CHAPTER

CONCLUSIONS, DISCUSSION AND RECOMMENDATIONS
CONCLUSIONS

Identification of voice problems after treatment of early glottic cancer is important, especially since so many patients with early glottic cancer can be cured of their disease, and voice problems have an important impact in daily life activities.

The purpose of this thesis was to enhance our knowledge regarding voice outcome in patients after treatment of early glottic cancer, to investigate the relation between voice outcome and quality of life, and to assess the efficacy of voice therapy in patients with voice problems after treatment of early glottic cancer. In order to achieve this goal, 8 research questions were formulated as described in the introduction and can be addressed based on the studies reported on in this thesis.

Research questions

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?

The study described in Chapter 2 demonstrated that voice problems after treatment of early glottic cancer frequently occur: 44% of the patients treated with radiotherapy and 29% of the patients treated with endoscopic laser surgery experience voice problems (no significant difference p= 0.079). Patients with voice problems following treatment of early glottic cancer can be identified in clinical practice using a short 5-item screening questionnaire.

2. To assess the impact of voice problems after treatment of early glottic cancer on daily life activities.

The study described in Chapter 3 demonstrated that many patients (58% of the patients following radiotherapy and 40% of the patients following endoscopic laser surgery (p<0.05) experience voice problems after treatment of early glottic cancer, leading to restrictions in their social life, mental well-being and overall health, as was shown by significant correlations between the VHI (tool to assess patient reported voice problems) and COOP/WONCA charts (tool to assess patient reported functional health status).

3. To investigate the applicability of the Voice Handicap Index (VHI) as a tool to assess patient reported voice problems in laryngeal cancer patients.

The study described in Chapter 4 demonstrated the VHI to be an adequate tool for detailed assessment of perceived voice problems after treatment of early glottic cancer. A validated cut-off point of 15 (or higher) on the total VHI score was recommended to identify patients with voice problems in daily life. To interpret significant changes or differences, a validated difference score of 10 points for individuals in clinical practice and 15 points for study group designs was recommended.
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.**

The study described in Chapter 4 demonstrated that voice problems among patients after treatment of early glottic cancer are comparable to voice problems perceived by patients with benign vocal fold pathology as was demonstrated by similar VHI scores in both groups.

5. **To investigate 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.**

The study described in Chapter 5 demonstrated that, except for fundamental frequency, no significant long-term (24 months) differences in voice outcome between radiotherapy and laser surgery treated patients with early glottic cancer were identified, as measured by acoustic analyses. Fundamental frequency remained higher pitched in patients treated by laser surgery.

However, voice recovery following treatment, as determined by acoustic analysis, occurred more rapidly in patients treated with laser surgery than in patients treated with radiotherapy. Moreover, long term voice outcome (one year or more following treatment), as reported by the patients themselves as assessed with the VHI, significantly favours laser surgery above radiotherapy as described in Chapter 3 with a mean VHI for the laser surgically treated group of 12.0 and a mean VHI of the radiotherapy treated group of 18.2.

6. **To investigate whether voice outcome following treatment for early glottic cancer differs from normal voices.**

The study described in Chapter 5 demonstrated that compared to normal voices, in the long-term (24 months) the patients treated with laser surgery had a higher than normal vocal pitch and the patients treated with radiotherapy had a higher than normal jitter value. Based on the new validated cut-off point for voice impairment as determined in Chapter 4 (considering a VHI score lower than 15 as normal instead of a score lower than 10), 50% of the patients after radiotherapy achieve normal VHI-scores, whereas 70% of the patients after laser surgery achieve normal VHI scores (significant difference, p<0.05) (as recalculated using the data from Chapter 3).

7. **To assess the efficacy of voice therapy for voice problems after treatment of early glottic cancer.**

The study described in Chapters 6 and 7 demonstrated that, compared to a randomized control group without voice therapy, voice therapy has a beneficial effect on voice quality of the patients with voice problems following treatment of early glottic cancer. This
positive effect was found with respect to patient reported voice outcome (VHI) as well as to acoustic voice quality assessment. These beneficial effects of voice therapy on voice outcome persisted for at least 1 year after completing voice therapy.

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.

