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T3-T4 laryngeal cancer in The Netherlands Cancer Institute; 10-year results of the consistent application of an organ-preserving/-sacrificing protocol

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ABSTRACT: *Background.* Both organ-preserving concurrent (chemo)radiotherapy ((C)RT) and organ-sacrificing surgery (total laryngectomy) are used for treatment of advanced laryngeal cancer. The purpose of this study was to present the assessment of our treatment protocol for T3 (C)RT and T4 disease (total laryngectomy + postoperative RT).

Methods. We conducted a retrospective cohort study in 182 consecutive patients (1999–2008). The primary outcome was overall survival (OS) in relation to stage and treatment.

Results. One hundred two patients received RT (82.4% T3), 20 patients CRT (60.0% T3), and 60 patients total laryngectomy + RT (91.7% T4). Five-year OS: T3 52%, T4 48%, for RT 50%, for CRT 43%, and for total laryngectomy + RT 52%. Five-year laryngectomy-free interval was 72% after RT, and 83% after CRT.

Conclusion. There were no differences in survival according to T classification or treatment modality. Because the majority of T3 laryngeal cancers were treated with (C)RT and the majority of T4 with total laryngectomy + RT, this gives food for thought on whether the present protocol for T3 laryngeal cancer is optimal. © 2014 Wiley Periodicals, Inc. *Head Neck* **37:** 1495–1503, 2015

KEY WORDS: laryngeal cancer, advanced stage, organ-preserving treatment, total laryngectomy, overall survival

INTRODUCTION

Over the last 2 decades, several studies have shown an overall increase of survival in head and neck cancer. Unfortunately, however, this does not seem to apply to all subsites and especially survival of laryngeal cancer seems to have decreased in the United States and to have remained stable in other countries (eg, The Netherlands and Canada).[1–4]

Historically, the advanced stages of laryngeal cancer have been treated with total laryngectomy with or without postoperative radiotherapy (RT). However, in an attempt to preserve the larynx, organ-preservation (chemo)radiotherapy ((C)RT) protocols are increasingly being applied. This is mainly based on the results of 2 "landmark" studies. The first was the Department of Veterans Affairs Laryngeal Cancer Study Group (1991) showing that 2-year survival rates in patients treated with induction chemotherapy (cisplatinum and fluorouracil) followed by RT were similar to those treated with total laryngectomy, except for T4N0 disease, which showed a significantly better survival in the total laryngectomy arm. The larynx was preserved in 64% of patients receiving organ preservation treatment, in contrast to the obvious 0% in the total laryngectomy arm of the study.[5–7] The second, purely RT-based organ-preservation study was the Radiation Therapy Oncology Group (RTOG) 91-11 trial, which assessed, in a 3-arm design, the effects of the addition of chemotherapy to RT, either induction with cisplatinum and fluorouracil, or concurrent with cisplatinum (CRT) only. At 2 years posttreatment, larynx preservation and locoregional control rates in this study were significantly higher in the CRT arm than in the other 2 arms. Overall survival (OS) in the 3 arms, however, did not differ significantly.[8] Recently, the 10-year results of this RTOG 91-11 trial were published. Similar, as in the 2-year report, locoregional control and larynx preservation still were highest in the CRT arm. However, also at 10-years, the addition of chemotherapy to the radiation treatment did not provide any OS benefit.[9]

Based on the results of the Veterans Affairs study, patients with large-volume T4 lesions with cartilage invasion or extending more than 1 cm into the tongue base were excluded from the RTOG 91-11 study. This means that only selected cases of advanced laryngeal cancer were studied and that the outcomes of this study cannot be generalized for all advanced laryngeal cancers, as often has been suggested.[8] Hoffman et al,[2] as already

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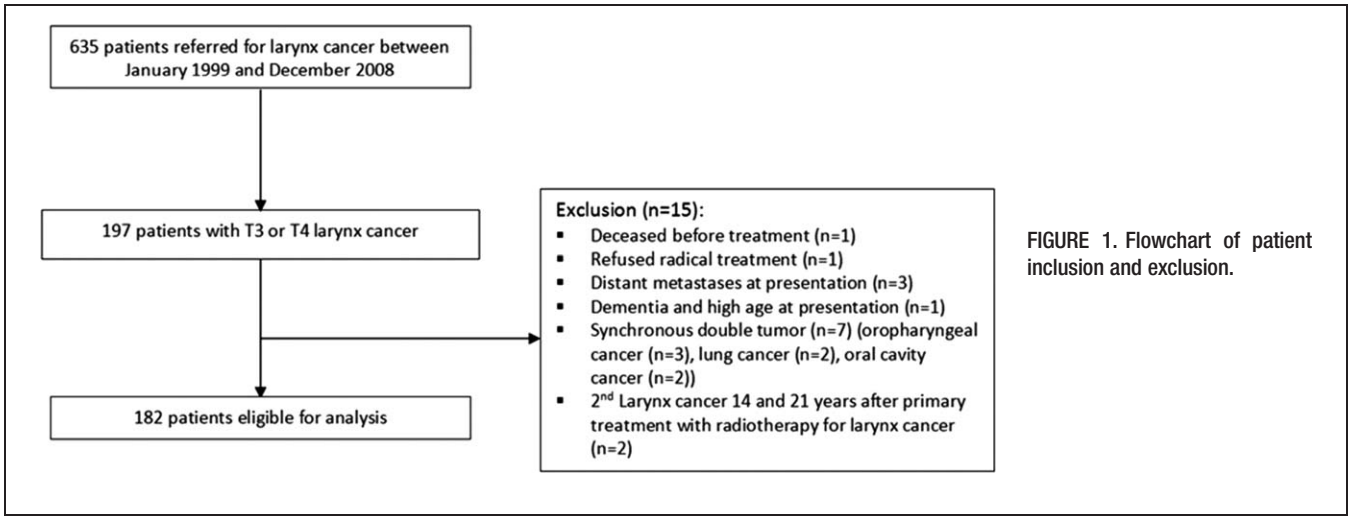


