, DMD, PhD[1,4]

[1] Department for Oral and Cranio-Maxillo and Facial Plastic Surgery, University of Cologne, Cologne, Germany. E-mail: mattheskreppel@yahoo.de
[2] Department of Pathology, University of Cologne, Cologne, Germany
[3] Department of Radiation Oncology, University of Cologne, Cologne, Germany
[4] Centre of Integrated Oncology (CIO) Cologne-Bonn, Cologne, Germany
[5] Department for Oral and Cranio-Maxillo and Facial Plastic Surgery, Julius–Maximilians University, Würzburg, Germany

Accepted 31 August 2010
Published online 29 November 2010 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/hed.21630

Abstract: *Background.* The purpose of this study was to evaluate the prognostic significance of different TNM-based stage groupings proposed in the literature.

Methods. We conducted a retrospective analysis of 300 patients with primary oral squamous cell carcinoma (T1–4, N0–2, M0). The stage grouping systems of the sixth edition of the Union Internationale Contre le Cancer (UICC), T and N Integer Score (TANIS), the Snyderman scheme, the Hart scheme, and the Berg scheme were tested for their prognostic significance. Disease free survival (DFS) was plotted by Kaplan–Meier analysis. Prognostic factors were identified through univariate and multivariate analysis.

Results. On univariate analysis, all systems revealed discriminatory power for DFS; however, on multivariate analysis, only the Hart scheme predicted DFS. The TANIS did not have a better prognostic ability than the UICC stage grouping.

Conclusion. Unlike in previous studies, the UICC stage grouping did perform worse than other TNM-based stage groupings, which may be due to the alterations made in the sixth edition.
 Head Neck **33:** 1467–1475, 2011

Keywords: oral cancer; stage grouping; prognosis; TANIS; multivariate analysis

The TNM classification is a globally accepted system to describe the anatomic extent of a tumor.[1] It has been developed from the observation that prognosis and treatment modalities are related to the extent of the tumor at the primary site (T classification), at the regional lymph nodes (N classification), and the presence or absence of distant metastases (M classification). Oral and oropharyngeal tumors must be classified before treatment (clinical staging, cTNM) and after resection (pathologic staging, pTNM) to obtain significant prognostic information, for example, cervical lymph node involvement, lymphangiosis carcinomatosa, and margin status.[2] Today's objectives in cancer staging are still the same as they were more than 40 years ago: support the planning of treatment, give some indication of prognosis, assist in evaluating treatment results, allow the unambiguous exchange of information between treatment centers, further the investigation of human cancer, and support cancer control activities.[3]

The various categories of T, N, and M offer a detailed description of the anatomic extent of the tumor and are recognized as the strongest predictor of survival. However, for purposes of tabulation and analysis, a further summarization is needed to obtain a reasonable number of homogeneous and distinct categories with respect to survival.[4,5] The 40 possible T, N, and M combinations can be reduced to the Union Internationale Contre le Cancer (UICC) stages I, II, III, and IV. In fifth edition in 1997, the UICC split stage IV for carcinoma of the oral cavity into 3 subgroups (IVa, IVb, and IVc). However, the improvements only yielded a modest improvement in the predictive value of the stage grouping.[6]

Too many tumors were classified as T4, as even localized small tumors in the oral cavity often invade adjacent structures such as the bone of the alveolar rim. There were suggestions that tumor thickness should be incorporated into the T classification, as tumor thickness is an important prognostic factor and can easily be assessed by modern imaging techniques.[7] As a result of these observations, T4 tumors in patients with oral cancer have been subdivided into T4a (lower risk) and T4b (higher risk) in the sixth edition of the UICC staging system for oral cancer, based on the involvement of vital anatomic structures.[3,8]

In attempts to achieve a higher level of discrimination among categories than in the UICC stage classification, various models using the same T and N data have

Correspondence to: M. Kreppel

been described.[9–12] The most popular example is the T and N Integer Score (TANIS). The TANIS scheme was first described by Jones et al[10] in 1993 due to the lack of prognostic relevance of the fourth edition of the UICC stage grouping. This graduation scheme consisted of the sum of integer values for the T and N classifications, and results in values from 1 to 7. The investigators analyzed a set of 86 patients with stage II to IV head and neck cancer and came to the conclusion that TANIS provides a better prognostic discrimination than UICC stage grouping. TANIS is based on the assumption that T and N are equally important and independent prognostic factors of survival and that the values of T and N can simply be added. Major advantages of the TANIS are that it is easy to use, its ability to define a reasonable number of groups, and the opportunity to be applied retrospectively if the TNM score is known.[13] Other authors have advocated further modifications such as a grouping of the score into 3 or 4 groups.[4,6,9,11,14,15] Snyderman and Wagner[11] modified the TANIS scheme. On the basis of visual examination of the TANIS survival graphs, they identified optimal stage groupings. Hart et al[9] derived a stage grouping scheme from the analysis of the disease-specific survival (DFS) in 640 patients with oropharyngeal cancer. The groupings were determined using a stepwise backward elimination model that included an indicator variable for each TNM combination in the beginning. Berg[14] analyzed survival rates of 470 patients with oropharyngeal carcinoma by assessing the degree of discrimination among survival curves.

The effects of the changes in the UICC staging system of the sixth edition for oral cancer have been evaluated in a previous study. However, the prognostic benefit of these alterations could not be confirmed, either for the subdivision of T4 or for the split of UICC stage IV.[8]

Because we did not find significant improvements of the TNM Classification and the UICC stage grouping in the first study, we evaluated the prognostic power of other stage groupings. Due to reasons of comparison, we used the same set of 300 patients with oral squamous cell carcinoma (OSCC) treated with neoadjuvant radiochemotherapy followed by radical surgical resection or primary surgery followed by radiochemotherapy.

