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HEAD AND NECK

Outcome of radiotherapy in T1 glottic carcinoma: a population-based study

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Abstract We evaluated the radiation outcome and prognostic factors in a population-based study of early (T1N0M0) glottic carcinoma. Survival parameters and prognostic factors were evaluated by uni- and multivariate analysis in 316 consecutive irradiated patients with T1 glottic carcinoma in the Comprehensive Cancer Center West region of the western Netherlands. Median follow-up was 70 months (range 1–190 months). Five and ten-year local control was 86 and 84%. Disease specific survival was 97% at 5 and 10 years. In multivariate analysis, pre-existent laryngeal hypertrophic laryngitis was the only predictive factor for local control (relative risk = 3.0, $P = 0.02$). Comorbidity was prognostic for overall survival. No factor was predictive for disease specific survival. Pre-existent laryngeal hypertrophic laryngitis is a new risk factor associated with reduced local control in T1 glottic carcinoma treated with radiotherapy.

Keywords Population-based · Glottic · Carcinoma · T1 · Radiotherapy · Local control · Prognostic factors

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Introduction

Laryngeal carcinoma is the most frequently diagnosed malignant head and neck tumor in Western Europe and the United States. Based on the records of the Netherlands Cancer Registry, 64% of these are glottic carcinomas of which more than half (56%) are diagnosed as "early glottic carcinomas" (T1) [1]. Radiotherapy provides successful treatment results with local control rates between 80 and 95% and disease-specific survival from 92 to 97% in large studies [2–5]. Rendering high-cure rates and what is generally accepted as good voice quality, irradiation as yet remains the cornerstone of treatment in many clinics with endoscopic laser surgery reserved only for small, selected mid-cord lesions [6]. However, despite high rates of local control, small number of tumors will recur. In many of these patients, laryngectomy will be unavoidable with severe impact on quality of life. To identify patient, tumor or treatment characteristics that are associated with failure of radiation therapy would therefore be of advantage, as these patients may need adjusted treatment or more thorough follow-up.

Many retrospective studies on prognostic factors have been undertaken and the literature is contradictory and often confusing. As of yet the evidence from randomized, prospective studies is minimal [7]. Table 1 shows treatment outcome (local control) and findings for prognostic factors in large

studies (more 100 patients) on T1 glottic carcinoma, treated with radiotherapy since 1990 [3, 5–21]. It is clear that in spite of reasonable steady rates of local control there are considerable discrepancies between findings on prognostic factors. What is also interesting is that most studies fail to show a significant impact on local control of the time-dose related factors, total dose, fraction dose and overall treatment time, which are generally considered important determinants of treatment outcome. The reasons for the contradictory results are several. Studies differ considerably in size and most studies are institution based, which may introduce referral bias. The choice of prognostic factors is diverse, cut-off points for subgroups within a specific prognostic factor are wide ranging and some studies do not perform stratification or multivariate analysis. Also, recurrences are relatively uncommon, which means there are few events within the subgroups of a specific prognostic factor. Several studies include T2 lesions in their analysis. These studies were purposely excluded from Table 1 as there is much evidence to suggest that T2 lesions have significantly worse treatment outcome than T1 lesions [2, 12, 22, 23]. We therefore believe that they should be treated as a separate entity. The conclusion must be that, after many years and many studies we are still not sure of the optimum time-dose related treatment schedule for T1 glottic carcinoma and of further factors that possibly predict radioresistance in these tumors.

The purpose of the present study was to evaluate treatment outcome and prognostic factors in T1 glottic carcinoma treated with radiotherapy within the Comprehensive Cancer Center West (CCCW) region of the Netherlands. By focusing on T1 tumors and using a population-based study design, we aimed to increase the validity of our findings on tumor and treatment related prognostic factors. The choice of prognostic factors was based on results of large studies on irradiated early glottic carcinoma [3, 5–21].

