Advanced larynx cancer. Trends and treatment outcomes
Timmermans, A.J.

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CHAPTER 4

Trends in treatment and survival of advanced larynx cancer: a 20-year population-based study in the Netherlands

A.J. Timmermans  
B.A.C. van Dijk  
L.I.H. Overbeek  
M.L.F. van Velthuysen  
H. van Tinteren  
F.J.M. Hilgers  
M.W.M. van den Brekel

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ABSTRACT

Background: Determining time trends for primary treatment modalities in advanced larynx cancer (LC), overall survival (OS) and laryngectomy-free interval (LFI) over the last two decades in the Netherlands.

Methods: Analysis of T3-4 LC data from two combined national (population-based, and pathology-based) cancer registries.

Results: 2,072 (14.7%) T3, and 1,722 (12.2%) T4 cases were identified. Total laryngectomy (TL) as primary treatment modality decreased, whereas radiotherapy (RT) increased. For T3 disease, 5-year OS after primary TL (+/- adjuvant-RT), RT and chemoradiotherapy (CRT) was 49%, 47% and 45% respectively. For T4 this was 48%, 34% and 42% (overall p<0.0001) respectively. 5-year LFI for T3 were 81% (RT) and 77% (CRT), and for T4 81%, and 87%, respectively.

Conclusions: From 1991-2010 TL as primary treatment modality for advanced LC decreased and RT increased. T3 disease showed similar survival rates for all primary treatment modalities. For T4 disease TL (+adjuvant-RT) showed the best survival.
INTRODUCTION

Primary treatment options for advanced larynx cancer are radiotherapy (RT), concomitant chemoradiotherapy or total laryngectomy (TL) with or without adjuvant RT. Of these treatments, TL with adjuvant RT has long been considered the gold standard. However, since this organ-sacrificing surgery often results in significant morbidity leading to psychosocial, vocal, pulmonary and olfactory problems, other options for treatment, e.g. partial laryngectomy and RT, have gained in popularity. After the publication of two randomized studies, organ-preserving (chemo-)radiotherapy treatment protocols are increasingly being used as alternative to TL (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 TL 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=0.05) higher survival rate after treatment with TL (3). A decade later, the 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 larynx cancer were excluded because of their better survival after TL in the VA study. The RTOG 91-11 study concluded that concurrent chemoradiation was superior to induction chemotherapy combined with RT or RT alone in terms of larynx preservation and loco-regional control, but similar in terms of overall survival (2, 4).

The shift towards organ-preserving treatment protocols has been postulated as a possible cause of the lack of gradual survival improvement for larynx cancer, when compared to other head and neck sites (5, 6). E.g., in 2006, Hoffman et al. reported decreasing survival for larynx cancer patients from the mid-80s to the mid-90s in the US (6). 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 2007, Chen et al. aimed to determine factors predictive for survival in patients with advanced larynx cancer. The authors reported a hazard ratio for death of 1.6 for RT and 1.3 for CRT when compared to treatment with TL (7). Since then, there has been a debate on whether or not TL should be performed more often in (a selection of) patients with advanced larynx 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 larynx cancer diagnostics and treatment in 1999 (9). This document contained evidence-based protocols on all stages of larynx 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 larynx
cancers in most centers preferably would be treated with TL, from then on patients with T3 larynx cancer received RT, in line with the consensus protocol then drafted. For T4 larynx cancer, TL plus adjuvant RT remained the preferred treatment modality. Van Dijk et al. (2013) recently published a study reporting a declining incidence and a stable relative survival of around 70% for all larynx cancer cases from 1989 to 2010 (11). Thus, although no decreasing survival was seen as in the US, survival rates did not increase either.

Since the introduction of RT and CRT as primary treatment modalities for patients with advanced larynx cancer, TL (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 TL 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 TL because of a dysfunctional larynx after prior RT or CRT (14).

