The Importance of Correct Stage Grouping in Oncology

Results of a Nationwide Study of Oropharyngeal Carcinoma in the Netherlands

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Background. **In the frame of a nationwide study of oropharyngeal carcinoma in the Netherlands (1986–1990), the current International Union Against Cancer 1992/American Joint Committee on Cancer 1988 staging system was evaluated with respect to patient distribution and prognostic value.**

Methods. **Data related to epidemiology, treatment and survival from 640 patients referred for primary treatment were analyzed. Staging was first evaluated in a proportional-hazard regression analysis controlled for these data. Next, all possible combinations of T, N, and M were tested in a stepwise backward elimination model until all remaining indicator variables had a *P* value of less than 0.05. New stages were defined, based on the coefficients of the remaining indicator variables.**

Results. **The revised stages revealed two advantages compared with the UICC 1992/AJCC 1988 version: a more balanced distribution of patients (31% in Stage I, 31% in Stage II, 18% in Stage III, 14% in Stage IV, and 5% unknown in the revised staging system versus 7% in Stage I, 17% in Stage II, 24% in Stage III, 50% in Stage IV, and 2% unknown in the UICC 1992/AJCC 1988 staging system), and an improved prognostic discrimination for the disease specific survival (5-year results in the revised staging were 67% in Stage I, 42% in Stage II, 28% in Stage III, and 11% in Stage IV, versus 68% in Stage I, 64% in Stage II, 44% in Stage III and 27% in Stage IV in UICC 1992/AJCC 1988).**

Conclusion. **Improvements in the current staging system in patient distribution in the stages in prognostic discrimination is feasible by regrouping the T, N, and M but without redefining the categories themselves. *Cancer* 1995;75:2656–62.**

Key words: oropharyngeal carcinoma, staging, patient distribution, disease specific survival, prognostic factors.

The results of diagnostic procedures in oncology are usually defined in terms of three tumor characteristics: T (size and extent of the primary tumor), N (size and extent of the regional metastasis), and M (evidence or absence of distant metastasis), each characteristic having a number of possible values. The purpose of this classification system is to provide a standard means of communication concerning individual patients or groups of patients. The T, N, and M can further be combined into three or four stages, each encompassing a population that is, ideally, homogenous with respect to prognosis under specified treatment strategies. For indi-

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Table 1. TNM Classification and Stage Grouping According to the International Union Against Cancer '92/American Joint Committee on Cancer '88 System

T1	≤2 cm
T2	2–4 cm
T3	>4 cm
T4	Extension to bone, muscle, skin, neck, etc.
N0	No evidence of lymph node metastasis
N1	Single ipsilateral metastasis <3 cm
N2a	Single ipsilateral metastasis 3–6 cm
N2b	Multiple ipsilateral metastasis <6 cm
N2c	Bi- or contralateral metastasis <6 cm
N3	Metastasis ≥6 cm
M0	No evidence of distant metastasis
M1	Distant metastasis
Stage grouping	
I	T1 N0 M0
II	T2 N0 M0
III	T3 N0 M0, T1–3 N1 M0
IV	T4 N0–1 M0, any T N2–3 M0, any T any N M1

vidual patients, staging should direct the choice of therapy and predict its success. In clinical studies, stage grouping should enable comparison of patient populations with the same tumor with respect to the results of different treatment modalities. The most widely used TNM classification for oropharyngeal carcinoma and stage grouping, the latter being common for all head and neck carcinomas, is shown in Table 1.[1]

In oropharyngeal carcinoma, at least 70% of patients present with advanced disease (Stages III–IV); more than half of the patients present with Stage IV disease.[2–5] Due to the low incidence of this tumor (0.3–0.5% of all malignancies),[4,6] few patients have Stages I–II at all. Stages III and IV, on the contrary, are large but heterogeneous. A more balanced distribution over the stages, leading to relative enlargement of Stages I and II and increased coherence of Stages III and, particularly, IV, might add practical value to the current stage grouping. Ideally, this should be obtained through redefining of each stage with respect to T, N, and M, which by themselves remain unchanged. Moreover, the stage grouping should have a stronger prognostic significance than the separate categories included.

In the frame of the nationwide study on oropharyngeal carcinoma in the Netherlands from 1986 until 1990 conducted by the Dutch Head and Neck Oncology Cooperative Group, data related to epidemiology, treatment, and survival of 640 patients were collected.[7] Current staging for this large patient population was critically assessed and revised.

Materials and Methods

The study was conducted in seven leading centers that participate in the Dutch Head and Neck Oncology Cooperative Group: the University Hospitals of Groningen, Leiden, and Maastricht in combination with the Radiotherapeutic Institute, Limburg; Nijmegen and Rotterdam in combination with the Dr. Daniel Den Hoed Cancer Centre, Utrecht; and the Netherlands Cancer Institute in combination with the University of Amsterdam. In each center, records of patients admitted for oropharyngeal carcinoma between 1986 and 1990 were reviewed. Data management was performed at the Comprehensive Cancer Centre, Amsterdam. Other details related to the organization of the study, data collection, and management were reported earlier.[7]

Patients

Six hundred forty patients who were admitted for primary treatment of histologically proven squamous cell carcinoma or undifferentiated carcinoma of the oropharynx were analyzed. Four hundred forty-one patients (69%) were males and 199 (31%) females, with a median age of 59 years (range, 30–92 years).

