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Trends in treatment and survival for advanced laryngeal cancer: A 20-year population-based study in The Netherlands

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ABSTRACT: *Background.* The purpose of this study was to determine time trends for primary treatment modalities in advanced laryngeal cancer, overall survival (OS), and laryngectomy-free interval (LFI) over the last 2 decades in The Netherlands.

Methods. We conducted an analysis of T3 to T4 laryngeal cancer data from 2 combined national (population-based and pathology-based) cancer registries.

Results. A total of 2072 T3 cases (14.7%) and 1722 T4 cases (12.2%) were identified. Total laryngectomy as primary treatment modality decreased, whereas radiotherapy (RT) increased. For T3 disease, 5-year OS after primary total laryngectomy (+/− adjuvant RT), RT, and chemoradiotherapy (CRT) was 49%, 47%, and 45%, respectively. For T4

disease, this was 48%, 34%, and 42% (overall $p < .0001$), respectively. Five-year LFI for T3 disease was 81% (RT) and 77% (CRT), and for T4 disease it was 81% and 87%, respectively.

Conclusion. From 1991 to 2010 total laryngectomy as primary treatment modality for advanced laryngeal cancer decreased and RT increased. T3 disease showed similar survival rates for all primary treatment modalities. For T4 disease, total laryngectomy (+ adjuvant RT) showed the best survival. © 2015 Wiley Periodicals, Inc. *Head Neck* 38: E1247–E1255, 2016

KEY WORDS: laryngeal cancer, treatment, total laryngectomy, radiotherapy, survival

INTRODUCTION

Primary treatment options for advanced laryngeal cancer are radiotherapy (RT), concomitant chemoradiotherapy (CRT) or total laryngectomy with or without adjuvant RT. Of these treatments, total laryngectomy with adjuvant RT has long been considered the gold standard. However, because this organ-sacrificing surgery often results in significant morbidity leading to psychosocial, vocal, pulmonary, and olfactory problems, other options for treatment (eg, partial laryngectomy and RT) have gained in popularity. After the publication of 2 randomized studies, organ-preserving CRT treatment protocols are increasingly being used as an alternative to total laryngectomy.^{1,2}

The first of these studies was published in 1991 by the Veterans Affairs Study Group (VA study).¹ The authors concluded that patients treated with either total laryngectomy or induction chemotherapy combined with RT had

similar survival rates. Moreover, in the latter group, the larynx could be preserved in 64% of the patients. It is worthy to note that, in a revision of the data of this study, patients with T4N0 cancer had a statistically significant ($p = .05$) higher survival rate after treatment with total laryngectomy.³ A decade later, the Radiation Therapy Oncology Group (RTOG) 91-11 study (2003) assessed whether any, and if so, which chemotherapy regimen had added value over RT alone. Patients with large-volume T4N0 laryngeal cancer were excluded because of their better survival after total laryngectomy in the VA study. The RTOG 91-11 study concluded that concurrent CRT was superior to induction chemotherapy combined with RT or RT alone in terms of larynx preservation and locoregional control, but similar in terms of overall survival (OS).^{2,4}

The shift toward organ-preserving treatment protocols has been postulated as a possible cause of the lack of gradual survival improvement for laryngeal cancer, when compared to other head and neck sites.^{5,6} In 2006, Hoffman et al⁶ reported decreasing survival for patients with laryngeal cancer patients from the mid-80s to the mid-90s in the United States. They also found an increase in the use of organ-preserving treatment modalities and a decrease in the use of surgery in the same period. In

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2007, Chen and Halpern⁷ aimed to determine factors predictive for survival in patients with advanced laryngeal cancer. The authors reported a hazard ratio for death of 1.6 for RT and 1.3 for CRT when compared to treatment with total laryngectomy.⁷ Since then, there has been a debate on whether or not total laryngectomy should be performed more often in (a selection of) patients with advanced laryngeal cancer.⁸

