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Laryngo-esophageal dysfunction free survival and propensity score matched analysis comparing organ preservation and total laryngectomy in hypopharynx cancer

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ABSTRACT

Aims: To assess the functional outcomes of patients treated for hypopharynx cancer and to obtain an unbiased estimate of survival difference between patients treated with chemoradiotherapy (CRT) or total laryngectomy (TL).

Methods: Retrospective cohort study of all patients treated with curative intent for T1-T4 squamous cell carcinoma of the hypopharynx in The Netherlands Cancer Institute (1990–2013). Functional outcome following radiotherapy (RT) or CRT was measured using laryngo-esophageal dysfunction free survival rate (LDFS). Using propensity score (PS) matched analysis, we compared survival outcome of TL to CRT in T2-T4 patients.

Results: We included 343 patients with T1T4 hypopharynx cancer. LDFS 2 and 5-years following CRT was respectively 44 and 32%. Following RT this was 39 and 30%. Patients were matched on the following variables: age, gender, TNM classification, subsite of tumor, decade of diagnosis, prior cancer, smoking, ACE27 score, BMI hemoglobin, albumin, and leukocyte level. With PS matching, we were able to match 26 TL patients with 26 CRT patients. The OS rates for TL and CRT in this matched cohort were respectively 56% and 46% at 5 years and 35% and 17% at 10 years.

Conclusion: In conclusion, functional outcomes following RT or CRT are suboptimal and require improved treatment strategies or rehabilitation efforts. The OS results challenge the preposition that CRT and TLE are equivalent in terms of survival.

Introduction

Each year, an estimated 3,000 people in the US will be diagnosed with hypopharynx cancer and face one of the worst prognoses of all head and neck squamous cell malignancies [1]. Intensive treatment protocols yield limited success in terms of overall survival (OS). The average 5-year OS rate varies between 28 and 41%, although this rate is improving [1–3].

While there is little doubt about organ preservation therapy in smaller tumors, for advanced T4 tumors there is no consensus whether organ preservation with chemoradiotherapy (CRT) versus a total laryngectomy (TL) yields higher OS rates. Recently, several publications have demonstrated the superiority of TL vs. CRT in advanced T4 larynx cancer [4,5], but there is a paucity of studies reporting on the effect of TL versus CRT on survival in advanced hypopharynx cancer [3,6,7]. Currently, most national guidelines advise to use organ preservation whenever possible, and as a consequence, the rate of primary TLs for hypopharynx cancer is gradually declining [8].

In light of the increasing use of organ preservation therapy, optimizing functional outcomes has become more important. Although CRT aims to spare the larynx surgically, laryngeal function can be severely hampered on the long term; patients can experience dysphonia,

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swallowing complaints, require repeated dilatations because of pharyngeal stenosis, be tube-feeding dependent, or can become tracheotomy dependent years after treatment [9,10]. Around 11% of patients are left with a non-functioning larynx after organ preservation treatment and require a TL for functional reasons [11]. On the other hand, following a TL, patients can also have severe functional problems and will have to master pulmonary, vocal and swallowing rehabilitation [12]. Furthermore, they might experience surgical complications on the short term, and social distress or loss of self-esteem on the long-term [13].

Given the lack of consensus as to whether TL or CRT is the optimal treatment for advanced hypopharynx cancer and the scarcity of RCTs on this topic, population-based observational studies provide the best possible evidence regarding oncological and functional survival. However, in these studies, confounding by indication can produce a significant risk of bias. Confounding by indication arises when (prognostic) baseline variables that influence choice of treatment are not properly accounted for. To control for this issue in the comparison of OS, a propensity score (PS) matched analysis can be performed. Therefore, the aim of this study was to assess the functional outcomes in patients treated with organ preservation (RT or CRT), by describing the laryngo-esophageal dysfunction free survival rate (LDFS), and to obtain an unbiased estimate of survival difference between patients treated with CRT or TL, using PS matching. Laryngo-esophageal dysfunction free survival rate is defined as the proportion of patients surviving without a local recurrence or laryngectomy and do not have a feeding tube or a tracheostomy in situ.

Materials and methods

We performed a retrospective cohort study of all patients diagnosed and treated with curative intent for hypopharynx cancer in The Netherlands Cancer Institute between February 1990 and February 2013, allowing for a minimum follow-up of 5 years for all patients. Patient numbers were received from the scientific information department, who record all patients treated in our institute with the tumor location according to the International Classification of Disease for Oncology (ICD-0-3), date of diagnosis, status and last date of follow-up. Patient and tumor specific variables were retrospectively collected from the (scanned) patient files to assess their impact on overall survival and LDFS. Events for the composite endpoint LDFS were death from any cause, recurrence, TL, and presence of a tracheotomy or feeding tube2-years or 5 years following treatment [14].