The studies described in Chapters 3 and 5 demonstrated that there are differences in voice outcome between radiotherapy and laser surgery for early glottic cancer, especially during the first period following treatment, and that patients treated with laser surgery demonstrate an earlier recovery of normal voice values and more patients (70%) achieve normal VHI scores than patients following radiotherapy (50%). Therefore voice outcome can be considered an important factor in deciding on a preferred treatment modality.
DISCUSSION

Treatment of choice for early glottic cancer

Obviously cure remains the most important factor for patients who are diagnosed with a malignancy. But when primary cure rates of different treatment options are equal, this is no longer a factor determining the primary choice of treatment. This thesis revealed that it is worth considering to include (speed of) recovery of voice outcome in (shared) decision making on treatment choice.

Besides voice outcome, other factors such as morbidity, remaining options for salvage therapy, treatment options for a regional second primary malignancy, quality of life, patient’s general health and costs also play a prominent role in the decision making for the individual patient concerning cancer treatment as well as post treatment supportive cancer care. In the following section we will discuss the factors determining the choice of preferred treatment modality in more detail.

Oncological outcome in broader perspective

Recent data support the generally held opinion that both laser surgery as well as radiotherapy have good local control rates for early glottic carcinoma of 71-94% and 73-94% respectively\(^1\)\(^-\)^\(^3\). However, oncological outcomes of laryngeal cancer are not only determined by the local control rates, but also by the salvage treatment options in case of a recurrence of the primary tumor, preferably without sacrificing the larynx or its functions. Literature reports larynx preservation rates of 95-98% and 77-95% for respectively primary laser surgery and primary radiotherapy\(^1\)\(^-\)^\(^3\). Although this was not the main purpose of this thesis, similar results as in the above mentioned studies were found in our own study group described in Chapter 5 (including 106 patients; 67 treated with endoscopic laser surgery and 39 patients treated with radiotherapy) with local control rates of 97% and 95%, and larynx preservation rates of 100% and 95% for respectively laser surgery and radiotherapy 2 years after treatment of T1a glottic cancer.

Given the excellent and almost identical primary local control rates of both treatment modalities it makes sense to take the salvage options into account when trying to determine a preferred treatment of choice.

Given the fact that patients, who have once developed a head and neck malignancy\(^4\), have a higher risk of developing a second primary tumor, the above mentioned also holds true for taking into account how previous treatment of an early glottic cancer will influence the possibilities of treating a regionally developed second primary tumor.
Salvage treatment after primary radiotherapy

In case of radiotherapy as primary treatment, Kasperts et al. demonstrated, in a systematic review, that re-irradiation for recurrent and second primary head and neck cancer has a relatively high risk of both acute and late complications. Soft tissue necrosis and osteonecrosis are the most frequently occurring complications but also (fatal) haemorrhages and fistulas are described.

This can be expected to hold true for re-irradiation of a recurrent cancer as well as for irradiation of a second primary tumor, should that second primary tumor develop within a previously irradiated area. Kasperts et al. conclude that salvage surgery, when feasible, is the treatment of choice for recurrences or second primaries following primary radiotherapy. We have to bear in mind that this study was not restricted to cases of early glottic cancer, usually treated with lower over-all doses of radiotherapy than more extensive head and neck tumors. In contrast with Kasperts, Wang et al., who studied the possibilities of re-irradiation following recurrences of early glottic cancer, concluded that re-irradiation is a good alternative for laryngectomy.

Without any doubt total laryngectomy remains an oncological safe salvage procedure but it severely compromises quality of life. Several studies report good results with external partial laryngectomy as organ preserving salvage therapy for limited recurrences (T1-T2) after primary radiotherapy. However, these procedures performed as salvage therapy after radiotherapy carry an increased risk of postoperative complications, like chondritis, chondronecrosis and fistulas. Furthermore quality of life can be compromised by temporary or permanent tracheostomy and swallowing problems.

Several studies proved laser surgery to be an adequate organ preserving salvage procedure for selected recurrences after primary radiotherapy for early glottic cancer. In spite of the occasional (17-19%) need for repetition of salvage laser surgery this can eventually result in 5-year disease-specific survival rates of 68% to 94%, local control rates of 42% to 84%, and larynx preservation rates of 74% to 87% for treatment of recurrent cancer.

To our knowledge only Del Bon et al. studied voice outcome after salvage laser surgery. In a small series they found no significant differences in VHI and acoustical analyses between 10 patients following primary laser surgery for early glottic cancer as compared to 10 patients following laser salvage treatment for irradiation failure.

