The Journal of Laryngology & Otology

cambridge.org/jlo

Long-term functional outcomes in tumour stage T_2 glottic carcinoma after radiotherapy

M Hendriksma[1], B J Heijnen[1], B M Verbist[2], M A de Jong[3], A P M Langeveld[1], P P G van Benthem[1] and E V Sjögren[1]

Departments of [1]Otorhinolaryngology, Head and Neck Surgery, [2]Radiology and [3]Radiation Oncology, Leiden University Medical Center, Leiden, the Netherlands

Abstract

Objective. To evaluate the long-term functional outcomes in patients who received primary radiotherapy for tumour–node stage T_2N_0 glottic carcinoma, stratified for tumour extension.
Methods. A cross-sectional study was performed on patients who were treated with radiotherapy for T_2N_0 glottic carcinoma. Four questionnaires were used to measure different aspects of functional outcome. In addition, objective evaluation and perceptual analysis were performed.
Results. Fourteen patients were included in this study. The median time between the start of radiotherapy and assessment was 42 months (range, 26–143 months). Patients reported high-level functioning, with low symptom scores and good swallowing function, and showed a median dysphonia grade of 1.5. The median Voice Handicap Index-30 score was 17.5.
Conclusion. Patients with T_2N_0 glottic carcinoma treated with radiotherapy had good long-term quality of life, with low symptom scores, good swallowing functioning and slightly elevated voice outcome parameters.

Main Article

Dr M Hendriksma takes responsibility for the integrity of the content of the paper

Cite this article: Hendriksma M, Heijnen BJ, Verbist BM, de Jong MA, Langeveld APM, van Benthem PPG, Sjögren EV. Long-term functional outcomes in tumour stage T_2 glottic carcinoma after radiotherapy. *J Laryngol Otol* 2023;**137**:685–690. https://doi.org/10.1017/S0022215122001682

Accepted: 15 July 2022
First published online: 25 July 2022

Key words:
Laryngeal Neoplasms; Radiotherapy; Quality Of Life; Voice; Deglutition

Author for correspondence:
Dr Martine Hendriksma, Department of Otorhinolaryngology, Head and Neck Surgery, H5-Q, Leiden University Medical Center, Albinusdreef 2, PO Box 9600, 2300 RC, Leiden, the Netherlands
E-mail: m.hendriksma@lumc.nl

Introduction

Radiotherapy is one of the two main treatment modalities for tumour–node stage T_2N_0 glottic carcinoma, yielding high rates of both local control and larynx preservation.[1] However, because of the high rates of disease control, it is clear that outcome evaluation must include functional outcomes, as patients will generally live out their lives with the handicap the treatment causes. Multidimensional functional parameters such as quality of life (QoL), voice outcome (voice quality, function and performance) and swallowing performance should be included in the appraisal of treatment results.

Although there is a sizeable amount of oncological outcome data available, reported functional outcomes after treatment for T_2 glottic carcinoma with radiotherapy are sparse, especially in the long term. Most studies have investigated T_1 glottic carcinoma alone, or grouped T_1 and T_2 tumours together, such that data on T_2 tumours are not extractable. The few studies that have reported functional outcomes after radiotherapy in T_2 glottic carcinoma patients demonstrate an improvement in post-treatment voice, although parameters do not normalise.[2–5] Studies also show that radiotherapy can affect the functional outcome after a longer period of time, probably due to progressive fibrosis in the glottic tissue.[6,7] However, T_2 glottic carcinoma comprises a heterogeneous group of tumours with varying extension – some have a large surface area without deep extension, whereas others may have a smaller diameter but penetrate deep into the vocal fold muscle.

To our knowledge, so far only one study has reported outcomes according to tumour extension in T_2 glottic carcinoma,[5] which is of interest when comparing the outcomes of radiotherapy with those of defects created by surgical modalities. Therefore, this cross-sectional study aimed to evaluate the long-term functional outcomes in patients who received primary radiotherapy for T_2N_0 glottic carcinoma at our centre between 2007 and 2016, stratified for tumour extension.

