Radiotherapy of Tonsillar and Base of the Tongue Carcinoma. Prediction of Local Control

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119 patients with squamous cell carcinoma of the tonsillar region (68) and the base of the tongue (51), who received external radiotherapy with curative intent between 1966 and 1984, are analysed with respect to overall treatment results, local tumour control and prognostic factors. Radiation doses were equivalent to 60–70 Gy in 6–7 weeks, with a mean fraction dose of 2.4 Gy on the cobalt 60 equipment and 2 Gy on the linear accelerator. Significant differences were found between both oropharyngeal subsites. Three-year overall survival was 57% in tonsillar carcinoma and 38% in base of the tongue ($P = 0.006$); disease-specific survival was 70% and 47%, respectively ($P = 0.005$); and local control rates were 82% and 61% ($P = 0.02$). Late damage to normal tissues, like persistent dysphagia and osteomyelitis, were seen in 11% of patients. Patients with large tumours in the tongue based developed significantly more complications ($P = 0.04$). T-stage and tumour subsite predicted local control independently before start of the treatment ($P = 0.02$ in both cases). A significant nonlinear correlation between Normalised Total Dose (using an α/β ratio of 15 Gy) and local control rate was found ($P = 0.006$), the middle range having the worst prognosis. The size of radiation field and overall treatment time did not correlate with local control in either site. Response at the end of radiotherapy and 6 weeks later have additional prognostic value for local control, irrespective of the initial stage or subsite ($P = 0.004$ and <0.001, respectively).
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INTRODUCTION

THE TONSILLAR region and the base of the tongue are the two most frequent subsites of origin in cancers of the oropharynx. Radiotherapy appears to be more effective for the tonsillar region than for the base of the tongue. For carcinoma of the tonsillar region a local control rate of approximately 65% [1–5], or incidentally lower [6, 7] is reported. For base of tongue carcinoma, the local control rate fluctuates around 50% in most studies [8–11], although some higher values have been noted [12–14]. In 1973 Gelinas and Fletcher reported on remarkably good results having 82% and 75% local tumour control, for the tonsillar region and base of the tongue, respectively [15].

In oropharyngeal tumours, control of the primary site emerges as the crucial parameter for the success of the therapy [6]. A reliable prediction of the control for the primary tumour before the start of radiotherapy can be based upon T-stage, as confirmed in many studies [2, 5–8, 10, 12, 14–17], N-stage [7, 12, 14, 16] and infiltration of tonsillar tumours in base of

the tongue correlate with local control, the latter being a poor prognostic sign [1, 2, 4, 7, 18]. Of the treatment parameters, increasing target volume [4, 19] and decreasing overall treatment time [2, 6, 20, 21] were found predictive for improved local control rates. A dose–response relationship is still disputed; it could be demonstrated in some studies [6, 20, 22], but not in others [2, 4, 7]. In fact it is the mechanism of repopulation during radiotherapy, with respect to overall treatment time and dose as important factors, presently debated [23, 24]. Regression of tumour during radiotherapy and total clearance following treatment are reliable predictors of tumour control [8, 25–28]. Finally, age above 60 [1] and male sex [29–31] correlate with low survival rates, but not with local control.

Radiotherapy to the oropharyngeal region can lead to xerostomia and dysphagia, and in a small number of patients severe nutritional problems will follow [5]. Late damage to normal tissues leading to fibrosis, soft tissue and mandibular bone necrosis, or cervical spine myelitis are reported to occur in 10–35% of the patients [5, 32, 33]. Generally, more complications are expected after high-dose treatment [22].