Patients and methods

The study was conducted in the region of the Comprehensive Cancer Center West (CCCW), with 1.6 million inhabitants. This region harbors one of nine cancer registries in the Netherlands where all cancers are registered. It covers a heterogeneous district in the west of the Netherlands with both urban and rural areas. Four irradiation centers serve this district. All patients diagnosed with primary early glottic carcinoma, diagnosed in this region between 1982 and 1993, were included in this study. The cut-off date was chosen based on the fact that from 1994 onwards laser surgery was being used in selected cases, first as an experimental therapy and later as a routine treatment procedure. Five patients were eventually irradiated outside the region, but were fully included in the study. Treatment consisted of radiotherapy in 282 patients, radiotherapy and microsurgery in 34 patients and microsurgery alone in 1 patient. Dual treatment involved surgical excision prior to radiotherapy. Two patients were not treated at all due to advanced lung disease at the time of diagnosis. Thus, a total of 316 patients were treated with radiotherapy and qualified for analysis.

Data were collected by retrospective review of patient charts as well as of hospital and regional cancer registries. The regional cancer registry was actively updated by trained health workers for this project. All patients had been staged by direct laryngoscopy and biopsy. Characteristics of patient (age, sex, comorbidity, pre-existent laryngeal hypertrophic laryngitis, smoking habit, smoking during irradiation and symptom duration), tumor (substage, anterior commissure involvement, differentiation and size) and radiotherapy (beam energy, total dose, dose per fraction, overall treatment time, treatment regimen, field size, treatment delay, additional mode and treatment era) were recorded.

Patient characteristics

Patient characteristics are summarized in Table 2. Age ranged from 37 to 91 (median 66 years) and was divided into four categories. Pre-existent laryngeal hypertrophic laryngitis was defined as non-malignant lesions (chronic laryngitis, leukoplakia or hyperkeratosis) recorded clinically or by pathological examination at some time prior to diagnosis. Evidence for pre-existent laryngeal hypertrophic laryngitis was found in 24 patients. To further characterize this subgroup, pathology reports were traced in the hospital and national database (Table 3). Comorbid disease was scored as present or absent disregarding the number and severity of the individual diseases. In the category smoking habits, ex-smokers were defined as patients who had stopped at least 10 years prior to diagnosis. Symptom duration was defined as time between first symptoms and diagnosis in months and was divided into three groups.

Tumor characteristics

Tumor characteristics are summarized in Table 4. Tumor stage was T1a or T1b. Seven tumors, localized only in the anterior commissure were excluded from analysis of substage, as they were neither T1a nor T1b. The size of the tumor was estimated by summating the number of affected thirds of the vocal cords and was divided into three groups.

Treatment characteristics

The treatment characteristics are summarized in Table 5. Radiotherapy was delivered with ^{60}Co or linear accelerator. Treatment with a linear accelerator was 4-MV ($n = 4$), 5-MV ($n = 85$), 6 MV ($n = 59$) or 8 MV ($n = 4$). There were four

Table 1 Local control and prognostic factors in multivariate analysis (large cohort studies of T1 glottic carcinoma treated with radiotherapy)

Study and year	Number of T1 tumors	Local control (%)	Factor significance in multivariate analysis									
			Tumor substage	Tumor size	Anterior commissure involvement	Beam energy	Total dose	Fraction size	Overall treatment time	Fractionation schedule	Field size	Waiting time
T1 multivariate (retrospective cohort: institution based)												
Terhaard 1991	194	84		Yes	No						No	
Small 1992	103	89		No			No	No			Yes	
Chatani 1993	244	88		Yes								
Le 1997	315	85			No		No	No	No			
Yu 1997	126	78	No		No	No		Yes			No	
Reddy 1998	114	82	No	Yes	No		No	No	No			
Voet 1998	352	89		No	No				Yes	Yes	No	
Canaday 1999	139	84			No		No	No	No		No	
Skladowski 1999	235	84					Yes		Yes			
Dinshaw 2000	460	82		No		No				No	Yes	
Brouha 2000	362	83										No
Jing Jin 2002	238	82	No	Yes	Yes	No	No		No		No	
Cellai 2005	831	86	No	Yes	Yes	Yes	No	No	No		No	
T1 multivariate (retrospective cohort: population based)												
Groome 2006	491	82				No		No	No		No	
Sjogren (this study)	316	86	No	No	No	No	No	No	No	No	No	No
T1 mulivariate (prospective randomized)												
Chatani 1996	237	88		No							No	
Yamazaki 2006	180	86	No	No	No				Yes	Yes	No	

