

**SUMMARY**

When someone is diagnosed with cancer, obviously the prognosis regarding cure and survival is the most important issue. However, other factors, such as functional outcome and quality of life following treatment, can also play an important role in determining the treatment of choice. In early glottic cancer cure rates are very high with percentages of more than 90%, irrespective of type of treatment (endoscopic laser surgery or radiotherapy). Voice outcome, being at risk in glottic cancer and its treatment, is generally considered to be the most important functional outcome measure, with expected high impact on the quality of life, and therefore forms the prominent theme of this thesis.

**Chapter 1**

This Chapter provides a general introduction of voice production, and the anatomy and physiology of the larynx in relation to phonation. Several methods of voice assessment are described. Furthermore a description of the staging of laryngeal carcinomas and more specifically early glottic carcinomas (Tis, T1 and T2) is given. These early glottic laryngeal carcinomas were traditionally treated by radiotherapy or even open surgery. But the last decades laser surgery has gained its place as an alternative to radiotherapy in the treatment of early glottic carcinomas. Based on the literature review in this Chapter, specific research goals are formulated:

1. To assess whether or not patients experience voice problems after treatment of early glottic carcinomas. And if so, how can we identify these patients?
2. To assess the impact of voice problems after treatment of early glottic cancer on daily life activities.
3. To investigate the applicability of the Voice Handicap Index (VHI) as a tool to assess patient reported voice problems in laryngeal cancer patients.
4. To assess whether voice problems perceived by patients after treatment of early glottic cancer are comparable to the voice problems perceived by patients with benign vocal fold pathology.
5. To investigate the differences in voice outcome and voice recovery after treatment of early glottic cancer by radiotherapy as compared to voice outcome and voice recovery after endoscopic laser surgery.
6. To investigate whether the voice outcome following treatment for early glottic cancer differs from normal voices.
7. To assess the efficacy of voice therapy for voice problems after treatment of early glottic cancer.
8. To investigate whether voice outcome can be an indicator of preferred treatment modality for early glottic cancer, given the fact that the cure rates of both treatment modalities (radiotherapy and endoscopic laser surgery) are excellent.

Chapter 2

Even though there are several studies concerning ‘voice quality’ after treatment of early glottic cancer, the results are difficult to compare and sometimes even contradictory, most likely as a result of differences in patient selection, voice assessment tools and study designs. Nevertheless, it seems that a considerable number of patients end up with deteriorated voice quality after treatment of early glottic cancer. In order to detect voice problems, a 5-item questionnaire on a 10 point scale (1 = very much 10 = not at all) was developed. The assessment of the psychometric properties and value of this 5-item questionnaire is described in this chapter. In total, 177 patients after treatment of early glottic cancer (51 treated by laser surgery vs 126 by radiotherapy) filled in the questionnaire. 104 patients responded to our request to complete the questionnaire a second time after at least one month (median interval period 5 months; range1-10 months). Furthermore the same questionnaire was completed by 110 healthy, age and sex matched, controls. The psychometric properties of the questionnaire, as specified by the reliability, the internal consistency and the predictive validity, were good. The questionnaire therefore proved to be a reliable screening instrument resulting in a useful differentiation between normal and abnormal voices. Patients scoring a 5 or less on at least one of the five questions were considered to have overall voice impairment. In this study a relatively high number of patients report voice problems after treatment of early glottic cancer: 44% of the patients treated by radiotherapy vs. 29% of the patients treated with laser surgery (not significant; p=0.079).

Chapter 3

This chapter describes a cross-sectional study to gain more insight concerning the impact of voice problems after treatment of early glottic cancer on daily life activities. The self-reported outcome measure Voice Handicap Index of patients was used to assess voice-related problems in daily life and COOP/WONCA charts were used to assess their functional health status. The VHI is a 30-item questionnaire measuring voice-related quality of life and the COOP/WONCA charts represent self-assessment in six domains: physical fitness, mental well-being, daily activities, social activities, change in health, and overall health. Results show that voice-related problems in daily life (VHI) were significantly related to social activities, mental wellbeing, and overall health (COOP/WONCA). In this study 58% of the patients following radiotherapy and 40% of the patients following endoscopic laser surgery for early glottic cancer, experience voice problems, leading to restrictions in their social life, mental well-being and overall health. It must be mentioned that these results
were calculated with the initially presumed cut-off point of 10 on the VHI. Where a VHI-score below 10 was considered a normal score without self-assessed voice impairment. In Chapter 4 the psychometric properties of the VHI were re-evaluated and the cut-off point was validated at 15. Recalculation lead to voice problems in 50% of the patients treated with radiotherapy versus 30% of the patients treated with endoscopic laser surgery.

Chapter 4
This Chapter describes (psychometric) research on the Voice Handicap Index. The VHI scores of patients with voice problems after treatment of early glottic cancer were compared to the VHI scores of patients with voice problems caused by benign voice disorders, and to VHI scores of a sample of the Dutch general population, without voice problems. Patients were asked to fill out the questionnaire twice with an interval period of mean 3,5 months. Reliability of the VHI was proven by good internal consistency and high test-retest stability. A cut-off point of 15 (or higher) on the total VHI scale was defined to identify patients with voice problems in daily life. A difference score of 10 points was defined for use in individual patients in clinical practise, and of 15 points for use in study group research designs. Overall the VHI proved to be a reliable, validated tool to assess voice problems in daily life, in clinical practice and for research purposes. Furthermore results showed that patients after early glottic cancer have comparable voice problems to patients with benign voice disorders with similar scores on the VHI.