Salvage after primary laser surgery

In case of recurrence after primary laser surgery for early glottic carcinoma many retreatment options are available. First of all repeated laser surgery proves to be a good salvage treatment for recurrences after primary laser surgery for early glottic cancer. Both Huang et al. and Roedel et al. justify salvage laser surgery for the less advanced re-
currences (rTis-T2) with a 5-year disease-specific survival rate of 97.9% and 81%, a larynx preservation rate of 86% and 91% and a 5-year local control rate of 70% and 64% respectively (16% and 34% required repeated laser surgery). Both authors stress the importance of experience with salvage laser surgery, good exposure of the tumor and patients who are closely followed-up. Furthermore they state that advanced recurrences, infiltration of both arytenoids, and/or deep cervical tumor spread are not suitable for laser salvage.

Salvage radiotherapy, is also a reliable therapeutic option for recurrences after initial laser surgery\textsuperscript{17,18}.

Furthermore partial laryngectomies (for the less advanced recurrences) and total laryngectomies (for the more advanced recurrences) are oncological safe salvage procedures for laser failures, with less morbidity than when performed after primary radiotherapy\textsuperscript{18,21}.

Voice outcome

When endoscopic laser treatment came “en vogue”, the initially by many authors held opinion was that voice outcome following laser treatment was worse compared to voice outcome than following radiotherapy\textsuperscript{22-27}. Since then many studies addressed voice outcome after laser surgery and radiotherapy for early glottic cancer, but results remained contradictory\textsuperscript{28-45}. Our studies clearly demonstrate that voice problems indeed occur in patients after treatment of early glottic cancer, either following laser surgery or radiotherapy, and that this may interfere with the daily life activities of patients.

The most important differences between both treatment options that we found, were more rapid voice recovery, less often patient reported voice problems in daily life, and higher pitched voice, in patients after laser surgery in comparison to patients after radiotherapy.

The persisting higher pitched fundamental frequency of the voice following endoscopic laser surgery (Chapter 5), is in accordance with recent literature\textsuperscript{46,47} and may be explained by loss of mass and increased stiffness of the vocal fold, which both can result in an increase of the fundamental frequency. Cheng\textsuperscript{46} et al. compared acoustical voice outcome (fundamental frequency, jitter, shimmer and harmonics to noise ratio) between patients treated by radiotherapy or endoscopic laser surgery for early glottic cancer (Tis-T2). Measured at least one year after treatment no difference was found between both groups concerning jitter, shimmer and harmonics to noise ratio. Only fundamental frequency was significantly higher in the patients of the endoscopic laser group. Unfortunately, their study had a cross-sectional (not longitudinal) design and their data can therefore not support nor deny our finding that voices of patients recovered more rapidly after laser surgery than after radiotherapy. The study by Cheng et al. as well as other studies\textsuperscript{36,37,46} supported our finding that fundamental voice frequency in irradiated patients does not differ significantly from normal controls. It may be that the changes in structure of the vocal folds follow-
ing radiotherapy, such as radiation-induced tissue fibrosis, atrophic changes, and mucosal dryness on the one hand and post radiation oedema on the other hand, compensate each other, with respect to vocal fundamental frequency outcome, but future physiological studies are needed to investigate this hypothesis.

Although we did not find a significant difference for jitter between radiotherapy and laser surgery 6 months after treatment, jitter remained (even after 24 months) significantly higher after radiotherapy in comparison to normal speakers.

Although voice quality of patients following treatment for early glottic cancer over-all differs from the standard, especially in the first months following treatment, this does not mean that all patients indeed experience a voice problem in daily life. Voice problems six months or more after either radiotherapy or endoscopic laser surgery were reported by 44% and 29% respectively in a group of 177 patients with early glottic cancer as determined by a voice screening questionnaire (Chapter 2). In Chapter 3, among a group of 92 patients, at least 12 months after radiotherapy or laser surgery, these percentages were respectively 58% and 40% as determined by the VHI questionnaire with a cut-off point taken at that time at 10 points. In the more recent study as described in Chapter 4 the new, validated cut-off point of the VHI changed to 15 points. If the results presented in Chapter 3 are re-calculated taking into account the validated cut-off point of 15, 50% and 30% of the patients experience voice problems following respectively radiotherapy and endoscopic laser surgery. The results support the screening questionnaire (5 items) to be a good tool to identify voice problems, comparable with the slightly more elaborate VHI (30 items). Contrary to the sometimes still held opinion that radiotherapy25-27 is the most voice preserving therapy for early glottic cancer, our results demonstrated that voice recovery after laser surgery is faster and it is less likely that patients treated with laser surgery experience voice problems in daily life compared to patients following radiotherapy.