In the Netherlands, there are two unique databases for cancer: the Netherlands Cancer Registry (NCR) and the PALGA foundation database (‘the nationwide network and registry of histo- and cytopathology in the Netherlands’ (15)). Combining these two databases now makes it possible to conduct a population-based cohort study on advanced larynx cancer with the following research questions: (1) What is the trend in proportion of TLs for T3-T4 larynx cancer in the period from 1991 to 2010? (2) What is the trend in primary treatment (primary TL (+/- adjuvant RT), RT and CRT) for T3-T4 larynx cancer? (3) What is the 5-year overall survival (OS) of patients with T3-T4 larynx cancer? (4) What is the laryngectomy-free interval (LFI) after RT or CRT for T3-T4 larynx 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 MREC. 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 larynx cancer, to identify whether “surgery” meant TL and whether TL was conducted for salvage or for a dysfunctional larynx.
Patient selection

The database from the NCR included 14,080 patients diagnosed with invasive larynx 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; according to the International Classification of Disease for Oncology (ICD-O-3)(16)), primary treatment (surgery/RT/CT), follow-up status (alive, emigrated, deceased), and follow-up time. Follow-up time was defined as time from date of incidence to date of last follow-up (31 December 2013). Date of incidence was defined as date of first histological or cytological confirmation of the tumor, or first admission in relation to this tumor.

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

Clinical staging was used, since the pathological stage is unavailable in case of primary treatment with RT and/or CRT. cT1A and cT1B were grouped as T1 and cT4A and cT4B as T4. cNX/missing was coded as N0 in case a cT-classification was known. cT0 or cTis larynx 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. cT-classification will be referred to as T-classification. Patients with T1 larynx cancer (N=5,573), T2 larynx cancer (N=4,008), distant metastases prior to primary treatment (N=150), cTX (N=499), non-squamous cell cancer (N=56) were excluded leaving 3,794 patients with T3-4N0-3M0 larynx cancer for analysis.

Treatment

Merging the databases enabled identifying primary treatment coded as “surgery” in the NCR database as a primary TL or partial laryngectomy. In case primary treatment was not a TL or a partial laryngectomy, “surgery” was coded as “treatment 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 TLs that were not part of the primary treatment. To determine the indication for a TL, a cut-off value was chosen of 120 days between date of incidence and date of TL. TL performed within these 120 days was considered a primary TL. In case the TL was performed at least 120 days after the incidence date, the TL was coded as salvage procedure, or as TL for a dysfunctional larynx. The distinction between salvage TL and TL for a dysfunctional larynx was made based on the presence of malignancy (salvage) or not (dysfunctional larynx) in the pathology report. We chose a cut-off 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 (TL (+/-RT), RT and CRT), laryngectomy-free Interval (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 date of incidence until TL or censoring (death or last date of follow-up). Patients at risk were defined as patients that 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 31 December 2013. Patients without follow-up (date of incidence and date of loss-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 TLs over the years (1993-2010). The percentage of TLs (total numbers and per indication) was calculated counting the number of TLs divided by the number of patients diagnosed with T3 or T4 larynx cancer. The percentage of TL, RT and CRT was calculated counting the number of treatments divided by the number of all patients diagnosed with T3 or T4 larynx 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 in 5 groups. Hazard ratios and 95% confidence levels were estimated. Variables with a p-value < 0.05 were considered statistically significant. Analyses were performed using IBM® SPSS® Statistics 20.0.

RESULTS

Patient, tumor and treatment characteristics
Detailed information on patient, tumor and treatment characteristics is shown in Table 1. The male to female ratio was 3.7:1 and the mean age was 64.1 years (range 28-100 years). Overall, most T3-4 patients had supraglottic cancer (63.1%), followed by glottic cancer (31.0%). A minority had subglottic cancer (2.6%) or larynx not otherwise specified (3.3%). Noteworthy is that the distribution of subsite was reversed for patients with T1-T2 larynx cancer (N=9581): glottic cancer occurred in 78.6% of the patients, followed by supraglottic cancer (19.9%) (Figure 1).
Over this 20-year period, the number of patients with T3 larynx cancer increased (Linear-by-Linear: p=0.001) and with T4 larynx cancer decreased (Linear-by-Linear: p=0.003) (Figure 2).

Table 1. Patient and tumor characteristics at time of primary treatment (N=number; NOS=not otherwise specified; TL=total laryngectomy; RT=radiotherapy; CRT=chemoradiotherapy)