Statistical analysis

Descriptive statistics were used to describe patient characteristics. Differences between groups (TL and (C)RT) were calculated using students' T test, Pearson's Chi Square test or linear-by-linear as appropriate. Analysis of the LDFS rate was conducted in the original unmatched cohort of (C)RT patients with T1-T4 hypopharynx cancer, using Kaplan-Meier (KM) analysis; the log rank test was used to test differences in LDFS rates between patients treated with RT or CRT.

Propensity score matching

To obtain an unbiased estimate of treatment effect we used propensity score matching to compare TL with CRT [15]. Based on knowledge from literature and clinical expertise, biological plausibility of prognostic value, and availability [15], we used the following variables to construct the propensity score model: age at diagnosis, gender, TNM classification, subsite of tumor, prior cancer, smoking (current smoker, stopped > 5 years ago, never smoked), alcohol (current user, stopped > 5 years ago, never used alcohol), ACE 27 comorbidity score, and levels of BMI and the peripheral blood parameters hemoglobin (mmol/L), albumin (g/L) and leukocyte(10E9/L). Additionally, we included decade of diagnosis as a predictor, to account for the time trends in treatment choice. The propensity score for each patient, representing the estimated probability that this patient will receive TL treatment based on the observed baseline covariates, was calculated using a logistic regression model. We used "greedy matching" to match TL patients 1:1 to similar CRT patients [15]. We set the caliper (the maximum acceptable difference in propensity score in a matched pair) at 0.25 standard deviation (SD), and used complete cases only. To evaluate the success of our matching procedure, we visually compared the distribution of the propensity scores between the matched groups, and we calculated standardized mean differences (SMD) of baseline characteristics [16]. To assess whether the results were sensitive to hidden bias as a result of misspecification of the propensity score model, we performed a sensitivity analysis as described by Olmos et al. [17] This sensitivity analysis results in a Gamma value, indicating by how much the odds of hidden treatment bias needs to change before the statistical significance of the outcome shifts. The larger the value, the more robust the results will be to hidden treatment bias. Gamma values close to 1 indicate that a study is sensitive to such bias [18]. Finally, survival analysis in the matched cohort was performed using KM analysis and a Cox-proportional hazards model. The latter employed a cluster term and robust standard errors, to account for the matched nature of the sample. All analyses were performed using the packages 'matching' and 'survival' in R software [19–21].

Ethics

This study does not fall under the scope of the Medical Research Involving Human Subjects Act, which was confirmed by the institutional review board.

Results

Patients

We initially retrieved a database with 441 patients. After exclusion of 98 patients (see Fig. 1), we were left with 343 patients diagnosed with squamous cell carcinoma (SCC) of the hypopharynx who were treated with curative intent in The Netherlands Cancer Institute, between February 1990 and February 2013. Mean age was 61 years (sd 10, range 32–91), 81% was male and the majority of patients received CRT (54%), followed by TL (26%) and RT (19%). Three patients were treated with primary laser surgery (0.9%). The first patient was treated with CRT in 1997. Before 1997, 75% of patients (n = 79) were laryngectomized and 25% received primary RT. This changed to 17% RT, 70% CRT and 11% TL from 1997 and onwards (n = 264). The majority of patients were diagnosed in an advanced stage: 21% in stage III, 45% in IVA and 15% in IVB. Patient characteristics are shown in Table 1.

Most patients were current smokers (85%), 8% were former smokers and the median amount of pack years of both groups was 40. Alcohol was consumed by 85% of patients, who drank a median amount of 28 units per week. Seventeen percent of patients had a history of cancer other than basal cell carcinoma, and half of these carcinomas were located in the head and neck area. Nine percent of patients were diagnosed with a synchronous tumor (89% in the head and neck area), 22% developed a second primary during follow-up and 6% a third primary.

Functional outcomes

We assessed the functional outcomes in the original (unmatched) cohort of patients treated with RT (n = 66), CRT (n = 185) or TL (n = 89). Function of the larynx and feeding status for all treatment options at 6 months, 2- and 5-years following treatment are reported in Table 2. Of the patients that were alive and not lost to follow-up two years following treatment, respectively 82, 89 and 94% of patients treated with RT, CRT and TL were able to consume full oral intake. This