Chapter 5
In Chapter 5 the difference in voice outcome and voice recovery after treatment of early glottic cancer either by radiotherapy or endoscopic laser surgery was evaluated. A prospective cohort study investigated acoustical voice outcome from baseline (before treatment) to 2 years after treatment in a group of patients treated with radiotherapy or endoscopic laser surgery for T1a glottic carcinomas. Voice parameters, jitter, shimmer, and normalised noise energy (NNE), recovered sooner in patients treated with laser surgery than those of patients treated with radiotherapy. Already 3 months after endoscopic laser surgery voices were comparable to normal voices except for the fundamental frequency, which remained higher pitched, even after 24 months. Three months after radiotherapy pathological results were obtained for jitter, shimmer and NNE. Six and twelve months after radiotherapy pathological results were still obtained for jitter and fundamental frequency. Two years after radiotherapy, no difference as compared to normal voices was found except for the jitter, which remained on a pathological level.

Six months after treatment there was no longer a difference between the two treatment modalities, except for the fundamental frequency, which remained higher pitched, even after 24 months, in patients treated with laser surgery.
Given the fact that widely reported oncological outcome is excellent following both treatment modalities, these voice results favour endoscopic laser surgery as the first treatment of choice in T1a glottic carcinoma.

Chapter 6

Chapter 6 describes a randomized controlled trial to assess the efficacy of voice therapy in a group of patients with voice problems at least 6 months after treatment of early glottic cancer (by radiotherapy or endoscopic laser surgery). Patients were included following an abnormal score on the 5-item screening questionnaire described in Chapter 2, and their consent to enter the study with the possibility that they would be assigned to voice therapy. Included patients were randomly assigned into the voice therapy group or control group. To assess the effect of voice therapy, a multidimensional voice assessment protocol, with the VHI as primary outcome measure, was performed. All patients’ voices were examined twice: once at baseline (study entry assessment) and once after voice therapy or after 3 months for patients in the control group (study exit assessment). The voice complaints of the patient, as assessed by the VHI, improved significantly in the voice therapy group, with a mean improvement of 15 points. In the control group a mean VHI difference of 3 points was found between the two measurements. A beneficial significant effect of voice therapy was also observed on secondary voice quality outcome measures (acoustical measures: Noise to Harmonics Ratio and jitter, and perceptual rating of vocal fry).

A striking finding in this study was that nearly 60% of the patients, all of whom reported voice problems in daily life on the 5 item screening questionnaire, were not willing to participate in the study. This high percentage may be explained by the time-consuming nature of voice therapy and the fact that many patients accepted their voice problem as an inevitable consequence of their treatment for a potentially life-threatening disease, but more research is needed to obtain insight in possible barriers and facilitators of referral to voice therapy. The study described in this Chapter provides evidence that voice therapy is effective for patients with voice problems after treatment of early glottic carcinoma.

Chapter 7

While the previous chapter provided evidence of short-term efficacy of voice therapy in patients with voice problems after treatment of early glottic cancer, it is of course also of interest to determine whether this positive result of voice therapy is long lasting. In this study we focussed on the VHI, as the primary outcome measure. Patients were re-evaluated at least 6 months after completing voice therapy. Results showed no significant change in VHI measured after 6 months or more as compared to the VHI score measured directly after voice therapy. The mean VHI score at follow-up assessment (6 months or more after voice therapy) remained significantly better than the baseline assessment measured be-
fore voice therapy. The findings in this study prove that the beneficial short-term effect of voice therapy in patients who experienced voice problems after treatment are long lasting (at least 6 months or more).

Chapter 8

In Chapter 8, the outcomes of the initially formulated research goals are summarized and discussed and put into broader perspective. Furthermore some recommendations were made, based upon the literature and the results presented in this thesis.

The overall conclusion of this thesis is that voice problems are prevalent and interfere with daily life activities, in patients after treatment of early glottic cancer, either following endoscopic laser surgery or radiotherapy.

Recommendation regarding treatment of choice for early glottic cancer

It is our considered opinion that endoscopic laser surgery should be recommended as the treatment of choice for most early glottic carcinomas. Although radiotherapy offers the same excellent oncological outcomes as endoscopic laser surgery, the morbidity as well as the options for salvage therapy in the unlikely event of recurrence, are less favourable. Moreover, voice quality recovers more rapidly following laser resection and patients less often report voice problems in daily life. Furthermore radiotherapy is less cost effective than endoscopic laser surgery. In clinical practice however there may be individual reasons, e.g. co-morbidity precluding general anaesthesia or other factors which favour radiotherapy as a good alternative.

Recommendation regarding voice screening and voice therapy

Based upon this thesis we recommend active screening for voice impairment after treatment of early glottic cancer in clinical practise and, if indicated, to carry out a more extensive voice assessment. Patients experiencing voice problems after treatment for early glottic cancer (endoscopic laser surgery or radiotherapy) should be offered the option of voice therapy, an evidence based intervention, as proven in this thesis.

Recommendation for future research

Future studies on the (cost-)effectiveness of the optimal choice of treatment and rehabilitation of patients diagnosed with early glottic cancer are needed and can be designed as randomized controlled trials, but other designs as case–control and cohort studies may also be considered to be more suitable for “personalized medicine” approaches. In any case, choice of outcome measures should be based on consensus and existing evidence, such as provided in the present thesis.