<table>
<thead>
<tr>
<th>Total (N, %)</th>
<th>Primary TL (N, %)</th>
<th>RT (N, %)</th>
<th>CRT Partial laryngectomy (N, %)</th>
<th>CT (N, %)</th>
<th>No treatment/treatment NOS (N, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=3794 (100)</td>
<td>1172 (30.9)</td>
<td>2018 (53.2)</td>
<td>265 (7.0)</td>
<td>27 (0.7)</td>
<td>14 (0.4)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2991 (78.8)</td>
<td>971 (82.8)</td>
<td>1554 (77.0)</td>
<td>191 (72.1)</td>
<td>19 (70.4)</td>
</tr>
<tr>
<td>Female</td>
<td>803 (21.2)</td>
<td>201 (17.2)</td>
<td>464 (23.0)</td>
<td>74 (27.9)</td>
<td>8 (29.6)</td>
</tr>
<tr>
<td>Mean age (range)</td>
<td>64.1 (28-100)</td>
<td>62.8 (31-89)</td>
<td>64.7 (28-100)</td>
<td>58.4 (34-80)</td>
<td>59.0 (39-71)</td>
</tr>
<tr>
<td>Subsite</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supraglottic</td>
<td>2394 (63.1)</td>
<td>651 (55.5)</td>
<td>1307 (64.8)</td>
<td>220 (83.0)</td>
<td>26 (96.3)</td>
</tr>
<tr>
<td>Glottic</td>
<td>1175 (31.0)</td>
<td>420 (35.8)</td>
<td>625 (31.0)</td>
<td>35 (13.2)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Subglottic</td>
<td>98 (2.6)</td>
<td>44 (3.8)</td>
<td>39 (1.9)</td>
<td>5 (1.9)</td>
<td>-</td>
</tr>
<tr>
<td>Larynx NOS</td>
<td>127 (3.3)</td>
<td>57 (4.9)</td>
<td>47 (2.3)</td>
<td>5 (1.9)</td>
<td>-</td>
</tr>
<tr>
<td>TN T3NO</td>
<td>1329 (35.0)</td>
<td>177 (15.1)</td>
<td>1011 (50.1)</td>
<td>53 (20.0)</td>
<td>8 (29.6)</td>
</tr>
<tr>
<td>T3N+</td>
<td>743 (19.6)</td>
<td>147 (12.5)</td>
<td>447 (22.2)</td>
<td>89 (33.6)</td>
<td>5 (18.5)</td>
</tr>
<tr>
<td>T4N0*</td>
<td>983 (25.9)</td>
<td>495 (42.2)</td>
<td>362 (17.9)</td>
<td>35 (13.2)</td>
<td>7 (25.9)</td>
</tr>
<tr>
<td>T4N+*</td>
<td>739 (19.5)</td>
<td>353 (30.1)</td>
<td>198 (9.8)</td>
<td>88 (33.2)</td>
<td>7 (25.9)</td>
</tr>
</tbody>
</table>

* The total of 1722 patients with a T4 larynx cancer, there were 1208 non-specified T4 cases, 489 T4a cases and 25 T4b cases (of which 4 underwent a TL).

Figure 1. The distribution of tumor site per T-classification
Figure 2. Number of patients diagnosed with T3 larynx cancer and T4 larynx cancer from 1991 to 2010. Over this 20-year period, the number of patients with T3 larynx cancer increased (p=0.001) and with T4 larynx cancer decreased (p=0.003)

**Trends in total laryngectomy**

Figure 3 shows the total number of TLs and per indication (primary TL, salvage TL and TL for a dysfunctional larynx) as a percentage of all patients with T3-T4 larynx cancer over the years 1991-2010 (N=3,794). There was a decrease of 3.07 TLs per year (p < 0.0001; calculated from 1993 to 2010). The use of a TL as primary treatment declined (-3.30 TLs per year; p < 0.0001), whereas numbers of salvage TLs and TLs for a dysfunctional larynx remained stable.

Figure 3. Number of total laryngectomies (TL). Lines indicate total number of TLs and per indication (primary TL, salvage TL and TL for a dysfunctional larynx) as percentage of patients with T3-T4 larynx cancer over the years 1991-2010 (N=3,794; absolute numbers for the years 1995, 2003 and 2010)
Trends in treatment and survival of advanced larynx cancer

Trends in treatment of advanced larynx cancer

When compared to TL (mean age: 62.8 years (range 31-89)), patients primarily treated with CRT were significantly younger (mean age: 58.4 years (range 34-80 years; p < 0.0001)) and patients undergoing RT significantly older (mean age: 64.7 years (range 28-100 years; p=0.001)).

Figures 4a and b show the trend in primary treatment for T3 and T4 larynx cancer patients from 1991 to 2010. For both T3 and T4 larynx cancer the use of primary TL as proportion of all patients with T3 or T4 larynx cancer decreased, whereas the use of RT increased. In both figures, the trend appears to change in 2000-2002 with an increase in RT and a decrease in TL which levels off a few years later.

