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Longitudinal Patient-Reported Voice Quality in Early-Stage Glottic Cancer

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Abstract

Objective. Patient-reported voice quality is an important outcome during counseling in early-stage glottic cancer. However, there is a paucity of adequate longitudinal studies concerning voice outcomes. This study aimed to investigate longitudinal trajectories for patient-reported voice quality and associated risk factors for treatment modalities such as transoral CO_2 laser microsurgery, single vocal cord irradiation, and local radiotherapy.

Study Design. A longitudinal observational cohort study.

Setting. Tertiary cancer center.

Methods. Patients treated for Tcis-T1b, N0M0 glottic cancer were included in this study (N = 294). The Voice Handicap Index was obtained at baseline and during follow-up (N = 1944). Mixed-effects models were used for investigating the different trajectories for patient-reported voice quality.

Results. The mean follow-up duration was 43.4 (SD 21.5) months. Patients received transoral CO_2 laser microsurgery (57.8%), single vocal cord irradiation (24.5%), or local radiotherapy (17.5%). A steeper improvement during the first year after treatment for single vocal cord irradiation (−15.7) and local radiotherapy (−12.4) was seen, compared with a more stable trajectory for laser surgery (−6.1). All treatment modalities showed equivalent outcomes during long-term follow-up. Associated risk factors for different longitudinal trajectories were age, tumor stage, and comorbidity.

Conclusion. Longitudinal patient-reported voice quality after treatment for early-stage glottic cancer is heterogeneous and nonlinear. Most improvement is seen during the first year of follow-up and differs between treatment modalities. No clinically significant differences in long-term trajectories were found. Insight into longitudinal trajectories can enhance individual patient counseling and provide the foundation for an individualized dynamic prediction model.

Keywords

larynx, longitudinal studies, patient-centered care, quality of life measures, voice assessment

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Early-stage glottic cancer (ESGC) is a common malignancy of the head and neck area and is mostly found in an early stage due to functional complaints like dysphonia.[1,2] ESGC can be treated with transoral CO_2 laser microsurgery (TLM), local radiotherapy (LRT), or single vocal cord irradiation (SVCI).[3] The choice for the best treatment differs per patient and should be made during a shared decision-making process. Although all treatment modalities have comparable and good five-year survival rates,[4-9] they differ in duration, side effects, laryngeal preservation, and functional outcomes.[4-7,10-16] TLM is performed in 1 session and enables targeted resection and preservation of tissue. However, it requires special equipment and trained professionals. On the other hand, radiotherapy is a widely available therapy and does not require anesthesia. But it takes multiple sessions and comes with sequelae like xerostomia. Moreover, in the case of recurrent disease, the need for partial laryngectomy is less when treated with TLM.[11] SVCI is

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a new technique, developed in our institution, that uses a mild hypofractionated scheme with limited volumes and highly conformal target coverage. This resulted in a significant reduction of the radiation dose to the adjacent organs.[17-19] In the case of ESGC, it was found to be noninferior to LRT.[18,20,21]

Patient-reported voice quality is considered an important outcome during counseling in ESGC. It is compromised by the disease and its treatment, which impact social communication and interaction and, as a result, the psychological and social well-being of the patient. Within our institute, patient-reported voice quality is structurally assessed and used as guidance for individual patient contacts in the consultation room using the Healthcare Monitor.[22]

Despite the increasing literature concerning patient-reported voice outcomes in ESGC, it is considered a limitation that many studies are not able to provide insight into longitudinal dynamic evolution because these studies are based on nonrandomized, cross-sectional data with varying time frames or short-term data comprising small sample sizes.[4-9,23,24] There is a need for long-term longitudinal patient-reported outcome data with a large sample size, as this type of data can improve our understanding of the dynamic trajectories of voice quality. In addition to survival and practical information, this data can be pivotal in empowering both patients and healthcare professionals for improved counseling.[25,26] Furthermore, when systematically collected, these data can be used for individualized prediction modeling,[27] quality monitoring, and improvement.[28-30]

Our structurally collected outcome data can be used to obtain longitudinal insight into patient-reported voice quality. So, this study aimed to investigate longitudinal dynamic trajectories for the 3 different treatment modalities, such as TLM, LRT, and SVCI, as well as associated risk factors for patient-reported voice quality in patients treated for ESGC.