Staging

Staging was done according to the 1992 rules of the International Union Against Cancer (UICC),[1] which are in accordance with those of the American Joint Committee on Cancer (AJCC), as proposed in 1988[8] (Table 1). Distribution by T and N is shown in Table 2. Distant metastases were present in 9 patients (1%), absent in 602 patients (94%), and unknown in 29 patients (5%). Distribution by stage according to the UICC 1992 classification, shown in Figure 1, was as follows: 44 patients (7%), Stage I; 106 (17%), Stage II; 157 (24%), Stage III; 319 (50%), Stage IV, and 14 (2%), unknown stage.

Vital Status and Survival

At the end of the follow-up, 225 patients (35%) were alive with no evidence of disease (NED), 17 (3%) were alive with tumor, 74 (12%) were dead with NED, 316 (49%) were dead with tumor, and 8 (1%) were lost to follow-up. In surviving patients, median follow-up was at 3 and 6 years, and maximal follow-up was at 7 years. When split up by center, tumor status at death appeared to range from 7–27% of patients having NED, but these differences were likely to have been caused by chance ($P = 0.35$).

Definitions and Statistical Analysis

Patients were followed up for at least 3 years or until death. Survival was defined as the time between the

Table 2. International Union Against Cancer '92 Distribution by T, N, and M, and by Stage

	T1 no. (%)	T2 no. (%)	T3 no. (%)	T4 no. (%)	Unknown no. (%)	Total no. (%)
N0	48 (7)	110 (17)	63 (10)	37 (6)	—	258 (40)
N1	14 (2)	33 (5)	53 (8)	48 (8)	3 (<1)	151 (24)
N2	11 (2)	47 (7)	63 (3)	61 (9)	—	182 (28)
N3	6 (1)	7 (1)	17 (3)	16 (2)	—	46 (7)
Unknown	—	—	—	3 (<1)	—	3 (<1)
Total	79 (12)	197 (31)	196 (31)	165 (26)	3 (<1)	640 (100)
Stage I		44 (7)				
Stage II		106 (17)				
Stage III		157 (24)				
Stage IV		319 (50)				
Stage unknown		14 (2)				

date of diagnosis and the end of follow-up or death. For the disease specific survival, only those patients who died of oropharyngeal tumor (local, regional, and/or distant) were considered dead. Survival curves were calculated using the life-table method.

Univariate analyses were performed with the log rank statistic. Cox's proportional hazards model was used for multivariate analyses. In the main analysis of stage, we controlled for all variables, as listed in Table 3.

These data were available for 594 patients. Treatment modality was used to define strata, and all other variables were used as covariates. To find an optimal combination of T, N, and M categories, we created dummy variables (0 or 1) indicating whether a patient had a T (or N) category larger than a particular value and also all possible products of these dummy variables for T, N, and M resulting in a total of $4 \times 6 \times 2 - 1 = 47$ dummy variables. However, because not all possible combinations of T, N, and M existed, four had to be deleted. Then, in a stepwise manner (with P values of 0.15 to enter and remove, as standardly used in analysis of prognostic factors), these dummy variables were added to the model, until no one had a P value of the size indicated, thereby recombining the T, N, and M categories into a new staging.