The above-mentioned studies were based on patients from the United States. In The Netherlands, the Dutch Head and Neck Society (former Dutch Cooperative Head and Neck Oncology Group) published a consensus document on laryngeal cancer diagnostics and treatment in 1999.⁹ 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 treatment modalities and results in all participating centers.¹⁰ Whereas before, T3 and T4 laryngeal cancers in most centers preferably would be treated with total laryngectomy, from then on patients with T3 laryngeal cancer received RT, in line with the consensus protocol then drafted. For T4 laryngeal cancer, total laryngectomy plus adjuvant RT remained the preferred treatment modality. In 2013, van Dijk et al¹¹ published a study reporting a declining incidence and a stable relative survival of around 70% for all laryngeal cancer cases from 1989 to 2010.¹¹ Thus, although no decreasing survival was seen as in the United States, survival rates did not increase either.

Since the introduction of RT and CRT as primary treatment modalities for patients with advanced laryngeal cancer, total laryngectomy (plus adjuvant RT in case of T4) is thus no longer considered the only curative option. However, recurrent or residual disease is not uncommon and still often requires salvage total laryngectomy with an accompanying higher risk of complications.^{12,13} Furthermore, the function of the larynx, especially its vital role in aspiration prevention, can become so impaired that some patients require a total laryngectomy because of a dysfunctional larynx after prior RT or CRT.¹⁴

In The Netherlands, there are 2 unique databases for cancer: the Netherlands Cancer Registry (NCR) and the PALGA foundation database (the nationwide network and registry of histopathology and cytopathology in The Netherlands¹⁵). Combining these 2 databases now makes it possible to conduct a population-based cohort study on advanced laryngeal cancer with the following research questions. (1) What is the trend in proportion of total laryngectomies for T3 to T4 laryngeal cancer in the period from 1991 to 2010? (2) What is the trend in primary treatment (primary total laryngectomy [+/- adjuvant RT], RT, and CRT) for T3 to T4 laryngeal cancer? (3) What is the 5-year OS of patients with T3 to T4 laryngeal cancer? (4) What is the laryngectomy-free interval (LFI) after RT or CRT for T3 to T4 laryngeal cancer?

MATERIALS AND METHODS

This study does not fall under the scope of the Medical Research Involving Human Subjects Act (WMO), which means that it does not have to be reviewed by an accredited Multicentre Research Ethics Committee. The privacy

committees of the NCR and the PALGA foundation approved this study.

Study design

A population-based cohort study with NCR data and PALGA was conducted. The NCR receives data from PALGA, from the registry of hospital discharges, and through trained administrators reviewing patient-related medical records. The NCR covers at least 95% of all malignancies. The PALGA Foundation manages a database covering all pathology reports in The Netherlands. All pathology laboratories collaborate and send in their pathology reports on a daily basis. Data from the latter database were used to verify the histopathology of the laryngeal cancer, to identify whether “surgery” meant total laryngectomy, and whether total laryngectomy was conducted for salvage or for a dysfunctional larynx.

Patient selection

The database from the NCR included 14,080 patients diagnosed with invasive laryngeal cancer between 1991 and 2010. Patient-specific information retrievable was: patients' age (at incidence) and sex, TNM classification/staging, site of the tumor (supraglottic, glottic, subglottic, or larynx not otherwise specified [NOS]; according to the International Classification of Disease for Oncology¹⁶), primary treatment (surgery/RT/CT), follow-up status (alive, emigrated, or deceased), and follow-up time. Follow-up time was defined as the time from the date of incidence to the date of last the follow-up (December 31, 2013). Date of incidence was defined as the date of first histological or cytological confirmation of the tumor, or first hospital admission in relation to this tumor.

PALGA delivered all pathology records (free text conclusion of the report) possibly reporting a total laryngectomy. The pathology records dated from January 1, 1991 until October 1, 2012. These pathology records were manually screened to identify total laryngectomies. Subsequently, the NCR and PALGA databases were merged.