Methods

Setting and Participants

All patients treated for ESGC (Tcis-T1b, N0M0) with TLM, LRT, and SVCI at the Erasmus Medical Center between 2013 and 2018 and participating in the Healthcare Monitor were included in this nonrandomized, longitudinal outcome study. The Healthcare Monitor is our electronic patient-reported outcome-based clinical support system.[22] The questionnaires were completed by all the patients before every outpatient clinic visit. This was done either at home or in the clinic with an iPad before the appointment. When patients had low-grade dysplasia and were appointed to strict follow-up, had synchronous tumors, had a prior head and neck malignancy, had no patient-reported outcome measures (PROM) data available, or did not provide informed consent on using data for research purposes, they were excluded from the study.

Ethical Considerations

This project was approved by the institutional review board and ethics committee (MEC-2020-0314) from the Erasmus Medical Center Cancer Institute and follows the principles of the Declaration of Helsinki. All participating patients provided electronic, written informed consent.

Main Outcomes and Measures

In this study, we used the prospectively obtained Dutch version of the Voice Handicap Index (VHI),[31,32] which is a validated 30-item questionnaire that measures the perceived psychosocial voice impairment in daily life.[33] Each item is scored on a 5-point Likert scale (0 = never, 5 = always). The VHI was measured at baseline and during follow-up, starting 2 to 4 months after the completion of the treatment. During the 1st, 2nd, 3rd, 4th, and 5th years, the VHI was obtained every 2, 3, 4, 6, and 12 months, respectively. The total score is the sum of all scores and ranges from 0 to 120. A higher outcome indicates greater voice impairment. A difference of 10 points on the VHI was used as the cutoff point for clinical relevance.[34]

The treatment modalities in this study are TLM[35] and radiotherapy. The latter can be divided into LRT with 66 Gy, and SVCI.

The tumor-specific and patient-specific data were retrospectively obtained from Erasmus Medical Center patient records. The variables were treatment, age (in years), gender, adult comorbidity evaluation 27 (ACE-27) score (0-3), World Health Organization (WHO) performance score (0-4), smoking status (yes, no, or former), tumor stage (Tcis, T1a, or T1b), and involvement of the anterior commissure (yes or no). The performance score includes a score for the physical ability of the patient to function in daily life. Comorbidity was scored at the time of diagnosis by the ACE-27, which varies between 0 (no comorbidity) and 3 (severe comorbidity), and was developed specifically for head and neck cancer.[36,37]

Statistical Analyses

Statistical analyses were performed using R version 4.0.2.[38] Descriptive statistics were used to summarize the characteristics of patients, tumors, and treatment modalities. Means (standard deviation [SD]) and medians (quartiles [Q1-Q3]) were used for continuous variables, and numbers (%) for categorical variables. The VHI measurements taken shortly before, and after the development of a recurrence were excluded from the analysis. Starting points for longitudinal analysis after treatment were calibrated for all treatment modalities. Mixed-effects models were used to investigate different longitudinal trajectories of voice quality over time, which uses all available measurements and accounts for unbalanced data, meaning that time points of questionnaires differ between patients and should be assessed accordingly.

Moreover, these models account for the correlation between measurements from the same patients. Above mentioned tumor-specific and patient-specific data were used during the model development. During development, we first checked whether different time structures (linear or nonlinear) for the fixed and random effects improved the model's fit, assuming all the aforementioned variables and their interaction with time. Then, it was investigated whether different interactions and main effects could be removed. Natural cubic splines were used for nonlinear structures.[39] The Akaike information criterion (AIC) and likelihood ratio test were used for observing the final model. The AIC criteria is an estimator of prediction error and, thus, the relative quality of statistical models. From the final model, coefficients, standard errors [SE], and *p*-values are obtained. Effect plots are used for the interpretation of interactions and nonlinear terms.

Results

Between January 1, 2013, and December 31, 2018, 344 patients treated for ESGC were identified. Fifty patients were excluded, as 24 (48.0%) were assigned to strict follow-up with smoking cessation advice if applicable, 11 (22.0%) had synchronous tumors, 7 (14.0%) had a prior head and neck malignancy, and 8 (16.0%) did not want the data to be used for research purposes. In total, 294 patients were included in this study for further analysis.