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

Figure 4a. Treatment modalities for T3 larynx cancer from 1991 to 2010 (primary treatment divided by total number of patients diagnosed with T3 larynx cancer that year, in%).

Figure 4b. Treatment modalities for T4 larynx cancer from 1991 to 2010 (primary treatment divided by total number of patients diagnosed with T4 larynx cancer that year, in%).
Figure 4b. Treatment modalities for T4 larynx cancer from 1991 to 2010 (primary treatment divided by total number of patients diagnosed with T4 larynx cancer that year, in %).

**Overall survival**

The OS for T3 and T4 larynx cancer after 5 years for T3 larynx cancer was 44% and for T4 39% (Log-Rank: p<0.0001; including all treatment modalities). Median OS was 3.81 years for T3 (95% CI: 3.42-4.20) and 2.83 years (95% CI: 2.51-3.15) for T4 larynx cancer.

Figure 5a shows the OS for patients with T3 larynx cancer. OS rates after TL, RT and CRT were similar: 49%, 47% and 45% respectively after 5 years (Log-rank: overall p=0.539). No significant differences were found between the patients that did and did not receive adjuvant RT after TL (47% and 56% respectively; Log-Rank: p=0.442) (Figure 5b). When analyzed for supraglottic and glottis tumors separately, no significant differences were found between tumor site.
Figure 5a. Overall survival for T3 larynx cancer for total laryngectomy (TL; n=324), radiotherapy (RT; n=1456) and radiotherapy combined with chemotherapy (CRT; n=142) separately.

Figure 5b. Overall survival for T3 larynx cancer for total laryngectomy (n=324) without radiotherapy (RT; n=75) or with RT (n=249).

Figure 6a shows the OS for patients with T4 larynx cancer. For these patients, 5-year OS after TL (48%) was better than after RT (34%) or after CRT (42%) (Log-Rank: overall p<0.0001). Patients who received adjuvant RT after TL had significant better survival than patients not undergoing RT (49% and 42% respectively; Log-Rank: p=0.047) (Figure 6b). When analyzed for supraglottic and glottis tumors separately, no significant differences were found between tumor site.
Table 2 shows a multivariable analysis for OS of primarily treated T3 or T4 larynx cancer patients. Patients with T4 larynx cancer have a higher hazard ratio (HR) for dying when compared to patients with T3 larynx cancer (HR 1.21 (95% CI 1.11-1.32; p<0.0001)). This was also the case for patients with positive lymph nodes when compared to patients without positive lymph nodes (HR 1.62 (95% CI 1.49-1.77; p<0.0001). Primary treatment with RT or CRT resulted in poorer survival (HR 1.33 (95% CI 1.21-1.47; p<0.0001) respectively HR 1.26 (95% CI 1.07-1.49; p=0.006)) compared to treatment with TL+adjuvant RT. HRs for dying increased with increasing age. Females had a lower hazard ratio for dying when compared to males (HR 0.88 (95% CI 0.80-0.97; p=0.01).
Table 2. Multivariable analysis calculating overall survival using Cox regression analysis including all patients with T3 or T4 larynx cancer and separately for T3 and T4 larynx cancer (HR = hazard ratio; TL = total laryngectomy; adj RT = adjuvant radiotherapy; CRT = chemoradiotherapy; NOS = not otherwise specified). The given hazard ratios are hazard ratios for death.