In our previous papers we have analysed the prognostic factors for the tumour control in tonsillar carcinoma [29] and carcinoma of the base of the tongue [34]. Of the tested parameters (T- and N-category and the stage of the disease according to UICC 1982 and UICC 1987 systems and extension of the tonsillar tumours to adjacent sites), the T-category appeared to be the single most important prognostic factor in both subsites. In each subsite the majority of patients were

Table 1. Carcinoma of the tonsillar region. Distribution of patients by the T- and the N-categories and the stage of the disease according to UICC (1982) staging system [49] in absolute figures and (percentages)

	T1	T2	T3	T4	Total
N0	5 (8)	11 (16)	7 (10)	6 (9)	29 (43)
N1	2 (3)	8 (12)	10 (15)	11 (16)	31 (46)
N2	—	—	1(1)	—	1(1)
N3	1(1)	1(1)	3 (5)	2 (3)	7 (10)
Total	8 (12)	20 (29)	21 (31)	19 (28)	68 (100)

Stage I, 5 (8%) patients; stage II, 11 (16%) patients, stage III, 27 (40%) patients, stage IV, 25 (37%) patients.

treated with radiotherapy, and significantly better tumour control and survival were reported in tonsillar carcinoma. In this paper we continue the study focussing upon those patients who were treated with radiotherapy only. The efficacy of treatment is evaluated in terms of local control and survival. Late damage to normal tissues, and significance of tumour and treatment parameters for prediction of late damage were studied. Dose-effect and time factor are tested in relation to local control in our patients. The impact of tumour subsite on effects on treatment was studied in particular; therefore the results are presented separately for tonsillar carcinoma and base of the tongue carcinoma.

PATIENTS AND METHODS

Patients

133 consecutively treated patients were registered. 14 patients were excluded from the analysis of treatment. These include 2 patients who did not complete radiotherapy, 2 patients treated with an implant only and 10 patients treated only with fast neutrons. For the remaining 119 patients (68 with tonsillar carcinoma and 51 with base of the tongue carcinoma) all data was available, except for the response at the end of radiotherapy in 7 patients and the response 6 weeks after the end of radiotherapy in 6 patients. All patients had histologically proven squamous cell carcinoma.

In patients with tonsillar carcinoma, 55 (81%) were male and 13 (19%) female; median age was 66 (range: 42–89) years. In the tongue base carcinoma group, 39 (76%) patients were male and 12 (24%) female; median age was 67 (range: 43–81) years. In both groups, about 80% of patients had tumours in stage III or IV on admission (Tables 1 and 2).

Table 2. Carcinoma of the base of the tongue. Distribution of patients by the T- and the N-categories and the stage of the disease according to UICC (1982) staging system [49] in absolute figures and (percentages)

	T1	T2	T3	T4	Total
N0	2 (4)	7 (14)	7 (14)	5 (10)	21 (41)
N1	3 (6)	6 (12)	3 (6)	5 (10)	17 (33)
N2	—	—	3(6)	2(4)	5(10)
N3	—	2 (4)	2 (4)	4 (8)	8 (16)
Total	5 (10)	15 (29)	15 (29)	16 (31)	51 (100)

Stage I, 2 (4%) patients; stage II, 7 (14%) patients, stage III, 19 (37%) patients, stage IV, 23 (45%) patients.

Treatment

Megavoltage radiotherapy was delivered through opposing lateral fields either with cobalt 60 equipment (1966–1973) or an 8 MV linear accelerator (1972–1984). From 1966 to 1975, 250 kV radiotherapy and electron beams were incidentally applied in the treatment of tonsillar carcinoma (3 patients and 1 patient, respectively). The total dose was equivalent to 60–70 Gy in 6–7 weeks. Fraction doses ranged from 1.8 to 3.1 Gy, but were generally higher in the early period when cobalt 60 was used (mean 2.4 Gy) than in the later period (mean 2 Gy). To take into account the biological effect of the dose per patient, normalised total doses (NTD) [35] were calculated in all patients both for tumour control and for late damage, according to the equation

$$NTD = nd\{2 + d/(\alpha/\beta)\}/\{1 + 2/(\alpha/\beta)\} \qquad (1)$$

where n is equal to the number of fractions, d is the dose per fraction in Gy and α/β is 15 Gy (35) for local tumour control (NTD_{15}) and 2 Gy for late damage to normal tissue (NTD_2) [36, 37].