Clinical staging was used, because the pathological stage is unavailable in case of primary treatment with RT and/or CRT. The cT1A and cT1B were grouped as T1 and cT4A and cT4B as T4. The cNX/missing was coded as N0 in case a cT classification was known. The cT0 or cTis laryngeal cancer were included in the T1 group ($n = 10$). One patient was scored as having a cT0 or cTis, but had a pT4 and was subsequently scored as having a T4. The cT classification will be referred to as T classification. Patients with T1 laryngeal cancer ($n = 5573$), T2 laryngeal cancer ($n = 4008$), distant metastases before primary treatment ($n = 150$), cTX ($n = 499$), and nonsquamous cell carcinoma ($n = 56$) were excluded from this study, leaving 3794 patients with T3, 4N0, and 3M0 laryngeal cancer for analysis.

Treatment

Merging the databases enabled identifying primary treatment coded as “surgery” in the NCR database as a primary total laryngectomy or partial laryngectomy. In case primary treatment was not a total laryngectomy or a partial laryngectomy, “surgery” was coded as “treatment

TABLE 1. Patient and tumor characteristics at time of primary treatment.

Characteristics	Total no. (%)	Primary total laryngectomy (%)	RT (%)	RT + CT (%)	Partial laryngectomy (%)	CT (%)	No treatment/treatment NOS (%)
Sex	3794 (100)	1172 (30.9)	2018 (53.2)	265 (7.0)	27 (0.7)	14 (0.4)	298 (7.9)
Male	2991 (78.8)	971 (82.8)	1554 (77.0)	191 (72.1)	19 (70.4)	13 (92.9)	243 (81.5)
Female	803 (21.2)	201 (17.2)	464 (23.0)	74 (27.9)	8 (29.6)	1 (7.1)	55 (18.5)
Mean age, y (range)	64.1 (28–100)	62.8 (31–89)	64.7 (28–100)	58.4 (34–80)	59.0 (39–71)	58.4 (44–71)	70.8 (40–98)
Subsite							
Supraglottic	2394 (63.1)	651 (55.5)	1307 (64.8)	220 (83.0)	26 (96.3)	13 (92.9)	177 (59.4)
Glottic	1175 (31.0)	420 (35.8)	625 (31.0)	35 (13.2)	1 (3.7)	1 (7.1)	93 (31.2)
Subglottic	98 (2.6)	44 (3.8)	39 (1.9)	5 (1.9)	—	—	10 (3.4)
Larynx NOS	127 (3.3)	57 (4.9)	47 (2.3)	5 (1.9)	—	—	18 (6.0)
T and N classification							
T3N0	1329 (35.0)	177 (15.1)	1011 (50.1)	53 (20.0)	8 (29.6)	2 (14.3)	78 (26.2)
T3N+	743 (19.6)	147 (12.5)	447 (22.2)	89 (33.6)	5 (18.5)	5 (35.7)	50 (16.8)
T4N0*	983 (25.9)	495 (42.2)	362 (17.9)	35 (13.2)	7 (25.9)	5 (35.7)	79 (26.5)
T4N+*	739 (19.5)	353 (30.1)	198 (9.8)	88 (33.2)	7 (25.9)	2 (14.3)	91 (30.5)

Abbreviations: RT, radiotherapy; CRT, chemoradiotherapy; NOS, not otherwise specified.

* Of the total of 1722 patients with T4 laryngeal cancer, there were 1208 with unspecified T4 cases, 489 with T4a cases, and 25 with T4b cases (of which 4 underwent a total laryngectomy).

NOS.” In case surgery, RT, or CT were not coded as primary treatment, treatment was coded as “no treatment/treatment NOS.” By merging the databases we were also able to identify total laryngectomies that were not part of the primary treatment. To determine the indication for a total laryngectomy, a cutoff value was chosen of 120 days between the date of incidence and the date of total laryngectomy. Total laryngectomy performed within these 120 days was considered a primary total laryngectomy. In case the total laryngectomy was performed at least 120 days after the incidence date, the total laryngectomy was coded as salvage procedure, or as total laryngectomy for a dysfunctional larynx. The distinction between salvage total laryngectomy and total laryngectomy for a dysfunctional larynx was made based on the presence of malignancy (salvage) or not (dysfunctional larynx) in the pathology report. We chose a cutoff value of 120 days because we felt confident that the primary treatment would be finished within this time window, also because the time delay between date of incidence and onset of (mostly centralized) primary treatment in The Netherlands rarely exceeds 40 days.