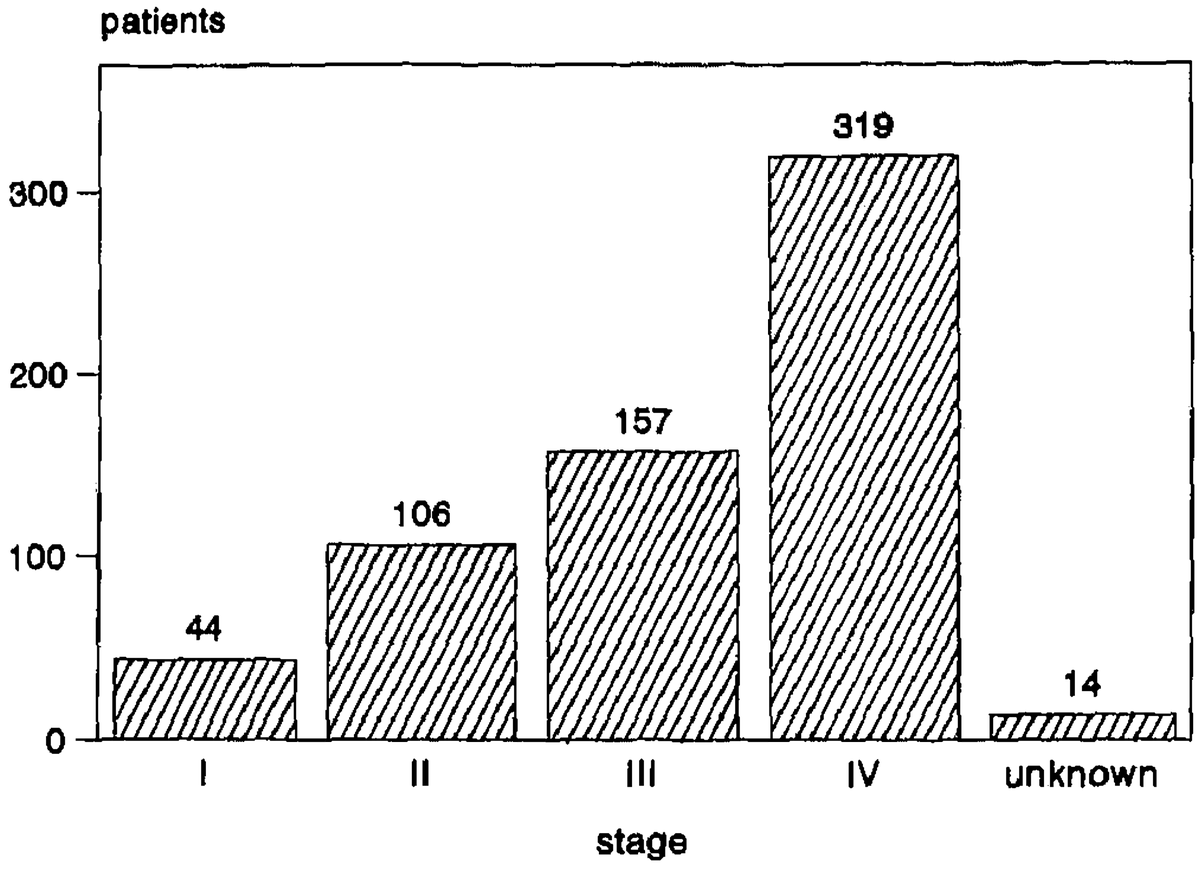

Figure 1. Distribution of the UICC 1992 staging system.

Results

The overall survival at 5 years was 28%. The 5-year disease specific survival was 41%; 35% in males and 51% in females ($P = 0.003$); in soft palate/uvula, 54%; tonsillar region, 42%; base of the tongue, 33%; and in posterior oropharyngeal wall, 32% ($P = 0.003$); Stage I (UICC, 1992), 68%; II, 64%; III, 44%; and IV, 27% ($P < 0.0001$) (Fig. 2); treatment by surgery alone, 80%; surgery and radiotherapy, 51%; radiotherapy alone, 36%; other treatments, 7%; and no treatment, 5% ($P < 0.0001$); 5-year disease specific survival ranged over the centers from 24% to 64% ($P = 0.009$).

Revised Staging

Controlled for the variables listed in Table 2, stage grouping was still associated with survival ($P < 0.0001$). However, when additionally controlled for stage grouping, there is still some evidence that T category (test for linear ln [hazard]; $P = 0.028$) as well as N category ($P = 0.031$) carry additional prognostic information.

In the stepwise procedure, which is used to find an optimal combination of T, N, and M categories, we chose to include M category ($P = 0.035$) regardless of its P value. Next, T3-4N1–3 ($P < 0.0001$), N3 ($P = 0.0002$), N1-3 ($P = 0.032$), T3-4 ($P = 0.015$), and T4N1-3 ($P = 0.077$) were included consecutively. Finally, T3-4N1-3 ($P = 0.36$) was again removed.

At this stage, T4N3 had a P value of 0.031, and T2–4N3 had a P value of 0.13, but both had a negative log (relative hazard), indicating that the associated disease specific survival was better than expected on the basis

Table 3. Variables Related to Treatment, Tumor, and Epidemiology Used in Cox's Proportional Hazard Method Analysis With Related Categories and Distribution of Patients

Variable	No.	Variable	No.
Treatment		Tumor (*cont*)	
Modalities		Side	
surgery alone	(42)	left	(269)
RT alone	(408)	right	(298)
surgery and RT	(147)	midline	(73)
other treatment	(14)	Histopathology	
no treatment	(29)	squamous	(628)
Neck dissection		undifferentiated	(12)
radical	(142)	Referral	
modified	(58)	primary tumor	(627)
selective	(17)	otherwise, not recurrence§	(13)
none	(423)	Epidemiology	
Type of surgery		Center	
combined resection	(133)	UH‖ Groningen	(70)
PT* and NN† in one session but discontinuous	(17)	UH Leiden	(43)
		UH Maastricht/RTIL¶	(70)
Resection of mandibula		UH Nijmegen	(93)
yes	(55)	UH Rotterdam/DDHCC#	(212)
no	(135)	UH Utrecht	(75)
Brachytherapy		NKI**/UH Amsterdam	(77)
yes	(73)	Incidence	
no	(567)	1986	(97)
Chemotherapy		1987	(133)
yes	(54)	1988	(139)
no	(584)	1989	(146)
Other treatments		1990	(125)
yes	(14)	Sex	
no	(626)	men	(441)
Standard protocol‡		women	(199)
yes	(530)	Age (yrs)	
no	(98)	<50	(151)
Tumor		50–59	(181)
Subsite		60–69	(175)
tonsillar region	(372)	≥70	(133)
soft palate/uvula	(62)		
base of the tongue	(179)		
posterior wall	(27)		