<table>
<thead>
<tr>
<th></th>
<th>T3+T4 larynx cancer</th>
<th>T3 larynx cancer</th>
<th>T4 larynx cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 95% CI p-value</td>
<td>HR 95% CI p-value</td>
<td>HR 95% CI p-value</td>
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<tr>
<td><strong>Primary treatment</strong></td>
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<tr>
<td>TL+adj RT</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>TL alone</td>
<td>1.09 0.93-1.29 0.29</td>
<td>0.94 0.70-1.26 0.66</td>
<td>1.12 0.92-1.37 0.25</td>
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<tr>
<td>RT</td>
<td>1.33 1.21-1.47 &lt;0.0001</td>
<td>1.09 0.93-1.28 0.28</td>
<td>1.50 1.33-1.71 &lt;0.0001</td>
</tr>
<tr>
<td>CRT</td>
<td>1.26 1.07-1.49 0.006</td>
<td>1.11 0.86-1.43 0.41</td>
<td>1.27 1.01-1.59 0.04</td>
</tr>
<tr>
<td><strong>Age</strong></td>
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<tr>
<td>&lt; 50</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>50-59</td>
<td>1.34 1.14-1.58 &lt;0.0001</td>
<td>1.55 1.22-1.97 &lt;0.0001</td>
<td>1.20 0.96-1.49 0.11</td>
</tr>
<tr>
<td>60-69</td>
<td>2.00 1.71-2.33 &lt;0.0001</td>
<td>2.22 1.76-2.79 &lt;0.0001</td>
<td>1.81 1.46-2.24 &lt;0.0001</td>
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<td>70-79</td>
<td>3.01 2.56-3.55 &lt;0.0001</td>
<td>3.62 2.85-4.59 &lt;0.0001</td>
<td>2.52 2.01-3.17 &lt;0.0001</td>
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<tr>
<td>≥ 80</td>
<td>5.20 4.28-6.35 &lt;0.0001</td>
<td>6.92 5.21-9.18 &lt;0.0001</td>
<td>4.06 3.08-5.37 &lt;0.0001</td>
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<tr>
<td><strong>Sex</strong></td>
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<tr>
<td>Male</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Female</td>
<td>0.88 0.80-0.97 0.01</td>
<td>0.85 0.75-0.97 0.02</td>
<td>0.91 0.78-1.05 0.20</td>
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<td><strong>T-classification</strong></td>
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<tr>
<td>T3</td>
<td>1.00</td>
<td></td>
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</tr>
<tr>
<td>T4</td>
<td>1.21 1.11-1.32 &lt;0.0001</td>
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<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>N+</td>
<td>1.62 1.49-1.77 &lt;0.0001</td>
<td>1.66 1.48-1.87 &lt;0.0001</td>
<td>1.56 1.37-1.76 &lt;0.0001</td>
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<td><strong>Subsite</strong></td>
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<tr>
<td>Supraglottic</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Glottic</td>
<td>0.92 0.84-1.01 0.09</td>
<td>0.92 0.82-1.05 0.22</td>
<td>0.92 0.80-1.05 0.21</td>
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<tr>
<td>Subglottic</td>
<td>1.01 0.79-1.29 0.96</td>
<td>1.09 0.66-1.83 0.73</td>
<td>0.98 0.73-1.30 0.87</td>
</tr>
<tr>
<td>Larynx NOS</td>
<td>1.45 1.18-1.78 &lt;0.0001</td>
<td>1.16 0.83-1.61 0.38</td>
<td>1.71 1.31-2.24 &lt;0.0001</td>
</tr>
</tbody>
</table>

When analyzed separately by T-classification, patients with T3 larynx cancer had higher HRs for dying in case of positive lymph nodes (HR 1.66 (95% CI 1.48-1.87; p<0.0001)), in case they were male, and with increasing age. For patients with T4 larynx cancer, HRs for dying were higher in case of positive lymph nodes (HR 1.56 (95% CI 1.37-1.76; p<0.0001)), primary treatment with RT or CRT (when compared to TL+adjuvant RT: HR 1.50 (95% CI 1.33-1.71; p<0.0001) respectively HR 1.27 (95% CI 1.01-1.59; p=0.04)) and with increasing age.

In figure 4a and 4b it appears that there is a change in treatment around 2000-2002 with an increase in RT and a decrease in TL, which levels off a few years later. As mentioned earlier in the Introduction, a consensus document on larynx cancer diagnostics and treatment was published in 1999 and implemented in 2000 (9). Therefore, in multivariable analysis, separately for T3 and T4 larynx cancer, we also compared the first with the second decade, adding an interaction term for the two decades and primary treatment (because of their changes over time). This additional analysis revealed that there is no significant difference in survival between the two decades based on treatment (data not shown).
Laryngectomy-free interval

Eighty-one percent of the T3 larynx cancer patients 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 larynx 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=0.076; figure 7b).