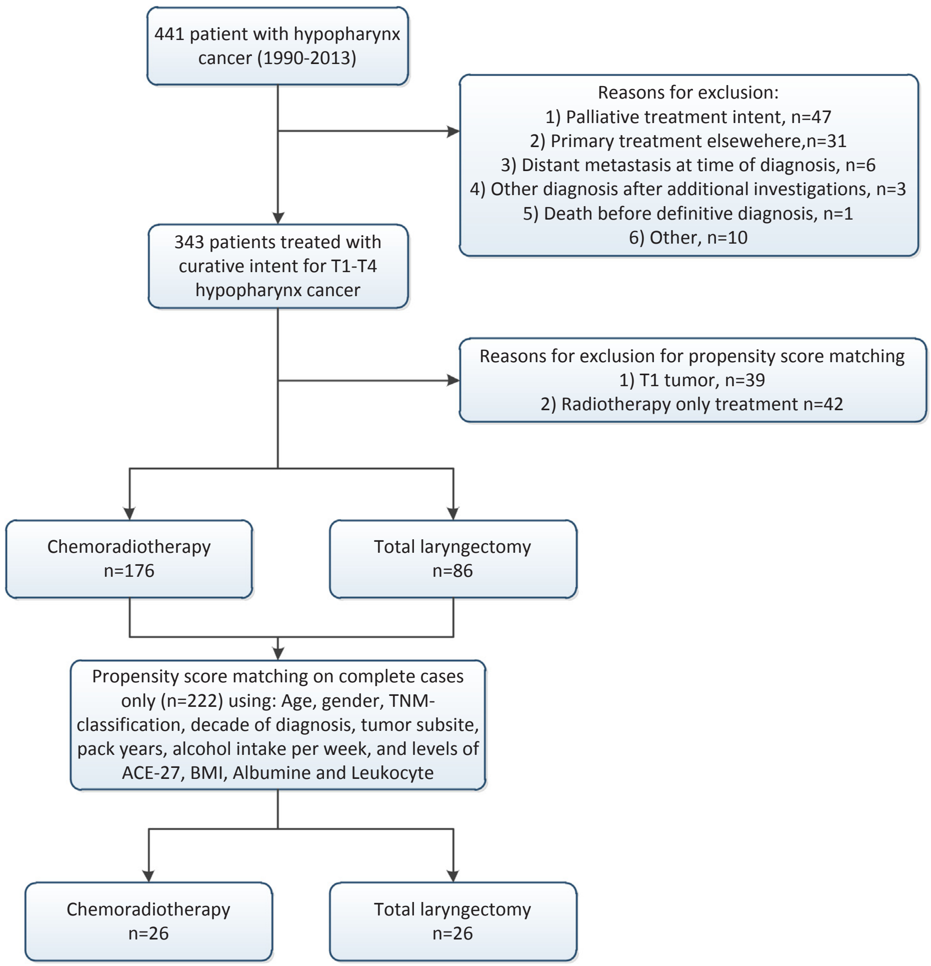

Fig. 1. Inclusion of patients in total cohort and propensity score matched analysis of chemoradiotherapy and total laryngectomy patients.

changed to 92, 89 and 91% at 5 years. The percentage of patients that required one of more dilatation procedures during follow-up was respectively 14%, 8% and 36% following treatment with RT, CRT or TL.

In the total cohort, 251 patients were treated with CRT or RT. Of these patients, the LDFS rate at 2-years and 5-years was respectively 42% and 31%. The LDFS rates in patients treated with RT at 2-years was 39% vs. 44% in the CRT group ($p = 0.90$), at 5-years this was 30% for RT vs. 32% for CRT patients ($p = 0.96$). To compare, the unadjusted 2- and 5 year OS rates in the RT group were 54% and 42%, and in the CRT group 63% and 43%.

Propensity score matching

To create an unbiased comparison of survival rates between CRT and TL we used propensity score matching. For propensity score matching we excluded patients with a T1 tumor ($n = 39$) since these patients are rarely treated with CRT or TL. Furthermore, patients treated with radiotherapy only ($n = 42$) were excluded as this is convincingly proven to be inferior to CRT and TL in terms of survival [2,22]. After excluding patients with missing data on predictors for the propensity score model ($n = 40$, 15%), 68 TL patients were available for matching. Based on the variables age at diagnosis, gender, TNM classification, subsite of tumor, decade of diagnosis, prior cancer, smoking, alcohol, ACE27 and levels of BMI and the peripheral blood parameters albumin, and leukocyte count, we were able to match 26 TL patients to 26 CRT patients with similar propensity scores (see Table 1 for their clinical characteristics). Sensitivity analysis resulted in a Gamma value of 2.7, indicating that the results of matching were not very sensitive to hidden bias.

Before matching, patients in the TL group were significantly older and had a lower nodal stage. After matching there were relatively more T4 patients in the CRT group (13 vs. 9) but due to the small sample size, this difference was considered acceptable. Other than that, there were no clinically relevant differences between groups (see Table 1).

Survival

In the matched cohort, the HR for death in the TL group compared to CRT was 0.65 (95% CI 0.34–1.24, $p = 0.19$). The 5-year overall survival rate for the patients treated with TL was better compared to CRT: 56% (95% CI 40–79) versus 46% (95% CI 31–70), but the difference was not statistically significant ($p = 0.19$). The 10-year OS rate was 35% (95% CI 20–60) for TL versus 17% (95% CI 7–41) for CRT (see Fig. 2).

Discussion

In this consecutive cohort of T1-T4 hypopharynx cancer patients treated with RT or CRT the LDFS rate was respectively 39% vs. 44% ($p = 0.90$), and 30% vs. 32% ($p = 0.96$), 2- and 5 years following treatment. In the PS matched pair cohort of T2-T4 patients treated with TL or CRT, we observed a higher 5-year OS rate (56%) in the TL group compared to the CRT group (46%), although the difference was not statistically significant.