Outcome measures

Outcome measures were trends in primary treatment (total laryngectomy [+/- RT], RT, and CRT), LFI (sometimes also referred to as larynx preservation rate) after primary RT and CRT, and OS per T classification and treatment. LFI was determined using follow-up time, which was calculated starting from the date of incidence until total laryngectomy or censoring (death or last date of follow-up). Patients at risk were defined as patients who were primarily treated with either RT or CRT. For OS, the follow-up of vital status was calculated as the time from incidence to death, emigration, or until December 31, 2013. Patients without follow-up (date of incidence and date of lost to follow-up were equal or

negative [$n = 7$]), were excluded from the survival analysis.

Statistical analysis

Descriptive statistics were performed. The independent *t* test was used to calculate if mean ages between treatment groups were significantly different (age was normally distributed). Linear-by-Linear was used to assess the association between T classification and incidence years. Linear regression was used to calculate the trends in total laryngectomies over the years 1993 to 2010. The percentage of total laryngectomies (total numbers and per

indication) was calculated counting the number of total laryngectomies divided by the number of patients diagnosed with T3 or T4 laryngeal cancer. The percentage of total laryngectomy, RT, and CRT was calculated counting

the number of treatments divided by the number of all patients diagnosed with T3 or T4 laryngeal cancer. For OS and LFI, Kaplan–Meier curves were plotted. Log-rank tests were used to compare groups. For multivariable analysis, Cox regression analysis was applied. The variables: primary treatment, age, sex, T and N classification, and subsite were included in the model. The continuous variable age was categorized into 5 groups. Hazard ratios (HRs) and 95% confidence levels (95% CIs) were estimated. Variables with a p value $< .05$ were considered statistically significant. Analyses were performed using SPSS Statistics 20.0 (IBM, Armonk, NY).

FIGURE 5. (A) Overall survival for T3 laryngeal cancer for total laryngectomy ($n = 324$), radiotherapy (RT; $n = 1456$), and RT combined with chemotherapy ($n = 142$) separately. (B) Overall survival for T3 laryngeal cancer for total laryngectomy ($n = 324$) without RT ($n = 75$) or with RT ($n = 249$).

RESULTS

Patient, tumor, and treatment characteristics

Detailed information on patient, tumor, and treatment characteristics is shown in Table 1. The male:female ratio was 3.7:1 and the mean age was 64.1 years (range, 28–100 years). Overall, most patients with T3 to T4 disease had supraglottic cancer (63.1%), followed by glottic cancer (31.0%). A minority had subglottic cancer (2.6%) or larynx NOS (3.3%). Noteworthy is that the distribution of subsite was reversed for patients with T1 to T2 laryngeal cancer ($n = 9581$): glottic cancer occurred in 78.6% of the patients, followed by supraglottic cancer (19.9%; see Figure 1).

Over this 20-year period, the number of patients with T3 laryngeal cancer increased (Linear-by-Linear: $p = .001$) and with T4 laryngeal cancer decreased (Linear-by-Linear: $p = .003$; see Figure 2).

Trends in total laryngectomy

Figure 3 shows the total number of total laryngectomies and per indication (primary total laryngectomy, salvage total laryngectomy, and total laryngectomy for a

dysfunctional larynx) as a percentage of all patients with T3 to T4 laryngeal cancer over the years 1991 to 2010 ($n = 3794$). There was a decrease of 3.07 total laryngectomies per year ($p < .0001$; calculated from 1993–2010). The use of a total laryngectomy as primary treatment declined (-3.30 total laryngectomies per year; $p < .0001$), whereas the numbers of salvage total laryngectomies and total laryngectomies for a dysfunctional larynx remained stable.