MATERIALS AND METHODS

Patients. This retrospective study included 300 treatment-naive patients with biopsy-proven primary OSCC of stages I to IV who were treated with curative intent at our institution between October 1995 and June 2005. The patients' clinical characteristics are listed in Table 1. For patients who presented before 2003, clinical and pathologic staging was retrospectively updated to the sixth edition of the UICC for carcinoma of the oral cavity. Patients with a tumor of the category T4 classification were assigned to the categories T4a and T4b using the UICC staging criteria of the sixth edition.[3] Clinical staging was updated using the CT, MRI, and scintigraphic pretreatment reports from the department of radiology. Pathologic staging was updated through the histopathologic reports after primary surgery. Patients with distant metastases were excluded from our study. None of our patients met the criteria to be classified as N3. Clinicopathologic parameters were obtained from the medical records including the histopathologic and surgical reports. Follow-up data were gathered from a combination of medical record review and the local government office for registration of residents. At the time of analysis, 138 patients were dead—98 of them (71%) died because of the tumor—and 162 patients were alive. The average follow-up time was 54.7 months. Median follow-up time was 48.0 months. The follow-up ranged from 0 to 146 months.

Patients with stage I disease were treated solely surgically, patients with stage II to IVb received a multimodal treatment. All patients, including those presenting with stage I, were treated with neck dissection because of the high incidence of occult nodal metastases and the tendency to regional recurrences. Before October 2002, patients with stage II to IVb received a

Table 1. Patient and tumor characteristics of the 300 patients with oral squamous cell carcinoma.

Characteristic	Value
Age, y	
Mean ± SD	58.9 ± 11.1
Median	59.0
Minimum/maximum	24/90
Follow-up, mo	
Mean	54.7
Median	48.0
Minimum/maximum	0/146
Sex, no. of patients (%)	
Male	208 (69.3%)
Female	92 (30.7%)
Treatment regime, no. of patients (%)	
Neoadjuvant treatment	138 (46.0%)
Primary surgical treatment	162 (54.0%)
Tumor sites, no. of patients (%)	
Floor of mouth	120 (40.0%)
Tongue	63 (21.0%)
Gingiva	58 (19.3%)
Palate	31 (10.3%)
Oropharynx	11 (3.7%)
Cheek	17 (5.7%)
T classification, no. of patients (%)	
T1	26 (8.7%)
T2	125 (41.7%)
T3	37 (12.3%)
T4a	89 (29.7%)
T4b	23 (7.7%)
N classification, no. of patients (%)	
N0	128 (42.7%)
N1	40 (13.3%)
N2	132 (44.0%)

simultaneous neoadjuvant radiochemotherapy with 39.6 Gy and carboplatin area under the curve (AUC) 5 during the first week of treatment followed by radical surgery. Patients with stage II to IVb after October 2002 were treated with radical surgery and an adjuvant concomitant radiochemotherapy consisting of 61 to 66 Gy and carboplatin AUC 5 during the first and fifth week of treatment. Patients who did not complete the treatment regime were excluded from our study.

Stage Grouping Schemes. Apart from the UICC sixth edition stage grouping, various other schemes were tested. Because we used the sixth edition of the UICC staging with a split of T4 into T4a and T4b, we had to extend the TANIS-7 to 8 subgroups, as T4 is divided into T4a and T4b (TANIS-8). T4a was assigned the value of 4, and T4b was assigned the value of 5. The groups for TANIS-3 were as follows: 1: 1 to 3; 2: 4; and 3: 5 to 8.[6,10] Apart from TANIS-3 and TANIS-8, we tested the schemes proposed by Snyderman and Wagner,[11] Hart et al,[9] and Berg.[14] We were unable to test a staging system that was proposed by Hall et al[4] as they subdivided N2 into N2a and N2b and N2c, and this information was not available in our data.

The stage groupings analyzed in this study are shown in Figure 1 below.

UICC-6th edition

	T1	T2	T3	T4a	T4b
N0	I	II	III	IVa	IVb
N1	III	III	III	IVa	IVb
N2	IVa	IVa	IVa	IVa	IVb
N3	IVb	IVb	IVb	IVb	IVb

TANIS-8

	T1	T2	T3	T4a	T4b
N0	1	2	3	4	5
N1	2	3	4	5	6
N2	3	4	5	6	7
N3	4	5	6	7	8

TANIS-3

	T1	T2	T3	T4a	T4b
N0	1	1	1	2	3
N1	1	1	2	3	3
N2	1	2	3	3	3
N3	2	3	3	3	3

Snyderman

	T1	T2	T3	T4a	T4b
N0	1	1	2	3	3
N1	1	2	3	4	4
N2	2	3	4	4	4
N3	3	4	4	4	4

Hart

	T1	T2	T3	T4a	T4b
N0	1	1	2	2	2
N1	1	1	2	3	3
N2	2	2	3	4	4
N3	3	3	4	4	4

Berg

	T1	T2	T3	T4a	T4b
N0	1	2	3	3	3
N1	1	2	3	4	4
N2	2	3	3	4	4
N3	3	3	4	4	4

FIGURE 1. Stage grouping schemes tested in this study. UICC, Union Internationale Contre le Cancer; TANIS, T and N Integer Score.

Table 2. Distribution of the T and N classification of the 300 patients.