Blank spaces indicate that factor was not studied

Table 2 Histology in patients with pre-existent laryngeal pathology

Histological diagnosis	*n*	Time before T1
No prior histological examination	13	–
Prior histological examination[a] (hyperkeratosis, hyperplasia or light dysplasia corresponding to clinical leukoplakia and/ or chronic laryngitis)	11	Mean 16 months Median 13 months Range 6–36 months

[a] As the pathological diagnosis is often a mix of histological entities incidence per entity is not detailed separately

Table 3 Patient characteristics and 5-year local control for T1 tumors

	n = 316 (%)	Local control (%)	*P* value (log-rank)
Sex			
Male	284 (90)	86	0.52
Female	32 (10)	90	
Age			
<50 years	32 (10)	84	0.77
50–59 years	65 (21)	88	
60–69 years	104 (33)	89	
≥70 years	115 (36)	83	
Pre-existent hypertrophic laryngitis			
Yes	24 (8)	77	0.07
No	292 (92)	87	
Comorbidity			
Yes	116 (37)	87	0.23
No	200 (63)	84	
Smoking[a]			
Non-smoker	70 (23)	89	0.27
Ex-smoker	36 (12)	94	
Smoker	198 (65)	84	
Smoking during RT[a]			
Yes	51 (24)	81	0.12
No	165 (76)	89	
Symptom duration[a]			
1–3 months	108 (37)	86	0.91
4–6 months	95 (32)	84	
7 or more months	91 (31)	86	

[a] Smoking: 12 missing values. Smoking during RT: 100 missing values. Symptom duration: 22 missing values. Irradiation center: five patients excluded due to treatment in other centers

different treatment centers (a–d). Dosage was prescribed at midplane, isodose level or according to ICRU 29. For the purpose of this study, all doses were re-calculated according to ICRU 29. Total dose ranged from 54 to 76 Gy (median 60 Gy) and was divided into two groups, 60 Gy or less and more than 60 Gy. Dose per fraction ranged from 2 to 2.8 Gy (median 2 Gy) and was divided into two groups,

Table 4 Tumor characteristics and 5-year control for T1 tumors

	n = 316 (%)	Local control (%)	*P* value (log-rank)
Stage[a]			
T1a	210 (68)	87	0.38
T1b	99 (32)	85	
Anterior commissure			
Yes	106 (34)	85	0.38
No	210 (66)	87	
Differentiation[a]			
Good	63 (27)	83	0.24
Moderate	154 (66)	88	
Poor	17 (7)	100	
Size[a]			
1/3	88 (28)	91	0.07
2/3	114 (37)	80	
3/3–6/3	110 (35)	89	

[a] Stage: 7 tumors localized solely in the anterior commissure are excluded. Differentiation: 82 missing values. Size: 4 missing values

2 Gy and more than 2 Gy. Because of the complex time-dose relationship we compared not only separate treatment variables but also whole treatment schedules. Due to variations in dosage prescription, however, there were too many treatment schedules for individual, comparative analysis. Therefore we divided schedules in two groups: group 1 consisting of the most frequent schedule of 30 × 2 Gy (including 1 patient with 27 × 2 Gy) and group 2 consisting of "additional treatment" either through a higher dose than 2 Gy per fraction or a higher number of fractions than 30. Treatment duration was divided in two groups: 42 days or shorter and longer than 42 days.

To exclude confounding influence of varying total doses and fraction doses on the effect of overall treatment time on local control, overall treatment time was also tested separately in the subgroup of patients that all received 60 Gy (30 × 2) total dose. The local control rates for a treatment duration of 42 days or shorter were compared to that of a duration of longer than 42 days by log-rank testing. Field size ranged from 25 to 100 cm^2 (median 36 cm^2) and was divided into two groups: smaller than 35 cm^2 and 35 cm^2 or larger. Treatment delay from time of diagnosis to time of radiotherapy ranged from 1 to 183 days (median of 21 days) and was divided into two groups: smaller or equal to 25 days and more than 25 days. Thirty-four patients received additional microsurgery prior to radiotherapy. Finally, the study period was divided into three eras of 4 years each.