FIGURE 1. Flowchart of patient inclusion and exclusion.

mentioned, suggested that the decreased survival in the United States was in parallel with the declining use of surgery in favor of organ-preserving treatment modalities. Since then, there is a growing concern about the decreasing survival in advanced laryngeal cancer because of this shift in the therapeutic approach.

In 1999, the Dutch Head and Neck Society (former Dutch Cooperative Head and Neck Oncology Group) published a consensus document on laryngeal cancer diagnostics and treatment.[10] This document contained evidence-based protocols on all stages of laryngeal cancer and was, in part, based on the results of earlier national studies on the treatment modalities and results in all participating centers.[11] Since then, the therapeutic approach in The Netherlands Cancer Institute followed the national consensus protocols and remained unchanged over the last 10 years. For advanced (T3 and T4) laryngeal cancer, this protocol consisted of accelerated RT for T3 disease, supplemented with concurrent chemotherapy in case of extensive neck disease, and of total laryngectomy with planned postoperative RT in case of T4 disease. This protocol remained unchanged also after the publication of the RTOG 91-11 results in 2003.

In view of the ongoing discussion about the status of the (C)RT-based larynx-preservation approach in both T3 and T4 cancer, and its possible impact on survival, a retrospective analysis was conducted to assess whether the commonly found difference in survival between T3 and T4,[12] obviously also depending on neck node status, still exists despite the fact that T3 disease was not treated surgically any longer in our institute.

MATERIALS AND METHODS

A total of 635 patients with laryngeal cancer were treated at The Netherlands Cancer Institute between January 1999 and December 2008. Of these, 197 patients with T3 and T4 tumors were selected for this study. In total, 182 patients were eligible for further analysis, and the reasons for the exclusion of 15 patients are given in the flow chart in Figure 1.

The following data were collected for each patient, if available: age and sex, American Society of Anesthesiologists (ASA) classification, staging according to the seventh edition of the Union for International Cancer Control (UICC) TNM staging manual (2009), primary tumor site, tracheotomy and/or debulking before primary treatment (yes/no), treatment characteristics, recurrences, outcome, and last date of follow-up.

Tumors were clinically staged according to the seventh edition of the UICC TNM staging manual (2009). As patients treated before 2002 were staged following the fifth edition, restaging was necessary because the fifth edition differs from the sixth and seventh editions, especially for the delineation between T3 and T4. For restaging, clinical records, CT scans, and pathology examinations were reviewed by 2 of the authors in consensus.

The primary endpoint was OS. Although we do provide information on recurrences, disease-free survival was not calculated because information about the cause of death in our database was deemed not to be reliable enough, because most patients died at home. OS was defined as the period of time the patients were diagnosed with laryngeal cancer until the last follow-up or death. The last follow-up date was defined by the last visit to the outpatient clinic of our institute. The last follow-up date and survival status were updated on August 1, 2012.

Statistical analysis

Descriptive statistics were performed. To find differences between the groups, we used the Pearson chi-square, 1-way analysis of variance and linear-by-linear. Univariate analysis was performed by Cox regression analysis to reveal factors associated with a higher likelihood of mortality in patients with T3 or T4 laryngeal cancer. Furthermore, for multivariable analysis, Cox regression analysis was performed using backward elimination with a significance level of 10% (2-sided) to eliminate parameters. Hazard ratios (HRs) and 95% confidence levels (CIs) were estimated. For OS, locoregional control, and laryngectomy-free interval, Kaplan–Meier curves were plotted. To determine locoregional control, local, regional, and locoregional recurrences were included. In case of a second primary or distant metastasis only, the date of diagnosis was used as the moment of censoring. Other cases were censored at the date of the last follow-up or the date the patient died. For the laryngectomy-free interval, patients at risk (treated with RT or CRT) were

TABLE 1. Patient and tumor characteristics listed by primary treatment.