Materials and methods

Patients

Between January 2019 and April 2019, a cross-sectional study on functional outcomes after treatment for T_2N_0 glottic carcinoma was performed in the Leiden University Medical Center. The target population of the study was patients with T_2N_0 glottic carcinoma who were treated with radiotherapy between January 2007 and December 2016. Exclusion criteria were: an inability to speak and read Dutch language, treatment for recurrent disease, treatment for other head and neck tumours, and the presence of any cognitive conditions hampering compliance with the study (e.g. dementia).

This study was approved by the Local Medical Ethics Committee (approval code: P18.150) in the Leiden University Medical Center, and all patients signed informed consent forms prior to inclusion in the study.

https://doi.org/10.1017/S0022215122001682 Published online by Cambridge University Press

Treatment and radiology

Radiotherapy was applied with a linear accelerator using a 4–6 MV photon beam. For T_{2a} tumours, the total dose ranged from 60 to 70 Gy (median of 70 Gy), administered in five fractions ranging between 2.0 and 2.4 Gy (median of 2.4 Gy) per week for six weeks. For T_{2b} tumours, the total dose consisted of 70 Gy, administered in five fractions of 2.0 Gy per week for seven weeks. Additionally, patients with T_{2a} tumours received unilateral elective radiotherapy to the neck at levels II, III and IV, consisting of a total dose ranging between 46.0 and 57.75 Gy (median of 54.25 Gy). Patients with T_{2b} tumours received bilateral elective radiotherapy to the neck at levels II, III and IV, consisting of a total dose of 54.25 Gy administered in fractions of 1.55 Gy bilaterally. The field area was 6×6 cm. The upper limit was the hyoid bone, the lower limit was the cricoid cartilage, and the skin was the anterior border.

Chronic complications were analysed with the Common Terminology Criteria for Adverse Events version 5.0.

All available pre-operative computed tomography (CT) scans were reviewed by one radiologist (BMV), and scored for superficial spread versus vocal fold muscle infiltration. If tumours were not visible on CT, they were classified as superficial.

Questionnaires

Four self-administrated questionnaires were utilised: the Voice Handicap Index-30,[8] the European Organization for Research and Treatment of Cancer 'QLQ-C30'[9] and 'QLQ-HN35'[10] QoL questionnaires, and the MD Anderson Dysphagia Inventory.[11] Patients were asked to complete the questionnaires after the voice recording during their visit to the outpatient clinic.

Voice Handicap Index

The Dutch-language version of the Voice Handicap Index is a validated questionnaire measuring voice problems in daily life.[12] It consists of 30 questions with 3 subscales (functional, emotional and physical), and it is scored with a 5-point Likert scale ranging from 0 (never) to 4 (always). The total score ranges from 0 to 120, with 120 points indicating a maximal voice handicap. A total score of 15 points or more is taken to indicate voice problems in daily life.[8,12]

'QLQ-C30' questionnaire

The Dutch-language version of the European Organization for Research and Treatment of Cancer QLQ-C30 is a validated questionnaire measuring health-related QoL in patients with cancer.[9] It comprises 30 questions that address patient function and symptomatology over the preceding week. The questionnaire includes: a global health scale; five functional scales (assessing physical, role, emotional, cognitive and social functioning); three multi-item symptom scales, each containing multiple questions on the items of fatigue, pain, and nausea and vomiting; and six single item scales, each containing one single question on the items of dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties. All items are answered on a four-point Likert scale (1 = not at all, 4 = very much), except for the global health status, which is scored on a seven-point Likert scale (1 = very poor, 7 = excellent). Calculated scores range between 0 and 100. Depending on the item, a higher score can represent a higher (better) level of functioning or a higher (worse) level of symptoms.