T classification	No. of patients (%) by N classification			Total no. of patients (%)
	N0	N1	N2	
T1	25 (19.5%)	0	1 (0.8%)	26 (8.7%)
T2	66 (51.6%)	18 (45.0%)	41 (31.1%)	125 (41.7%)
T3	9 (7.0%)	10 (25.0%)	18 (13.6%)	37 (12.3%)
T4a	21 (16.4%)	9 (22.5%)	59 (44.7%)	89 (29.6%)
T4b	7 (5.5%)	3 (7.5%)	13 (9.8%)	23 (7.7%)
Total no. of patients	128	40	132	300

Statistical Analysis. The Kaplan–Meier survival analysis method was used to estimate the events of interest for DFS, and the time interval from the beginning of primary therapy until a locoregional recurrence or death. Patients who were alive and free of tumor at the last date of follow-up were classified as censored observations.[26] The log-rank test was used to compare DFS times among patients with different characteristics. Any p values of less than .05 were considered as statistically significant and printed in bold. For multivariate analysis, a Cox proportional hazard model with forward selection was calculated to estimate the prognostic impact of patient-related and tumor-related factors on survival, which were significant in univariate analysis.[27] Furthermore, we used the Cox proportional hazard model to determine the hazard ratio stage groupings by setting up indicator variables for each group. We compared the risk of each group to a reference group, which was the one with the least advanced stage. The method was described by Groome et al[6,28,29] to determine relative severity of disease in study groups with different kinds of head and neck cancer.

All statistics were carried out with PASW Statistics 18.0.

RESULTS

On average, our patients were 59.8 years old at the time of diagnosis of their disease, and 69.3% of our patients were men. Most frequent tumor sites in the oral cavity were floor of mouth (40.0%) and tongue (21.0%). According to the UICC sixth edition, the distribution of the T classification was as follows: T1, 8.7%; T2, 41.7%; T3, 12.3%; T4a, 49.7%; and T4b, 7.7%. A total of 42.7% of our patients had no cervical lymph node metastases. Cervical lymph node categories N1 and N2 were found for 13.3% and 44.0%, respectively. The UICC sixth edition stage distribution consisted of 8.3% with stage I disease, 22.0% stage II, and 12.3% stage III. A total of 57.4% showed an advanced disease stage at the time of diagnosis, 45.7% were stage IVa and 11.7% were stage IVb. Of our patients, 46% received a neoadjuvant radiochemotherapy followed by radical surgery, whereas 54% of our patients were treated with primary surgery followed by adjuvant radiochemotherapy.

Table 2 shows the sample size for the T and N subgroups.

Table 3 shows the hazard ratio for each subgroup. The hazard ratios were calculated with the Cox proportional hazard model. Each subgroup was compared to the reference group T1N0. There is a strong association between risk and increasing size of the primary tumor and cervical lymph node metastases. For the subgroups T1N1 and T1N2, we did not calculate hazard ratios due to the small number of patients (no patients for T1N1 and 1 patient for T1N2). Patients with a cervical lymph node status of the category N2, only had a small increase of risk with a larger primary tumor (4.06 for a patient with T2N2 and 4.42 for a patient with T4N2). Patients with categories T3N2 and T4aN2 were at a lower risk than patients with T2N2 (Table 4).

Table 5 shows the hazard ratios for the different staging schemes. All 6 staging schemes served as a good predictor for survival ($p < .05$). The UICC sixth edition exhibited a steady increase of risk with an increasing stage of disease. Stage II had a risk of 1.28 compared to stage I; however, the difference was not statistically significant ($p = .653$). Stages IVa and IVb were at a significantly higher risk than patients with stage I. The TANIS-3 stage grouping showed that patients in groups 2 and 3 were at a significantly higher risk than patients in group 1. The differences in relative risk between group 2 and 3 were small (2.14 vs 2.46). In TANIS-8, groups 2 and 3 did not have a significantly worse prognosis than the reference group 1.

Univariate Analysis. Univariate analysis using the log-rank test revealed that T classification ($p = .012$) and N classification ($p < .001$) had a significant impact on the

Table 3. Relative risks for each subgroup in comparison to the least severe stage (T1N0).

T classification	N0 (p value)	N1 (p value)	N2 (p value)
T1	1.00	No data	No data
T2	1.29 (.648)	1.96 (.274)	4.06 (**.009**)
T3	2.49 (.174)	2.67 (.145)	3.69 (**.024**)
T4a	2.24 (.199)	2.46 (.239)	3.85 (**.011**)
T4b	3.24 (.080)	5.77 (**.022**)	4.42 (**.009**)

Note: Significant p *values are printed in bold. They indicate that the relative risk of the subgroup is significantly higher than for the T1N0 subgroup.*

Table 4. Distribution of patients in the different stage groupings.

	No. of patients (%)					
Group (UICC stage)	UICC-6th edition	TANIS-3	TANIS-8	Snyderman	Hart	Berg
Group 1 (I)	25 (8.3%)	119 (39.7%)	25 (8.3%)	91 (30.3%)	109 (36.3%)	25 (8.3%)
Group 2 (II)	66 (22.0%)	72 (24.0%)	66 (22.0%)	28 (9.3%)	89 (29.6%)	85 (28.3%)
Group 3 (III)	37 (12.3%)	109 (36.3%)	28 (9.3%)	79 (26.4%)	30 (10.0%)	106 (35.3%)
Group 4 (IVa)	149 (49.7%)		72 (24.0%)	102 (34.0%)	72 (24.0%)	84 (28.0%)
Group 5 (IVb)	23 (7.7%)		34 (11.3%)			
Group 6			2 (20.7%)			
Group 7			13 (4.3%)			
Group 8			0			

Abbreviations: UICC, Union Internationale Contre le Cancer; TANIS, T and N Integer Score.

patients' DFS. The 5-year DFS rate decreased steadily from 73.3% (T1) to 34.3% (T4b); however, patients with T4a (40.2%) had a slightly lower survival rate than patients with T3 tumors (44.6%). Patient sex and tumor site had no significant impact on the DFS. Histopathologic grading showed a trend of decreasing survival with decreasing differentiation of the tumor; however, the trend did not prove to be significant ($p = .160$). No significant statistical differences regarding survival were observed between the 2 treatment groups ($p = .123$; Table 6).