	Total laryngectomy	RT	CRT	*p* value
No. of patients	60	102	20	
Sex (%)				.022*
Male	51 (85.0)	75 (73.5)	11 (55.0)	
Female	9 (15.0)	27 (26.5)	9 (45.0)	
Age at diagnosis (range)	Mean 64.1 y (44–85)	Mean 62.1 y (36–87)	Mean 57.2 y (43–72)	.053†
ASA (%)				.297‡
1	11 (18.3)	22 (21.6)	1 (5.0)	
2	26 (43.3)	47 (46.1)	16 (80.0)	
3 or 4	23 (38.3)	25 (24.5)	3 (15.0)	
Missing	0	8 (7.8)	0	
Body mass index (%)				.250‡
<18	7 (11.7)	3 (2.9)	4 (20.0)	
18–25	39 (65.0)	55 (53.9)	10 (50.0)	
25–30	10 (16.7)	30 (29.4)	4 (20.0)	
30–40	2 (3.3)	6 (5.9)	1 (5.0)	
>40	1 (1.7)	1 (1.0)	0	
Missing	1 (1.7)	7 (6.9)	1 (5.0)	
Tracheotomy before primary treatment (%)				.014*
No	53 (88.3)	97 (95.1)	15 (75.0)	
Yes	7 (11.7)	5 (4.9)	5 (25.0)	
Debulking before primary treatment (%)				.287*
No	49 (81.7)	82 (80.4)	19 (95.0)	
Yes	11 (18.3)	20 (19.6)	1 (5.0)	
Origin tumor (%)				.001*
Supraglottic	21 (35.0)	64 (62.7)	19 (95.0)	
Glottic	11 (18.3)	19 (18.6)	1 (5.0)	
Subglottic	2 (3.3)	1 (1.0)	0	
Transglottic	26 (43.3)	18 (17.6)	0	
T classification of origin tumor, following criteria of 7th edition (%)				.001‡
T3	5 (8.3)	84 (82.4)	12 (60.0)	
T4a	54 (90.0)	18 (17.6)	6 (30.0)	
T4b	1 (1.7)	0	2 (10.0)	
N classification of origin tumor (%)				.006‡
N0	33 (55.0)	62 (60.8)	3 (15.0)	
N1	5 (8.3)	21 (20.6)	0	
N2a	2 (3.3)	0	0	
N2b	6 (10.0)	9 (8.8)	1 (5.0)	
N2c	13 (21.7)	9 (8.8)	12 (60.0)	
N3	1 (1.7)	1 (1.0)	4 (20.0)	
Stage (%)				.001‡
Stage III	2 (3.3)	68 (66.7)	2 (10.0)	
Stage IV	58 (96.7)	34 (33.3)	18 (90.0)	

Abbreviations: RT, radiotherapy; CRT, concurrent chemoradiotherapy; ASA, American Society of Anesthesiologists.
* Pearson chi-square.
† One-way analysis of variance.
‡ Linear-by-linear.
Body mass index was calculated as weight in kilograms divided by height in meters squared.

included. Date of total laryngectomy was the date of the event. Other cases were censored at the date of the last follow-up or at the date the patient died.

To compare groups, log-rank tests were performed. Variables with a p value $< .05$ were considered statistically significant. Analyses were performed with IBM SPSS Statistics software, version 20.0.

RESULTS

Patients

Patient and treatment data are shown in Table 1. Of the 182 primary T3 and T4 laryngeal cancer cases, 137 were men and 45 were women. There were 104 supraglottic, 31 glottic, 44 transglottic, and 3 subglottic tumors and 101 were T3 lesions and 81 were T4 lesions. As a result of restaging to the 2009 UICC classification, 10 of the 182 patients were downstaged from T4 to T3 and 5 patients were upstaged.

Primary total laryngectomy followed by planned postoperative RT was used in 60 patients. Of these 60, 9 patients did not undergo the planned postoperative RT because of the following reasons: refusal of the additional treatment ($n = 6$), a very favorable histology (no extralaryngeal spread; ie, T3 instead of T4; $n = 1$), or interfering comorbidity ($n = 2$). Primary single-modality RT was given to 102 patients and CRT to 20 patients.

Viewed by T classification, 82.4% of the patients treated with RT had a T3, 60.0% of patients treated with CRT had

a T3, and 91.7% of the patients treated with total laryngectomy had a T4 lesion. According to treatment (RT, CRT, or total laryngectomy ± RT), there were significant group differences with respect to sex (more women in the CRT group: 45.0%; compared to the total laryngectomy: 15.0%; and RT group: 26.2%; $p = .020$), and tumor origin (more supraglottic lesions in the RT and CRT groups; 62.7% and 95.0%, respectively, compared to 35.0% in the total laryngectomy group; $p = .001$).

Moreover, obviously as a result of the prevailing protocol, there were significant group differences for T classification (T3 laryngeal cancer was mainly treated with RT or CRT, whereas T4 laryngeal cancer was treated with total laryngectomy), N classification (patients in the CRT group had more positive lymph nodes of 85.0% compared to 39.2% in the RT group and 45.0% in the total laryngectomy group; $p = .006$; and tracheotomy before primary treatment CRT more often than total laryngectomy + RT and RT; $p = .014$). The treatment groups were comparable with respect to age, ASA classification, body mass index, and debulking before primary treatment.