'QLQ-HN35' questionnaire

The Dutch-language version of the European Organization for Research and Treatment of Cancer QLQ-HN35 is a validated questionnaire that evaluates health-related QoL specifically in head and neck cancer patients.[10] It consists of 35 questions that address symptoms and side effects of treatment, social function, and body image and sexuality. The questionnaire incorporates 7 multi-item scales (pain, swallowing, senses (taste and smell), speech, social eating, social contact and sexuality) and 11 single items (teeth, mouth opening, dry mouth, sticky saliva, coughing, feeling ill, analgesic use, nutritional supplement use, feeding tube use, weight loss and weight gain), which are answered on 4-point Likert scales. Calculated scores range between 0 and 100. A higher score represents more severe problems or symptoms.

MD Anderson Dysphagia Inventory

The Dutch-language version of the MD Anderson Dysphagia Inventory is a validated questionnaire that evaluates the impact of dysphagia on QoL.[13] It comprises 20 questions answered on 5-point Likert scales ranging between 1 (strongly agree) and 5 (strongly disagree). Two questions are scored in the opposite direction, whereby 1 represents 'strongly disagree' and 5 reflects 'strongly agree'. The questionnaire is subdivided into a global score and three subscales (emotional, functional and physical). A higher score indicates higher functioning.[11,13]

Perceptual evaluation

Perceptual analysis was performed using the Grade, Roughness, Breathiness, Asthenia, Strain rating scale on a 30-second running speech sample.[14] The speech sample consisted of a standard phonetically balanced Dutch-language text, '80 Dappere Fietsers' ('80 Brave Cyclists'). The rating scale comprises five subscales (grade, roughness, breathiness, asthenia and strain), of which only the grade was rated. A panel of two experienced speech and language pathologists (including BJH), familiar with the Grade, Roughness, Breathiness, Asthenia, Strain rating scale, who were blinded to all data, conducted the perceptual evaluation. Each speech sample was scored from 0 (normal) to 3 (severely dysphonic); a higher score therefore indicates a more dysphonic voice.[14]

Objective evaluation and voice recording

The voice recordings were taken in a noise-free environment, and were acquired at a sampling frequency of 44.1 kHz with a dual microphone headset recorder (Alphatron Medical Systems, Rotterdam, the Netherlands) and an Opus 56 microphone (Beyerdynamic, Heilbronn, Germany). The voice parameters consisted of aerodynamic parameters (maximum phonation time) and acoustic parameters (dynamic range, fundamental frequency, percentage jitter, percentage shimmer and harmonics-to-noise ratio). The acoustic parameters were measured with Praat software.[15] The maximum phonation time was determined by measuring the duration of the sustained letter /a/ sound at the most comfortable pitch and loudness. The longest maximum phonation time from two attempts was taken as the representative maximum phonation time. Jitter, shimmer and harmonics-to-noise ratio were measured on a stable 2-second mid-section of the sustained /a/ sound. The dynamic range (in decibels) and the fundamental frequency (in Hertz) were extracted from the patient's

https://doi.org/10.1017/S0022215122001682 Published online by Cambridge University Press

phonetogram, recorded with a voice range profile program (2007; Alphatron Medical Systems).

Statistical analysis

Statistical analysis was performed using SPSS software, version 25.0 (IBM, Armonk, New York, USA). First, descriptive statistics of the median with range were calculated for all different outcomes. Then, Spearman correlation co-efficients were calculated between the grade and the other voice outcome parameters and between the time to assessment and the different voice outcome parameters. The Voice Handicap Index-30 score was compared between tumours with superficial spread and those with vocal fold muscle infiltration; the Mann–Whitney U test was used to test this difference.

Results and analysis

Patients

In total, 68 patients were treated with radiotherapy for a T_2N_0 glottic carcinoma between 2007 and 2016. Forty patients were excluded: 5 patients had disease recurrence and 35 patients died. In total, 28 patients were approached, of whom 14 agreed to participate in this study (response rate of 50.0 per cent). Baseline characteristics are presented in Table 1. The median time between the start of treatment and assessment was 42 months (range, 26–143 months).