Baseline Characteristics

The mean follow-up duration was 43.4 (SD 21.5) months, and a total of 1944 VHI measurements were retrieved. The mean age at diagnosis was 67.2 (SD 10.6) years, with 81.3% of patients being male. Patients were treated with TLM (57.8%), SVCI (24.5%), and LRT (17.7%). Patients endured Tcis (35.0%), T1a (52.7%), and T1b (12.2%) malignancies. In total, 37 patients (12.6%) had recurrent disease, with a mean time to recurrence of 26 (SD 18.8) months. Per treatment group, the recurrent disease was observed in 6 (8.5%) patients for SVCI, 26 (15.3%) for TLM, and 5 (9.4%) for LRT. No significant differences between treatment modalities were observed ($p = .26$).

At baseline, the mean VHI was 31.1 (SD 22.8). At baseline, 38.8% of patients scored below 20, 30.2% between 20 and 40, 19.4% between 40 and 60, and 11.6% above 60. No significant differences between the predicted mean VHI scores at baseline were observed: TLM (32.0, SE: 2.8), SVCI (30.6, SE: 3.3), and LRT (33.3, SE: 4.7). **Table I** shows all baseline characteristics.

Model Development

Figure I depicts all the VHI trajectories for the different treatment modalities as well as highlights individual patients with varying trajectories. This figure illustrates both the heterogeneity and nonlinearity of the VHI over time. Most patients start with a relatively high VHI score before treatment (t = 0), with a gradual decline over time. Other patients start with lower scores and show a more variable course after treatment.

After visual inspection of the individual VHI profiles and using the AIC criteria, we observed that the nonlinear structure for time assuming natural cubic splines with 3 and 6 degrees of freedom (2 and 5 internal knots) provided us with the best fit, and we decided to use this time structure for further interpretation. A diagonal matrix for the variance-covariance of the random effects was assumed. The following 5 models with different fixed effects structures were tested: Voice outcome as a function of the interaction of time with (1) only treatment as well as the main effects of age, gender, comorbidity, performance score, smoking status, tumor stage, involvement of the vocal cord (VC); (2) treatment, comorbidity, smoking status, tumor stage and involvement of VC as well as the main effects of age, gender, and performance score; (3) treatment, tumor stage and involvement of VC as well as the main effects of comorbidity, smoking status, age, gender, and performance score; (4) treatment, age, gender, tumor stage, and involvement of VC as well as the main effects of smoking status, comorbidity and performance score; (5) all variables. Corresponding formulas can be found in Appendix I. Using the likelihood ratio test, we observed that the more complicated models did not improve the fit; therefore, we decided to continue with the simplified Model 1. A subanalysis, in which patients with recurrent disease were excluded, showed no differences in longitudinal trajectories.

Longitudinal Dynamic Trajectory

Figure 2 shows the average predicted longitudinal trajectory with confidence intervals of the VHI for the different treatments, based on Model 1. No clinically significant differences in longitudinal trajectories between treatment modalities were found. Predicted values after 12 months were 15.9 (SE 3.4), 25.8 (SE 2.8), and 20.9 (SE 4.8) for SVCI, TLM, and LRT, respectively. During the first year of follow-up, a steeper clinically significant improvement was seen for SVCI (−15.7) and LRT (−12.4), which was followed by a nonclinically significant deterioration. Patients treated with TLM show a clinically nonsignificant improvement during the first 12 months (−6.1). All treatment modalities show equivalent outcomes during longitudinal follow-up. Two-, three-, and our-year follow-up VHI outcomes were 20.2, 23.6, and 22.9 for SVCI, 24.1, 23.5, and 23.4 for TLM, and 23.5, 24.6, and 21.7 for LRT, respectively.