Trends in treatment of advanced laryngeal cancer

When compared to total laryngectomy (mean age, 62.8 years; range, 31–89 years), patients primarily treated with CRT were significantly younger (mean age, 58.4 years; range, 34–80 years; $p < .0001$), and patients undergoing RT were significantly older (mean age, 64.7 years; range, 28–100 years; $p = .001$).

Figures 4A and 4B show the trend in primary treatment for patients with T3 and T4 laryngeal cancer from 1991 to 2010. For both T3 and T4 laryngeal cancer, the use of primary total laryngectomy as proportion of all patients with T3 or T4 laryngeal cancer decreased, whereas the use of RT increased. In both figures, the trend seems to

FIGURE 6. (A) Overall survival (OS) for T4 laryngeal cancer for total laryngectomy ($n = 848$), radiotherapy (RT; $n = 560$), and RT combined with chemotherapy ($n = 123$) separately. (B) OS for T4 laryngeal cancer for total laryngectomy ($n = 848$) without RT ($n = 148$) or with RT ($n = 700$).

TABLE 2. Multivariable analysis calculating overall survival using Cox regression analysis including all patients with T3 or T4 laryngeal cancer and separately for T3 and T4 laryngeal cancer.

	T3 + T4 laryngeal cancer			T3 laryngeal cancer			T4 laryngeal cancer		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
Primary treatment									
Total laryngectomy + adjuvant RT	1.00			1.00			1.00		
Total laryngectomy alone	1.09	0.93–1.29	.29	0.94	0.70–1.26	.66	1.12	0.92–1.37	.25
RT	1.33	1.21–1.47	< .0001	1.09	0.93–1.28	.28	1.50	1.33–1.71	< .0001
CRT	1.26	1.07–1.49	.006	1.11	0.86–1.43	.41	1.27	1.01–1.59	.04
Age, y									
<50	1.00			1.00			1.00		
50–59	1.34	1.14–1.58	< .0001	1.55	1.22–1.97	< .0001	1.20	0.96–1.49	.11
60–69	2.00	1.71–2.33	< .0001	2.22	1.76–2.79	< .0001	1.81	1.46–2.24	< .0001
70–79	3.01	2.56–3.55	< .0001	3.62	2.85–4.59	< .0001	2.52	2.01–3.17	< .0001
≥80	5.20	4.28–6.35	< .0001	6.92	5.21–9.18	< .0001	4.06	3.08–5.37	< .0001
Sex									
Male	1.00			1.00			1.00		
Female	0.88	0.80–0.97	.01	0.85	0.75–0.97	.02	0.91	0.78–1.05	.20
T classification									
T3	1.00								
T4	1.21	1.11–1.32	< .0001						
N classification									
N0	1.00			1.00			1.00		
N+	1.62	1.49–1.77	< .0001	1.66	1.48–1.87	< .0001	1.56	1.37–1.76	< .0001
Subsite									
Supraglottic	1.00			1.00			1.00		
Glottic	0.92	0.84–1.01	.09	0.92	0.82–1.05	.22	0.92	0.80–1.05	.21
Subglottic	1.01	0.79–1.29	.96	1.09	0.66–1.83	.73	0.98	0.73–1.30	.87
Larynx NOS	1.45	1.18–1.78	< .0001	1.16	0.83–1.61	.38	1.71	1.31–2.24	< .0001

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; RT, radiotherapy; CRT, chemoradiotherapy; NOS, not otherwise specified. The given HRs are HRs for death.

change in 2000 to 2002 with an increase in RT and a decrease in total laryngectomy, which levels off a few years later.

Over the study period from 1991 to 2010, the main treatment modality for T3N0 and T3N+ laryngeal cancer was RT (76.1% and 60.2%, respectively). Only 13.3% and 19.8%, respectively, underwent total laryngectomy as primary treatment. Of these patients, 76.9% received postoperative RT. For patients with T4N0 and T4N+ laryngeal cancer, the main treatment modality was total laryngectomy (50.4% and 47.8%, respectively), followed by postoperative RT in 82.5% of the cases. RT as a primary treatment for T4N0 and T4N+ laryngeal cancer was administered in 36.8% and 26.8%, respectively, of the patients. Only 3.6% and 11.9% of these patients received CRT as primary treatment.