Voice Handicap Index

The median Voice Handicap Index-30 score was 17.5, with a range of 1–54 (Table 2). Six of the 14 patients (42.9 per cent) reported a Voice Handicap Index-30 score within the normal range (less than 15 points). The physical subscale showed the highest score with a median of 9.0 (range, 0–22).

Table 1. Patient characteristics

Characteristics	Values
Total group (*n* (%))	14 (100)
Patient characteristics	
Sex (*n* (%))	
– Male	11 (78.6)
– Female	3 (21.4)
Age at RT (median (range); years)	64.0 (47–84)
Clinical characteristics	
Vocal fold mobility (*n* (%))	
– Normal	12 (85.7)
– Impaired	2 (14.3)
AC involvement? (*n* (%))	
– Yes	5 (35.7)
– No	9 (64.3)
Radiological characteristics	
Tumour extension (*n* (%))	
– Superficial spread	6 (42.9)
– Deep vocal fold muscle infiltration	8 (57.1)

RT = radiotherapy; AC = anterior commissure

Table 2. Voice outcome parameters

Voice parameters	Median (range)
Voice Handicap Index score	17.5 (1–54)
– Superficial spread patients (*n* = 6)	8.0 (3–39)
– Deep vocal fold muscle infiltration patients (*n* = 8)	23.5 (1–54)
Grade (from GRBAS)	1.5 (0–3)
MPT (seconds)	17.4 (4.7–34.3)
Dynamic range (dB)	36.0 (26–50)
Fundamental frequency (Hz)	
– Male (*n* = 11)	98 (86–181)
– Female (*n* = 3)	171 (147–194)
Jitter (%)	0.66 (0.30–3.50)
Shimmer (%)	5.5 (1.65–15.7)
HNR (dB)	17.5 (9.02–21.7)

Total *n* = 14. GRBAS = Grade, Roughness, Breathiness, Asthenia, Strain rating scale; MPT = maximum phonation time; HNR = harmonics-to-noise ratio

The emotional and physical subscales showed lower scores, with median values of 6.0 (range, 0–16) and 2.0 (range, 0–16), respectively. Patients with deep infiltration of the vocal fold muscle had a higher Voice Handicap Index-30 score (median of 23.5 (range, 1–54)) than patients with superficial spread (median of 8.0 (range, 3–39)); however, this result was not statistically significant ($p = 0.272$).

'QLQ-C30' questionnaire

Patients showed a good global health status with a median of 79 points at the time of assessment (Table 3). The results of the different functional scales also showed high levels of functioning, ranging between 87 and 100 points. The most frequently reported complaints were fatigue (median of 22 (range, 0–78)) and insomnia (median of 17 (range, 0–100)).

'QLQ-HN35' questionnaire

The symptom scale showed low symptom scores (Table 4). After a median of 42 months, the most registered complaints were dry mouth (median of 33 (range, 0–100)), sticky saliva (median of 33 (range, 0–100)), coughing (median of 33 (range, 0–100)) and a decrease in sexuality (median of 50 (range, 0–100)). Notably, few patients complained about speech problems in this questionnaire; the median score of 6 on this item is considered to be low.

MD Anderson Dysphagia Inventory

The MD Anderson Dysphagia Inventory showed high functioning, with a median score of 95.0 (range, 32–100) (maximum score is 100) (Table 5). In this questionnaire, there was one outlier with a total score of 32. We cannot exclude the possibility that this was caused by a misunderstanding of the instructions, as all other questionnaires indicated a high level of functioning in this individual.

