Disease outcome in T1 glottic carcinoma

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Chapter 11

Conclusions and recommendations for further research

- introduction
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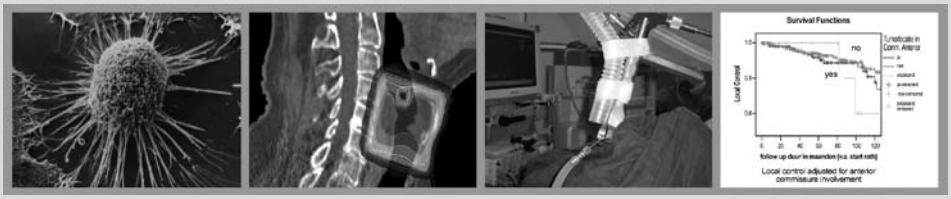

Introduction

The general aim of this thesis is to determine and compare disease and voice outcome for T1 glottic carcinoma treated with radiotherapy or laser surgery. Apart from giving the main findings and conclusions of the previous chapters, this concluding chapter will also focus on the unresolved issues, as well as explore the implications, opportunities and strategies for future research.

Main findings and conclusions of this thesis

Chapter 1 is a general introduction which briefly describes basic anatomy and physiology, as well as the pathophysiology of "early glottic" and "T1 glottic" carcinoma. The scope of this thesis is also given.

Chapter 2 describes the epidemiology of head and neck squamous cell carcinoma (HNSCC) of the larynx in the Netherlands from 1989 to 2002. In this time period 8097 men and 1347 women were diagnosed with HNSCC of the larynx, averaging 674 cases per year. This corresponds to a standardized incidence rate of 4.2 / 100.000 person-years making it the most frequent form of head and neck cancer in the Netherlands for this time period. As 64% of these laryngeal HNSCC's was diagnosed in the glottis, of which 56% in the T1 stage, this corresponds to an average of 242 T1 glottic carcinomas per year. Although common as a head and neck cancer, in absolute terms T1 glottic carcinoma is rare and in 2001 it represented only 0.53% of all cancers in men and 0.12% of all cases in women. The implications, which these data have for clinical studies on T1 glottic carcinoma, are discussed in chapter 10.

Chapter 3 is a population-based, retrospective cohort study of the outcome and prognostic factors for T1 glottic carcinoma treated with radiotherapy. The 5-year rate of local control was high at 85% with 93% laryngeal preservation. None of the conventional patient, tumor, or treatment factors taken from literature had a significant influence on local control or disease-specific survival. As this was a population-based study of considerable size we believe that for factors with well-defined, universally accepted values such as sub stage (T1a/b) and anterior commissure involvement (yes/no) our results are reliable. We therefore conclude that these factors have no prognostic value in the treatment of T1 glottic carcinoma with radiotherapy. For factors with more variable definitions such as tumor size (defined as number of affected 1/3's of vocal fold in this study), the validity becomes more uncertain as the values and cut-off points chosen to represent these factors may not have been optimal. Also, the results for these factors are only comparable to studies using the same definitions. Therefore, more care should be taken when interpreting these results. Also, our finding that treatment parameters such as total dose, fraction size and overall treatment time were not prognostic for local control is only valid for the range

of values included. In our study this range was limited. The only factor with a significant impact on local control was a new factor not reported on before: pre-existent hypertrophic laryngitis, showing a decrease in 5-year local control from 87% to 77% in patients where this factor was present. In multivariate analysis, pre-existent hypertrophic laryngitis was associated with a relative risk of local failure of 3.0 (95% C.I. 1.2 - 7.2, p = 0.02). We speculate that this could be linked to chronic inflammation but further research is needed to support this theory.

Chapter 4 is a population-based, retrospective cohort study of the risk of synchronous and metachronous tumors in patients with Tis-T1 glottic carcinoma. It shows that observed-to-expected ratios in males are elevated for cancers of the pancreas (3.8), lung (3.6), bladder (2.7), and colorectum (1.9). Contrary to general expectation, the observed-to-expected ratio for cancers of the mouth, oro- and hypopharynx (2.4.), although elevated, was not found to be statistically significant and the ratio for esophagus cancer was not elevated (1.1). Therefore, apart from lung cancer, the risk of cancers outside the upper-aerodigestive tract outweighs the risk of multiple malignant neoplasias in the mouth, oro- and hypopharynx or the oesophagus and is more likely to influence survival in patients with Tis-T1 glottic carcinoma. From this we conclude that the low incidence of head and neck and esophageal tumors does not seem to support routine panendoscopy in these patients. Furthermore, physician awareness of the high incidence of tobacco related multiple malignant neoplasia outside the upper aerodigestive tract is necessary for early detection and counseling of patients.