In line with other studies, we report an increase in the use of (C)RT at the expense of TL as primary treatment [8]. Therefore, in recent

Table 1
Patient characteristics.

	Total group	(C)RT original cohort	TL original cohort	P value	CRT matched cohort	TL matched cohort	SMD
No. patients	343*	251	89		26	26	
Age at diagnosis (mean, SD)	61 (10.4)	60.1 (9.5)	63.3 (12.1)	**0.013**	59 (9.4)	59 (12.1)	0
Male gender	276 (81)	202 (80)	72 (81)	1.00	20 (77%)	23 (88%)	0.29
T classification				**0.001**			
T1	39 (11)	33 (13)	3 (3.4)		–	–	
T2	106 (31)	82 (33)	24 (27)		8 (31)	9 (35)	0.08
T3	85 (25)	65 (26)	20 (23)		5 (19)	8 (31)	0.28
T4	108 (31)	70 (28)	38 (43)		13 (50)	9 (35)	0.30
TX	5 (1.5)	1 (0.4)	4 (4.5)				
N classification				**0.001**			
N0	107 (31)	66 (26)	38 (43)		8 (31)	9 (35)	0.08
N1	70 (20)	46 (18)	24 (27)		6 (23)	8 (31)	0.18
N2	125 (36)	105 (42)	20 (23)		9 (35)	6 (23)	0.26
N3	39 (11)	33 (13)	6 (7)		3 (12)	3 (12)	0
NX	2 (0.6)	1 (0.4)	1 (1.1)				
Subsite				**0.005**			
Pyriform sinus	263 (77)	203 (81)	57 (64)		20 (77)	21 (81)	0.10
Posterior wall	34 (10)	19 (8)	15 (17)		2 (8)	1 (4)	0.90
Postcricoid region	22 (6)	16 (6)	6 (7)		1 (4)	2 (8)	0.90
Other	24 (7)	13 (5)	11 (12)		3 (12)	2 (8)	0.13
ACE27				0.139			
0	110 (32)	84 (34)	25 (28)		9 (35)	9 (35)	0
1	130 (38)	91 (37)	38 (43)		10 (39)	11 (42)	0.06
2	84 (25)	58 (23)	25 (28)		6 (23)	6 (23)	0
3	17 (5)	16 (6)	1 (1)		1 (4)	0 (0)	0.4
Unknown	2 (0.6)	2 (0.8)					
Prior cancer: yes	59 (17)	23 (9)	25 (39)	< **0.001**	7 (27)	5 (19)	0.18
Smoking				0.219			0.44
Never	25 (7)	16 (6)	9 (10)		3 (12)	2 (8)	0.13
Yes	290 (85)	217 (87)	70 (79)		21 (81)	24 (92)	0.33
Stopped > 5yrs ago	28 (8)	18 (7)	10 (11)		2 (8)	0 (0)	0.58
Alcohol				0.564			
Never	39 (11)	29 (12)	9 (10)		2 (8)	3 (12)	0.13
Yes	291 (85)	214 (85)	75 (84)		24 (92)	22 (85)	0.22
Stopped > 5yrs ago	13 (4)	8 (3)	5 (6)		0 (0)	1 (4)	0.40
BMI (mean, SD)	23 (4.4)	23 (4.4)	23 (4.5)	0.685	23 (4.1)	24 (5.6)	0.21
Hb (mean, SD)	8.7 (1.0)	8.8 (1.07)	8.5 (0.9)	0.069	8.3 (0.9)	8.6 (0.9)	0.33
Albumin (mean, SD)	43 (4.9)	43.5 (4.8)	42 (5.2)	**0.033**	44 (6.1)	43 (4.6)	0.19
Leukocyte (mean, SD)	9.9 (4.2)	9.7 (4.1)	10.2 (4.0)	0.306	9.6 (3.4)	9.5 (3.4)	0.03

Values in bold are statistically significant.
Abbreviations: SD standard deviation, SMD standardized mean difference, BMI body mass index, Hb Hemoglobine.
* There were 3 patients in our cohort treated with laser surgery that were not analyzed separately. Values in parentheses are percentages unless indicated otherwise.

Table 2
Functional outcomes measured 6 months, 2- and 5-years post treatment.