End points and statistical analysis

Data were analyzed using SPSS10. Follow-up was calculated in months from the first day of radiotherapy to the

Table 5 Treatment characteristics and 5-year local control for T1 tumors

	$n = 316$ (%)	Local control (%)	P value (log-rank)
Unit[a]			
Cobalt	161 (51)	87	0.50
Linear accelerator	152 (49)	85	
Irradiation center[a]			
a	133 (43)	86	0.65
b	25 (8)	84	
c	49 (16)	87	
d	104 (33)	87	
Schedule[a]			
1 (30 × 2 Gy)	157 (50)	84	0.08
2 (other)	157 (50)	89	
Overall treatment time[a]			
<42 days	89 (28)	83	0.18
≥42 days	226 (72)	88	
Total dose[a]			
≤60 Gy	158 (50)	84	0.09
>60 Gy	156 (50)	89	
Fraction dose[a]			
=2 Gy	209 (67)	86	0.38
>2 Gy	105 (33)	88	
Field area[a]			
≤35 cm	116 (38)	86	0.80
>35 cm	190 (62)	87	
Treatment delay[a]			
≤25 days	164 (52)	83	0.10
>25 days	151 (48)	89	
Treatment mode			
RT only	282 (89)	86	0.34
RT and surgery	34 (11)	90	
Treatment era			
1982–1985	102 (32)	85	0.18
1986–1989	112 (36)	82	
1990–1993	102 (32)	92	

[a] Unit and norm: three missing values. Overall treatment time and treatment delay: one missing value. Schedule, total dose and fraction dose: two missing values. Field area: ten missing values

date of the last follow-up or time of death. The recurrence free interval for local control ran from the first day of radiotherapy to the date of the first recurrence, time of death or withdrawal from the study. Follow-up data of patients lost to follow-up were included in analysis up to the point of loss. Local recurrence was defined as all recurrences involving the initial tumor site. Treatment outcome was evaluated by 5- and 10-year overall survival, disease specific survival and local control, using the Kaplan–Meier method. Univariate analysis was carried out by means of log-rank testing. All significant factors along with those of borderline significance (defined as $P \leq 0.20$) were then entered into multivariate analysis using the Cox proportional hazard model. The variable smoking during radiotherapy, although qualifying for entry, was left out of multivariate analysis as the large amount of missing values in this category would considerably weaken the analysis.

Results

In 316 patients included the study, there was a male to female ratio of 8:1 (284 males and 32 females). Age ranged from 37 to 91 with a median of 66 years. Median follow up was 70 months (range 1–190 months). The median follow-up for patients still alive was 80 months with 80% of these patients having at least 5 years of follow-up. In total, there were 46 cases of recurrent disease of which 38 were local, 5 local with regional involvement, 1 regional and 2 distant. In ten cases, the local recurrence consisted of residual disease adjacent to treatment.

Local control

Five- and 10-year local control rates were 86 and 84%. The results of the univariate analysis of the influence of patient, tumor and treatment characteristics on local control are shown in Tables 2, 4 and 5. No single factor showed true significance. However, pre-existent laryngeal hypertrophic laryngitis ($P = 0.07$), tumor size ($P = 0.07$), total doses ($P = 0.09$), treatment duration ($P = 0.18$), treatment delay ($P = 0.10$), treatment era ($P = 0.18$) and regimen ($P = 0.08$) were of borderline significance, as defined earlier, and were therefore entered into multivariate analysis. Smoking during radiotherapy was also of borderline significance ($P = 0.12$) but was left out of analysis as explained earlier. To exclude confounding influence of varying total doses and fraction doses on the effect of overall treatment time on local control, overall treatment time was also tested separately (log-rank) in the subgroup of patients that all received 60 Gy (30 × 2) total dose. In this test, overall treatment time did not affect local control ($P = 0.95$) in this group. In multivariate analysis, only pre-existent laryngeal hypertrophic laryngitis was found to be of significant influence on recurrent disease. Patients with pre-existent laryngeal hypertrophic laryngitis had a higher rate of recurrence ($P = 0.02$) with a relative risk of 3.0 (95% CI 1.2–7.2) (Table 6).

Disease-specific survival

Twelve patients died as a result of their glottic tumor. Ten of these patients had undergone total laryngectomy, one

Table 6 Multivariate analysis (Cox regression)

	P value	RR	95% CI interval
Pre-existent hypertrophic laryngitis	0.02	3.0	1.2–7.2
Tumor size	0.07		
Total dose	0.90		
Treatment era	0.64		
Treatment delay	0.20		
Overall treatment time	0.48		

$N = 313$, three cases dropped due to missing values

had undergone a chordectomy and one had irradiation for mediastinal metastasis. In nine cases, death was caused by general deterioration due to a second recurrence, one patient suffered a fatal bleeding from the tumor and two patients died of post-operative complications (one myocardial infarction and one cerebral vascular accident). The ultimate 5- and 10-year disease-free survival was 97%. In univariate analysis, age was the only variable of significant influence on disease free survival ($P = 0.03$). Pre-existent laryngeal hypertrophic laryngitis was of borderline significance ($P = 0.20$). Ultimately, in multivariate analysis, neither was found to be of prognostic value (data not shown).