Table 7 displays the 5-year survival rates and their impact on DFS in univariate analysis. The UICC stage grouping had a very strong impact on the DFS ($p < .001$; Figure 2). The 5-year survival rate steadily decreased from each stage to the next higher stage. Survival differences between the stages IVa and IVb were small (3.1%). TANIS-3, the Snyderman scheme, the Hart scheme, and the Berg scheme also showed a decreasing DFS with increasing stage. All 4 stage groupings had a significant impact on DFS in univariate analysis ($p < .001$ for TANIS-3; $p = .002$ for Snyderman; $p = .012$ for Hart; and $p < .001$ for Berg). TANIS-8 also had a significant impact on DFS ($p = .004$). Patients in group 4 had lower 5-year survival rates (39.8%) than patients in group 5 (44.9%).

Multivariate Analysis. In multivariate analysis, we tested 6 models, each containing age, T classification, N classification, and 1 of the stage groupings. Only 1 of the 6 stage groupings had a significant impact on DFS, when age, T classification, and N classification were included in a model (UICC, $p = .079$, TANIS-3, $p = .089$; TANIS-8, $p = .175$; the Snyderman scheme, $p = .059$; the Hart scheme, $p = .043$; and the Berg, scheme $p = .058$). The stage grouping schemes proposed by Snyderman and Berg did not quite reach the 95% significance level. The TANIS-8 showed the worst performance in multivariate analysis.

DISCUSSION

Correct staging is mandatory in the management of patients with cancer, otherwise the patients cannot be assigned to the best treatment scheme for their individual situation, and the treatment effects cannot be evaluated properly.[1,4] The purpose of this study was to compare the prognostic validity of the sixth edition of the TNM classification of the UICC for carcinoma of the oral cavity with other TNM-based stage groupings. The TANIS was introduced in 1993 due to a lack of prognostic significance of the UICC stage grouping, and it was reported that the TANIS is more strongly associated with survival than the UICC stage grouping in oral cancer and in other head and neck cancers.[1,4,6,9,11,28,30,31] However, all these studies used TNM data of the fourth or fifth edition of the UICC. To the best of our knowledge, there is no study that

Table 5. Relative risks for each staging scheme in comparison to the least severe stage.

	Relative risks for each stage grouping scheme (p value)					
Group (UICC stage)	UICC-6th edition ($p < .001$)	TANIS-3 ($p < .001$)	TANIS-8 ($p = .034$)	Snyderman ($p = .021$)	Hart ($p < .001$)	Berg ($p = .036$)
Group 1 (I)	1.00	1.00	1.00	1.00	1.00	1.00
Group 2 (II)	1.28 (.653)	2.14 (< **.001**)	1.29 (.649)	1.85 (.071)	2.43 (< **.001**)	1.48 (0.468)
Group 3 (III)	2.25 (.144)	2.46 (< **.001**)	2.26 (.151)	2.75 (< **.001**)	2.73 (**.001**)	3.33 (**.020**)
Group 4 (IVa)	3.63 (**.012**)		3.39 (**.020**)	3.17 (< **.001**)	2.90 (< **.001**)	3.92 (**.008**)
Group 5 (IVb)	4.19 (**.009**)		3.13 (**.038**)			
Group 6			4.12 (**.007**)			
Group 7			4.41 (**.009**)			

Abbreviations: UICC, Union Internationale Contre le Cancer; TANIS, T and N Integer Score.
Note: Significant p values are printed in bold. They indicate that the relative risk of the group is significantly higher than for the reference group. The p values in brackets behind the staging scheme indicate the prognostic impact of the scheme.

Table 6. Five-year DFS with regard to age, sex, T classification, N classification, histopathologic grading, and treatment regime.

Univariate analysis of prognostic factors using the log-rank test		
Parameter	5-year DFS	*p* value
All 300 patients	48.4%	
Age		**.007**
≤59 y (lower half of median)	54.0%	
>59 y (upper half of median)	43.2%	
Sex		.512
Male	49.8%	
Female	45.6%	
Tumor site		.736
T classification		**.012**
T1	73.3%	
T2	55.8%	
T3	44.6%	
T4a	40.2%	
T4b	34.3%	
N classification		**<.001**
N0	66.1%	
N1	52.4%	
N2	33.2%	
Grading		.160
G1	64.3%	
G2	49.1%	
G3	44.0%	
G4	0%	
Treatment regime		.123
Neoadjuvant regime	43.5%	
Primary surgery regime	51.8%	

Abbreviation: DFS, disease-free survival.
Note: Significant p *values are printed in bold.*

compares the UICC stage grouping to the TANIS using the sixth edition of the UICC staging system for oral cancer. Due to these findings, we used the same set of patients to evaluate whether different TNM-based stage groupings led to an improvement of the prognostic quality.

