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## CANCER OF THE SUPRAGLOTTIC LARYNX WITH NECK NODE METASTASIS TREATED BY RADIATION THERAPY ONLY

The revised 1987 UICC classification system as prognostic indicator

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### Abstract

In 1987, a thoroughly renewed TNM classification was published; the revision was a conjunct effort of the International Union Against Cancer (UICC) and American Joint Committee on Cancer (AJCC). With respect to the former UICC classification, a major change was introduced regarding the regional lymph node subcategories in head and neck cancer; that is compared to the 1978 edition the subjective subcategory of fixation was eliminated and size of the lymph node has become of paramount importance. To see whether the 1987 UICC classification system is indeed more predictive and discriminatory than the 1978 edition, we have analysed patients with supraglottic cancer with clinically detectable lymph node metastasis (T1-4, N+). All patients treated between 1965 and 1980 by radiation therapy only were staged according to both editions of the UICC classification system. From these data we conclude that the prognosis of patients with lymph nodal involvement indeed worsens from N1 to N3 when classified according to the 1987 edition; in contrast, no difference is seen between the N1, N2 or N3 subcategories when staged according to the 1978 classification rules.

*Key words:* Larynx, cancer, supraglottic, neck node metastasis, staging, UICC classification, radiotherapy.

Classification systems permit consistency in describing the extent of malignant diseases. Proper classification and staging will allow the physician to determine treatment for the patient and evaluate results of management; moreover, data on treatment results reported from various institutions can be compared more reliably. The TMM system for the classification of malignant tumours was developed first by Pierre Denoix between 1943 and 1952 (1). In Europe, for tumours in the head and neck, the most commonly used system is the one developed by the Inter-

national Union Against Cancer (UICC). This organization (UICC) revised its system in 1987 thoroughly and for head and neck cancer in particular with respect to the classification of cervical lymph node metastasis (2). It has been shown that for the curability of tumours, volume of disease is of paramount importance, specifically when radiation therapy (RT) is used as a single modality treatment (3-5). In the recently revised UICC classification system, measured size, that is volume, is now used specifically to stratify neck nodes into different subclasses, which is in marked contrast to the 1978 edition (Table 1). In this paper we have therefore tried to analyse retrospectively if the 1987 UICC classification system is indeed more predictive and discriminatory than the 1978 edition, in particular with regard to neck nodes. For this purpose we have chosen a particular cohort of patients, that is those with supraglottic laryngeal cancer with clinically detectable regional metastasis treated by RT only.

### Material and Methods

All charts of patients treated between 1965 and 1980 in the Dr. Daniël den Hoed Cancer Center and Dijkzigt University Hospital for histologically confirmed squamous cell carcinoma of the supraglottic larynx, were retrospectively reviewed. Only patients without distant metastasis at the time of admission (M0) were included in the analysis. Staging was done according to the so-called old UICC

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**Table 1**  
*UICC classification systems for cervical lymph node metastases*

Nodal class	
UICC (1978)	UICC (1987)
N0 None	N0 None
N1 Mobile ipsilateral nodes	N1 Single ipsilateral nodes; ≤ 3 cm
N2 Contra- or bilateral nodes	N2A Single ipsilateral nodes; 3–6 cm
	N2B Multiple ipsilateral nodes; ≤ 6 cm
	N2C Bilateral or contralateral nodes; ≤ 6 cm
N3 Fixed nodes	N3 Lymph node(s) > 6 cm

**Table 2**  
*UICC classification systems for tumour (T-) staging*

T-stage	
UICC (1978)	UICC (1987)
T1A Laryngeal surface epiglottis or aryepiglottic fold	T1 One subsite, normal cord mobility
T1B Epiglottis and extending to ventricular cavities or bands	
T2 Confined to the larynx with extension to adjacent site or sites or to the glottis without fixation	T2 More than one subsite, normal cord mobility
T3 Vocal cord fixation and/or evidence of deep infiltration	T3 Vocal cord fixation and/or invasion postcricoid, preepiglottic space, medial wall piriform sinus
T4 Direct extension beyond larynx	T4 Invasion through thyroid cartilage and/or extension tissues beyond larynx