Overall survival

Five- and 10-year overall survival for all 316 patients was 80 and 59%, respectively. Univariate analysis showed only co-morbidity to be predictive of overall survival ($P < 0.01$) with borderline significance for smoking during RT ($P = 0.18$), radiation unit ($P = 0.18$), field ($P = 0.09$) and additional microsurgery ($P = 0.15$). In multivariate analysis, only co-morbidity was prognostic for overall survival with a relative risk of 1.8 (95% CI 1.25–2.69) (data not shown).

Salvage treatment

Salvage treatment was given in 43 patients. Thirty-eight patients underwent macro-laryngeal surgery, of whom 35 underwent total laryngectomy, 1 had a hemi-laryngectomy and 2 had chordectomies. Nine patients with a total laryngectomy also underwent a neck dissection, two of them had positive lymph nodes. Five patients underwent micro-laryngeal surgery of whom four were laser excisions and one was an excisional biopsy.

Complications of radiotherapy

Three cases of laryngeal edema and two cases of hypothyroid necessitating treatment were recorded.

Discussion

This study reports on treatment results and prognostic factors for local control in a large, population-based series of consecutive patients treated for T1 glottic carcinoma with radiotherapy. The average 5-year local control rate of radiotherapy for T1 glottic cancer in 16 large studies is 84% (range 78–89%), with an average larynx preservation of 93% [32]. We found a 5-year local control rate of 86% and a disease-specific survival of 97%, which is in accordance with the literature and supports the consensus that good, consistent treatment results are achieved with radiotherapy in T1 glottic carcinoma.

Pre-existent laryngeal hypertrophic laryngitis

Pre-existent laryngeal hypertrophic laryngitis was the only independent prognostic factor for local control in this study. It was defined as pre-existent non-malignant disease of the larynx, such as leukoplakia or chronic laryngitis recorded in the charts prior, and separate, to the diagnosis of invasive carcinoma. In 11 out of 24 patients with pre-existent laryngeal hypertrophic laryngitis there had been histological confirmation of the clinical diagnosis (Table 3). Pre-existent laryngeal hypertrophic laryngitis was associated with a relative risk of recurrence of 3.0 (95% confidence interval 1.2–7.2).

To our knowledge, no other study has yet incorporated this factor and how exactly pre-existent laryngeal hypertrophic laryngitis may influence local recurrence is not clear. One preliminary hypothesis is that the clinical diagnosis of chronic laryngitis, leukoplakia or hyperkeratosis is linked to inflammation. Inflammatory mediators, such as Cox-2-derived prostaglandins are potent inflammatory mediators that promote tumor growth and metastasis through stimulation of cell proliferation, invasion and angiogenesis, and have been identified in laryngeal carcinoma [24–26]. It is possible that these mediators may also promote radioresistance. Molecular inhibition of this signaling system with Cox-2 inhibitors, also in combination with an EGRF inhibitor, is currently being investigated for potential combination with radiotherapy in head and neck squamous cell carcinoma [27, 28]. Another possibility is that pre-existent laryngeal hypertrophic laryngitis may be indicative of the large fields of genetically damaged mucosa containing precursor lesions, which are often encountered in head and neck squamous cell carcinoma [29]. Such precursor lesions, known to be the origin of local recurrence in surgically treated head and neck cancer [30] may also be less sensitive to radiotherapy and therefore go on to develop recurrences which are actually second field tumors. Further investigations are warranted to confirm if, and by what mechanism, chronic, pre-existent laryngeal hypertrophic laryngitis

contributes to low but steady rate of local recurrence in T1 glottic carcinoma treated with radiotherapy.