In the 68 patients with tonsillar carcinoma, the mean NTD_{15} was 58 Gy. In 26 patients (38%) NTD_{15} was <60 Gy, in 18 (27%) equal to 60–65 Gy and in 24 (35%) >65 Gy. In the 51 patients with base of the tongue carcinoma, mean NTD_{15} was 61 Gy. The NDT_{15} was less than 60 Gy in 20 patients (39%), equal to 60–65 Gy in 16 (31%) and >65 Gy in 15 (30%). No significant differences were observed with respect to NTD_{15} between T-stages.

Overall treatment time in tonsillar carcinoma was 25–73 days (mean 37 days), 28 patients (41%) having had radiotherapy for 34 days or shorter, 23 (34%) patients for 35–48 days, and 17 (25%) patients for 49 days or longer. In base of the tongue carcinoma patients, the mean overall treatment time was 38 days (range: 22–53). 22 patients (43%) had radiotherapy over 34 days or shorter, 19 patients (37%) for 35–48 days and 10 patients (20%) for more than 48 days.

In tonsillar carcinoma the largest radiation field size was smaller than 70 cm² in 18 patients (26%), 70–120 cm² in 23 (34%), while in the remaining 27 patients (40%) the largest field was larger than 120 cm². In base of the tongue cancer the largest field was smaller than 70 cm² in 18 patients (35%), 70–120 cm² in 20 (39%) and larger in 13 patients (25%). In case shrinking fields or boosts were used, the calculations were based on the largest radiation field.

Responses were estimated by routine ENT examinations and palpation. In case of recurrent, residual and/or metastatic disease, the possibilities for secondary treatment were evaluated individually, based on the patient's general condition and tumour extent. Treatment consisted of surgery, chemotherapy or radiotherapy, depending on the individual situation.

Definitions and statistical analysis

Minimal follow-up was 3 years or until death. Patients who died without tumour were considered lost to follow-up. Time to local recurrence is defined as the time from start of treatment until the first evidence of failure in the primary site. Recurrence is a renewed manifestation of the tumour in the area that was previously irradiated. Tumour manifestation outside the radiation treatment field found during follow-up is considered as a metastasis. Lesions, not disappearing after the initial treatment, irrespective of time, are considered as residual tumour.

Table 3. Variables, related categories and numbers of patients per category, that were used in the analysis of the local control

Variable	Category	N
Sex	Men	94
	Women	25
Age	≤59	41
	60–74	50
	≥75	28
Subsite	Tonsil	68
	Tongue base	51
T-stage	T1	13
	T2	35
	T3	36
	T4	35
Field size	<70 cm^2	36
	70–119.9 cm^2	43
	≥120 cm^2	40
NTD$_{15}$	≤60 Gy	46
	60.1–65 Gy	34
	>65 Gy	39
Overall treatment time	<35 days	50
	35–48 days	42
	>48 days	27
Response end RT*	NED	31
	Unclear	46
	Residual tumour	35
Response 6 wk.†	NED	95
	Unclear	12
	residual tumour	6

*Missing values in 7 patients; †missing values in 6 patients.

In testing the prognostic value for local control, the following variables were used: age, sex, tumour subsite, t-stage, size of the radiation treatment field, the NTD$_{15}$, overall treatment time, response at the end of treatment and response 6 weeks later (Table 3).

For possible prediction of late normal tissue damage, the following variables were tested: age, sex, tumour subsite, T-stage, radiotherapeutic equipment, the NTD$_2$ and radiation field size.

Surival curves were calculated using the product-limit method of Kaplan and Meier [38]. In determination of overall survival, all deaths were included, regardless of tumour status. Calculation of disease specific survival is based only on those patients who died with cancer. Cox's proportional hazard regression analysis [39] was used to estimate and test the independent contribution of multiple variables to prognosis in a forward stepwise manner. At each step we tested linearity of variables and interaction between all variables and the subsite of primary tumour. In cases where the association of variables had to be analysed, the χ^2 test for contingency tables was performed for nominal and ordinal variables and the Kruskall–Wallis test for ordinal and interval variables.