system (1978 edition) as well as to the new UICC classification (1987 edition). Both staging systems are briefly summarised in Tables 1 and 2. A total number of 312 files of patients with supraglottic cancer with or without regional metastasis (T1–4, N±) were retrieved. For this particular study only patients treated by RT exclusively were eligible; therefore those treated by RT and/or surgery (n=60) were excluded from the present analysis. Moreover, 14 files were discarded due to inadequate treatment (total dose less than 40 Gy/early death). In summary 238 patients were treated by RT only, that is 165 with T1–4, N0 disease and 73 with T1–4, N+ disease. A previous report dealt with the 165 T1–4, N0 patients with particular emphasis to the relapse rate of the clinically negative neck (6). The 73 patients with clinically detectable lymph node metastasis in the neck form the basis of the present analysis. For the patient population under study a mean age of 60 years and a male to female ratio of 5 to 1 was found. The distribution of the tumours with respect to the T- and N-stage according to the 1978 and 1987 classification systems is shown in Tables 3 and 4 respectively. All patients were irradiated by a linear accelerator with a 4 MV photon beam with a once-a-day conventional fractionation scheme, that is 2 Gy per fraction, 5 times per week by 2 lateral opposed fields. During the treatment the head was fixed in a supine position on the treatment couch with a custom made plastic cast. According to the protocol at the time, the response of all tumours was evaluated after a total dose of 40 Gy had been applied. In case a good

**Table 3**

T	N1	N2	N3	Total
T1A	5	2	1	8
T1B	1		1	2
T2	10	2	1	13
T3	10		2	12
T4	17	5	14	36
TX	1		1	2
Total	44	9	20	73

Distribution of T- and N-stages of patients with epidermoid cancer of the supraglottic larynx with lymph nodal metastasis. Staging according to the UICC classification system—1978 edition.

**Table 4**

T	N1	N2A	N2B	N2C	N3	Total
T1	1				1	2
T2	9	4	5	3		21
T3	11	2	4	1	4	22
T4	6	7	4	4	5	26
Tx	1			1		2
Total	28	13	13	9	10	73

Distribution of T- and N-stages of patients with epidermoid cancer of the supraglottic larynx with lymph nodal metastasis. Staging according to the UICC classification system—1987 edition.

response was observed, the RT was continued to a full dose (RT-I). Patients with a poor response of their primary tumour and/or neck disease were preferably subjected to surgery (these are not included in the present study). However, in case of patient refusal and/or if medically unfit for operation, some patients were offered a second course of RT in spite of a poor response of their tumours to the first series of radiation (RT-II, included in this study). Tables 5 and 6 show the distribution according to T-stage and N-stage for the patients of the RT-I and RT-II subgroups when staged according to the UICC 1987 classification. After a dose of 40 Gy had been delivered to the primary cancer and both sides of the neck, the primary and the clinically palpable neck nodes were boosted to a higher dose by a shrinking field technique. The average dose to the primary site was 63.3 Gy (range 50–79), the average dose delivered to the node(s) 66.8 Gy. For different T- and N-stages, the number of patients treated by either a continuous or split course technique are also depicted in Tables 5 and 6; as is apparent, 58 out of 73 (80%) N+ patients were treated by a split course technique with a mean split period of 28 days (range 17–69).

**Table 5**

Tumour stage	RT-I		RT-II	
	Continuous	Split course	Continuous	Split course
T1 N+	1	1		
T2 N+	4	13		4
T3 N+	2	9		11
T4 N+	8	9		9
Tx N+		1		1
Total	15	33		25

Patients treated by radiation alone (RT) for cancer of the supraglottis with clinically detectable lymph node metastasis (N+). Staging according to the UICC 1987 edition. RT-I: Full course of RT as first choice treatment modality. RT-II: Full course of RT in patients who refused and/or were medically unfit for operation. RT was given either by a continuous or a split course technique.

**Table 6**

N-stage	RT-I		RT-II	
	Continuous	Split course	Continuous	Split course
N1	0	22		6
N2A	5	4		4
N2B	2	7		4
N2C	4	2		3
N3	4			6
Total	15	35		23

Patients treated by radiation alone (RT) for T1–4, N+ epidermoid cancer of the supraglottic larynx. N category staged according to the UICC 1987 edition. RT-I: Full course of RT as first choice of treatment modality. RT-II: Full course of RT in patients who refused and/or were medically unfit for operation. RT was given by either a continuous or a split course technique.