Other factors in local control

No other factor was found to be predictive for local control in this study. As stated in the introduction, the literature on early glottic carcinoma is extensive and contradictory. For instance, several publications find a significant influence of tumor size/extension on local control, whereas others do not (Table 1). Also, although the majority of studies, including our own population-based study, find no evidence of influence of anterior commissure involvement on local control, three studies do find an influence, including a large Italian study of 831 patients [6]. It is interesting, however, that the only prospective randomized trial to date does not find a significant influence of anterior commissure involvement on local control [7]. Accurate data on the impact of these two factors (size/extension and anterior commissure involvement) on treatment outcome is particularly relevant today with regard to defining the indications for laser surgery. Other prognostic factors identified with a varying degree of consistency are continued smoking during and after radiotherapy [5], low hemoglobin levels [15], poorly differentiated tumors (ref), large fields (>36 cm^2) [12, 19] and the time-dose parameters that will be discussed separately below. As of yet, no systematic review or meta-analysis of these data has been published. Due to Lack of reliable comparative outcome analysis, identifying dependable prognostic factors remains a problem. Inconsistencies in the definition of prognostic factors (such as tumor size/extension) may be one explanation for the conflicting results, although the discrepancy between the relatively steady failure rates and the fluctuating findings on prognostic factors suggests that there may be important prognostic factors that are as of yet insufficiently identified.

However, a few cautious conclusions can be drawn from current data. Firstly, there is insufficient ground to distinguish between T1a versus T1b stage tumors as far as radiotherapy is concerned. The overwhelming majority of studies do not find this sub-staging a prognostic factor. Secondly, several studies have shown that the time-dose parameters have a significant impact on treatment outcome. At the same time, several authors have also warned for the complex relationship between total dose, fraction size and overall treatment time [18, 20]. The total dose given often varies within a study, thus compensating and possibly masking the effect of smaller fraction sizes or longer treatment times. Although most studies enter factors individually into multivariate analysis, comparing whole fractionation schedules is therefore preferable to analyzing individual factors. Van der Voet [20] showed that locoregional control increased when the total dose was given in higher fractions and thus shorter time. These results were confirmed in the prospective, randomized trial of Yamazaki [7]. Both authors argued that overall treatment time was the determinant factor in the time-dose relationship and both recommend the use of fraction sizes higher than that of the conventional 2 Gy (van der Voet 2.4 Gy and Yamazaki 2.25 Gy) to reduce overall treatment time. Dinshaw [12], however, found equal outcomes for his different fractionation schedules. In our study, 157 patients (50%) were treated with a standard regimen of 30 × 2 Gy [12]. The other half was treated with varying schedules. In all cases but one these schedules resulted in a higher total dose either through a higher dose per fraction or through a higher number of fractions. As there were too many different schedules for analysis in this second group, we chose to combine them and to compare them to the standard schedule of 30 × 2 Gy. The alternative schedules showed a borderline impact in univariate analysis (Table 3). This significance was, however, lost in multivariate analysis.

As stated, several authors have argued that of the individual time-dose parameters *overall treatment time* is the most important, finding decreased local control rates with prolong overall treatment time [2, 4, 7, 20]. Rudoltz [4] showed a decrease in local control with increasing treatment time (<43 days: 100%; 43–46 days: 91%, 47–50 days: 74%, 51–54 days: 65% and >55 days 50%). Gowda and Mendenhall [31] also showed that, shorter treatment time/larger fraction doses resulted in higher rates of local control and larynx preservation without a significant increase in acute morbidity. Skladowski [18] showed that prolonging treatment time due to interruption had a negative influence on local control with each day of extension producing a 1.3% loss in local control in his model and Groome [13] found the same for more than four treatment brakes. The above-mentioned studies recommend limiting treatment duration by avoiding interruption due to holidays, as well as using shorter fractionation schedules.

Interestingly, as seen from Table 1 most studies actually fail to show a significant impact on local control of the time-dose related factors. Most likely, this is because the complex relationship between the factors may mask their significance in simple univariate/multivariate analysis as discussed earlier. It has also been suggested that any differences may be obscured by the fact that schedule variation is limited and the doses used in most series are already on the plateau of the sigmoid tumor-curve [18]. Despite this discrepancy, the concept of increased local control with shorter treatment time has become commonly accepted, as has that of the negative influence of treatment brakes. In the year 2000, the positive impact of shorter treatment times on local control led to the introduction of an accelerated schedule of 25 × 2.4 Gy as an alternative to the standard schedule of 30 × 2 Gy in the Dutch national guideline for the treatment of laryngeal cancer (ref).