Logistic regression was used for the analysis of complications at 1 year. Patients not surviving for 1 year or longer were not included in this analysis, regardless of their status, with respect to complications. Both for inclusion and exclusion a *P*-value of 5% was used.

RESULTS

Response to radiotherapy

Response of the primary tumour at the end of radiotherapy was recorded in 62 out of 68 patients with tonsillar carcinoma as follows: no evidence of disease (NED) in 37%, unclear

whether there was residual tumour or scar tissue in 40%, residual tumour in 23% of the patients. For base of the tongue carcinoma response at the end of treatment was known in 50 of 51 patients: NED in 16%, unclear in 42%, residual tumour in 42%.

Response to treatment 6 weeks after completion of therapy was recorded in 64 of 68 patients suffering from tonsillar carcinoma: NED in 91%, unclear in 8% and residual tumour in 1% of the patients. For base of the tongue group, the response at this time was known in 49 of 51 patients: NED in 76%, unclear in 14% and residual tumour in 10%.

All patients with no evidence of disease at the end of the radiotherapy were controlled in the primary site at 6 weeks follow-up as well. From the patients with residual tumour or unclear tumour status at the end of treatment, 87% were tumour-free at the primary site at 6 weeks for tonsillar carcinoma and 70% for base of the tongue carcinoma. At both evaluation points the reponse of the primary tumour to treatment was significantly better in tonsillar carcinoma than in base of tongue cancer (*P*=0.005 and 0.02, respectively). In none of the patients with residual tumour at 6 weeks after completion of radiotherapy local control was reached later during the follow-up.

Treatment results and follow-up

Tonsillar region. For tonsillar carcinoma, NED was observed in 65 patients in a period following radiotherapy, whereas 3 patients had residual disease (local, regional or both, see Table 4) that did not resolve later in the follow-up. Of the 65 patients with NED, 14 developed a local and/or regional recurrence and another 8 patients distant metastases. 43 patients never had a relapse, but 11 patients died of other causes in the first 3 years of follow-up resulting in 32 patients being at risk from recurrence after 3 years.

In total, 25 patients had a relapse at some site; and secondary treatment was given to 15 (60%) of these patients. Median survival after diagnosis of failure was 10 months in patients who recieved secondary treatment, versus 2.5 months in the non-treated group. Tumour control was achieved in 3 patients, but 2 of them died from intercurrent disease within 6 months.

Base of the tongue. In this group of 51 patients, NED in a period following radiotherapy was reached in 41 patients, while 10 patients had permanent residual cancer at some site (Table 4). 14 of these 41 patients had local and/or regional

Table 4. Crude treatment results (i.e. figures are not corrected for the length of the follow-up). The first sites of failure are reported

	Tonsil	Base of tongue	Total
Tumour control	43	20	63
Local failure	4	13 (1)*	16
Regional failure	6 (1)*	7 (3)†	12
Local + regional failure	7	4	13
Distant metastasis	8	7	15
Total	68	51	119

*Of these patients, 1 had recurrence at the margin of the field.
†Of these patients, 2 had recurrence at the margin of the field and 1 had metastasis low in the neck.
Residual tumours are included: 1 locoregional and 2 regional in tonsillar carcinoma and 6 local, 2 locoregional and 2 regional residual tumours in base of the tongue carcinoma.

failure during the follow-up. 7 patients had distant metastases with controlled locoregional site. Of the 20 patients who remained tumour-free after radiotherapy, 9 patients died of other causes during the first 3 years of follow-up and 11 patients were still at risk.

Of the 31 patients who failed radiotherapy, 11 (35%) were submitted to secondary treatment. In this group mean survival after diagnosis of failure was 9.5 months, versus 4 months in patients who were not treated any further. The tumour was controlled in 2 patients, who survived 22 months and more than 10 years after relapse, respectively.

Local control. In the total group of 119 patients, a 3-year local control rate of 73% was achieved. Failure to control tumour at the primary site occurred in 29 patients, all within 26 months after onset of treatment.