Associated Risk Factors

Table 2 presents the results of the final mixed-effects model. In particular, the coefficients, SE, and *p*-values are presented. Older age, increased tumor stage, and severe

Table 1. Baseline Characteristics

Variable	TLM	SVCI	LRT	Overall
Patients	170 (57.8%)	72 (24.5%)	52 (17.7%)	294 (100%)
Mean age, SD	66.2 (10.7)	68.5 (9.5)	68.9 (11.4)	67.4 (10.6)
Gender				
Male	127 (74.7%)	64 (88.9%)	48 (92.3%)	239 (81.3%)
Female	43 (25.3%)	8 (11.1%)	4 (7.7%)	55 (18.7%)
T-stage				
Cis	74 (43.5%)	16 (22.5%)	14 (26.4%)	103 (35.4%)
1a	92 (54.1%)	55 (77.5%)	12 (22.6%)	155 (54.1%)
1b	4 (2.4%)	0 (0.0%)	27 (50.9%)	36 (12.2%)
Comorbidity (ACE-27)				
0	40 (23.5%)	22 (30.6%)	16 (30.8%)	78 (26.5%)
1	78 (45.9%)	31 (43.1%)	20 (38.5%)	129 (43.9%)
2	37 (21.8%)	10 (13.9%)	13 (25.0%)	60 (20.4%)
3	15 (8.8%)	9 (12.5%)	3 (5.8%)	27 (9.2%)
ECOG performance status				
0	132 (77.6%)	56 (77.8%)	41 (78.8%)	229 (77.9%)
1	27 (15.9%)	11 (15.3%)	10 (19.2%)	48 (16.3%)
2 + 3	11 (6.5%)	5 (6.9%)	1 (1.9%)	17 (5.8%)
Anterior commissure				
Yes	46 (27.1%)	29 (40.3%)	33 (63.5%)	108 (36.7%)
No	124 (72.9%)	43 (59.7%)	19 (36.5%)	186 (63.3%)
Smoking				
Yes	83 (48.8%)	26 (36.1%)	29 (55.8%)	138 (46.9%)
No	6 (3.5%)	8 (11.1%)	2 (3.8%)	16 (5.4%)
Former	81 (47.6%)	38 (52.8%)	21 (40.4%)	140 (47.6%)
Mean pack years, SD	35.1 (17.2)	31.4 (19.9)	36.5 (18.2)	34.4 (18.1)
Alcohol				
Yes	99 (58.2%)	45 (62.5%)	39 (75.0%)	183 (62.2%)
No	55 (32.4%)	21 (29.2%)	10 (19.2%)	86 (29.3%)
Unknown	16 (9.4%)	6 (8.3%)	3 (5.8%)	25 (8.5%)
Weight loss				
Yes	17 (10.0%)	13 (18.1%)	5 (9.6%)	35 (11.9%)
No	142 (83.5%)	56 (77.8%)	44 (84.6%)	242 (82.3%)
Unknown	11 (6.5%)	3 (4.2%)	3 (5.8%)	17 (5.8%)
Marital status				
Married/living together	113 (66.5%)	51 (70.8%)	35 (67.3%)	199 (67.7%)
Alone	51 (30.0%)	21 (29.2%)	16 (30.8%)	88 (29.9%)
Unknown	6 (3.5%)	0 (0.0%)	1 (1.9%)	7 (2.4%)
Education				
Low	69 (40.6%)	25 (34.7%)	20 (38.5%)	114 (38.8%)
Intermediate	58 (34.1%)	24 (33.3%)	18 (34.6%)	100 (34.0%)
Tertiary	17 (10.0%)	15 (20.8%)	3 (5.8%)	35 (11.9%)
Missing	26 (15.3%)	8 (11.1%)	11 (21.2%)	45 (15.3%)
Work				
Employed	38 (22.4%)	15 (20.8%)	11 (21.2%)	64 (21.8%)
Not employed	25 (14.7%)	10 (13.9%)	8 (15.4%)	43 (14.6%)
Retired	92 (54.1%)	45 (62.5%)	31 (59.6%)	168 (57.1%)
Missing	15 (8.8%)	2 (2.8%)	2 (3.8%)	19 (6.5%)
VHI at baseline, SE	32.0 (2.8)	30.6 (3.3)	33.3 (4.7)	31.1

Abbreviations: LRT, local radiotherapy; SE, standard error; SVCI, single vocal cord irradiation; TLM, transoral CO_2 laser microsurgery; VHI, Voice Handicap Index.