	6 months post treatment			2 years post treatment			5 years post treatment		
	RT	CRT	TL	RT	CRT	TL	RT	CRT	TL
Initial cohort	66	185	89	66	185	89	66	185	89
Censored*	9	24	12	31	69	37	42	105	55
Patients in FU	57	161	77	35	116	52	24	80	34
Larynx function									
Larynx in situ	51 (89)	152 (94)	–	31 (89)	106 (91)	–	18 (75)	68 (85)	–
Tracheotomy	4 (7)	7 (4)	–	0	4 (3)	–	0	4 (5)	–
Salvage TL	2 (4)	2 (1)	–	4 (11)	6 (7)	–	6 (25)	8 (10)	–
Feeding status									
Normal	38 (67)	108 (67)	58 (75)	29 (82)	103 (89)	49 (94)	22 (92)	71 (89)	31 (91)
Pureed food only	8 (14)	7 (4)	9 (12)	1 (3)	4 (3)	1 (2)	1 (4)	2 (2.5)	0
NG feeding tube	5 (9)	12 (7)	3 (4)	2 (6)	1 (1)	1 (2)	1 (4)	1 (1)	1 (3)
PRG/PEG/jejunostomy	6 (11)	33 (20)	7 (9)	3 (9)	8 (7)	1 (2)	0	6 (7.5)	2 (6)
TPN	0	1 (0.6)	0	0	0	0	0	0	0

Values in parentheses are percentages.
Abbreviations: FU follow-up, NG nasogastric (feeding tube), PRG Percutaneous radiologic gastrostomy (feeding tube), PEG Percutaneous endoscopic gastrostomy (feeding tube) , TPN total parenteral nutrition
* Censored patients were died or lost to follow-up at the respecting point in time. Percentages are calculated over the number of patients that were alive and not lost follow-up for each treatment and point in time.

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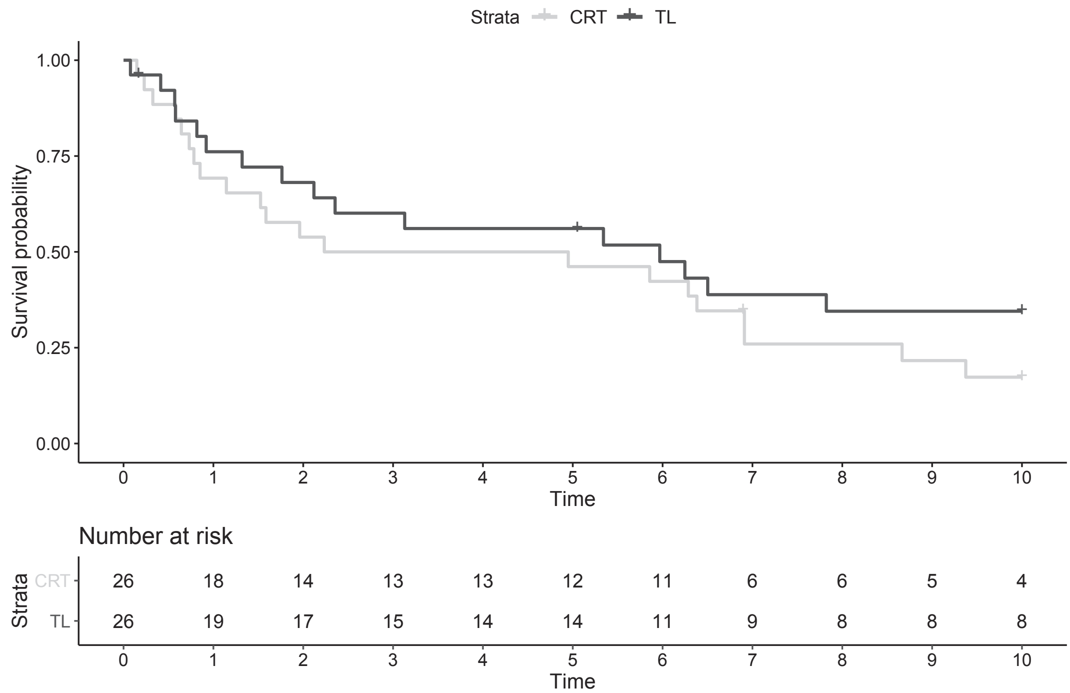

Fig. 2. Kaplan Meier curve of the matched cohort demonstrating the 10-year overall survival for the CRT (light grey) and TL (black) patient.

years, functional outcomes and long term toxicity following organ preservation have received more focus. However, heterogeneity in patients, treatment protocols, outcome measurements and definitions make direct comparisons between studies difficult and reported LDFS rates in literature vary widely [23–27].

The first RCT in hypopharynx cancer reported a LDFS of 17% at 5 years, although when only death from local disease was used as endpoint instead of death from any cause, this rate was 35% [28]. Much higher LDFS rates were reported in the long-term results of the GORTEC-2000-01 comparing induction CT with cisplatin (P) and 5-fluorouracil (F) with or without docetaxel (T) followed by RT. They reported an LDFS of 67% in the TPF group versus 47% in the PF group at 5 years [29]. However, their LDFS rate included ‘the presence of natural speech, absence of a tracheostomy, absence of a feeding tube for ≥2 years after treatment or recurring pneumonia that required hospitalization’. Despite the improved results following induction CT with TPF, concerns regarding dose limiting toxicity compromising the concurrent component have prevented this from becoming standard of care [30]. While a recent *meta*-analysis analyzing induction CT followed by concurrent CRT in head and neck cancer demonstrated a significant improved disease control and complete response rate, they were unable to demonstrate significant improved OS rate in patients treated with induction CT [31].