**Figure 7a.** Laryngectomy-free interval (LFI) for patients with T3 larynx cancer (N=1598) primarily treated with radiotherapy (N=1456) or radio- and chemotherapy (N=142) using Kaplan-Meier survival analysis (LFI was determined using follow-up time, which was calculated starting from date of incidence until total laryngectomy or censoring (death or last date of follow-up))

**Figure 7b.** Laryngectomy-free interval (LFI) for patients with T4 larynx cancer (N=683) primarily treated with radiotherapy (N=560) or radio- and chemotherapy (N=123) using Kaplan-Meier survival analysis (LFI was determined using follow-up time, which was calculated starting from date of incidence until total laryngectomy or censoring (death or last date of follow-up))
DISCUSSION

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

For both T3 and T4 larynx cancer, the use of primary TL as a proportion of all patients diagnosed with T3 and T4 larynx cancer decreased, whereas the use of RT increased. Hoffman et al. (2006) also observed a decrease in number of TLs as primary treatment for larynx cancer and an increase in RT and chemotherapy (1985-2001), but that study included all larynx cancer cases and not only the advanced cases as in the present study (6). The decrease in TLs and increase in RT for T3 larynx cancer in our study is not unexpected, since the Dutch guidelines for treating larynx cancer changed in 1999 after the publication of a consensus document by the Dutch Head and Neck Society (DHNS, former Dutch Cooperative Head and Neck Oncology Group) (9, 17). Until that time, patients with T3 and T4 larynx cancer in most centers preferably were treated with TL 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 larynx cancer were preferably irradiated and patients with T4 larynx 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 larynx cancer differs significantly (44% and 39% respectively after 5 years). When analyzed per treatment, OS is similar for T3 larynx cancer after treatment with TL, RT or CRT. For T4 larynx cancer however, patients treated with RT or CRT have poorer survival compared to patients treated primarily with TL and adjuvant RT. In a population-based study in the Province Alberta, Canada, Dziegielewski et al. (2012) also found superior survival rates after treatment with TL for T4 larynx cancer (18). Furthermore, Chen et al. (2007) reported HRs for death of 1.61 and 1.43 for RT and CRT respectively when compared to TL for stage IV larynx 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 (7).

A possible explanation for the inferior survival after RT for T4 larynx cancer may be due to unknown selection biases, such as co-morbidity, 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 larynx cancer had inoperable disease or had significant co-morbidity and was treated with palliative intent.
The majority of the T4 cases who were primarily treated with TL, received postoperative RT. These patients had superior survival rates when compared to those not undergoing RT. In the Dutch consensus document on larynx 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 oncological outcome (19, 20), which is underlined (again) in the present study.

As reported earlier by Van Dijk et al. (2013) the decrease in survival that was seen in the United States does not seem to apply for the Netherlands (11). Hoffman et al. (2006) 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 larynx cancer after treatment with TL, RT or CRT might be due to several factors. Firstly, head and neck cancer care is highly centralized in the Netherlands in the 8 centres participating in the DHNS, which guarantees treatment by dedicated head and neck specialists. This possible centralisation effect (bigger volume - better outcome) is underlined by the comparatively favorable survival figures for larynx cancer achieved in the Netherlands according to the European cancer statistics published by Sant et al. in 2009 (21). Secondly, since the late nineties in the Netherlands altered fractionated RT is widely used for advanced larynx 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 larynx cancer in this study is that patients should be extensively counseled about the various pro’s and con’s of the three options, i.e. TL, RT and CRT, in order to be able to take a well-informed choice.

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

LFI for patients with T3 or T4 larynx 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-T4 larynx cancer, when compared to T1-T2 larynx 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 TN 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 co-morbidity 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 Egelmeer et al. and Sherman et al. might become more useful (27, 28).

**Limitations**

In the NCR and PALGA database, data regarding co-morbidity, treatment intentions, loco-regional 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 is that in 2003 the definition of T-classification changed (5th to 6th edition of TNM-staging of the UICC). This is probably (in part) the explanation of the fact that patients with T3 larynx cancer increased over the study period, whereas the number of patients with T4 larynx cancer decreased. In the description for T3 and T4 larynx cancer in the 5th edition, the presence of cartilage erosion or invasion was reserved for T4. In the 6th edition however, (minor) cartilage erosion was de-classified as a T3 larynx cancer, with extra-laryngeal 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 larynx cancer decreased, most likely as a result of a decrease in smoking.

In 1991 and 1992, there was a smaller number of TLs than expected. This can be explained by the fact that only patients were included that were *diagnosed* with larynx cancer between 1991 and 2010. Patients diagnosed in the years preceding 1991 and laryngectomized in 1991 and 1992 for recurrent disease, were thus not included in this study.

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


Trends in treatment and survival of advanced larynx cancer