Univariate analysis showed that age ($p = .007$), T classification ($p = .012$), and N classification ($p < .001$) are useful parameters to predict DFS in patients with OSCC. With regard to the N classification, these findings are consistent and feasible to compare with the literature as no changes have been made from the fifth to the sixth edition. The N classification is commonly regarded as the most powerful indicator because the development of cervical lymph node metastases leads to an adverse prognosis.[18] The T classification of the fifth edition of the UICC is widely accepted as a prognostic indicator for patients with OSCC.[32] Using univariate analysis, our study revealed that T classification in the sixth edition is a valid prognostic factor for DFS ($p = .012$). In a previous study, we were able to demonstrate that T classification of the sixth edition of the UICC has a significant impact on overall survival in patients with OSCC; however, no significant differences regarding survival could be detected between categories T4a and T4b.[8]

On univariate analysis, the UICC stage grouping ($p < .001$), TANIS-3 ($p < .001$; Figure 3), TANIS-8 (.004; Figure 4), the Snyderman scheme ($p = .002$; Figure 5), the Hart scheme ($p = .012$; Figure 6), and the Berg scheme ($p < .001$; Figure 7) all had a significant impact on DFS. Multivariate analysis including age, T classification, N classification, and the stage groupings revealed that only the Hart scheme was a significant prognostic indicator for DFS ($p = .043$). The stage groupings proposed by Snyderman ($p = .059$) and Berg ($p = .058$) narrowly missed the 95% significance level. The TANIS-3 ($p = .089$) and TANIS-8 ($p = .175$) yielded the least significant results in multivariate analysis. The UICC sixth edition stage grouping did not have a significant impact on the patients' prognosis in multivariate analysis ($p = .079$). As shown in Table 5, the stages II ($p = .653$), and III ($p = .144$) did not have a significantly poorer prognosis than the patients in the reference group with the smallest hazard (stage I). In the Hart scheme, which achieved the most significant result of all schemes in multivariate analysis, all categories exhibited a higher risk for death or locoregional recurrence than the patients in the reference group ($p < .05$).

We could not confirm that TANIS-8 and TANIS-3 and the scheme originally proposed by Jones et al[10] are more strongly associated with survival than the UICC stage grouping as it was reported in previous studies.[6,11,12,30] This may be due to different reasons: other studies did not include patients of all stages, and

Table 7. Five-year DFS with regard to the stage groupings.

	Univariate analysis of the different stage groupings (5-year DFS, *p* value)					
Group (UICC stage)	UICC-6th edition (***p* < .001**)	TANIS-3 (***p* < .001**)	TANIS-8 (***p* = .004**)	Snyderman (***p* = .002**)	Hart (***p* = .012**)	Berg (***p* < .001**)
Group 1 (I)	77.2%	67.1%	77.2%	71.9%	68.5%	77.2%
Group 2 (II)	70.7%	40.3%	70.7%	58.7%	41.4%	66.7%
Group 3 (III)	58.3%	35.7%	58.7%	40.3%	38.0%	41.2%
Group 4 (IVa)	37.4%		39.8%	35.7%	35.1%	37.4%
Group 5 (IVb)	34.3%		44.9%			
Group 6			32.9%			
Group 7			32.1%			

Abbreviations: DFS, disease-free survival; UICC, Union Internationale Contre le Cancer; TANIS, T and N Integer Score.
Note: The p *values in brackets behind the staging scheme indicate the prognostic impact of the scheme. Significant* p *values are printed in bold. As none of our patients exhibited N classification N3, we had no patients in the subgroup 8 of TANIS-8.*

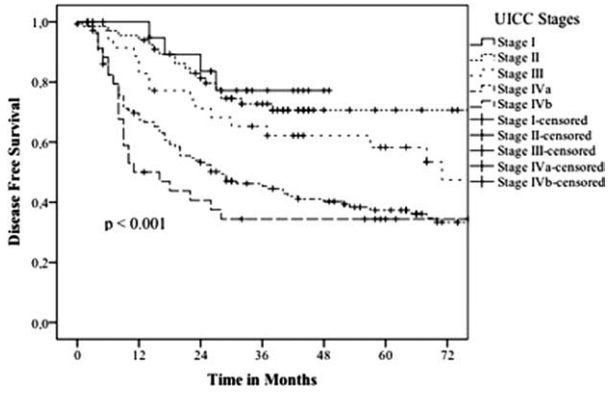

FIGURE 2. Disease-free survival with regard to the Union Internationale Contre le Cancer (UICC) stage grouping.

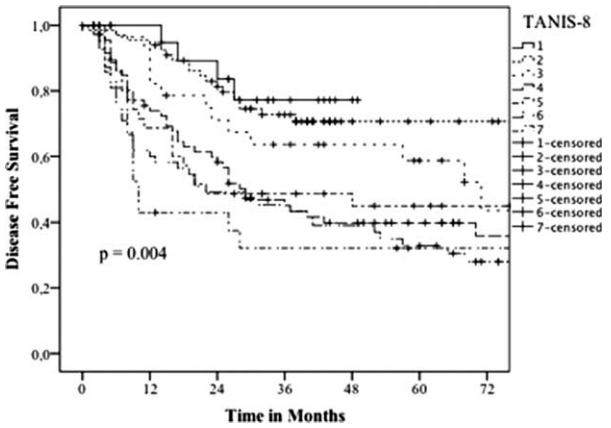

FIGURE 4. Disease-free survival with regard to the T and N Integer Score (TANIS)-8.