**Results**

The present report only attempts to evaluate the ability to the 1987 UICC classification system to better prognosticate patients in comparison to the 1978 UICC edition. However, it seems appropriate to first briefly summarise the overall treatment results of the patient population under study. The median follow-up time for the N+ patients was 28.9 months. Fig. 1 shows the local regional and distant failures of the 73 patients with T1–4, N+ disease. Ultimately 51 out of 73 (70%) relapsed locally and/or regionally at some point in time; 22 (30%) patients died with distant metastasis. A summary of the cause of death is presented in Table 7; 13 patients (18%) died due to intercurrent disease and for 58 patients (78%) the cause of death was tumour related. To study the influence of T-stage per se in the two (classification) editions, data on the causes of death and survival for T1–4, N0 patients were taken from a previous publication on the same patient population (T1–4, N0 patients Tables 7 and 8 (6)). From Table 7 the large impact on tumour related deaths of lymph nodal disease in the N+ patient category is evident; i.e. on the average three times as many deaths in the N+ (78%) versus N0 (26%) patients are tumour related. The 5-year overall and corrected survival rates for stage I through IV for the old and new UICC classification edition can be seen in Table 8; no significant differences were found comparing both systems stage by stage. The corrected survival curves for patients classified according to both classifications are depicted for the different T-stages

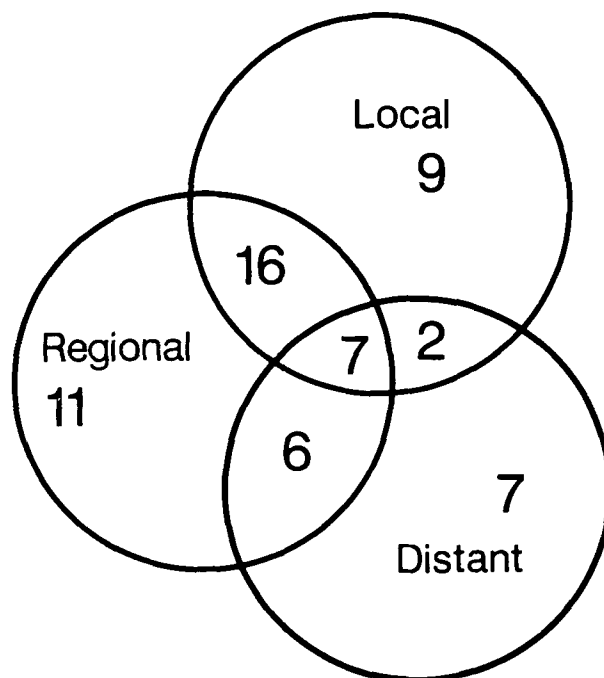


Fig. 1. Sites of failure for patients with epidermoid carcinoma of the supraglottic larynx with clinically palpable lymph nodes (T1–4, N+) treated between 1965–1980 by radiation therapy only.

**Table 7**

T and N patient category	No. of patients			
	Intercurrent deaths	Tumour related deaths	Alive	Total
T1-4, N0	61	42	62	165
T1-4, N+	13	58	2	73
All patients	74	100	64	238

Tumour related deaths, that is local and/or regional failures and/or distant metastasis, and death of other causes of patients with epidermoid carcinoma of the supraglottic larynx (N+) treated between 1965-1980 by radiation therapy only.

\*For comparison purposes causes of death for N0 patients are depicted as well; these data were retrieved from a previous publication on the same patient population database of the same institution (ref. 6).

**Table 8**

Stage*	UICC-1978		UICC-1987			
	Patients (No.)	Survival (%)		Patients (No.)	Survival (%)	
		Corr. 5-yrs	Overall 5-yrs		Corr. 5-yrs	Overall 5-yrs
I	65	80	60	7	88	88
II	31	96	70	93	84	60
III	47	38	28	42	32	28
IV	95	36	28	96	34	28
Total	238			238		

Patient distribution and survival stage by stage for patients with epidermoid carcinoma of the supraglottic larynx classified according to the UICC system—1978 and 1987 edition.

\*To study the influence of (T-) stage per se, data on T-4, N0 patients were retrieved from a previous publication on supraglottic patients from the same institution (ref. 6).

in Figs 2 and 3, for the N-stages in Figs 4 and 5. A worsening of the corrected survival for higher T-stages was found, varying from 70% (5 years T1) to 35% (5 years/T4); however, with respect to the T categories no significant differences could be observed between the 1978 and revised edition. Seventy per cent of the patients without clinically detectable lymph node metastasis (N0) versus only about 20% of patients with palpable lymph nodes (N+) survived 5 years. With respect to the N+ subgroups no differences were seen for N1, N2 or N3 when staged according to the 1978 edition. A significant difference (generalized Wilcoxon test,  $p = 0.05$ ) was found between the nodal subclasses of the revised UICC classification; the prognosis worsened in an orderly way from N1 to N3.