In a subset of patients, significant long term toxicity can be expected following organ preservation treatment. The GORTEC 2000–01 study reported most late toxicities to occur in the mucous membrane, salivary gland, larynx and subcutaneous tissues. In their cohort, significantly fewer grade III-IV toxicities of the larynx were observed in the TPF regimen versus PF (9 vs. 17%), but the cisplatin and 5-FU dose was lower in the TPF treatment arm [29]. Rütten et al. reported on a cohort of 77 stage III-IV head and neck cancer patients treated with CRT and reported long-term toxicity rates at 5 years of 52% grade III and 25% grade IV [10]. Only 15.6% of patients were able to consume a normal diet. Kraaijenga et al. reported that 10 years after treatment with CRT, 50% of patients had impaired swallowing and 14% were tube feeding dependent [9]. Meanwhile, hypopharyngeal dose has been reported as a prognostic factor for severe late toxicity following CRT [32,33].

Although organ preservation can lead to significant long term toxicity following treatment, a TL will, on the other hand, likewise interfere with important basic life functions such as breathing, swallowing and the production of speech, and can lead to significant short and long-term toxicity or complications [34]. The percentage of patients that needed dilatations for dysphagia was highest in the TL group with a crude incidence of 36%, versus 14 and 8% in patients treated with RT or CRT. Granting that vocal rehabilitation is quite successful with modern day voice prostheses, only few are genuinely satisfied with their altered voice, many patients still suffer from pulmonary complaints, have difficulty swallowing and experience social distress [12,13,23,35].

Although less pronounced than in our study, the first RCT comparing organ preservation with TL in hypopharynx cancer reported a similarly better but also non-significant higher OS rate in the TL group versus CRT. In their cohort, the 5-year OS was reported to be 35% for surgery versus 30% for CRT, and the final results showed a 10-year OS of 13.8% in the surgery arm versus 13.1% in the CRT arm [28,36]. Later, several retrospective studies have reported a significant survival benefit for surgery versus radiotherapy [3,7,37,38]. In 2014, Kuo et al. analyzed 3,958 patients from a SEER database and reported a survival benefit in the surgery plus radiotherapy arm over radiotherapy, with 5-yr OS rates of 34.5% vs. 22.6% [7]. A later study by Newman et al., analyzing 6,647 patients from the SEER database, similarly reported a survival benefit in the surgery plus radiotherapy arm versus radiotherapy, with 5-yr OS rates of 49% versus 37.8% [8]. Both SEER studies are however limited by the fact that important details regarding the use of chemotherapy, the type of surgery and the functional outcomes are missing and a subset of the radiotherapy arm in both studies will have been treated with chemoradiotherapy. As demonstrated by Blanchard et al., the addition of concomitant chemotherapy leads to an absolute benefit of 3.9% at 5 years among patients with hypopharynx cancer [39]. This benefit does not fully explain the observed OS difference between surgery and radiotherapy in the SEER cohorts, suggesting TL is indeed superior in terms of OS.

In a subsequent analysis, Kuo et al. reported on the effect of chemotherapy, but in this study the number of patients treated with surgery plus chemotherapy that were used for analysis represented only 4.9% of the total cohort. While they reported no significant difference in OS between TL and CRT, the small sample of the surgical subgroup limits interpretability of the results [7]. In 2019, Tassler et al. performed a propensity score adjusted analysis, controlling for year of diagnosis and T-stage. In their retrospective cohort of 137 hypopharynx cancer patients treated with CRT or TL, a significant survival benefit in favor or TL was observed [40].

With the increasing amount of evidence questioning the presumed equality between TL and CRT, there clearly is no consensus on the 'best treatment option'. However, since both options significantly impact a patients' life, it is extremely important to counsel future hypopharynx cancer patients about all the associated risks and possible consequences of the treatment options, so they can make a well informed decision on treatment [41]. Laccourreye et al. demonstrated how improved knowledge about the potential risk on a tracheotomy or feeding tube following organ preservation therapy shifted the treatment preferences of patients [41]. Improving patient counseling and shared decision making has been shown to lead to improved patient outcomes [42]. Therefore, especially in a setting with no 'best treatment' and/or treatment options with will have a significant effect on quality of life such as for hypopharynx cancer, optimal shared decision making should be the standard of care.

There are certain limitations to this study. Inherent to the retrospective nature and the long inclusion time of patients, certain prognostic variables that could affect oncological or functional outcomes could not be retrieved. While we tried to equalize treatment groups by performing a propensity score matched pair analysis, variables that were not included in our PS-model due to unavailability might have potentially influenced the outcome. The sensitivity analysis suggested that the analysis was robust for such bias, however. Although there is low risk of bias due to confounding, after matching, we were not able to match all TL patients, and only 26 patients per group were left for analysis. This makes the observations relatively vulnerable to sample idiosyncrasies, and left us with low power to detect statistical significance, as reflected in the wide CI for the hazard ratio.