Pretreatment parameters in relation to local control. For 68 patients with tonsillar carcinoma, local control at 3 years was 82% while for 51 patients with base of the tongue carcinoma, there was only a 61% local control rate (Fig. 1). The significant difference between these results ($P=0.02$) exists mainly because 8 patients had local or locoregional residual tumour in the tongue base, versus only 1 patient with local residual disease in the tonsillar region. After exclusion of these patients, the 3-year local control rates are no longer significantly different (82% vs. 72%).

Despite small numbers of patients in T1 group in both subsites (8 in tonsillar- and 5 in base of the tongue carcinoma), a significant difference in local control by T-stage was found in each subsite ($P=0.02$), (Fig. 2).

No relation was found between local control and patients' sex or age.

Treatment parameters in relation to local control. A statistically significant non-linear correlation ($P=0.006$) between NTD_{15} and local control was found, with the middle range (60–65 Gy) showing the worst results. Three-year local control rate by NTD_{15} for tonsillar tumours was as follows: NTD_{15} <60 Gy was 82%, NTD_{15} equal to 60–65 Gy was 69%, NTD_{15} higher than 65 Gy was 93%. Corresponding values for the base of the tongue tumours were 71%, 34% and 78%, respectively.

In an attempt to explain this significant non-linear relation, the association of NTD_{15} with the following variables was

Fig. 1. **Local control in tonsillar region and in base of the tongue.**

analysed: sex, age, subsite, T-stage, field size, overall treatment time and radiotherapeutic device. An association with the field size ($P<0.0001$), overall treatment time ($P<0.0001$) and radiotherapeutic device ($P<0.0001$) was found. However, these cannot explain the non-linear relation between NTD_{15} and local control as the main difference is observed between the high dose group ($NTD_{15}<65$ Gy) and the other two, and not between the low and the middle dose groups.

Post-treatment parameters in relation to local control. After the relation of pretreatment and treatment factors to local control was assessed, relation of response to treatment and local control was studied. Strong correlation between lasting local control and response to treatment at the end of radiotherapy ($P=0.0004$) and 6 weeks later ($P<0.0001$) was found in both subsites.

The prognostic value of all these variables was tested using Cox's proportional hazard regression model. In the multivariate analysis of pretreatment and treatment parameters, all variables were controlled for the tumour subsite, T-stage, and NTD_{15}. Tumour subsite and T-stage have prognostic value for local recurrence, i.e. tonsillar region and small tumours are predictive for higher local control rates ($P=0.0005$ and 0.03, respectively). The non-linear relation between NTD_{15} and local recurrence remained significant ($P=0.004$).

Responses to radiotherapy at the end of treatment and 6 weeks later, when controlled for the initial tumour stage, subsite and NTD_{15}, have additional prognostic value for local recurrence ($P=0.03$ and <0.0001, respectively). When controlled for the response at 6 weeks, the only significant parameter in the multivariate analysis remains the NTD_{15} (Table 5).

Late damage to normal tissue

Of 83 patients (50 with tonsillar carcinoma and 33 with base of the tongue carcinoma) who were still alive after 1 year of follow-up, 9 patients (11%) had severe late damage secondary to the radiotherapy. In the tonsillar carcinoma group, 6 patients (12%) developed the following sequelae: persistent dysphagia with (1) or without (2) pain, osteomyelitis (2) and myelopathy (1). In base of the tongue carcinoma group, late damage was observed in 3 patients (9%): persistent dysphagia in 1 patient and osteomyelitis of the mandibula in a further 2 patients.

All complications were entered in the logistic regression model. Univariately, only a site-dependent relation between T-stage and complications was observed ($P=0.04$) in patients with extensive tumours in base of the tongue having a higher complication rate. Controlling for this factor, no other variable attained statistical significance.

Survival

Overall survival and disease-specific survival were significantly higher in tonsillar carcinoma than in base of the tongue carcinoma. Three-year rates for the two subsites were 57% and 38%, respectively ($P=0.006$) in case of overall survival (Fig. 3). Disease specific survival at 3 years was 70% in the tonsillar region and 47% in the base of the tongue ($P=0.005$) (Fig. 4).