carcinoma from all head and neck sites were analyzed.[10] It has been demonstrated previously that the site of origin has a significant impact on the prognosis in head and neck cancer. OSCC had a lower 5-year overall survival than squamous cell carcinoma from the larynx and hypopharynx.[33] Additionally, in none of the previous studies was the sixth edition of the UICC for T, N, or M classification and stage grouping used. The fourth edition of the UICC from 1987 had a generic stage IV category that comprised a wide range of categories from T4N0M0 to T4N3M1 and, therefore, contained patients with various degrees of different prognosis. At this time, the TANIS provided a more detailed picture of patients with advanced carcinoma of the oral cavity.[10,11,14,15] The changes made to the TNM staging in fifth and sixth edition of the UICC, as described above, were aimed to compensate these shortcomings. Although a trend for a better discrimination of survival between stages T4a and T4b and IVa an IVb was observed recently, no significant improvement of the prognostic quality of the TNM system of the sixth edition could be confirmed as no significant differences in survival were found between the patients in these advanced stages of disease, although a trend for a higher 5-year overall survival rate was observed for patients with T4a and IVa.[8]

Although the schemes suggested by Hart et al,[9] Snyderman and Wagner,[11] and Berg[14] achieved a higher prognostic ability in our study, all staging systems based on the TANIS carry 2 major flaws in comparison to the UICC stage grouping: patients with simultaneous distant metastases only account for 2% to 4% of all patients, but it has not been clearly defined how to stage this group.[13] It has been suggested to classify these patients in the group of the highest TANIS score, but no data are available so far.[15] The second and more important disadvantage of the TANIS is that it is based on the empirical and false notion of equivalence and independence in survival prediction between T classification and N classification. First, cervical lymph node metastases are widely accepted as the strongest independent prognostic factor in patients with OSCC having a stronger impact on survival than T classification.[34] Second, T classification and N classification are not independent. An association between T classification and the incidence of cervical lymph node metastases has been shown.[35,36] A general problem with the alternative staging systems is that

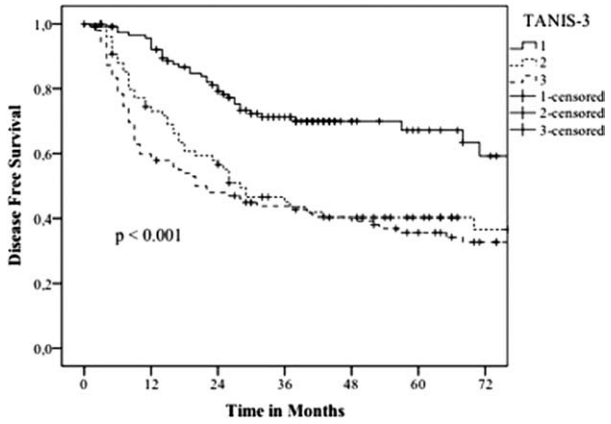

FIGURE 3. Disease-free survival with regard to the T and N Integer Score (TANIS)-3.

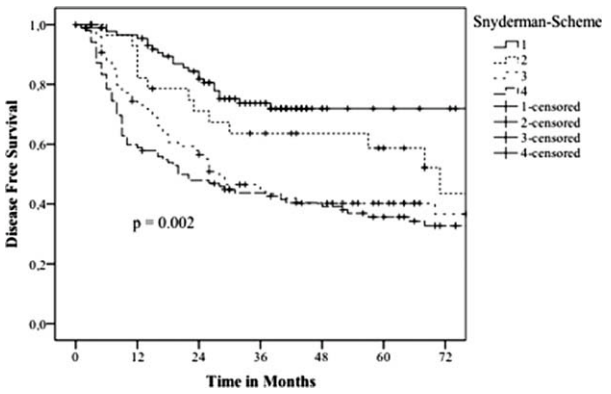

FIGURE 5. Disease-free survival with regard to the Snyderman scheme.

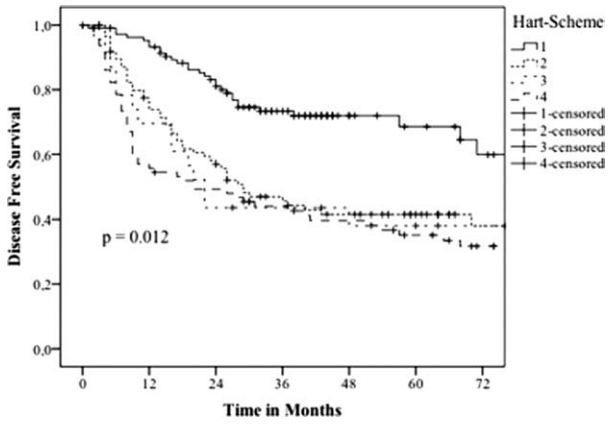

FIGURE 6. Disease-free survival with regard to the Hart scheme.

each system has its advocates and data to support the contention that makes it difficult to determine which system should be used. Furthermore, none of the suggested alternative staging systems is able to address the larger issue of patient, tumor, and treatment-related factors which is regarded as an essential part in prognostication today.[37]

In addition to this, the TANIS and its derivatives are affected by problems that arise from the point that they are also TNM-based just like the UICC stage grouping: staging data of head and neck carcinoma is that locally advanced carcinoma are often treated with nonsurgical organ preservation strategies as the first-line of management today. Combining these strategies offers the opportunity of tissue preservation and retained functional integrity.[18] Hence, surgical data to obtain a pTNM are often not available. As a consequence, meticulous clinical examinations including imaging techniques such as CT, MRI, positron emission tomography, and endoscopic exploration of the upper aerodigestive tract are required to provide detailed and reliable staging information. In our study, 138 patients received a neoadjuvant treatment.