Radiotherapy

In 102 patients, primary treatment consisted of single modality RT. Two protocols were in place during this period. In the first protocol, in 85 of 102 patients (83.3%), RT consisted of 46 Gy in 23 fractions to the primary tumor and the elective bilateral neck. A boost of 24 Gy was given to the tumor-bearing areas, to a total dose of 70 Gy in 35 fractions. In 34 patients, also the pathologic lymph nodes in the neck received a total dose of 70 Gy. The vast majority (78 patients) received accelerated RT according to the Danish Head and Neck Cancer (DAHANCA) protocol with 6 fractions per week with a reduced overall treatment time of 6 weeks,[13] and 4 patients received conventional RT with 5 fractions per week (overall treatment time of 7 weeks). Data on the remaining 3 patients were missing. In 61 of these 85 patients, the RT was delivered with 3D conformal RT or intensity-modulated RT (IMRT). In 22 patients RT was delivered with 2 lateral fields. These RT data were missing in 2 patients. One patient did not finish treatment and died 21 days after the start of treatment. In the second protocol, 14 patients (13.6%) were treated in another accelerated/hyperfractionated RT national study protocol (69.5 Gy, in 40 fractions in 5 weeks). The primary tumor received 69.5 Gy (10×2.0 Gy $+15 \times 1.8$ Gy $+15 \times 1.5$ Gy), the elective bilateral neck 47 Gy (10×2.0 Gy $+15 \times 1.8$ Gy). In 2 patients (14%), a total dose was delivered on pathologic lymph nodes in the neck as well.

Three patients (2.9%) could not be assigned to 1 of these 2 protocols. Two patients received 74 and 80 Gy, respectively, in 7 and 10 weeks to compensate for too many "lost" RT days during the treatment time. One patient received a total dose of 70 Gy on the tumor-bearing area, but 54.25 Gy on the elective bilateral neck after a simultaneous integrated boost approach.

Concomitant chemoradiation

Twenty patients received CRT, 17 on the indication of N2 or N3 neck disease, 1 because of inoperable disease. The remaining 2 patients had T3N0 disease, and thus were protocol violations in hindsight. The RT protocols for these 20 patients were similar to those described above. In 14 patients (70.0%), the pathologic lymph nodes in the neck also received a total dose of 70 Gy. Nine patients underwent conventional RT, 11 patients followed the DAHANCA schedule. In 10 patients, the RT was delivered in 2 lateral fields, and in 10 patients with 3D conformal RT or IMRT. All patients received cisplatinum in high doses or low doses. High-dose 3 weekly cisplatinum consists of 100 mg/m^2, 3 courses ($n = 9$). Low-dose daily cisplatinum consists of 6 mg/m^2, 25 courses ($n = 11$).

The deviation from application of the institute's protocol (T3 primary RT, inoperability or N2c/N3 CRT T4 primary total laryngectomy + RT) over the study period was as follows (see Table 1). There were 5 T3 patients treated with total laryngectomy and 18 T4 patients treated with RT. The 5 patients with T3 lesions receiving total laryngectomy initially all were classified as T4 according to the fifth or sixth UICC edition, which explains the choice for surgery at that time. In the group of 18 patients with T4 laryngeal cancer, in 4 patients, the tumor was upstaged for this study (original T3 classification), which explains the choice for RT. Of the remaining 14 T4 patients treated with RT, the indication was refusal of total laryngectomy in 3 patients. In 1 patient with T4 there was inoperable disease (where CRT would have been indicated), and in the remaining 10 patients the reason to use RT instead of total laryngectomy could not be deducted from the charts in retrospect. This means that together with the 2 T3N0 patients receiving CRT, 16 patients (9%) should be considered protocol violations, whereas 166 (91%) were treated according to protocol.

Survival

Figure 2 shows the OS of T3 and T4 laryngeal cancer separately, and for the total group categorized by treatment. Five-year OS for T3 laryngeal cancer was 52%, and for T4 laryngeal cancer it was 48% (log-rank: $p = .528$). Five-year OS after total laryngectomy was 52%, after RT it was 50%, and after CRT it was 43% (log-rank: $p = .828$). In Figures 3A and 3B, the OS is analyzed per primary treatment for T3 laryngeal cancer and T4 laryngeal cancer, respectively. Figure 4 shows the OS analyzed per stage (stage III and stage IV). For stage III, the OS was 58% and for stage IV it was 44% ($p = .126$), the latter having a significant larger proportion of patients with positive nodal status compared to stage III (Figure 4). Figure 5 shows the influence of nodal status on OS when analyzed separately for T3 and T4 laryngeal cancer. Patients with T3N0 laryngeal cancer had a 5-year OS of 65% compared to 35% for patients with T3N+ laryngeal cancer ($p = .005$). Patients with T4N0 laryngeal cancer and T4N+ laryngeal cancer had 5-year OS of 58% and 35%, respectively ($p = .026$). Five-year OS between T3N0 and T4N0 laryngeal cancer was not significant (log-rank: $p = .549$).