Conclusion

In conclusion, we report a laryngo-esophageal dysfunction free survival rate at 5 years of 31% for RT and CRT, and a 5-year OS rate of 56% following TL as compared to 46% for CRT. Although these results should be interpreted with caution, they are in in line with results from previous studies, and challenge the preposition that CRT and TLE are equivalent in terms of survival. Moreover, the disappointing LDFS rate demands improved treatment strategies or rehabilitation efforts [43]. Until better alternative treatment strategies are found, counseling the patients about the expected outcome and quality of life should be a major point of focus of physicians treating these patients.

Declaration of Competing Interest

None declared

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References

[1] Gatta G, Botta L, Sanchez MJ, Anderson LA, Pierannunzio D, Licitra L. Prognoses and improvement for head and neck cancers diagnosed in Europe in early 2000s: The EUROCARE-5 population-based study. Eur J Cancer 2015.

[2] Petersen JF, Timmermans AJ, van Dijk BAC, et al. Trends in treatment, incidence and survival of hypopharynx cancer: a 20-year population-based study in the Netherlands. Eur Arch Otorhinolaryngol 2018;275:181–9.

[3] Newman JR, Connolly TM, Illing EA, Kilgore ML, Locher JL, Carroll WR. Survival trends in hypopharyngeal cancer: a population-based review. Laryngoscope 2015;125:624–9.

[4] Dyckhoff G, Plinkert PK, Ramroth H. A change in the study evaluation paradigm reveals that larynx preservation compromises survival in T4 laryngeal cancer patients. BMC Cancer 2017;17:609.

[5] Olsen KD. Reexamining the treatment of advanced laryngeal cancer. Head Neck 2010;32:1–7.

[6] Al-Mamgani A, Navran A, Walraven I, Schreuder WH, Tesselaar MET, Klop WMC. Organ-preservation (chemo)radiotherapy for T4 laryngeal and hypopharyngeal cancer: is the effort worth? Eur Arch Otorhinolaryngol 2018;276:575–83.

[7] Kuo P, Chen MM, Decker RH, Yarbrough WG, Judson BL. Hypopharyngeal cancer incidence, treatment, and survival: temporal trends in the United States. Laryngoscope 2014;124:2064–9.

[8] Kuo P, Sosa JA, Burtness BA, et al. Treatment trends and survival effects of chemotherapy for hypopharyngeal cancer: analysis of the National Cancer Data Base. Cancer 2016.

[9] Kraaijenga SA, Oskam IM, van der Molen L, Hamming-Vrieze O, Hilgers FJ, van den Brekel MW. Evaluation of long term (10-years+) dysphagia and trismus in patients treated with concurrent chemo-radiotherapy for advanced head and neck cancer. Oral Oncol 2015.

[10] Rutten H, Pop LA, Janssens GO, et al. Long-term outcome and morbidity after treatment with accelerated radiotherapy and weekly cisplatin for locally advanced head-and-neck cancer: results of a multidisciplinary late morbidity clinic. Int J Radiat Oncol Biol Phys 2011;81:923–9.

[11] Theunissen EA, Timmermans AJ, Zuur CL, et al. Total laryngectomy for a dysfunctional larynx after (chemo)radiotherapy. Arch Otolaryngol Head Neck Surg 2012;138:548–55.

[12] Petersen JF, Lansaat L, Timmermans AJ, van der Noort V, Hilgers FJM, van den Brekel MWM. Postlaryngectomy prosthetic voice rehabilitation outcomes in a consecutive cohort of 232 patients over a 13-year period. Head Neck 2019;41:623–31.

[13] Yilmaz M, Yener M, Yollu U, et al. Depression, self-esteem and sexual function in laryngeal cancer patients. Clin Otolaryngol 2015;40:349–54.

[14] Lefebvre JL, Ang KK. Larynx preservation clinical trial design: key issues and recommendations–a consensus panel summary. Head Neck 2009;31:429–41.

[15] Austin PC. An Introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011;46:399–424.

[16] Normand ST, Landrum MB, Guadagnoli E, et al. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. J Clin Epidemiol 2001;54:387–98.

[17] Olmos A, Govindasamy P. Propensity Scores: A Practical Introduction Using R. J MultiDisciplinary Evaluat 2015;11:68–88.

[18] Rosenbaum PR. Observational Studies. New York: Springer-Verlag, New York; 2002.

[19] RStudio: Integrated Development Environment for R. In: RStudio I, editor. Boston, MA: R Foundation for Statistical Computing; 2015.

[20] Sekhon JS. Multivariate and propensity score matching software with automated balance optimization: the matching package for R. J Stat Softw 2011;42:1–52.

[21] Therneau T. A Package for Survival Analysis in R Studio. version 2.38. In; 2015.