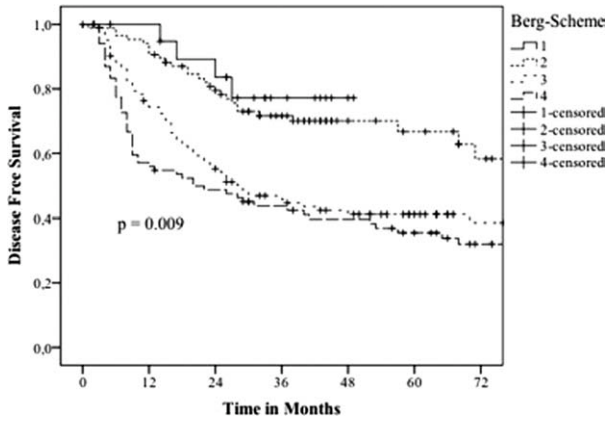

FIGURE 7. Disease-free survival with regard to the Berg scheme.

Thus, we were able to obtain a ypTNM but not a pTNM for these patients. Recent studies have shown that cTNM before a neoadjuvant radiochemotherapy has no predictive value for survival.[38] This may be mainly due to the fact that the diagnostic tools, which are available and applied, vary between different medical centers. However, this is 1 of the 2 major limitations of the TNM system.[39] First, the TNM system does not consider neoadjuvant radiochemotherapy and new molecular therapeutic approaches such as cetuximab for advanced recurrent head and neck carcinoma. Adding different therapeutic strategies to the TNM system leads to an exponential increase in staging groups, making it very difficult to evaluate the results because of the small number of patients in every stage group. To avoid this problem, a nomogram to predict the 5-year locoregional recurrence-free survival after surgery with and without adjuvant chemoradiation for patients with OSCC has been developed recently. It gives an estimate of the individual risk for a patient with OSCC as the nomogram comprises relevant patient factors beyond the TNM stages such as age, sex, surgical margin status, and tobacco use.[40]

Second, the TNM system is solely based on the anatomic extent of the tumor. It underlies the assumption that the tumor progresses continuously over time from local to regional to distant sites.[11] Other biological factors that reflect the biological aggressiveness of the disease have proven to be relevant, too.[41,42] In the last few years, several potential molecular and histopathological markers influencing the prognosis in patients with OSCC have been discovered.[36,43,44] One of the most promising biomarkers for survival and lymphatic spread seems to be podoplanin. Podoplanin is expressed frequently in OSCC and correlates with cervical lymph node metastases and clinical outcome.[45,46]

Exploring the function of biomarkers like podoplanin offers the opportunity to move from a tumor model of temporal determinism to one of biological determinism, as carcinogenesis is not defined by what stage the patient is in at detection but rather by molecular characteristics of the tumor and the host.

REFERENCES

1. Greene FL, Sobin LH. The staging of cancer: a retrospective and prospective appraisal. CA Cancer J Clin 2008; 58:180–190.
2. Woolgar JA, Hall GL. Determinants of outcome following surgery for oral squamous cell carcinoma. Future Oncol 2009;5:51–61.
3. O'Sullivan B, Shah J. New TNM staging criteria for head and neck tumors. Semin Surg Oncol 2003;21:30–42.
4. Hall SF, Groome PA, Irish J, O'Sullivan B. TNM-based stage groupings in head and neck cancer: application in cancer of the hypopharynx. Head Neck 2009;31:1–8.
5. Hermanek P, Sobin LH, Fleming ID. What do we need beyond TNM? Cancer 1996;7:815–817.
6. Groome PA, Schulze K, Boysen M, Hall SF, Mackillop WJ. A comparison of published head and neck stage groupings in carcinomas of the oral cavity. Head Neck 2001;23:613–624.
7. Patel SG, Shah JP. TNM staging of cancers of the head and neck: striving for uniformity among diversity. CA Cancer J Clin 2005;55:242–258; quiz 261–262, 264.