**Morbidity of primary treatment of early glottic cancer**

Radiotherapy is more time consuming for patients than laser surgery: patients undergoing radiotherapy have to go the clinic (depending on the radiation schedule) five days a week for 6 weeks on a row, while laser surgery can be performed in a one day clinical admission. Furthermore patients treated with radiotherapy often experience discomfort during and several weeks following the irradiation due to localized mucositis.

As a consequence of the narrow field of irradiation and the relatively low over-all dose of irradiation in cases of early glottic cancer, the incidence of major or long-term complications due to primary radiotherapy, such as glottic fibrosis and/or stenosis, cervical myelitis, laryngeal cartilage necrosis and hypothyroidism is low48-50. However, minor complications and discomforts, such as laryngitis, laryngeal dryness, swallowing disorders, radiation dermatitis or moderate oedema, not resolving within several weeks following the end of irradiation are reported to occur in up to 18% of patients48-51.
Major complications after laser surgery for early glottic carcinoma are also rare\textsuperscript{52,53}. Complications such as post-operative haemorrhaging, synechia of the anterior commissure, thermal tissue damage and oedema are described\textsuperscript{52,54,55}. Ellies\textsuperscript{52} et al treated 337 T1a and 30 T1b vocal fold carcinomas by endoscopic laser excision, with a low complication rate of 1.2% and 6.7% respectively. Postoperative hemorrhaging, requiring microlaryngoscopic hemostasis occurred in 3 cases. Furthermore they described 1 patient who developed a synechia, requiring treatment and 2 patients with laryngeal edemas which were managed conservatively. None of the cases required tracheotomy. In order to prevent synechia in the anterior commissure after laser surgery, Roh and Yoon\textsuperscript{55} suggest application of mitomycin C to the wound defect. Thermal tissue damage can be minimized by using proper laser settings of energy, pulse, time and focus.

**Treatment costs**

Treatment of early glottic cancer by radiotherapy is a time-consuming procedure lasting several weeks and mainly because of that the one day visit endoscopic laser surgery is much more cost-effective than radiotherapy\textsuperscript{42,56-59}. In our department Goor\textsuperscript{57} et al., studying patients with T1a glottic cancer, found the total costs of treatment to be 8322 euros for radiotherapy and 4434 euros for endoscopic laser surgery in the period 1995 to 1999. This amount included the costs of the treatment of a recurrence, should it occur. In addition to the above mentioned actual costs, Smith\textsuperscript{42} et al. showed that the hidden costs for radiation therapy versus endoscopic excision of early glottic cancer were all significantly higher for radiotherapy in terms of total number of hours of work missed, total travel time, and total travel distance.

**Voice therapy**

While voice therapy is commonly accepted as intervention in selected patients with benign voice disorders, patients with voice problems after treatment of early glottic cancer are usually not referred for voice therapy. This thesis revealed that patients after treatment of early glottic cancer encounter the same voice problems as patients with benign voice disorders and that voice therapy is beneficial for patients with voice problems following either radiotherapy or endoscopic laser surgery. The beneficial effect was observed not only immediately following voice therapy, but also in the long term (Chapter 6 and 7).

The prerequisite for effectiveness of voice therapy of course must be that a patient is sufficiently motivated to enter a voice therapy programme. It must be taken into consideration that the patients included in this study were motivated to follow a voice therapy program. The results may, therefore, be less favourable if patients are urged to enrol in a voice therapy program without clear motivation. A striking finding in our study was that nearly 60% of the patients with voice problems in daily life, did not express the need to be enrolled in a voice therapy program. This may be caused by the time-consuming nature of
voice therapy and the fact that patients may accept their voice problem as an unavoidable consequence of the treatment for a potentially life-threatening disease (adaptive coping strategy). To our knowledge there are no further recent studies about the efficacy of voice therapy in patients after treatment of early glottic cancer. Future research is needed to obtain more insight into the need and motivation for voice therapy. Nevertheless, based on the beneficial effect of voice therapy, it is recommended to offer patients with voice problems after treatment for early glottic cancer voice therapy as evidence based intervention.