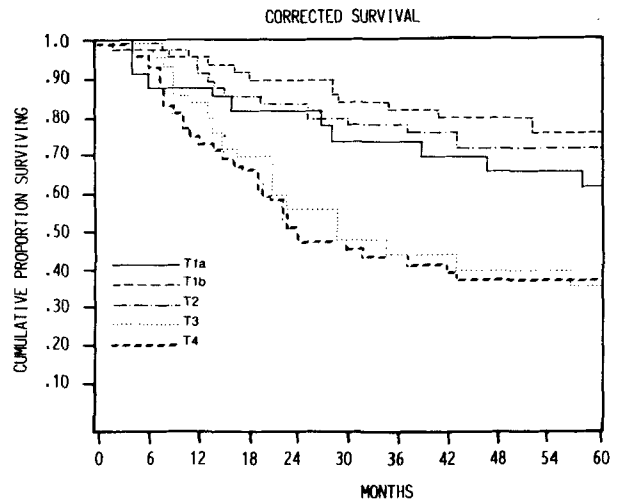


Fig. 2. Corrected survival rate considering death due to epidermoid cancer of the supraglottic larynx only for patients with T1A (n=27), T1B (n=48), T2 (n=44), T3 (n=32) and T4 (n=85) tumours treated by radiation therapy exclusively. Staging was done according to the 1987 UICC classification system. To study the influence of T-stage per se, data were partly derived from a previous publication on patients with T1-4, N0 epidermoid carcinoma of the supraglottic larynx. For details see ref. 6.

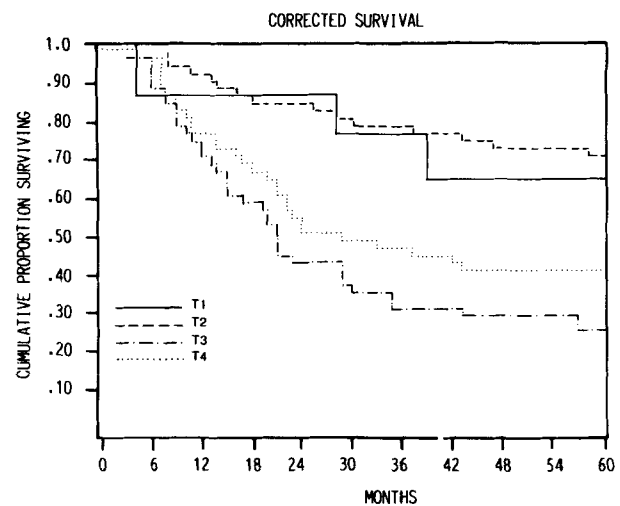


Fig. 3. Corrected survival rate considering death due to epidermoid cancer of the supraglottic larynx only for patients with T1 (n=9), T2 (n=114), T3 (n=42) and T4 (n=71) tumours treated by radiation therapy exclusively. Staging was done according to the 1987 UICC classification system.

**Discussion**

For supraglottic cancer per se, there is a large body of evidence in the literature that T-stage and cervical nodal involvement are indeed parameters of biological virulence (7-15). In a previous publication we discussed the influence of T-stage per se and relapse rate in the neck on local-regional control and survival in patients with supraglottic

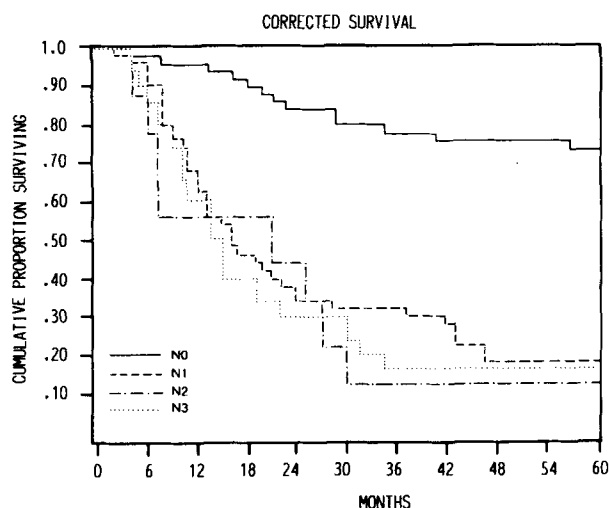


Fig. 4. Corrected survival rate considering death due to epidermoid cancer of the supraglottic larynx only for patients with N0 ( $n=165$ ), N1 ( $n=44$ ), N2 ( $n=9$ ) and N3 ( $n=20$ ) neck nodes. All primary tumours and neck nodes were treated by radiation therapy exclusively. Staging was done according to the 1978 UICC classification system. To study the influence of T-stage per se, data were partly derived from a previous publication on patients with T1-4, N0 epidermoid carcinoma of the supraglottic larynx. For details see ref. 6.