Overall survival

The OS after 5 years for T3 laryngeal cancer was 44% and for T4 laryngeal cancer was 39% (log-rank: $p < .0001$; including all treatment modalities). Median OS was 3.81 years for T3 laryngeal cancer (95% CI = 3.42–4.20) and 2.83 years for T4 laryngeal cancer (95% CI = 2.51–3.15).

Figure 5A shows the OS for patients with T3 laryngeal cancer. OS rates after total laryngectomy, RT, and CRT were similar: 49%, 47%, and 45%, respectively, after

5 years (log-rank: overall $p = .539$). No significant differences were found between the patients that did and did not receive adjuvant RT after total laryngectomy (47% and 56%, respectively; log-rank: $p = .442$; Figure 5B). When analyzed for supraglottic and glottic tumors separately, no significant differences were found between tumor sites.

Figure 6A shows the OS for patients with T4 laryngeal cancer. For these patients, 5-year OS after total laryngectomy (48%) was better than after RT (34%) or after CRT (42%; log-rank: overall $p < .0001$). Patients who received adjuvant RT after total laryngectomy had significant better survival than patients not undergoing RT (49% and 42%, respectively; log-rank: $p = .047$; Figure 6B). When analyzed for supraglottic and glottic tumors separately, no significant differences were found between tumor sites.

Table 2 shows a multivariable analysis for OS of patients primarily treated for T3 or T4 laryngeal cancer. Patients with T4 laryngeal cancer have a higher HR for dying when compared to patients with T3 laryngeal cancer (HR = 1.21; 95% CI = 1.11–1.32; $p < .0001$). This was also the case for patients with positive lymph nodes when compared with patients without positive lymph nodes (HR = 1.62; 95% CI = 1.49–1.77; $p < .0001$). Primary treatment with RT or CRT resulted in poorer survival (HR = 1.33; 95% CI = 1.21–1.47; $p < .0001$; and

HR = 1.26; 95% CI = 1.07–1.49; $p = .006$, respectively) compared to treatment with total laryngectomy + adjuvant RT. HRs for dying increased with increasing age. Women had a lower HR for dying when compared to men (HR = 0.88; 95% CI = 0.80–0.97; $p = .01$).

When analyzed separately by T classification, patients with T3 laryngeal cancer had higher HRs for dying in case of positive lymph nodes (HR = 1.66; 95% CI = 1.48–1.87; $p < .0001$), in case they were men, and with increasing age. For patients with T4 laryngeal cancer, HRs for dying were higher in case of positive lymph nodes (HR = 1.56; 95% CI = 1.37–1.76; $p < .0001$), primary treatment with RT or CRT (when compared to total laryngectomy + adjuvant RT: HR = 1.50; 95% CI = 1.33–1.71;

$p < .0001$; and HR = 1.27; 95% CI = 1.01–1.59; $p = .04$, respectively), and with increasing age.

In Figures 4A and 4B, it seems that there is a change in treatment around 2000 to 2002 with an increase in RT and a decrease in total laryngectomy, which levels off a few years later. As mentioned earlier in the Introduction, a consensus document on laryngeal cancer diagnostics and treatment was published in 1999 and implemented in 2000.⁹ Therefore, in multivariable analysis, separately for T3 and T4 laryngeal cancer, we also compared the first with the second decade, adding an interaction term for the 2 decades and primary treatment (because of their changes over time). This additional analysis revealed that there is no significant difference in survival between the 2 decades based on treatment (data not shown).

Laryngectomy-free interval

Eighty-one percent of the patients with T3 laryngeal cancer treated with RT retained their larynx at 5 years (5-year LFI: 81%) and 78% at 10 years (10-year LFI: 78%). After treatment with CRT, these rates were similar: both 77% after 5 and 10 years (Figure 7A). LFI for patients with T4 laryngeal cancer and primary treatment with RT were 81% and 75% after 5 and 10 years, respectively. After treatment with CRT, these numbers were higher: 87% and 82% after 5 and 10 years, respectively ($p = .076$; Figure 7B).