Perceptual evaluation

The median grade of dysphonia was 1.5, with a range between 0 and 3 (Table 2). The voice was scored as normal in three

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Table 3. Quality of life results according to EORTC 'QLQ C30'

QLQ-C30 parameter	Median (range)
Global health	
– Global health status	79 (42–100)
Functional scales	
– Physical functioning	87 (53–100)
– Role functioning	100 (67–100)
– Emotional functioning	92 (59–100)
– Cognitive functioning	100 (67–100)
– Social functioning	100 (17–100)
Symptom scales or items	
– Fatigue	22 (0–78)
– Nausea & vomiting	0 (0–33)
– Pain	8 (0–50)
– Dyspnoea	0 (0–67)
– Insomnia	17 (0–100)
– Appetite loss	0 (0–100)
– Constipation	0 (0–33)
– Diarrhoea	0 (0–100)
– Financial difficulties	0 (0–67)

EORTC = European Organization for Research and Treatment of Cancer

Table 4. Quality of life results according to EORTC 'QLQ-HN35'

QLQ-HN35 parameter	Median (range)
Pain	8 (0–25)
Swallowing	0 (0–42)
Senses problems	0 (0–50)
Speech problems	6 (0–56)
Trouble with social eating	0 (0–50)
Trouble with social contact	0 (0–33)
Less sexuality	50 (0–100)
Teeth	0 (0–67)
Opening mouth	0 (0–0)
Dry mouth	33 (0–100)
Sticky saliva	33 (0–100)
Coughing	33 (0–100)
Felt ill	0 (0–67)
Pain killers	0 (0–67)
Nutritional supplements	0 (0–0)
Feeding tube	0 (0–0)
Weight loss	0 (0–100)
Weight gain	0 (0–67)

EORTC = European Organization for Research and Treatment of Cancer

patients (21.4 per cent), as mildly dysphonic in four patients (28.6 per cent), and as moderately dysphonic in six patients (42.9 per cent); the voice of one patient (7.15 per cent) was rated as severely dysphonic. The grade was lower in the patients with deep infiltration of the vocal fold muscle (median of 1.0 (range, 0–2)) than in patients with superficial infiltration (median of 2.0 (range, 0–3)); however, this result was not statistically significant. No correlations were found between the grade and other voice parameters.

Table 5. Impact of dysphagia on quality of life*

Inventory parameter	Median (range)
Total score	95.0 (32.0–100)
Emotional subscore	90.0 (23.7–100)
Functional subscore	100 (28.0–100)
Physical subscore	95.0 (37.5–100)

*Measured by the MD Anderson Dysphagia Inventory

Acoustic and aerodynamic parameters

The median values for the different acoustic and aerodynamic parameters are shown in Table 2. The median maximum phonation time was 17.4 seconds (range, 4.7–34.23 seconds). The voice in the patient with the lowest maximum phonation time (4.7 seconds) was so severely dysphonic that the voice range profile software was unable to analyse the voice parameters because of the irregularity of the signal; the other acoustic parameters could not be analysed in this patient either. No correlations existed between assessment time and the different voice outcome measures.

Toxicity

Treatment was not interrupted in any of the patients. In two patients (14.3 per cent), a grade 3 acute adverse event was reported. One patient required a nasogastric feeding tube during treatment for grade 3 dysphagia, and one patient required hospital admission and medication because of grade 3 dyspnoea. Five patients reported late complications of hypothyroidism (35.7 per cent), of whom three were treated with medication. In the two other patients, treatment was not necessary.

Discussion

This cross-sectional study investigated long-term functional outcomes in patients with T_2N_0 glottic carcinoma treated with radiotherapy. Our results show good long-term results after a median follow up of 42 months. In general, the Voice Handicap Index score was slightly elevated, whereas the perceptual evaluation showed mild to moderate dysphonia. The QoL scores indicated high functioning with low symptom scores, and the swallowing function showed high functioning as well. Patients with vocal fold muscle infiltration showed a trend towards a higher voice handicap than those with superficial spread; however, this finding was not statistically significant. No correlations were found between voice outcome parameters and the time of assessment.