**Shortcoming**

The results as reported in this thesis would have been methodologically stronger if randomized treatment allocation of patients to either radiotherapy or surgery could have been performed. We have to take into consideration that our research as presented in this thesis started in a period that radiotherapy was the recommended treatment modality for these early glottic cancers, and a randomized controlled trial was not an option at that time.

Also, even if a RCT would have been an option, comparison of functional outcome of different treatment modalities for early glottic cancer is difficult and challenging, and multicentre studies are needed to guarantee adequate subject numbers. I agree with van Loon et al., who mentioned that a standardized method is needed to accurately measure tumor extent and depth in order to allow comparison of laser surgery versus radiotherapy. Also, agreement on functional outcome measures is a requirement for comparison of functional results of types of treatment and resection.

The initial Dutch national guideline on laryngeal cancer (2000) adopted laser surgery only as a possible alternative for radiotherapy in superficial midcord T1a lesions. The more recent Dutch guideline (2010) on laryngeal cancer recommends laser surgery as the treatment of choice for these T1a lesions, where a sufficient margin can be obtained within the affected fold, by either a subligamental or subepithelial resection which does not extend into the anterior commissure (type I and II cordectomy according to ELS classification).

Regarding surgical treatment, although achievement of local control is paramount, the ability to perform radical resection, while preserving adequate voice quality, has been an important consideration in treatment decision making and in the design of current guidelines.

Deep T1a lesions or lesions extending into the anterior commissure requiring a transmuscular, total, or extended cordectomy or a resection of the anterior commissure (type III, VI and V of the ELS classification) are commonly regarded as less suitable for laser surgery, because poor voice quality is expected after these procedures. Involvement of the anterior commissure can be considered slightly challenging because of its allegedly easy
local tumor spread. The anterior commissure is located very near to the thyroid cartilage: because of the absence of perichondrium or conus elasticus and early ossification of the cartilage at this level there is a poor local defence against tumor spread once the tumor has infiltrated more deeply in the vocal fold. Clearly this is not a big issue in case of only superficial tumor spread. Adequate radiological staging at this level, especially invasion of the cartilage can be challenging. Because of this and the fact that deep infiltration of tumor in the anterior commissure can occur without impairment of vocal cord mobility leads to a risk of understaging or overstaging in 25% to 50% of the cases. The more extensive the tumor, the more extended the endoscopic laser resection, the more extensive the scarring of the vocal folds and consequently the worse voice outcome is anticipated. Roh et al. indeed found that the extent of laser resection for Tis or T1 glottic carcinomas can affect the vocal function by influencing a patient’s QOL associated with social activities. The early glottic cancers with a limited extent and infiltration depth (type I and II cordecomies) had significantly better results on VHI as well as on GRBAS as on acoustic analysis, compared to those lesions requiring extensive laser resection (type III, IV and V cordecomies). Also both Ledda and Peretti found worse voice quality from type III and more extensive resections in comparison to the smaller resection types I and II.

Despite many studies concerning cure rates and functional outcomes, international consensus on the choice of treatment for early glottic cancer is still an utopia. In the United Kingdom, the ENT-UK Head and Neck Group achieved consensus that trans oral laser assisted microsurgical resection should be offered as a treatment modality to all patients with early glottic cancer. In Germany and Spain also more extensive tumor stages are treated by laser surgery.

Although treatment allocation in our studies was not randomized and conclusions therefore should be regarded with caution, it is important that no significant difference in the voice analyses was found before treatment between both patient groups (undergoing either laser resection or radiotherapy) with early glottic cancer, to be treated by laser surgery or radiotherapy. Therefore no patient selection has occurred on basis of voice quality. In the study on the effectiveness of voice therapy, we did perform a randomised controlled trial targeting patients with voice problems after treatment. This RCT involved a relatively small study sample and is therefore considered as a proof of principle.
RECOMMENDATIONS

Recommendation regarding treatment of choice for early glottic cancer

Taking into account the above mentioned considerations, it is our considered opinion that laser surgery should be recommended as the treatment of choice for most early glottic carcinomas. Although radiotherapy offers the same excellent oncological outcomes as laser surgery does, 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 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 (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 (early) rehabilitation of patients diagnosed with early glottic cancer are needed and can be designed as randomized controlled trials, but other designs such as case–control and cohort studies may also be considered 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.
REFERENCES


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Conclusions, discussion and recommendations