[22] Pignon JP, le Maitre A, Maillard E, Bourhis J, Mach-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92:4–14.

[23] Terlingen LT, Pilz W, Kuijer M, Kremer B, Baijens LW. Diagnosis and treatment of oropharyngeal dysphagia after total laryngectomy with or without pharyngoesophageal reconstruction: a systematic review. Head Neck 2018.

[24] Forastiere AA, Ismaila N, Lewin JS, et al. Use of larynx-preservation strategies in the treatment of laryngeal cancer: American society of clinical oncology clinical practice guideline update. J Clin Oncol 2017. Jco2017757385.

[25] Forastiere AA, Trotti AM. Searching for less toxic larynx preservation: a need for common definitions and metrics. J Natl Cancer Inst 2009;101:129–31.

[26] Caudell JJ, Carroll WR, Spencer SA, Bonner JA. Examination of laryngoesophageal dysfunction-free survival as an endpoint in nonsurgical treatment of squamous cell carcinomas of the larynx and hypopharynx. Cancer 2011;117:4447–51.

[27] Chen AM, Hsu S, Meshman J, et al. Effect of daily fraction size on laryngoesophageal dysfunction after chemoradiation for squamous cell carcinomas of the larynx and hypopharynx. Head Neck 2017;39:1322–6.

[28] Lefebvre JL, Chevalier D, Luboinski B, Kirkpatrick A, Collette L, Sahmoud T. Larynx preservation in pyriform sinus cancer: preliminary results of a European organization for research and treatment of cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. J Natl Cancer Inst 1996;88:890–9.

[29] Janoray G, Pointreau Y, Garaud P, et al. Long-term Results of a multicenter randomized phase III trial of induction chemotherapy with cisplatin, 5-fluorouracil, +/- docetaxel for larynx preservation. J Natl Cancer Inst 2016;108.

[30] Corry J, Rischin D. Induction chemotherapy in head and neck cancer: closer to an answer? Lancet Oncol 2011;12:113–4.

[31] Vidal L, Ben Aharon I, Limon D, Cohen E, Popovtzer A. Role of induction chemotherapy prior to chemoradiation in head and neck squamous cell cancer-systematic review and meta-analysis. Cancer J 2017;23:79–83.

[32] Machtay M, Moughan J, Farach A, et al. Hypopharyngeal dose is associated with severe late toxicity in locally advanced head-and-neck cancer: an RTOG analysis. Int J Radiat Oncol Biol Phys 2012;84:983–9.

[33] Machtay M, Moughan J, Trotti A, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an

RTOG analysis. J Clin Oncol 2008;26:3582–9.
[34] Timmermans AJ, Lansaat L, Theunissen EA, Hamming-Vrieze O, Hilgers FJ, van den Brekel MW. Predictive factors for pharyngocutaneous fistulization after total laryngectomy. Ann Otol Rhinol Laryngol 2014;123:153–61.
[35] Hilgers FJ, Aaronson NK, Ackerstaff AH, Schouwenburg PF, van Zandwikj N. The influence of a heat and moisture exchanger (HME) on the respiratory symptoms after total laryngectomy. Clin Otolaryngol Allied Sci 1991;16:152–6.
[36] Lefebvre JL, Andry G, Chevalier D, et al. Laryngeal preservation with induction chemotherapy for hypopharyngeal squamous cell carcinoma: 10-year results of EORTC trial 24891. Ann Oncol 2012;23:2708–14.
[37] Elias MM, Hilgers FJ, Keus RB, Gregor RT, Hart AA, Balm AJ. Carcinoma of the pyriform sinus: a retrospective analysis of treatment results over a 20-year period. Clin Otolaryngol Allied Sci 1995;20:249–53.
[38] Sewnaik A, Hoorweg JJ, Knegt PP, Wieringa MH, van der Beek JM, Kerrebijn JD. Treatment of hypopharyngeal carcinoma: analysis of nationwide study in the Netherlands over a 10-year period. Clin Otolaryngol 2005;30:52–7.
[39] Blanchard P, Baujat B, Holostenco V, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. Radiother Oncol 2011;100:33–40.
[40] Tassler AB, Gooding WE, Ferris RL. Hypopharyngeal cancer treatment: Does initial surgery confer survival benefit? Head Neck 2019.
[41] Laccourreye O, Malinvaud D, Menard M, Consoli S, Giraud P, Bonfils P. Total laryngectomy or laryngeal preservation for advanced laryngeal cancer. Impact of the functional risk upon the patient's preferences. Eur Ann Otorhinolaryngol Head Neck Dis 2014;131:93–7.
[42] Stacey D, Legare F, Col NF, et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev 2014;1:Cd001431.
[43] Eerenstein SEJ, Verdonck-de Leeuw IM, Leemans CR. Swallowing and Voice Outcomes following Treatment of Hypopharyngeal Cancer: The Need for Supervised Rehabilitation. Adv Otorhinolaryngol 2019;83:118–25.