* Primary tumor.
† Neck nodes.
‡ Treatment according to the existing standard protocol in the different institutes.
§ Patient seen for second opinion and subsequently primarily treated in the "second opinion institute."
‖ University hospital.
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of the variables already in the model. Therefore, these variables were not included. The final result gives the following optimal score function:

$$1.28*\mathrm{M1} + 0.64*\mathrm{T3\text{–}4} + 0.45*\mathrm{N2\text{–}3} + 0.67*\mathrm{N3} + 0.39*\mathrm{T4N1\text{–}3}.$$

The associated standard errors in the same order are 0.48, 0.16, 0.15, 0.22 and 0.17, respectively, with P values at this stage of 0.018, <0.0001, 0.0024, 0.0041, and 0.023. On the basis of this score function, T, N and M were recombined into stages as shown in Table 4.

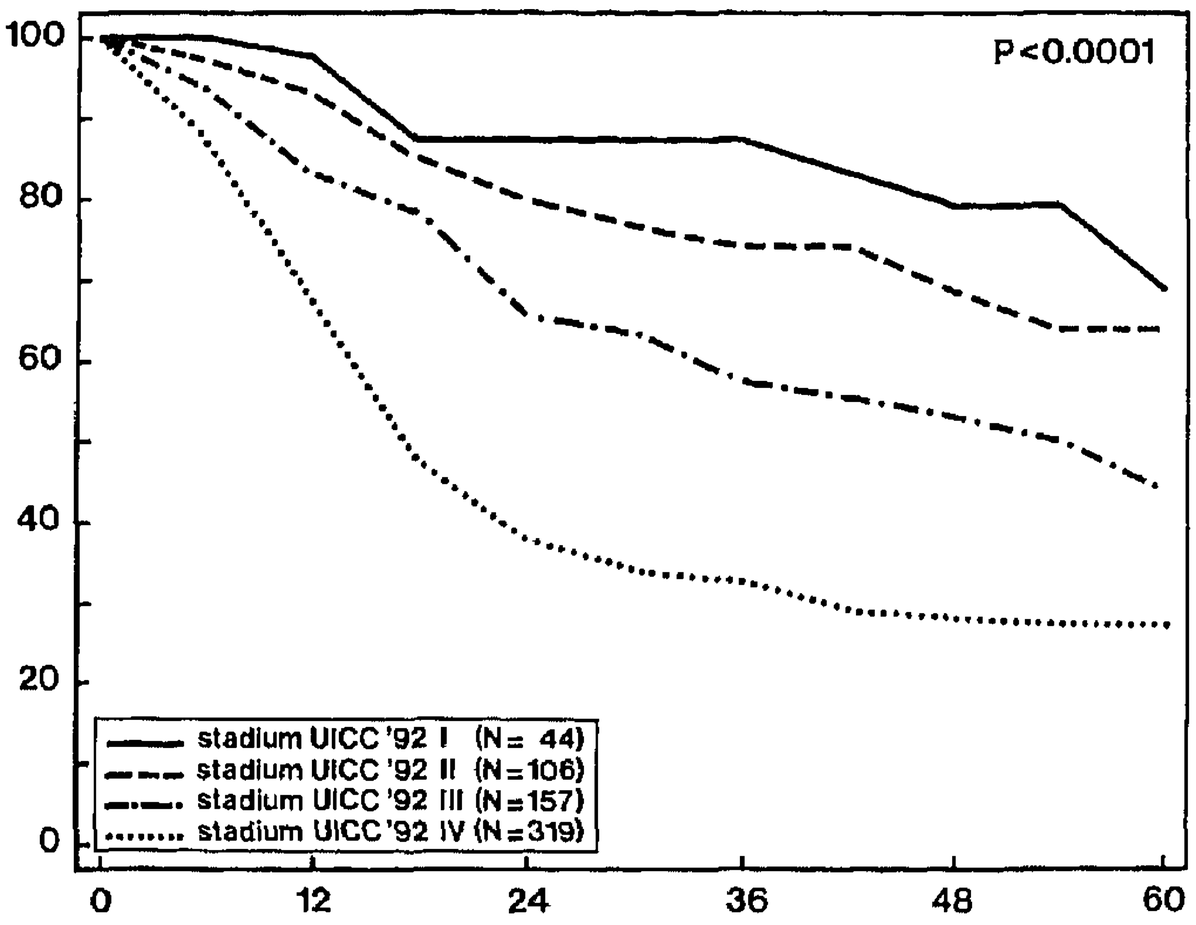

Figure 2. Disease specific survival according to the UICC 1992 stages.

Effects of the Revised Staging on Patient Distribution and Disease Specific Survival

When applied to our patient population, the revised staging resulted in the following distribution: Stage I, 197 patients (31%); Stage II, 200 (31%); Stage III, 118 (18%); Stage IV, 92 (14%); and unknown stage, 33 (5%). Compared with the UICC 1992 staging, relocation of patients toward lower stages is observed. It is noteworthy that revised Stage IV contains only 14% of patients (Fig. 3). A higher proportion of patients with unknown stage in the revised system is caused by the fact that less patients with unknown M categories could be assigned to Stage IV on the basis of T and N categories alone.