Univariate analysis was performed to reveal factors associated with a higher likelihood of mortality (Table 2). Patients with a positive N classification are more likely to die than patients with N0 (HR 2.16 95% CI = 1.40–3.33; $p = 0.001$). In addition, patients with higher ASA scores

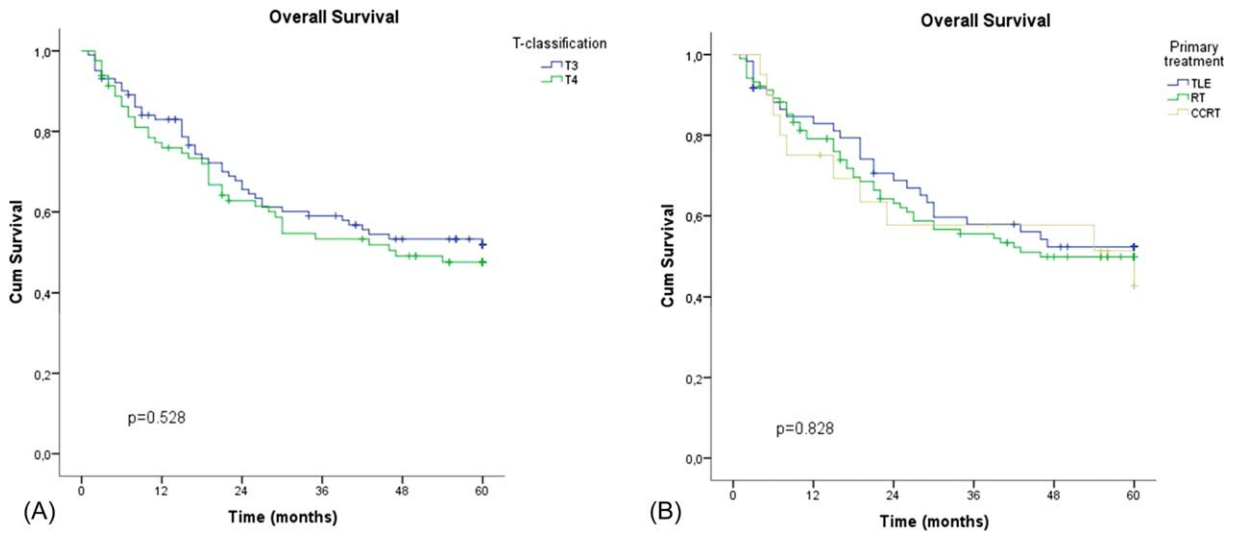


FIGURE 2. (A) Overall survival of T3 and T4 laryngeal cancer and (B) overall survival categorized by the 3 treatment groups. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

had worse survival. In multivariable analysis, N classification and ASA score remained significant (Table 3).

Locoregional control and laryngectomy-free interval

After total laryngectomy, single modality RT, and CRT 13.3%, 32.4%, and 30.0% of the patients, respectively, developed 1 or more recurrences (chi-square test: $p = .025$). The first recurrence was local in 50%, 72%, and 33%, respectively. Five-year locoregional control was 73% for the total group and 87%, 65%, and 76% for patients after treatment with total laryngectomy, RT, and CRT, respectively. Five-year laryngectomy-free interval was 72% after RT and 83% after CRT. Of the total 25 patients that underwent a total laryngectomy after RT or CRT, 20 had total laryngectomy for recurrent disease and 5 for a dysfunctional larynx.

DISCUSSION

In this retrospective cohort of 182 consecutive patients, no significant differences in OS were observed between T3 and T4 laryngeal cancer, nor between stage III and stage IV disease. The dominating prognostic factors in this study still were nodal status and comorbidity, as has been found in many other studies in head and neck cancer. The survival rates for stage III (58%) and stage IV disease (44%) in our institute are in line with the recently published survival figures from The Netherlands Cancer Registry over the period from 1999 to 2009: the 5-year