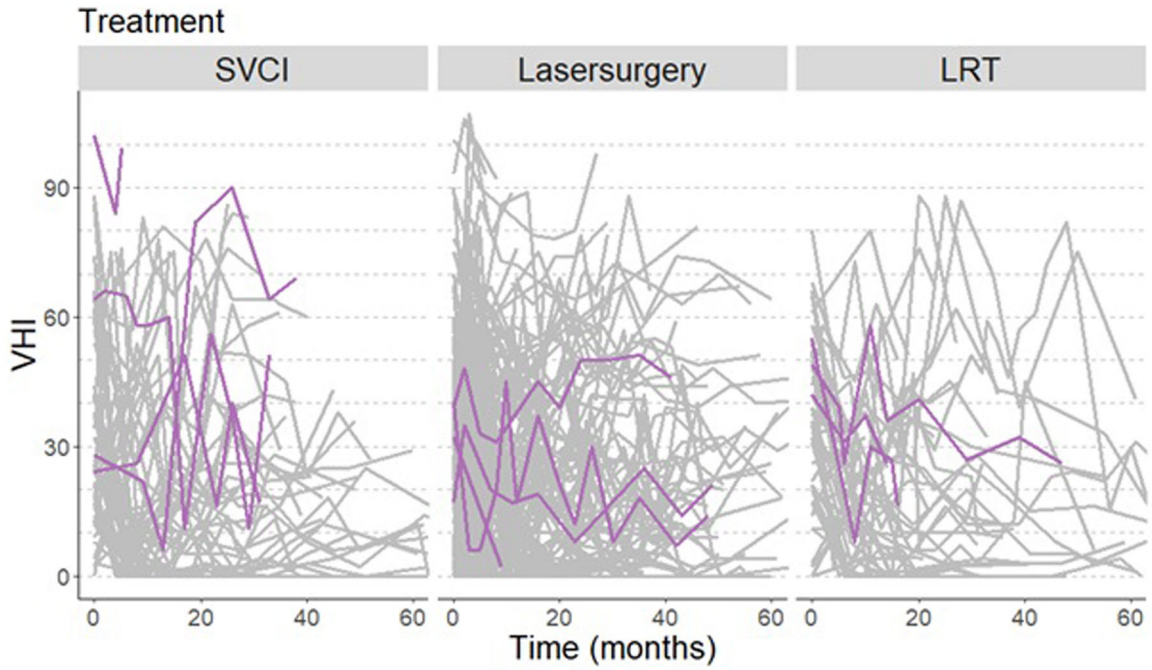

Figure 1. VHI profiles for all 294 patients, highlighting 5 individual patients. This figure shows the variability between patients in longitudinal outcomes. VHI, Voice Handicap Index.