Figure 4 shows the disease specific survival of the revised stages, which is superior in prognostic discrimination to the UICC 1992 system (Fig. 2) in the case of this sample. The 5-year results with the revised system were 67% in Stage I, 42% in Stage II, 28% in Stage III, and 11% in Stage IV ($P < 0.0001$). With the revised staging, a more pronounced difference between Stages I and II (25% vs. 4% in UICC 1992) seems to have been achieved, so that a small group of patients with an extremely poor prognosis corresponding to Stage IV might have been identified.

Revised Staging and Other Prognostic Factors

Univariately, there was strong evidence of a different prognosis between the centers ($P = 0.009$). After controlling for sex, age, and stage UICC 1992, the difference decreased to some extent ($P = 0.015$); when controlling additionally for midline origin, a further decrease was observed ($P = 0.051$). However, a much more impressive change emerged after controlling for the revised staging ($P = 0.08$) and midline origin in addition ($P = 0.17$).

Apart from stage, for midline origin ($P < 0.0001$) and sex ($P < 0.02$), there was persistent evidence for prognostic significance throughout all analyses. For age, this was only the case without controlling for treatment modalities ($P = 0.006$); controlling for this variable, the P value for age increased to 0.08.

Table 4. Revised Staging

Stage I	T 1–2	N 0–1	M 0
Stage II	T 1–2	N 2	M 0
	T 3	N 0–1	M 0
	T 4	N 0	M 0
Stage III	T 1–2	N 3	M 0
	T 3	N 2	M 0
	T 4	N 1	M 0
Stage IV	T 3	N 3	M 0
	T 4	N 2–3	M 0
	any T	any N	M 1

T, N and M are identical as in the International Union Against Cancer '92/'92 system.

Discussion

The advantages of a more balanced distribution of patients over the stages are obvious: the larger the group, the more powerful the statistical analyses based on that group can be. As stated in the introduction, the function of staging in directing the choice of therapy may gain practical value with increased Stages I and II, being the favorable groups, and decreasing Stages III and IV into the really unfavorable cases. This seems to be of great