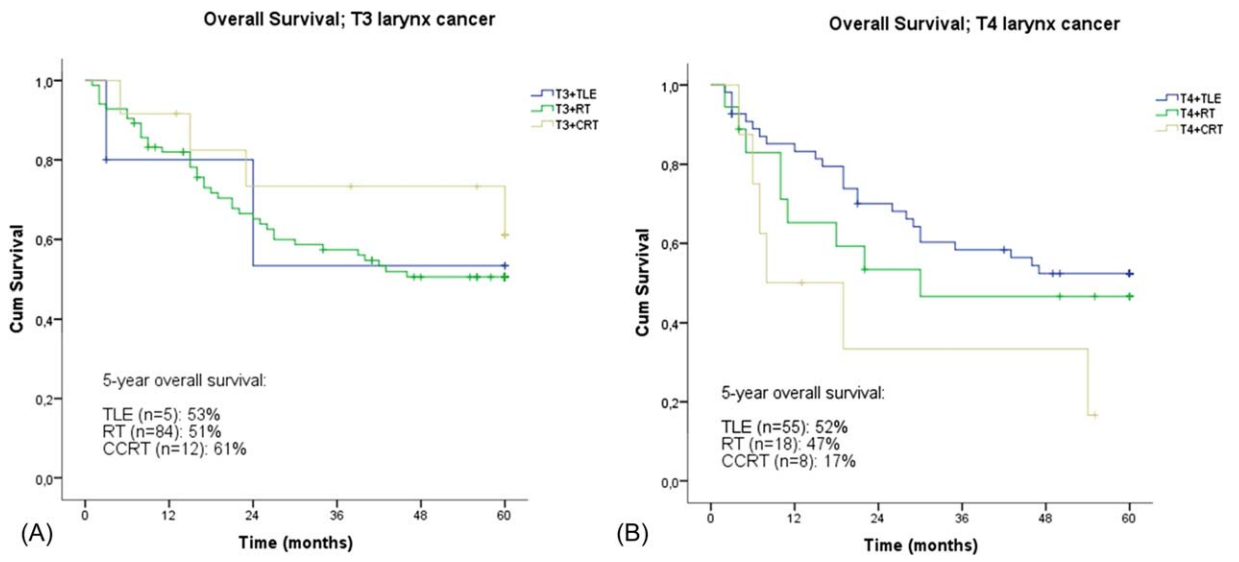
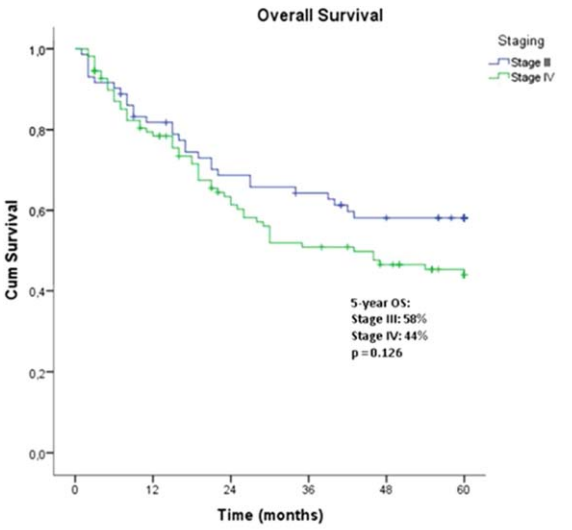


FIGURE 3. Overall survival analyzed per treatment-group for (A) T3 laryngeal cancer and (B) T4 laryngeal cancer. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



	N0	N+	Total
Stage III	54	18	72
Stage IV	44	66	110
	98	84	182
Chi-square: p=0.001			

FIGURE 4. Overall survival analyzed for stage III and stage IV. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

relative survival rates for stage III and IVa laryngeal cancer are 56% and 41%, respectively (1999–2002), and 55% and 42%, respectively (2003–2009).[14] However, it is important to note that T2N1 to 2 disease, also part of the "stage III-family," and T2N3 disease (stage IV) was not included in the present study.

Historically, survival of T3 laryngeal cancer has been better than that of T4 laryngeal cancer.[12,15] Robin et al[12] (1991) found that of all patients treated with total laryngectomy, T3 laryngeal cancer had better survival than T4 laryngeal cancer (supraglottis T3N0: 83%; total of 22 cases; T4N0: 45%; total of 10 cases; glottis: T3N0 50%; total of 107 cases; and T4N0 39%; total of 9 cases). Groome et al,[15] (2002), comparing different TNM-based stage groupings in laryngeal cancer using data from Canada and Norway, reported an HR for death of laryngeal cancer of 5.4 and 7.5 for T3N0, and of 10.5 and 9.0 for T4N0 laryngeal cancer (for Canada and Norway, respectively). However, the authors did not report on treatment but, including all T, N, and M classifications, >80% of the patients in both countries were irradiated. Thus, it is noteworthy that such difference in survival was absent in our cohort.

The treatment protocol consistently used in this patient cohort is based on a consensus document on laryngeal cancer diagnostics and treatment of the Dutch Head and Neck Society (former Netherlands Cooperative Head and Neck Tumor Group) published in 1999.[10] That document, in part, was based on an earlier national study reporting on the treatment results of T3 laryngeal cancer.[11,16,17] That study showed that planned combined treatment (consisting of surgery and RT) significantly increased corrected survival. Primary surgery and primary RT had similar effects. With the improved RT protocols emerging at that time (ie, reduction of the overall treatment time in the DAHANCA protocol), it was expected that locoregional control and survival would improve, and the need for total laryngectomy with or without adjuvant RT, at that time the standard treatment for T3 laryngeal cancer in most head and neck services in The Netherlands, would decrease.

The respective roles of organ preservation (C)RT treatment and organ sacrificing surgical treatment for advanced laryngeal cancer have been extensively