Only a few studies have presented long-term (more than 24 months) functional outcomes after radiotherapy. Only two studies described acoustic and aerodynamic parameters after radiotherapy in T_2N_0 glottic carcinoma patients.[2,4] Niedzielska *et al.* evaluated the phonatory function after one to three years in 11 male patients with T_2N_0 glottic carcinoma.[4] Their voice outcome parameters (jitter, shimmer, fundamental frequency and maximum phonation time) were comparable with our results. Agarwal *et al.* analysed the

https://doi.org/10.1017/S0022215122001682 Published online by Cambridge University Press

voice quality (jitter, shimmer and minimal intensity) before and after radiotherapy (between three and six months) in 50 patients, of whom 17 had T_2 glottic carcinoma.[2] We found similar scores for jitter but higher scores for shimmer. This difference might be explained by the fact that they used other testing conditions than ours.

A study by Remmelts *et al.* investigated the voice outcome with the physical subscale of the Voice Handicap Index-30 questionnaire.[16] They reported a mean score of 9.9 (range, 0–30) on this subscale in 38 patients with T_2 glottic carcinoma after a median time of 66 months. Our study revealed a similar score on this subscale after a median follow-up duration of 42 months. Al-Mamgani *et al.* investigated Voice Handicap Index scores in 223 patients with T_1–T_2 glottic carcinoma.[5] The Voice Handicap Index-30 score in patients treated for a T_{2a} tumour after 36 and 48 months was 24.3 and 23.8, respectively. The mean score in patients with T_{2b} tumours after 36 and 48 months was 36.2 and 39.7, respectively, showing that tumours leading to vocal fold movement impairment (T_{2b}) were associated with a higher voice handicap than tumours that did not lead to such impairment. In comparison, both our study and that by Remmelts *et al.* showed lower Voice Handicap Index scores for patients with T_2 tumours treated with radiotherapy.[16] However, in line with Al-Mamgani *et al.*,[5] we did find a trend towards higher Voice Handicap Index-30 scores in patients with more deeply infiltrating tumours, which in our case were defined as tumours that infiltrated the vocal fold muscle.

- Reported functional outcomes after treatment for tumour–node stage T_2N_0 glottic carcinoma with radiotherapy are sparse, especially in the long term
- However, reports demonstrate post-treatment voice improvement
- This study shows good long-term functional outcomes
- Patients with a tumour infiltrating the vocal fold muscle were examined with computed tomography
- Imaging showed a trend toward higher Voice Handicap Index scores than patients with superficial spread

It is possible that our study was positively influenced by the small numbers of participants and the fact that our cohort consisted mainly of T_{2a} tumours ($n = 12$ (85.7 per cent)). Even if seven (58.3 per cent) of these T_{2a} tumours infiltrated the vocal fold muscle, the vocal fold still showed normal mobility. Therefore, T_{2b} tumours with impaired vocal fold mobility were underrepresented in our cohort. Based on our results, we hypothesise that patients with T_2 glottic tumours infiltrating the vocal fold muscle may have a poorer voice outcome, with patients with a T_{2b} tumour and fixated vocal folds having the poorest result. This hypothesis will, however, have to be proven in larger studies. The study of Remmelts *et al.* did not describe the substage of T_2 tumours[16] (these substages are officially no longer part of the American Joint Committee on Cancer Staging[17]) and they only assessed the psychical subdomain of the Voice Handicap Index-30.[16] It is not known whether this subdomain is representative of the total score of the Voice Handicap Index-30.

More data on functional outcomes of different subcategories of T_2 tumours in radiotherapy are crucial for an adequate comparison of results with those of other treatment modalities. In surgical studies, for instance those on transoral laser microsurgery, it has long been recognised that T_2 glottic carcinomas are a heterogeneous group of lesions, requiring a variety of different types of resection, with varying functional and oncological outcomes.[18] Studies show that larger resection types as defined by the European Laryngological Society (European Laryngological Society type IV–VI resections) result in a worse voice outcome compared with superficial resection (European Laryngological Society type I–III resections).[19,20] As the study by Al-Mamgani *et al.*[5] and our study indicate, comparing functional outcomes of these different resections with a simple mean or median score for an overall cohort of patients with T_2 glottic tumours treated with radiotherapy is probably not adequate when determining the relative merits of the treatments and when counselling patients in therapy choice. Furthermore, it is our opinion that to harmonise outcome studies between modalities, the subcategorisation of tumours and comparison between modalities should be based on clinical and radiological extension of the tumour in addition to vocal fold mobility (T_{2a} or T_{2b}).