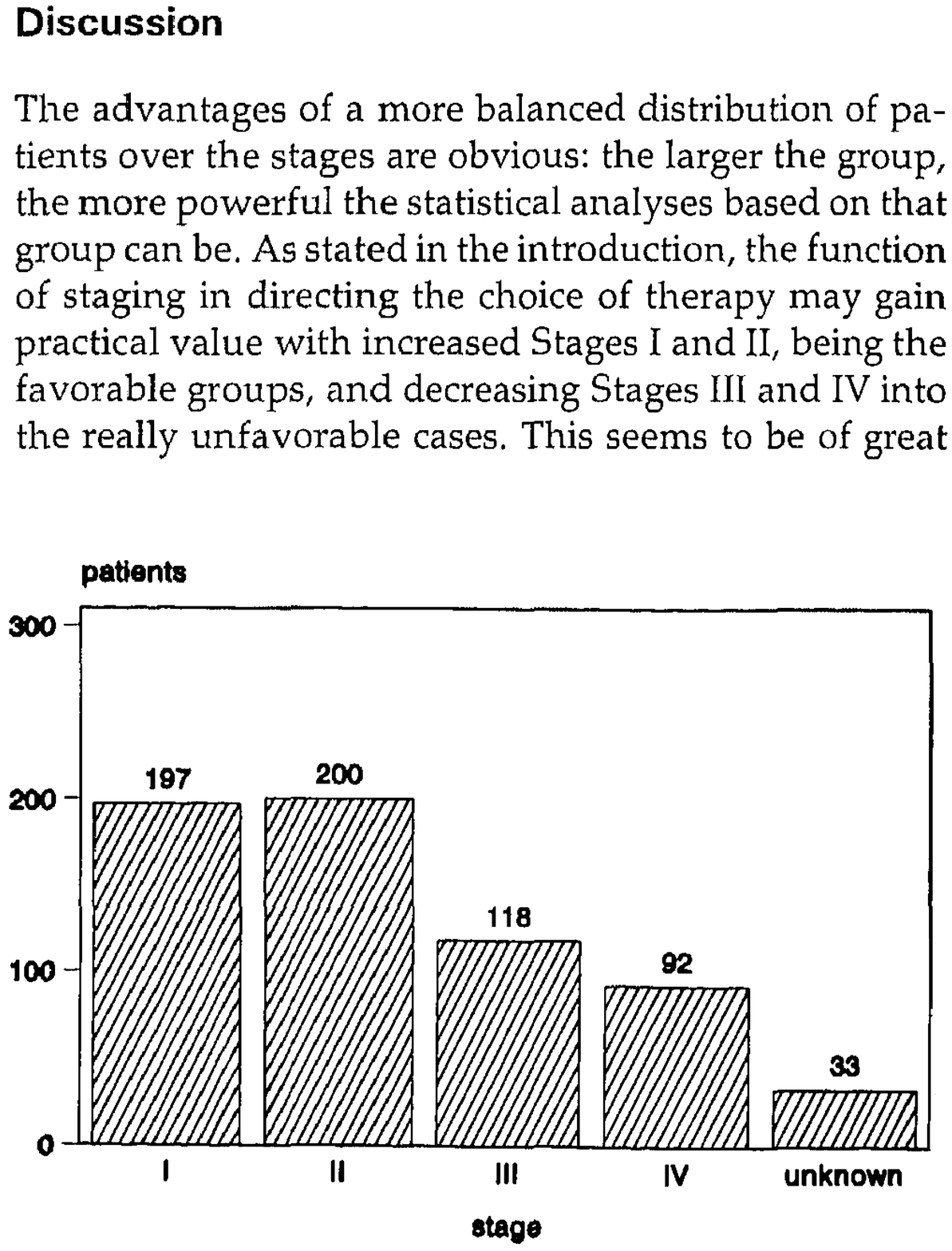

Figure 3. Distribution by the revised staging system.

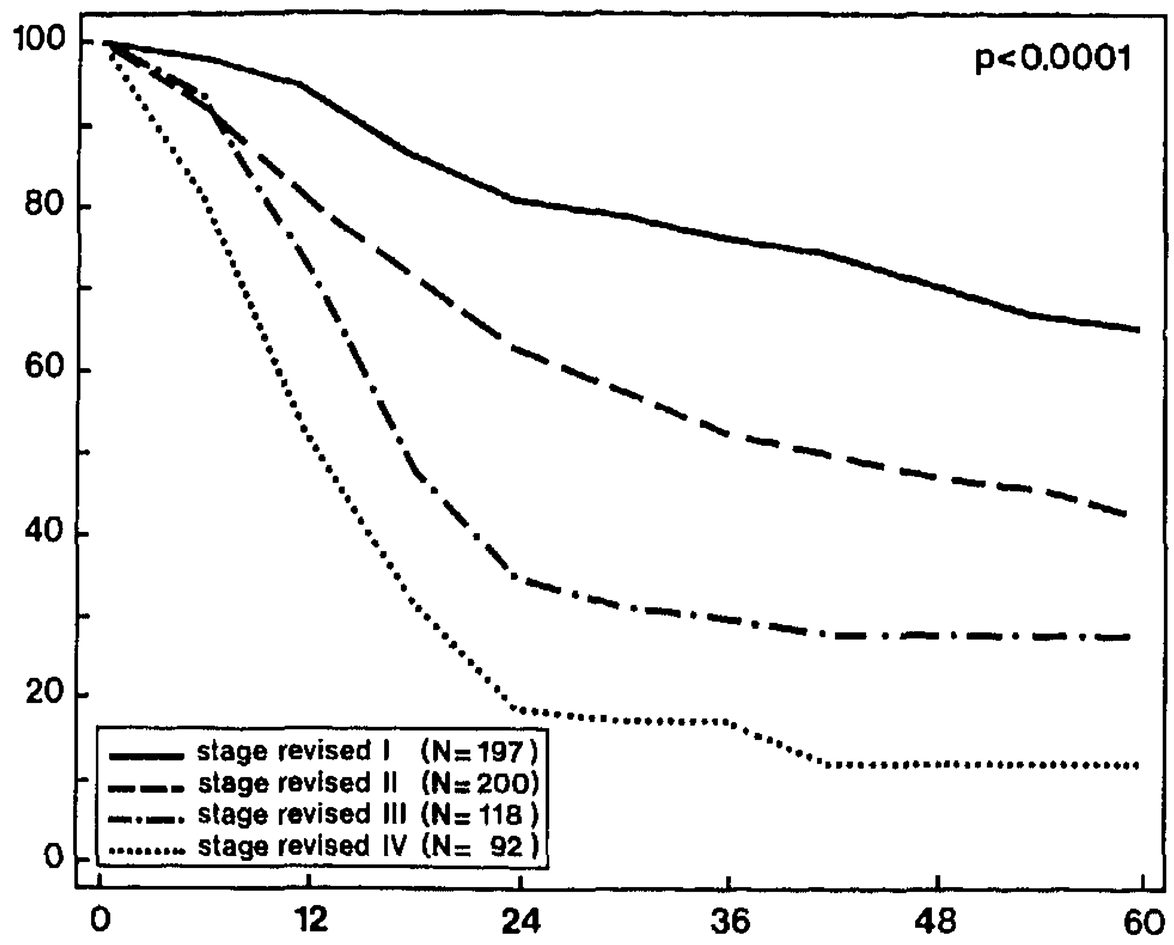

Figure 4. Disease specific survival according to the revised stages.

importance, because in many clinical trials (e.g., organ preservation studies[9]), all Stage III and IV patients are considered eligible candidates, and with the present staging system, this leads to heterogeneous groups of favorable and unfavorable patients. Stage IV, especially, should encompass only those patients with a poor prognosis. In our study, increased discrimination between revised stages suggests that such an improvement may have been obtained. However, it should be noted that our regrouping is optimized for the sample studied here. Therefore, it is to be expected that an application of this revised system to another group of patients would result in less diverging curves than shown in Figure 4. A study to get an independent evaluation of our stage system would be worthwhile. However, the fact that the original stage grouping can be improved on does not follow so much from a comparison of Figure 2 and Figure 4, but from our finding that T and N categories as such carry prognostic information in addition to that of the UICC 1992 stage grouping.