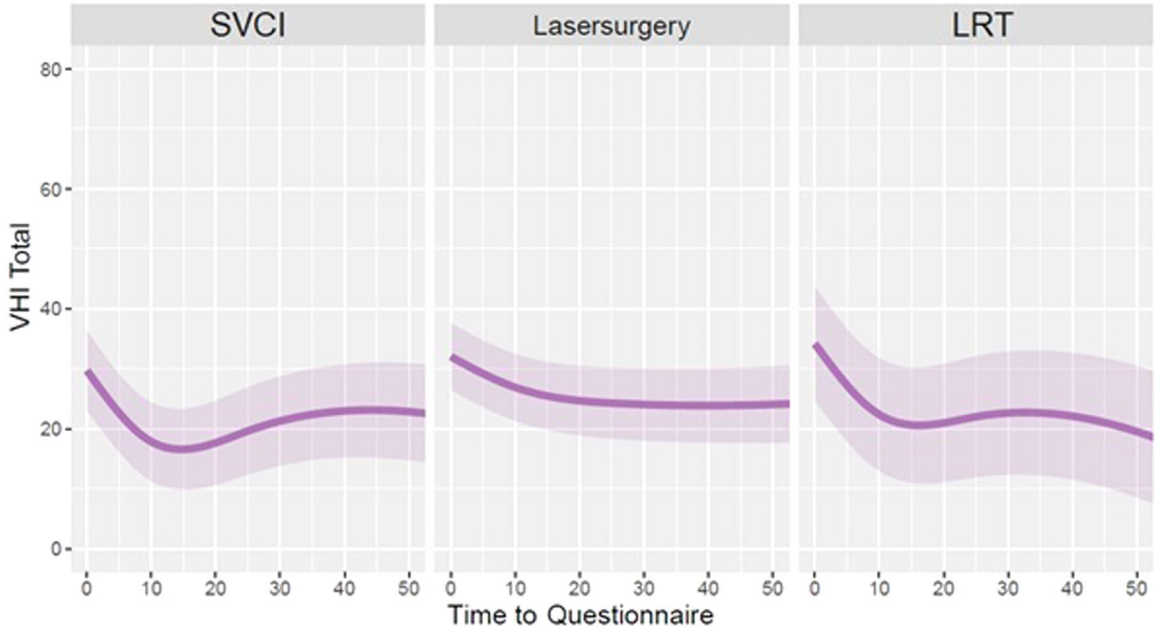

Figure 2. The predicted longitudinal dynamic trajectory for the VHI from baseline to 50 months posttreatment for SVCI, TLM, and LRT. LRT, local radiotherapy; SVCI, single vocal cord irradiation; TLM, transoral carbon dioxide laser microsurgery; VHI, Voice Handicap Index.

comorbidity were found to be associated with the longitudinal VHI profiles in the final model. A year increase in age comes with an overall lower VHI of 0.3 points (SE 0.1) at baseline, after correcting for the other covariates. The clinical significance of this difference is low. This also applies to patients with T1a tumors, who show an overall higher VHI of 6.2 points (SE 2.6) at baseline compared to patients with Tcis. However, patients with severe comorbidity (ACE 3) score overall 13.6 points (SE 4.8) higher on the VHI than patients with no comorbidity ($p = .005$) at baseline (correcting for the other covariates), which is considered clinically significant. Other variables, such as T1b and ACE 2 and 3, had no impact on the longitudinal VHI.

Table 2. Results of the Final Mixed-Effects Model

Variable	Estimates (*B*)	Standard error	*p* value
Age	−0.3	0.1	.02
Gender (ref: male)			
Female	−0.1	3.0	.97
Comorbidity ACE27 (ref: ACE 0)			
ACE 1	0.3	2.9	.92
ACE 2	1.1	3.7	.76
ACE 3	13.6	4.8	.005
WHO Performance score (ref: WHO 0)			
WHO 1	2.3	3.2	.49
WHO 2 + 3	2.3	5.5	.67
Smoking (ref: no)			
Yes	−9.8	5.37	.07
Former	−9.7	5.2	.07
T-stage (ref: Tcis)			
T1a	6.2	2.6	.02
T1b	8.7	4.9	.08
Anterior commissure (ref: no)			
Yes	−0.2	2.6	.94

Discussion

Patient-reported voice outcome has extensively been studied in ESGC with cross-sectional data. However, to our knowledge, this current large cohort study is the first to provide insight into longitudinal dynamic trajectories and associated risk factors for all three treatment modalities. Our outcomes are important as they enhance knowledge of the longitudinal dynamics of voice quality, which can be used during counseling in addition to oncological and practical considerations. At the same time, this data will provide the foundation for the development of an individualized prediction tool.

Longitudinal Patient-Reported Voice Quality

No clinically significant differences in longitudinal trajectories between treatment modalities were found. However, during the 1st year of follow-up, patients treated with both radiotherapy modalities showed a steeper and clinically significant improvement compared to a more stable and clinically insignificant improvement over time with TLM. The nonlinear stable trajectory for TLM has been described previously by Lane et al.[40] It is in accordance with the belief that full remodeling of the glottic tissue takes 12 to 24 months. However, because the first follow-up measurement is taken at 2 to 4 months, short deteriorations after surgery may go undetected. In our analysis, we found a "rebound" effect within the longitudinal trajectories for both radiotherapy modalities. This is, however, not clinically significant (<10 points on the VHI). The longitudinal outcomes of all treatment modalities are equivalent, which is in line with previous systematic reviews and meta-analyses.[5,6] Additionally, the longitudinal improvement in patient-reported voice quality was clinically significant for SVCI and LRT. This corresponds with a previous study that investigated 2-year follow-up data for TLM.[23]

Associated Risk Factors

By using all available patient- and tumor-specific variables, we were able to shed light on the risk factors associated with different longitudinal trajectories. Previous cross-sectional studies reported that associated risk factors can be divided into patient, tumor, and treatment factors.[41-43] The associated risk factors, such as age and tumor stage, from our findings are in alignment with these studies. However, comorbidity by means of ACE 27 has not previously been associated with patient-reported voice quality. It is worth noting that comorbidity was not considered in previous studies.[41-43] We would argue that this association is due to the fact that many patients with ACE 3 in our cohort had severe pulmonary comorbidity, which can also affect the VHI. There was no impact of the involvement of the anterior commissure, which was surprising because we believe these are more difficult to treat, especially with TLM, and thus have a lower patient-reported voice quality.[44] Due to missing data, we were unable to include the depth of the cordectomy and smoking cessation behavior, but both of them were found to be important factors for functional outcomes in ESGC.[41,45]