DISCUSSION

This population-based study, comprising all Dutch patients diagnosed with laryngeal squamous cell carcinoma between 1991 and 2010 present in 2 national cancer registries, indeed enabled answering the 4 research questions raised at the end of the Introduction (trends in proportion of total laryngectomy for T3 and T4, time trends for all treatment modalities, 5-year OS rates, and 5-year LFI).

For both T3 and T4 laryngeal cancer, the use of primary total laryngectomy as a proportion of all patients diagnosed with T3 and T4 laryngeal cancer decreased, whereas the use of RT increased. Hoffman et al⁶ also observed a decrease in the number of total laryngectomies as primary treatment for laryngeal cancer and an increase in RT and chemotherapy (1985–2001), but that study included all laryngeal cancer cases and not only the advanced cases as in the present study. The decrease in total laryngectomies and increase in RT for T3 laryngeal cancer in our study is not unexpected, because the Dutch guidelines for treating laryngeal cancer changed in 1999 after the publication of a consensus document by the Dutch Head and Neck Society (former Dutch Cooperative Head and Neck Oncology Group).^{9,17} Until that time, patients with T3 and T4 laryngeal cancer in most centers preferably were treated with total laryngectomy with or without adjuvant RT. After the publication of this consensus document, which was also based on published data from The Netherlands,¹⁰ patients with T3 laryngeal cancer were preferably irradiated and patients with T4 laryngeal cancers in most centers were still laryngectomized and received adjuvant RT. This policy, in essence, did not change after the publication of the RTOG 91-11 study

in 2003, although CRT became more popular in The Netherlands as well.

OS of T3 and T4 laryngeal cancer differs significantly (44% and 39%, respectively, after 5 years). When analyzed per treatment, OS is similar for T3 laryngeal cancer after treatment with total laryngectomy, RT, or CRT. For T4 laryngeal cancer, however, patients treated with RT or CRT have poorer survival compared with patients treated primarily with total laryngectomy and adjuvant RT. In a population-based study in the Province of Alberta, Canada, Dziegielewski et al¹⁸ also found superior survival rates after treatment with total laryngectomy for T4 laryngeal cancer. Furthermore, Chen and Halpern⁷ reported HRs for death of 1.61 and 1.43 for RT and CRT, respectively, when compared to total laryngectomy for stage IV laryngeal cancer, which are in line but slightly higher than found in the present study. It has to be kept in mind, though, that stage IV also includes T3N+ cancers and, thus, not solely T4 cancers.

A possible explanation for the inferior survival after RT for T4 laryngeal cancer may be due to unknown selection biases, such as comorbidity, the patient and physician preferences, intent of the treatment, and tumor characteristics, such as tumor volume and operability of the tumor. Possibly, a subgroup of patients who underwent RT for T4 laryngeal cancer had inoperable disease or had significant comorbidity and was treated with palliative intent.

The majority of the patients with T4 laryngeal cancer who were primarily treated with total laryngectomy, received postoperative RT. These patients had superior survival rates when compared to those not undergoing RT. In the Dutch consensus document on laryngeal cancer (1999), it is recommended to add RT in case surgery is the treatment of choice.⁹ This recommendation was based on several studies that suggest that RT in the postoperative setting improves oncologic outcome,^{19,20} which is underlined (again) in the present study.