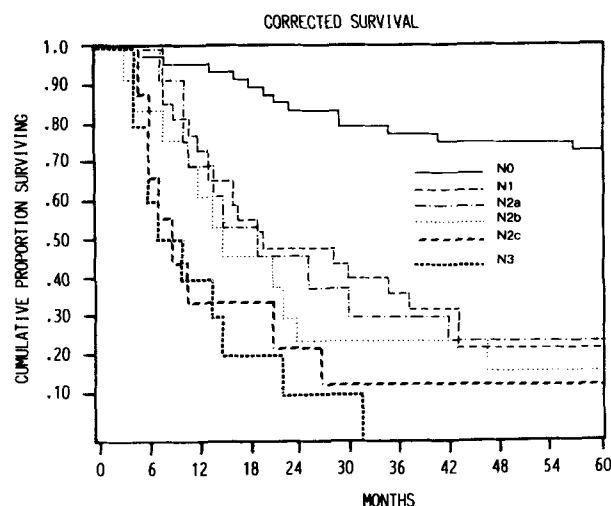


Fig. 5. Corrected survival rate considering death due to epidermoid cancer of the supraglottic larynx only for patients with N0 ( $n=165$ ), N1 ( $n=28$ ), N2A ( $n=13$ ), N2B ( $n=13$ ), N2C ( $n=9$ ) and N3 ( $n=10$ ) neck nodes. All primary tumours and neck nodes were treated by radiation therapy exclusively. Staging was done according to the 1987 UICC classification system. To study the influence of T-stage per se, data were partly derived from a previous publication on patients with T1-4, N0 epidermoid carcinoma of the supraglottic larynx. For details see ref. 6.

glottic laryngeal cancer without lymph node metastasis (T1-4, N0) treated by RT only (6).

The present communication deals with the question whether the classification systems used are sufficiently discriminatory for different subgroupings in terms of patient

outcome. As the in Europe most commonly used UICC classification system was recently revised thoroughly, in particular with regard to the neck nodal involvement, we carried out an analysis of patients with supraglottic cancer and clinically detectable lymph node metastasis (T1-4, N+) treated by a single modality, i.e. by radical RT. For comparison purposes patients were retrospectively staged according to the old (1978) and, in retrospect, according to the new (1987) edition. A brief overview of the obtained treatment results in the patient population under study shows that death from intercurrent disease has a strong impact on the overall survival; 18% (13/73) of our patients died of causes not related to their laryngeal cancer, a phenomenon which is coherent with the data of the literature (Table 7). Of the 73 patients with clinically detectable lymph node metastasis in the neck, only 2 (3%) were alive at 10 years, which is in marked contrast to the 37% (62 out of 165) of the N0 category (Table 7, see also ref. 6). The majority of the N+ patients (80%) died due to tumour-related causes with the major site of failure being the neck (Fig. 1); i.e. 40 out of 58 patients (69%) with a tumour related failure experienced at least a regional relapse, demonstrating again the major impact on survival of (uncontrolled) lymph node metastasis.

Tumour size (volume) has been shown to be a significant predictor of a given patient's potential for cure by RT (3-5, 16) and is part of current staging systems (T- and N-stage) for upper aerodigestive tract malignancies (17-19). In fact, the paramount importance of tumour volume has been stressed in the recent edition of the UICC classification in particular with regard to the neck nodes.

The influence of T-stage per se on tumour control for patients treated by RT only can be best discussed by the data as published in a previous paper in this journal on T1-4, N0 supraglottic cancer (6). In short, a somewhat worse corrected survival rate for the T3/T4 tumours (5 years/55%) versus the T1/T2 tumours (5 years/85%) was observed. No statistical significant difference was found with respect to T-stage comparing both classification systems. However, the larynx poses a problem for the clinical assessment of exact tumour extent (T-stage); it has even been suggested that newer generation CT- and/or MRI-scanners might prove valuable and could become even indispensable for assessing the accurate T category in the near future (18, 20-23). Moreover, besides these limitations, only minor changes have been introduced with regard to T-stage in the recent UICC classification system (Table 2). Both staging systems do agree on advanced T categories (T3/T4) and advanced tumour stages (III/IV) as being of poor prognostic significance.