Strengths and Limitations

A strength of our study is the use of statistical techniques for repeated measurement data. Mixed-effects models are

relatively new and have been shown to be superior to older methods such as linear regression, repeated measurements of analysis of variance, or paired *t*-tests for concluding repeated measurements data.[27,46-48] Another strength is the large number of patients included in this study and the corresponding number of measurements. The latter can be attributed to the fact that these PROMs are embedded in our routine care. A limitation of this study is that the VHI is not a multidimensional voice assessment and only provides limited subjective information. In our cohort, 60% underwent TLM, which could cause treatment bias. It is important to mention that no comparison between treatment modalities can be made due to confounding by indication.[49,50] This is caused by differences in the tumor or patient characteristics like tumor stage, anatomical difficulties, and so forth. Also, differences between healthcare professions in counseling cause bias. A randomized controlled trial would provide the opportunity to make a fair comparison. It should be noted that we did not exclude patients with recurrent disease prior to this study. We acknowledge the impact of recurrent disease in ESGC on patient-reported outcomes, especially due to a second treatment. By excluding measurements before and after the recurrence, we think the remaining measurements are valuable for further analysis. However, it would be more equitable and statistically correct to use joint modeling to account for and predict these events alongside longitudinal patient-reported voice quality.[27]

Impact on Clinical Practice

Our findings can be used for individual counseling and shared decision-making in addition to oncological and practical considerations. Our results can be used to help patients manage their treatment expectations. This data, however, cannot be used as a decision-making tool because it is susceptible to confounding by indications.[49,50] However, when counseling patients for whom TLM and radiotherapy are equivalent treatment options, insights into expected voice quality after treatment can be used in addition to oncological and practical considerations.[51,52] We believe PROMs, like the VHI, provide unique opportunities to provide patient-centered counseling by means of individualized dynamic prognostic models. In our institution, we have experience with developing prognostic models for overall survival,[53-56] and the next step is to do this for patient-reported outcomes as well. By doing this, we will be able to provide patients with individualized predictions on both quantity and quality of life aspects prior to their treatment and during follow-up. For patients, this can give a full perspective on what to expect from certain treatment modalities. This study will form the basis for a second study concerning the development of an individualized dynamic prediction model for longitudinal patient-reported voice outcome and recurrent disease in ESGC. We also would like to investigate whether longitudinal PROMs are helpful in predicting recurrent disease.

Conclusion

Longitudinal patient-reported voice quality after treatment of ESGC is heterogeneous and nonlinear. Most improvement is seen during the first year of follow-up and differs between treatment modalities. No clinically significant differences in long-term longitudinal trajectories over time for patient-reported voice quality were observed. Associated risk factors for different longitudinal trajectories for voice quality were older age, increased tumor stage, and severe comorbidity. These longitudinal dynamic trajectories can enhance individual patient counseling and provide the foundation for an individualized dynamic prediction model.

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None.

Author Contributions

Maarten C. Dorr, design, conduct, and analysis, presentation; **Aniel Sewnaik**, design, conduct, and presentation; **Elrozy Andrinopoulou**, analysis and presentation; **Diako Berzenji**, conduct; **Emilie A.C. Dronkers**, conduct; **Simone E. Bernard**, conduct; **Arta Hoesseini**, conduct; **Lisa Tans**, conduct; **Dimitris Rizopoulos**, analysis and presentation; **Robert J. Baatenburg de Jong**, design, conduct, and presentation; **Marinella P.J. Offerman**, design, conduct, and presentation.

Disclosures

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Data Availability Statement

The data can be obtained on request. Requests should be directed toward the data management team of the Head and Neck department of the Erasmus Medical Center Cancer Institute (hoofdhalschirurgie@erasmusmc.nl), which has a protocol for approving data requests. Because of restrictions based on privacy regulations and the informed consent of the participants, data cannot be made freely available in a public repository.

Supplemental Material

Additional supporting information is available in the online version of the article.

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