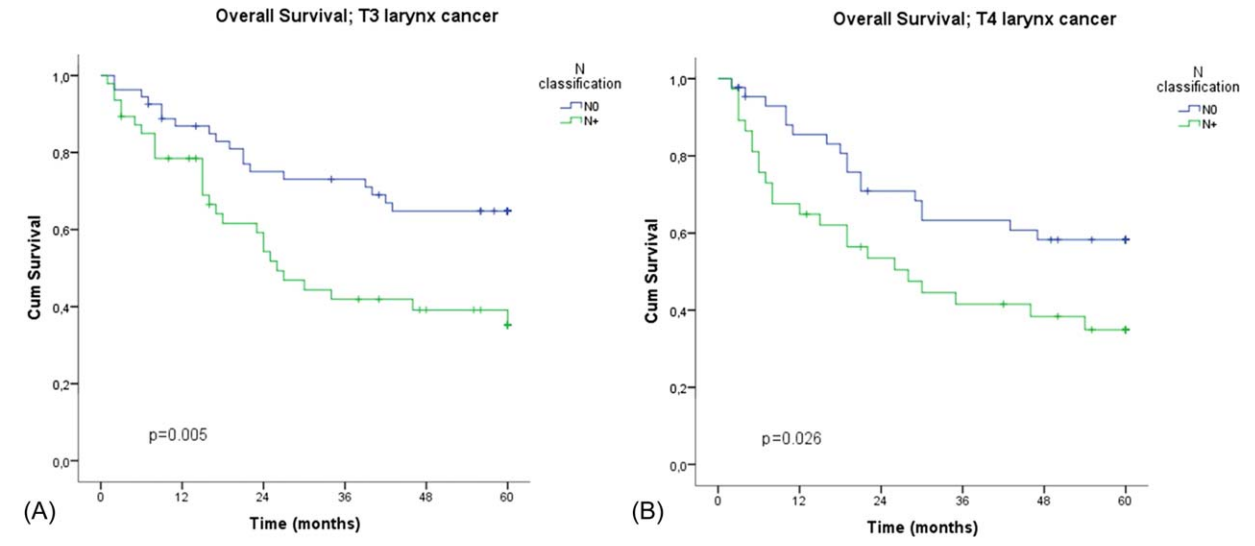


FIGURE 5. The influence of nodal status on overall survival analyzed for (A) T3 laryngeal cancer and (B) T4 laryngeal cancer. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE 2. Univariate analysis for factors influencing overall survival in patients with T3/T4 laryngeal cancer.

	No. of patients	HR (95% CI)	*p* value
Primary treatment ($n = 182$)			.831
Total laryngectomy	60	Ref	
RT	102	1.11 (0.69–1.78)	.664
CRT	20	1.23 (0.60–2.55)	.570
Sex ($n = 182$)			.066
Male	137	Ref	
Female	45	1.55 (0.97–2.47)	
ASA ($n = 174$)			**.015**
1	34	Ref	
2	89	2.26 (1.11–4.63)	**.026**
3 or 4	51	3.02 (1.43–6.38)	**.004**
Origin tumor ($n = 182$)			.551
Supraglottic	104	Ref	
Glottic	31	0.65 (0.34–1.24)	.193
Subglottic	3	0.00 (0.00–2.04^{237})	.966
Transglottic	44	1.09 (0.66–1.79)	.747
T classification, following criteria of 7th edition ($n = 182$)			.532
T3	101	Ref	
T4	81	1.15 (0.75–1.75)	
N classification ($n = 182$)			**.001**
N0	98	Ref	
N+	84	2.16 (1.40–3.33)	

Abbreviations: HR, hazard ratio; CI, confidence interval; RT, radiotherapy; CRT, chemoradiotherapy; ASA, American Society of Anesthesiologists.
HRs and *p* values were calculated using Cox regression.
The figures in bold indicate statistical significance.

addressed in the recent literature.[2,7,18–22] Gourin et al[18] (2009) found that patients with T4 disease had significantly better survival after total laryngectomy (55%) than after CRT (25%) or RT alone (0%). In addition, after controlling for nodal status, organ-preserving treatment was still a significant predictor of worse survival. Furthermore, Hoffman et al[2] (2006) studied patterns of care and survival after laryngeal cancer between 1985 and 2001 in the United States in 158,426 patients. These authors reported a decreasing trend in survival from the mid-1980s to the mid-1990s and, in the same period, an increase of chemoradiation as primary treatment with a decrease in surgery. For T3N0M0 laryngeal cancer specifically, a significant better 5-year relative survival was found for those patients treated with surgery and irradiation compared to patients treated with irradiation (with or without chemotherapy; 64.4% vs 49.4%). It should be noted, however, that specific data regarding RT and chemotherapy were not available. In addition, "surgery" was not further specified in total laryngectomy, endoscopic surgery, or other surgery. Recently, Dziegielewski et al[20] (2012) found better survival for patients with T3 and T4a laryngeal cancer treated with total laryngectomy (with (C)RT) compared to RT and CRT and suggest reassessment of current treatment guidelines. Also, Chen and Halpern[21] (2007) found total laryngectomy to be superior to RT and CRT as primary treatment in patients with stage IV laryngeal cancer in terms of OS. For stage III disease, total laryngectomy had better survival than RT in their series. The findings of a decreased survival for the advanced stages of laryngeal cancer are serious and warning. Several authors already have expressed their concerns about this issue.[7,22]

Especially in T3 laryngeal cancer, there is discussion about what treatment modality is best for which patient. Besides (C)RT and total laryngectomy, other treatment options for T3 disease are partial open laryngeal surgery or transoral laser microsurgery (TLM). With respect to the latter approach, recently, Canis et al[23] (2013) published the results of a cohort of 226 patients with pT3 laryngeal cancer treated with TLM. Sixteen percent of patients also underwent selective neck dissection and postoperative RT, and postoperative RT only was given in another 2% of the patients. Five-year OS was 64.4%. The functional results were also quite favorable; 6 patients (2.7%) required a temporary tracheotomy and 2 patients (0.9%) needed a permanent tracheotomy. Percutaneous endoscopic gastrostomy tubes were temporarily

TABLE 3. Multivariable analysis to reveal factors influencing overall survival in patients with T3/T4 laryngeal cancer.