Classification and staging systems in head and neck cancer are regularly evaluated and are being proposed for revisions.[1,10–16] Globally, two types of revisions can be distinguished: those affecting definitions of T, N, and/or M that may require changes in diagnostic procedures and clinical routine handlings, thus complex in practical implementation, and those limited to regrouping the existing categories, thereby affecting only administrative aspects of staging. In the update of the TNM classification by UICC in 1987, new definitions of the N category were introduced.[16] The latest update from 1992,[1] commented on in 1993,[17] did not involve oropharyngeal carcinoma. Stage grouping for head and neck carcinomas, however, has remained unchanged since 1978.[18] Of the recently published proposals for improving the UICC 1992/AJCC 1988 system, only a few papers proposed the easy-to-implement regrouping of existing categories.[10,15]

Recently, two other interesting propositions have been published concerning a revision of the staging in head and neck cancer. Jones et al. proposed the addition of the values for T and N into an integer score, while leaving the M category out: this is called the TANIS (tumor and nodes integer score) classification and leads to seven possible categories.[10] Furthermore, they propose a stage grouping into three stages, Stage I comprising TANIS 1–3, Stage II comprising TANIS 4, and Stage III comprising TANIS 5–7. The TANIS classification is advantageous in that it is easy to apply and recall. When applied to our patient material, Stage I would have included 267 patients; Stage II, 135; and Stage III, 205. Berg's classification method,[15] like our series, which was also specifically applied to oropharyngeal cancer, is comparable to that of the UICC and the one proposed here because, it includes the M category and results in four stages. When applied to our patient population, the

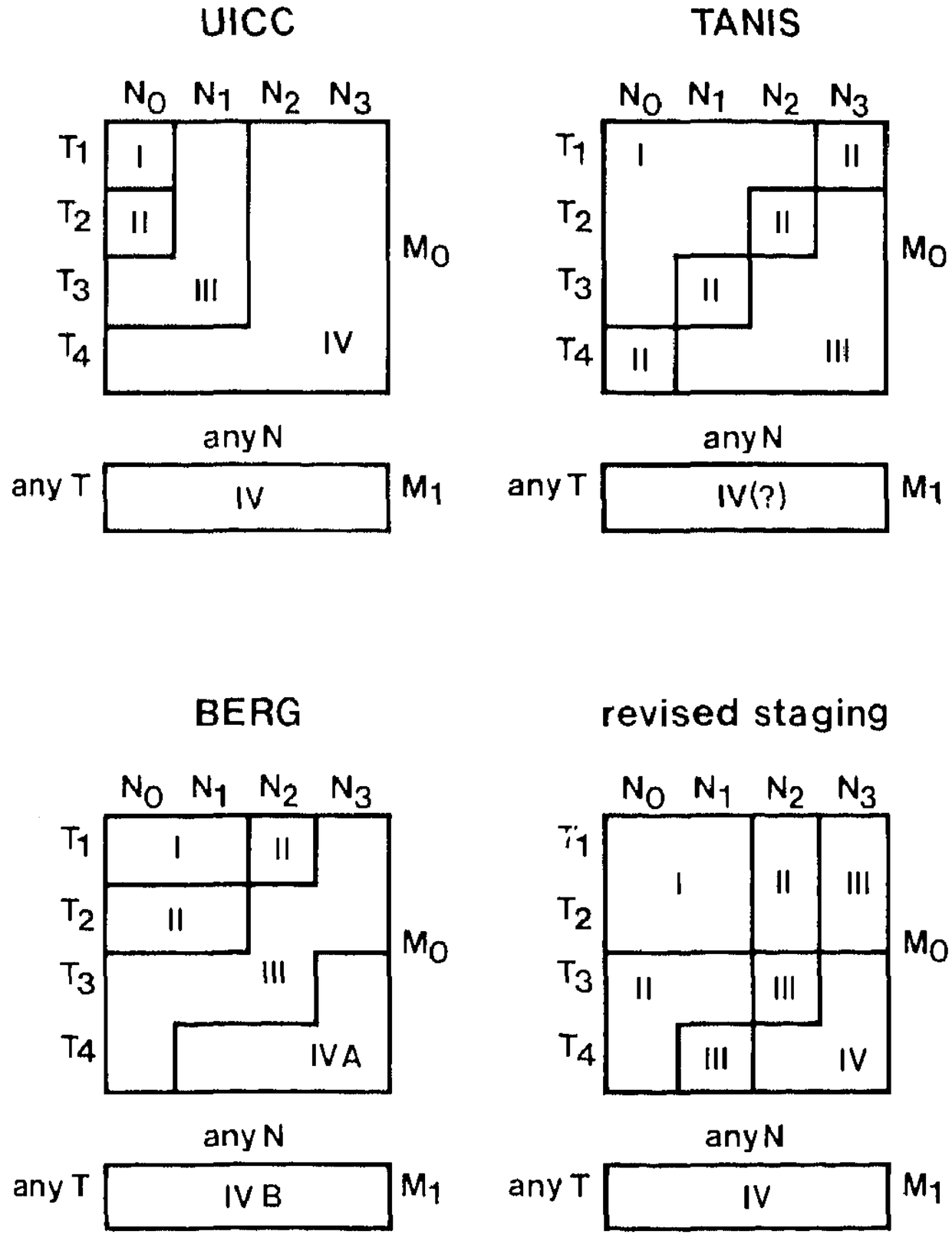

Figure 5. Diagramatic comparison of the stage grouping of the four different classification systems discussed (UICC 1992, TANIS, Berg, and the current revised staging).