DISCUSSION

The 3-year local control rate achieved in patients with tonsillar carcinoma was 82% in this series. Compared with other
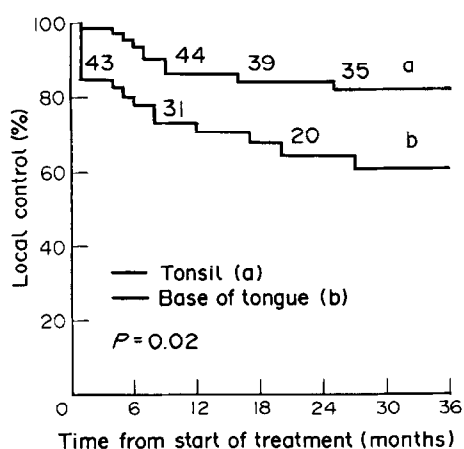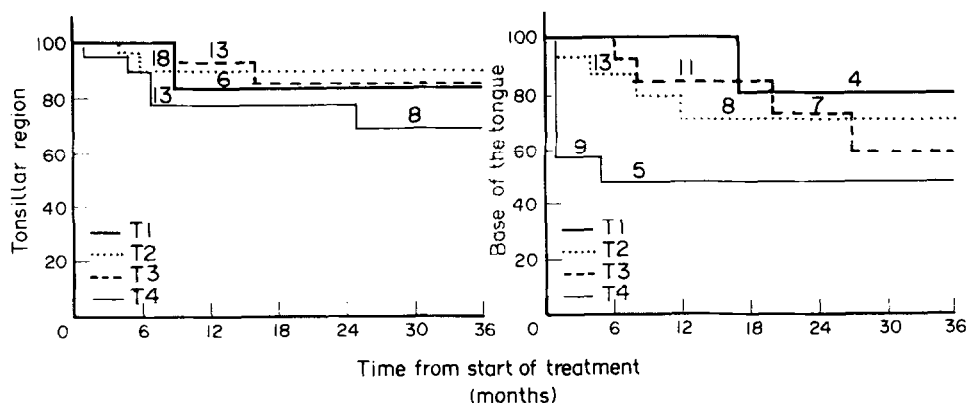
Fig. 2. Local control by T-stage in tonsillar and in base of tongue carcinoma (*P* = 0.045).

Table 5. *P-values of stepwise proportional hazard-regression analysis of prognostic factors for local control*

		Multivariately*	
	Univariately	Step 1†	Step 2‡
Sex	NS§	NS	NS
Age	NS	NS	NS
Subsite	0.02	0.0005	NS
T-stage	0.02	0.03	NS
NTD$_{15}$	0.006‖	0.004‖	0.0002‖
Field size	NS	NS	NS
Overall treatment time	NS	NS	NS
Response end RT	0.0004		NS
Response after 6 weeks	<0.0001		<0.0001

*In multivariate analysis all variables were controlled for subsite, T-stage and NTD$_{15}$.
†Multivariate analysis of pretreatment and treatment variables.
‡Multivariate analysis controlled for response to radiotherapy at 6 weeks.
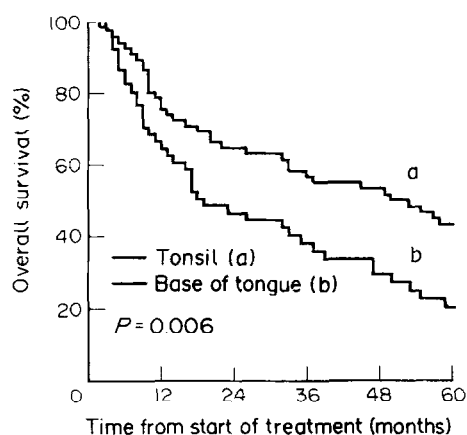§Not significant. ‖Including non-linearity.

Fig. 3. Overall survival of 119 patients split up by tumour site.