Overall and disease-specific survival

In multivariate analysis, we found no factor prognostic for disease-specific survival and only co-morbidity was prognostic for overall survival. The fact that age was not prognostic for overall survival, although the expected trend was seen for older age groups, was probably due to the relatively poor survival of the youngest age group (<50 years). This is also indicated by the fact that age, on the basis of the youngest age group, was a significant factor for decreased disease-specific survival in univariate analysis (data not shown).

As for the relevance of the current findings, the question arises if patients with pre-existent laryngeal hypertrophic laryngitis should be routinely treated with the alternative to radiotherapy: laser surgery. It has long been known that both radiotherapy and laser surgery are viable treatment options for T1 glottic carcinoma. For laser surgery, reported local control has typically been slightly higher than for radiotherapy (see above), although many studies consist only of selected and often superficial mid-cord T1a lesions treatable with a subepithelial or subligamental resection (type I/II ELS classification [32]. The average 5-year rate of local control was 92% (88–94%) with an average larynx preservation of 98% in ten such studies on *selected* T1a lesions [33]. Voice quality after laser resection of superficial, mid-cord T1a lesions is found to be good and often comparable to normal [30–33]. Although no randomized trial has yet been performed, from these retrospective data local control rates in selected T1a can be considered at least comparable to radiotherapy. Providing similar voice quality to radiotherapy [33–39] and the additional benefits of shorter treatment time, lower costs and the possibility of repeated procedures, laser surgery is already the preferred treatment for superficial T1a midcord lesions according to Dutch National Guidelines and at our institution.

In six studies on *unselected* T1 lesions (T1a and T1b) treated with laser surgery, the average 5-year local control was 88% (81–93%) and larynx preservation was 98% [32]. Seeing these results, the question, whether patients with T1 glottic carcinoma with pre-existent laryngeal hypertrophic laryngitis should be routinely treated with laser surgery, or whether all patients with T1 glottic carcinoma should be routinely treated with laser surgery rises. Theoretically, laser surgery as a primary treatment option should lead to higher rates of organ preservation as it allows for multiple resections with radiotherapy, kept as a reserve for surgical failures. This is illustrated by the difference in average larynx preservation between radiotherapy (93%) and laser surgery (98%) discussed earlier.

The main obstacle in extending the indications for laser surgery to larger T1 lesions is the uncertainty over functional outcome after more extensive resections. Although most surgeons would agree that larger and deeper lesions, and therefore more extensive resections, will have significantly worse functional outcome, there is still not much multidimensional voice data for how worse this will be. The conclusion of a recent Cochrane analysis was that "there is currently insufficient evidence to guide management decisions on the most effective treatment". Furthermore, investigations into prognostic factors for failure in laser surgery are currently limited to a few small studies [39–43]. For example, neither the influence of T-stage nor the anterior commissure invasion on local control is clear. The lack of reliable comparative outcome analysis for the two treatment modalities is likely to cause a lack of coherent practice guidelines for some time to come.

What then, in this general debate, can be said about patients with pre-existent laryngeal hypertrophic laryngitis? First of all, issues over functionality would seem equally relevant to patients with pre-existent laryngeal hypertrophic laryngitis. Whether these patients and their treating physicians would be willing to offer voice function for a higher chance of eventually preserving their larynx is unknown. Furthermore, one of the contraindications for laser surgery is the inability to delineate the circumference of the tumor. In patients with pre-existent laryngeal hypertrophic laryngitis, it may be particularly difficult to achieve a macroscopically radical resection making them less suitable for laser surgery. Therefore, theoretically these patients may end up having higher rates of residual disease than average for laser surgery. However, by choosing laser surgery in these patients the options of additional treatment via re-resection and/or radiotherapy have been kept open. Whether this advantage outweighs the higher chance of residual disease remains to be seen in further research.

In summary, the literature on prognostic factors in T1 glottic carcinoma is contradictory. Our population-based study has shown that patients with pre-existent laryngeal disease are at a greater risk of local recurrence. As this is the first study to identify this prognostic factor, further investigation of this and other variables in prospective, randomized trials are essential. Furthermore, laser surgery should be considered when treating patients with pre-existent laryngeal hypertrophic laryngitis and delineated disease.

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