Regarding QoL, the European Organization for Research and Treatment of Cancer 'QLQ-C30' questionnaire was designed as a general questionnaire for patients with cancer, whereas the head and neck module (European Organization for Research and Treatment of Cancer 'QLQ-HN35') was designed for head and neck cancer patients and is thus more sensitive for specific toxicities and symptoms related to the treatment. To our knowledge, there are no studies that report results with these questionnaires for T_2N_0 glottic carcinoma specifically.

Two studies that used the European Organization for Research and Treatment of Cancer QLQ-C30 and QLQ-HN35 questionnaires included both T_1 and T_2 glottic carcinoma patients and treated them with radiotherapy,[21,22] but did not report separately on the two categories. The study by Arias *et al.* investigated QoL in 59 patients, of whom 10 had T_2 tumours.[22] Their results showed similar elevated QLQ-C30 scores to our results. On the QLQ-HN35 questionnaire, they showed the highest scores on the items of dry mouth, sticky saliva, coughing, painkiller use and weight gain;[22] we reported the highest scores for less sexuality, dry mouth, sticky saliva and coughing. Stoeckli *et al.* investigated QoL in 16 patients with T_1 and T_2 tumours.[21] They did not specify how many patients had T_2 tumours. Their study also reported an elevated score for fatigue and insomnia on the European Organization for Research and Treatment of Cancer QLQ-C030 questionnaire, and showed the highest scores for dry mouth, sticky saliva and coughing,[21] which was similar to our results.

A comparison of our results with normative data from the general Dutch population on the QLQ-C30 questionnaire showed comparable scores, even on the elevated items (fatigue and insomnia).[23] Therefore, the question remains whether or not these elevated items are related to the treatment in the long term. Unfortunately, no normative data from the general Dutch population exist for the European Organization for Research and Treatment of Cancer QLQ-HN35 questionnaire. Therefore, a comparison was performed with a multinational study on 108 patients with newly diagnosed laryngeal cancer (stages I–IV) and 185 disease-free patients after treatment for laryngeal cancer.[24] Elevated scores in our study are comparable to their combined scores (patients undergoing active treatment and disease-free patients); only the sexuality item is higher in our study.

Our study has some limitations. Firstly, the sample size was small and T_{2b} tumours were underrepresented. As stated, this may have positively biased our results. Secondly, because of the cross-sectional study design, comparison between pre- and

https://doi.org/10.1017/S0022215122001682 Published online by Cambridge University Press

post-treatment findings was not possible. In addition, not all patients were assessed at the same time-point post radiotherapy, although there was a minimum follow up of 26 months, which in our opinion represents a long-term follow up.

Based on our findings, we conclude that patients with T_2N_0 glottic carcinoma treated with radiotherapy show overall good long-term QoL, with low symptom scores and slightly elevated voice outcome parameters, which do not return to normal values after a median follow up of 42 months. Patients with tumours infiltrating the vocal fold muscle show a trend towards a higher voice handicap, which is supported by data in the literature. More studies are needed to investigate (long-term) functional outcomes after treatment for T_2 glottic carcinoma, particularly to investigate the effect of tumour extension on functional outcomes after radiotherapy so as to allow a meaningful comparison of results with those of other treatment modalities and enable more accurate counselling of patients.

Acknowledgement. We would like to thank Mrs VAH van de Kamp for her assistance in the voice evaluation.

Competing interests. None declared

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https://doi.org/10.1017/S0022215122001682 Published online by Cambridge University Press