As reported earlier by van Dijk et al,¹¹ the decrease in survival that was seen in the United States does not seem to apply for The Netherlands. Hoffman et al⁶ attributed their decrease in survival to the increase of the use of organ-preserving treatment modalities, such as RT and CRT. That we do not see a difference in survival for T3 laryngeal cancer after treatment with total laryngectomy, RT, or CRT might be due to several factors. First, head and neck cancer care is highly centralized in The Netherlands in the 8 centers participating in the Dutch Head and Neck Society, which guarantees treatment by dedicated head and neck specialists. This possible centralization effect (bigger volume – better outcome) is underlined by the comparatively favorable survival figures for laryngeal cancer achieved in The Netherlands according to the European cancer statistics published by Sant et al²¹ in 2009. Second, since the late 1990s, The Netherlands altered fractionated RT as widely used for advanced laryngeal cancers in most centers, which seems to be superior to conventional schemes of RT regarding local control and survival in head and neck cancer.²² In some centers, the ARCON protocol was used for many years involving accelerated RT in combination with carbogen inhalation and nicotinamide.²³ The clinical relevance of

the similar survival figures for T3 laryngeal cancer in this study is that patients should be extensively counseled about the various pros and cons of the 3 options (ie, total laryngectomy, RT, and CRT), in order to be able to make a well-informed choice.

As expected, patients with positive lymph nodes in the neck have poorer survival when compared with patients without positive lymph nodes, which is in concordance with the literature.^{24,25}

LFI for patients with T3 or T4 laryngeal cancer after RT or CRT was 77% or higher after 5 years. This finding is in agreement with the literature. In the VA study, the larynx was preserved in 64% of the patients after 2 years for patients initially treated with induction chemotherapy combined with RT.¹ The RTOG 91-11 study reported larynx preservation rates (a synonymous term for LFI) after 10 years of 82% and 64% after treatment with concurrent chemoradiation and RT alone, respectively.⁴

An interesting and noteworthy finding is the reversed distribution of subsite for patients with T3 to T4 laryngeal cancer, when compared to T1 to T2 laryngeal cancer. In the advanced stages, supraglottic cancer occurred twice as often as glottic cancer. These numbers are in concordance with the distribution of patients in the RTOG 91-11 study.^{2,4}

Although T and N classification, sex, and age are important in predicting survival and larynx preservation, many other factors play a role in decision-making and patient counseling for treatment selection. Among these are comorbidity and general condition, tumor volume, and patient and doctor preferences. In the future, possibly, markers predicting response and larynx preservation will become more important.²⁶ Nomograms, as developed by Egelmeier et al²⁷ and Sherman et al,²⁸ might become more useful.

Limitations

In the NCR and PALGA database, data regarding comorbidity, treatment intentions, locoregional control, functional outcome, toxicity, patient and physician preferences, tumor characteristics, such as tumor volume and operability of the tumor, and quality of life are not recorded. These data are also important in evaluating and understanding treatment results.

Another limitation of this study was that, in 2003, the definition of T classification changed (fifth to sixth edition of TNM classification of the Union for International Cancer Control). This is probably (in part) the explanation of the fact that patients with T3 laryngeal cancer increased over the study period, whereas the number of patients with T4 laryngeal cancer decreased. In the description for T3 and T4 laryngeal cancer in the fifth edition, the presence of cartilage erosion or invasion was reserved for T4. In the sixth edition, however, (minor) cartilage erosion was declassified as a T3 laryngeal cancer, with extralaryngeal spread being required for T4 classification. The T3 category now might be more unfavorable than before, but at the same time the T4 category has “lost” its most favorable subgroup, and, thus, also would be more unfavorable. Furthermore, incidence of laryngeal cancer decreased, most likely as a result of a decrease in smoking.

In 1991 and 1992, there were smaller numbers of total laryngectomies than expected. This can be explained by

the fact that only patients were included that were “diagnosed” with laryngeal cancer between 1991 and 2010. Thus, patients diagnosed in the years preceding 1991 and laryngectomized in 1991 and 1992 for recurrent disease were not included in this study.

CONCLUSIONS

In conclusion, total laryngectomy as primary treatment for advanced laryngeal cancer decreased and RT increased between 1991 and 2010 in The Netherlands. T3 laryngeal cancer showed similar survival with all 3 primary treatment modalities (total laryngectomy, RT, or CRT). After RT or CRT, 4 of 5 larynges are preserved both in T3 and T4 cancers after 5 years. Patients with T4 laryngeal cancer treated with total laryngectomy and adjuvant RT have a better survival than after RT or CRT.

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