In contrast to the primary tumour, the neck nodes are more easily accessible for clinical examination. A major change has been introduced in the most recent UICC classification system. The neck node classification is now based on size, on the presence of single or multiple nodes

as well as on the ipsilateral, bilateral or contralateral neck involvement (2). Prior to its last revision, the UICC in principle only discriminated between ipsilateral, contralateral or fixed nodes (1). Moreover, the subjectivity of establishing fixation (N3—1978 edition) has been eliminated. In particular with regard to neck nodes, there is ample evidence in the current literature that the extent (volume) of lymph nodal metastasis is of extreme importance in terms of ultimate control (3, 24–28). Most authors on laryngeal carcinoma even postulate that N-stage is the major determinant of patient outcome (3, 24, 26, 28, 29). Hahn et al. (24) for instance showed that T-stage has a prognostic value only for patients with non- or limited (N1) lymph nodal involvement. Wall et al. (28) demonstrated a strong correlation between control of the disease in the neck and at the primary site, for both early and late T-stage supraglottic cancer. They suggested that radioresistance was due to inherent cellular characteristics reflected in the nodal metastasis.

With respect to the N-subclasses, only small numbers of patients are available in the present study population for data analysis (Tables 4 and 6). In light of the following discussion two factors are of importance. First of all, according to the running protocol at the time, all patients were treated somewhat irrespective of the extent of the T- and N-status of their disease, by a split course technique. This variable but significant split-period of several weeks (mean 27 days) is graphically summarised for the N0 as well as for the N+ patients in Fig. 6. Furthermore, the dose applied to the lymph nodes (average 66.8 Gy) was not tailored to the tumour volume. Both the standard dose irrespective of extent of disease and the substantial lengthening of the overall treatment time are somewhat inconsistent with radiobiological and clinical data having established firm dose-response relationships (4, 19, 30–32).

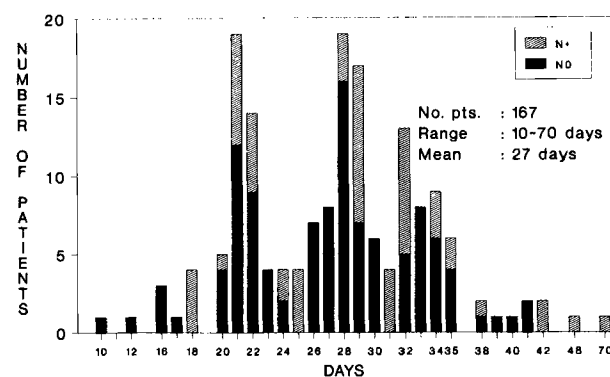


Fig. 6. Distribution of 167 patients with T1–4, N0+ supraglottic carcinoma treated by split course radiation. Number of patients and duration of rest interval in days (split period) between two radiation series is depicted. Besides N+ patients, for comparison purposes data on N0 patients with supraglottic cancer treated by RT only in same institutions are depicted as well. The N0 patients have been described in detail in ref. 6.

However, even though the numbers are small and, as we know now, suboptimal doses were in fact used, we did find a significant difference in corrected survival between the nodal subclasses of the revised UICC classification. The prognosis of patients with lymph nodal involvement worsened in an orderly way from N1 to N3 (Fig. 5). This is in contrast to those staged according to the old classification rules; that is for the 1978 edition of the UICC no difference was seen between N1, N2 or N3 (Fig. 4). Moreover, the lack of difference in prognosis of the N3 patients versus N1 patients, when staged according to the old UICC classification, demonstrates again that having established fixation does not reflect in a dismal outcome per se; i.e. fixation (UICC 1978—N3 disease) is not a reliable prognosticator. This is in contradistinction to the N3 patients when staged according to the UICC 1987 classification: N3 disease, now based on tumour volume (size) has an extremely poor prognosis (Fig. 5).

For patients with supraglottic carcinoma treated by RT only, the newly revised classification system thus seems to be indeed capable to prognosticate in a better way those with neck nodal disease. More patients are needed, however, to underline these findings with a higher statistical resolution.

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