	No. of patients	HR (95% CI)	*p* value
ASA ($n = 174$)			**.013**
1	34	Ref	
2	89	2.23 (1.09–4.56)	**.029**
3 or 4	51	3.08 (1.45–6.50)	**.003**
N classification ($n = 174$)			**.001**
N0	94	Ref	
N+	80	2.09 (1.35–3.24)	

Abbreviations: HR, hazard ratio; CI, confidence interval; ASA, American Society of Anesthesiologists.
HRs and *p* values were calculated using Cox regression.
The figures in bold indicate statistical significance.

necessary in 6 patients (2.7%) and permanently necessary in 3 patients (1.3%). Unfortunately, no data on the voice quality were available. The authors concluded that the results of TLM are satisfactory, but they also address that the data are only of one institution and that further prospective studies should be done.[23] For carefully selected cases, it may be a good alternative.

In the multivariable analysis in the present study, N classification and ASA score were found to be associated with mortality. Both findings are in line with the literature. Various studies reported that patients with positive neck nodes have worse prognosis.[18,24] Also, ASA scores have been reported to be predictive for morbidity and mortality as well as chance for successful organ preservation.[25–27]

Next to survival, quality of life, toxicity, and larynx preservation are important parameters in the decision-making process. Both organ sacrificing and preserving treatments for advanced laryngeal cancer significantly affect quality of life. Finizia et al[28] (1998) studied voice and quality of life of patients treated for laryngeal cancer with RT with or without total laryngectomy as salvage surgery. They found that irradiated patients and listeners rated their voices higher than that of laryngectomized patients using tracheoesophageal speech. In most studies, however, scores for quality of life were similar regarding most functions and symptoms.[28–30] Moreover, one has to keep in mind that, in the last 2 decades, major progress has been made with respect to vocal, pulmonary, and olfactory rehabilitation, making the functional deficits of total laryngectomy less debilitating than ever before.[31] Toxicity after (C)RT can be considerable, resulting in swallowing problems, difficulties with speech, and a dysfunctional larynx. Fortunately, the reduction of the radiation dose to the surrounding tissues achievable with IMRT has decreased RT side effects. Especially through preservation of the salivary glands, the reduction of xerostomia leads to less severe dysphagia. Nevertheless, in some cases, a total laryngectomy is still deemed to be the only solution to resolve the sequels of (C)RT, as recently published from our institute, where 11% of the total laryngectomies over the last decade was indicated for a "dysfunctional larynx."[32] It should be noted that, in that study, all patients previously treated with RT or CRT for any head and neck cancer site were included. In the present study, the 5-year laryngectomy-free interval was 72% after RT and 83% after CRT. Of these patients, 20 underwent total laryngectomy for recurrent disease and 5 for a dysfunctional larynx. However, this gives no complete information on how severe toxicity was in our CRT study population. Unfortunately, we could not retrieve reliable data on these aspects from the medical records.

An obvious shortcoming of this study was its retrospective character. In addition, the relative small sample size precludes drawing far-reaching conclusions. An aspect to stress is that retrospective (and this obviously also counts for prospective) studies like the one presented here should be based on uniform staging. Because the laryngeal cancers in this study originally were staged according to the fifth, sixth, and seventh editions of the UICC TNM staging manual, the necessity of restaging all tumors according to the seventh edition of the UICC TNM staging manual (2009) was obvious. A disadvantage of restaging is that comparison with literature based on earlier editions of the UICC TNM staging becomes difficult. In the sixth edition, the criterion "minor thyroid cartilage erosion" was added to the T3 classification of supraglottic and glottic laryngeal cancer. This means that tumors staged as a T4 in editions before the sixth edition, will be classified as a T3 now, resulting in a higher chance of treatment with (C)RT for a tumor that would have been treated surgically years ago. The move of the "minor cartilage erosion" cases from T4 to T3 means that the T3 category now might be more unfavorable than in the past, but, on the other hand, it is likely that the T4 category has "lost" its most favorable subgroup, so that the remaining T4s are the relatively more unfavorable cases, neutralizing the potential effects on survival this restaging has for both categories. An additional point to make with regard to the present study is that we did include all T3 and T4 tumors, also the large-volume tumors invading the larynx and with extralaryngeal spread, which means that there was no selection bias for the larger tumors in this cohort, something that has not always been the case in prospective studies and is a concern with regard to generalizing results for all laryngeal cancers.[8]

In conclusion, in this cohort, representing a single institution's treatment outcome based on a consistent application (91%) of treatment protocols over a 10-year period, survival according to staging (T3 vs T4 laryngeal cancer), and according to treatment modality (total laryngectomy + RT vs (C)RT) showed no differences for either of the two. Considering that the majority of T3 laryngeal cancers were treated with organ-preserving modalities and the majority of T4 laryngeal cancers were treated with total laryngectomy + RT, this gives food for thought on whether the present treatment protocol for T3 laryngeal cancer is optimal.

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