8. Kreppel M, Eich HT, Kübler AC, Zöller JE, Scheer M. Prognostic Value of the 6th Edition of the UICC's TNM Classification and Stage Grouping for Oral Cancer. J Surg Oncol [epub ahead of print].
9. Hart AA, Mak-Kregar S, Hilgers FJ, et al. The importance of correct stage grouping in oncology. Results of a nationwide study of oropharyngeal carcinoma in The Netherlands. Cancer 1995;75:2656–2662.
10. Jones GW, Browman G, Goodyear M, Marcellus D, Hodson DI. Comparison of the addition of T and N integer scores with TNM stage groups in head and neck cancer. Head Neck 1993;15:497–503.
11. Snyderman CH, Wagner RL. Superiority of the T and N integer score (TANIS) staging system for squamous cell carcinoma of the oral cavity. Otolaryngol Head Neck Surg 1995;112:691–694.
12. Carinci F, Farina A, Longhini L, Urso RG, Pelucchi S, Calearo C. Is the new TNM (1997) the best system for predicting prognosis? Int J Oral Maxillofac Surg 1999;28:203–205.
13. Lydiatt WM, Shah JP, Hoffman HT; Head and Neck Sites Task Force. American Committee on Cancer. AJCC stage groupings for head and neck cancer: should we look at alternatives? A report of the Head and Neck Sites Task Force. Head Neck 2001;23:607–612.
14. Berg H. The prognostic relevance of the TNM Systems for oropharynx carcinomas. [Article in German] Tumordiagn Ther 1992;13:171–177.
15. Carinci F, Pelucchi S, Farina A, Calearo C. A comparison between TNM and TANIS stage grouping for predicting prognosis of oral and oropharyngeal cancer. J Oral Maxillofac Surg 1998;56:832–836; discussion 836–837.
16. Freier K, Engel M, Lindel K, et al. Neoadjuvant concurrent radiochemotherapy followed by surgery in advanced oral squamous cell carcinoma (OSCC): a retrospective analysis of 207 patients. Oral Oncol 2008;44:116–123.
17. Kirita T, Ohgi K, Shimooka H, et al. Preoperative concurrent chemoradiotherapy plus radical surgery for advanced squamous cell carcinoma of the oral cavity: an analysis of long-term results. Oral Oncol 1999;35:597–606.
18. Klug C, Wutzl A, Kermer C, et al. Preoperative radiochemotherapy and radical resection for stages II-IV oral and oropharyngeal cancer: outcome of 222 patients. Int J Oral Maxillofac Surg 2005;34:143–148.
19. Mohr C, Bohndorf W, Carstens J, et al. Preoperative radiochemotherapy and radical surgery in comparison with radical surgery alone. A prospective, multicentric, randomized DOSAK study of advanced squamous cell carcinoma of the oral cavity and the oropharynx (a 3-year follow-up). Int J Oral Maxillofac Surg 1994;23: 140–148.
20. Slotman GJ, Doolittle CH, Glicksman AS. Preoperative combined chemotherapy and radiation therapy plus radical surgery in advanced head and neck cancer. Five-year results with impressive complete response rates and high survival. Cancer 1992;69:2736–2743.
21. Fan KH, Lin CY, Kang CJ, et al. Combined-modality treatment for advanced oral tongue squamous cell carcinoma. Int J Radiat Oncol Biol Phys 2007;67:453–461.
22. Soo KC, Tan EH, Wee J, et al. Surgery and adjuvant radiotherapy vs concurrent chemoradiotherapy in stage III/IV nonmetastatic squamous cell head and neck cancer: a randomised comparison. Br J Cancer 2005;93: 279–286.
23. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350:1945–1952.
24. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350:1937–1944.
25. Brizel DM, Sibley GS, Prosnitz LR, Scher RL, Dewhirst MW. Tumor hypoxia adversely affects the prognosis of carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 1997;38:285–289.
26. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Statist Assoc 1958;53: 457–481.
27. Cox D. Regression model and life-tables. J R Stat Soc 1972;34:187–220.
28. Groome PA, Schulze KM, Mackillop WJ, et al. A comparison of published head and neck stage groupings in carcinomas of the tonsillar region. Cancer 2001;92:1484–1894.
29. Groome PA, Schulze K, Boysen M, et al. A comparison of published head and neck stage groupings in laryngeal cancer using data from two countries. J Clin Epidemiol 2002;55:533–544.
30. Carinci F, Farina A, Pelucchi S, Brunelli G, Pastore A, Calearo C. Stage grouping of oropharyngeal cancer: evaluation of three systems by means of survival analysis. J Craniofac Surg 1999;10:73–78.
31. Carinci F, Farina A, Pelucchi S, Calearo C, Pastore A. Comparison between TANIS and UICC 1997 stage grouping in parotid gland carcinoma. J Craniofac Surg 2001;12:141–144.
32. Arduino PG, Carrozzo M, Chiecchio A, et al. Clinical and histopathologic independent prognostic factors in oral squamous cell carcinoma: a retrospective study of 334 cases. J Oral Maxillofac Surg 2008;66:1570–1579.
33. Lavaf A, Genden EM, Cesaretti JA, Packer S, Kao J. Adjuvant radiotherapy improves overall survival for patients with lymph node-positive head and neck squamous cell carcinoma. Cancer 2008;112:535–543.
34. Shaw RJ, Lowe D, Woolgar JA, et al. Extracapsular spread in oral squamous cell carcinoma. Head Neck 2010;32:714–722.
35. Kowalski LP, Bagietto R, Lara JR, Santos RL, Silva JF Jr, Magrin J. Prognostic significance of the distribution of neck node metastasis from oral carcinoma. Head Neck 2000;22:207–214.
36. Massano J, Regateiro FS, Januário G, Ferreira A. Oral squamous cell carcinoma: review of prognostic and predictive factors. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;102:67–76.
37. Burke HB. Outcome prediction and the future of the TNM staging system. J Natl Cancer Inst 2004;96: 1408–1409.
38. Driemel O, Ettl T, Kölbl O, et al. Outcome and histopathologic regression in oral squamous cell carcinoma after preoperative radiochemotherapy. Strahlenther Onkol 2009; 185:296–302.
39. Burke HB. The power of prediction. Cancer 2008;113: 890–892.
40. Gross ND, Patel SG, Carvalho AL, et al. Nomogram for deciding adjuvant treatment after surgery for oral cavity squamous cell carcinoma. Head Neck 2008;30: 1352–1360.
41. Vora HH, Shah ND, Patel DD, Trivedi TI, Chikhlikar PR. Prognostic significance of biomarkers in squamous cell carcinoma of the tongue: multivariate analysis. J Surg Oncol 2003;82:34–50.
42. Patel SG, Lydiatt WM. Staging of head and neck cancers: is it time to change the balance between the ideal and the practical? J Surg Oncol 2008;97:653–657.
43. Thomson PJ, Goodson ML, Booth C, Cragg N, Hamadah O. Cyclin A activity predicts clinical outcome in oral precancer and cancer. Int J Oral Maxillofac Surg 2006;35:1041–1046.
44. Shah NG, Trivedi TI, Tankshali RA, et al. Prognostic significance of molecular markers in oral squamous cell carcinoma: a multivariate analysis. Head Neck 2009;31: 1544–1556.
45. Yuan P, Temam S, El-Naggar A, et al. Overexpression of podoplanin in oral cancer and its association with poor clinical outcome. Cancer 2006;107:563–569.
46. Kreppel M, Scheer M, Drebber U, Ritter L, Zöller JE. Impact of podoplanin expression in oral squamous cell carcinoma: clinical and histopathologic correlations. Virchows Arch 2010;456:473–482.