Fig. 4. Disease-specific survival of 119 patients split up by tumour site.

published results [1–7, 15], and taking into account that the majority of the patients had advanced disease, this is a favourable result. The 3-year local control for base of the tongue carcinoma group was 61%. These results, even though higher than in many other series [8–14], are less satisfactory. The significant difference between local tumour control rates in the two subsites could not be explained by different treatment
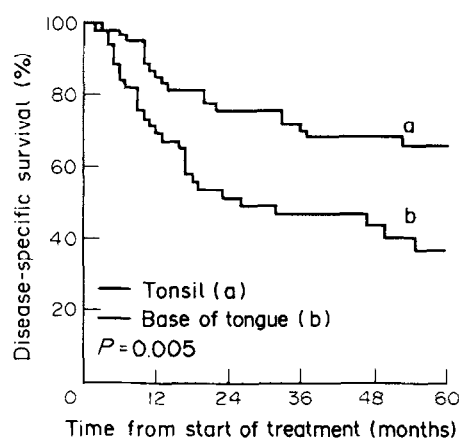
parameters. Thus, basically the same treatment, i.e. external radiotherapy with doses equivalent to 60–70 Gy in 6–7 weeks, controls effectively the primary site in tonsillar tumours, but not in base of the tongue tumours. Possibly, accelerated regimes [40–42] or combination with interstitial radiotherapy [43–45] could yield better results in this subsite. Hoffstetter *et al.* [45] observed improvement in local control of T1 and T2 tumours after combination of external radiotherapy and interstitial brachytherapy. Puthawala *et al.* [44] reported on only 10–20% local failure rates in advanced tumours of the base of the tongue when interstitial brachytherapy was added to external radiotheraphy. Consistent results, i.e. 2 years local failure rate of 23%, were also reported by Levendag and van Putten [43].

The significantly better results in tonsillar carcinoma in our series were observed at all evaluation points: at the end of the treatment, 6 weeks thereafter and during follow-up. The difference became evident very early, subsequent to a greater proportion of residual tumours in base of the tongue. The recurrence rate during follow-up were, on the contrary, similar in both subsites.

NED at the end of radiotherapy was highly predictive for local control in our patients. At that moment however, it was not possible to distinguish residual tumour from scar tissue in about 40% of patients. Six weeks later the vast majority of patients developed scar tissue, and could be clearly differentiated from patients with local residual disease. Local control

at 6 weeks appears to be essential for the prognosis; the decision to give secondary treatment should therefore be made at that point. At both subsites however, secondary treatment ultimately benefited only a very small number of our patients.

The high predictive value of status at 6 weeks after completion of treatment is consistent with some other reports [25–27], but is not surprising because later observations are expected to correlate better with local control.

Correlation of T-category with local control was found in this study, as well as in many other series [2, 5–8, 10, 12, 14–17]. We have tested other prognostic factors reported in the literature, i.e. total dose [6, 22], size of radiation fields [4, 19] and overall treatment time [2, 6, 20]; but a significant correlation with local control could not be confirmed in our series. A non-linear relation between normalised total dose and local control that was found in our patients, could not be explained with available tumour, patient or treatment parameters. The conflicting reports on dose–response relationships in oropharyngeal cancer were also discussed in a recent paper of Bentzen *et al.* [20]. Size of radiation fields need not correlate with local control under the assumption that all fields were designed, so to cover the tumour sufficiently. The low incidence of recurrences at the margin of the field in our patients suggests the fields were large enough as to cover the complete tumour.

Based on results presented in this study and in our earlier papers [29, 34], we conclude that tumour subsite is a separate early prognostic factor when the two most frequently involved subsites of oropharyngeal cancer are compared. The literature does not confirm this conclusion, although there is certainly enough evidence of poorer results for base for the tongue tumours [8–14], when compared to tumours of the tonsillar region [1–7, 15]. Studies of tumour–host relationship, potential doubling time [21, 46–48] and of histigical and histochemical aspects of these tumours might contribute to more accurate determination of prognosis for the individual patient with a tonsillar or base of tongue carcinoma.

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