distribution over the stages would have been as follows: Stage I 58; Stage II, 150; Stage III, 260; and Stage IV, 148 patients. Figure 5 shows diagrammatically the different stage groupings discussed here.

Both the TANIS and the Berg systems improve on the stage grouping of the UICC in our material with respect to prognostic power. The TANIS classification seems to be comparable in this respect with the regrouping proposed here, whereas there is some indication that Berg's staging is still somewhat inferior. With respect to the distribution of patients over stages, both are better than the UICC staging, but, as can be seen from the figures given above, are less balanced compared with the regrouping proposed here. However, a more formal comparison between the four stage grouping systems, performed on independent material, would provide a better evaluation of these systems.

From our study, one can conclude that it is possible to improve the stage grouping of the UICC, leading to a more balanced distribution of patients over the stages and to better discrimination of distinct prognostic groups. Because there is ample evidence that the latest redefinitions of the T and N categories in the UICC and the AJCC classification systems have been real improvements, a comparable refinement of the stage grouping is long overdue.

References

1. International Union against Cancer. Pharynx. In: TNM Classification of malignant tumours. 4th ed. 2nd rev. Hermanek P, Sobin LH, editors. Berlin: Springer-Verlag, 1992;21–4.
2. Bataini JP, Jaulerry C, Brunin F, Ponvert D, Ghossein NA. Significance and therapeutic implications of tumor regression following radiotherapy in patients treated for squamous cell carcinoma of the oropharynx and pharyngolarynx. *Head Neck* 1990;12:41–9.
3. Hussey DH, Latourette HB, Panje WR. Head and neck cancer: an analysis of the incidence, patterns of treatment, and survival at the university of Iowa. *Ann Otol Rhinol Laryngol* 1991; 100(Suppl):1–16.
4. Johansen LV, Overgaard J, Overgaard M, Birkler N, Fisker A. Squamous cell carcinoma of the oropharynx: an analysis of 213 consecutive patients scheduled for primary radiotherapy. *Laryngoscope* 1990;100:985–90.
5. Vernham GA, Crowther JA. Head and neck carcinoma—stage at presentation. *Clin Otolaryngol* 1993;19:120–4.
6. Vereniging van Integrale Kankercentra. Incidence of cancer in the Netherlands 1990. Utrecht: Vereniging van Integrale Kankercentra, 1993.
7. Mak-Kregar S, Hilgers FJM, Levendag PC, Manni JJ, Meeuwis CA, Lubsen H, et al. Epidemiology, treatment and survival of oropharyngeal carcinoma in the Netherlands: a nationwide study. *Eur Arch Otorhinolaryngol*, in press.
8. American Joint Committee on Cancer. Manual for staging of cancer. 3d ed. Philadelphia: J. B. Lippincott Co., 1988:33–5.
9. Wolf GT, Urba S, Hazuka M. Induction chemotherapy for organ preservation in advanced squamous cell carcinoma of the oral cavity and oropharynx. *Recent Results Cancer Res* 1994;134:133–43.
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. Howaldt HP, Frenz M, Pitz H. Proposal for a modified T-classification for oral cancer. *J Cranio Maxillofac Surg* 1993;21:96–101.
12. Ghouri AF, Zamora RL, Harvey JE, Spitznagel EL Jr. Sessions DG. Epidermoid carcinoma of the oral cavity and oropharynx: validity of the current AJCC staging system and new statistical tools for the prediction of subclinical neck disease. *Otolaryngol Head Neck Surg* 1993;108:225–32.
13. Kleinsasser O. Revision of classification of laryngeal cancer, is it long overdue? (proposals for an improved TN-classification). *J Laryngol Otol* 1992;106:197–204.
14. Sikand A, Flores AD, Morrison MD, Durham JS. Design and evaluation of a subclassification system for supraglottic laryngeal cancer. *J Otolaryngol* 1992;21:270–7.
15. Berg H. Die prognostische Relevanz des TNM-systems fuer Oropharynxcarcinome. *Tumordiagn Ther* 1992;13:171–7.
16. International Union Against Cancer. TNM Classification of malignant tumours. In: Hermanek P, Sobin LH, editors. 4th ed. Berlin: Springer-Verlag; 1987.
17. International Union Against Cancer. TNM Supplement 1993: a commentary on uniform use. Hermanek P, Henson DE, Hutter RVP, Sobin LH, editors. Berlin: Springer-Verlag; 1993.
18. International Union Against Cancer. TNM classification of malignant tumours. 3rd ed. Geneva: UICC, 1978.