Chapter 5 is a population-based, retrospective cohort study in patients with Tis-T1 glottic carcinoma, focusing on the impact of prior tumors on survival. We wished to determine the prevalence of prior tumors in this patient group and the impact of prior tumors on survival. These results show that prior tumors occur in (6%) of patients with early glottic carcinoma and that they have an independent impact on overall survival in this group. In this study, patients with early glottic carcinoma and a prior tumor as a group had 3.4 times the risk of dying during follow-up compared to patients without a prior tumor. This risk was time-related and decreased to 2.6 times if the tumor was diagnosed more than 6 months before the glottic tumor. The effect of prior tumors was stronger than that of other (non-malignant) comorbidity which was only of borderline significance. These findings show that although disease-specific survival is very high in early glottic carcinoma, overall survival is limited in patients with prior tumors. This supports the concept of incorporating data on prior malignancies (and other comorbidity) into the existing TNM tumor staging system to improve the accuracy of prognostication and to aid in treatment decisions for the individual patient.

Chapter 6 is a retrospective cohort study and reports on the clinical outcome of T1 glottic carcinoma at our institution since the introduction of CO_2-laser surgery as a treat-

ment option in 1996. As a rule, patients with superficial, midcord T1a carcinomas were selected for laser surgery. They had high rates of local control (91%) and larynx preservation (100%). However, the remaining T1 patients allocated to radiotherapy for reasons of voice preservation had a relatively poor outcome (local control 75% and larynx preservation 83%). Because of indication bias based on tumor extension these groups cannot be directly compared. However, the outcome in the radiotherapy group is poor, even when compared to average outcome for unselected T1 glottic carcinoma treated with radiotherapy. In chapter 3, tumor size defined by number of affected 1/3 parts of vocal fold seemed an uncertain prognostic factor. From the findings in chapter 6 we however conclude that: -tumor extension may be an important prognostic factor in radiotherapy for T1 glottic carcinoma, -this factor is not managed adequately in the current TNM staging system and -further investigations into the optimal definition of tumor size and extension are necessary. Furthermore, the relatively poor rates of local control after radiotherapy raise the question of a possible role for laser surgery in these lesions despite possible costs to functionality.

Chapter 7 is a retrospective cohort study in which we investigated whether a "typical" voice in terms of auditory perception may be defined after type I or II cordectomy and if other parameters in a multidimensional voice protocol correlate to this perceptual profile.
We found that the typical laser-treated voice was mildly breathy and that correlations between auditory perception and other parameters were weak. From this data we conclude that stroboscopy, VHI, perceptual and acoustic analyses measure separate, but complimentary aspects of the disordered voice, and these outcomes do not form one integrated voice profile. As the ELS concludes in their own proposal for the current multidimensional voice assessment protocol: "it is not to be considered as an ultimate way to basically assess the voice" and "new and more sophisticated measurement or evaluation techniques are to be encouraged". We agree that acoustic parameters need to be identified that adequately describe disordered voice production. Also, given the poor inter- and intra-rater reliabilities associated with both stroboscopy and perceptual rating, different assessment or rating approaches will have to be developed, so that voice professionals can establish clinically relevant, integrated voice profiles for use in patient counseling and clinical outcome studies. The discrepancy between perceptual analysis (quality) and patient self-assessment (impact) is particularly interesting. The fact that the severity of perceived dysphonia does not necessarily reflect the degree of impairment perceived by the patient, and that voice impairment experienced by this patient population was minimal may provide the flexibility necessary for performing larger resections in the future.

Chapter 8 is the first retrospective cohort study that compares post-treatment voice quality after radiotherapy (historic control group) and endoscopic laser surgery (subepithelial or subligamental resection) in patients with similar T1a midcord lesions. In this study, roughly half of the patients had mild to moderate dysphonia regardless of treatment

modality. There was no statistical difference in the severity and type of dysphonia between the groups as assessed by a multidimensional protocol (GRBAS, acoustic and aerodynamic analysis, stroboscopy and VHI); although indications are, that the profiles of the dysphonia may ultimately be different. Irradiated voices showed more roughness and laser treated voices more breathiness. Our results, supported by the modest trends found in literature, lead us to conclude that endoscopic laser surgery offers equivalent overall voice quality to irradiation for patients with T1a (midcord) glottic carcinoma. Providing similar disease outcome and the additional benefits of shorter treatment time, lower costs and the possibility of repeated procedures, we believe that endoscopic laser surgery is therefore the preferred treatment for superficial, midcord T1a glottic carcinoma.

Chapter 9 constitutes a review of the literature on T1 glottic carcinoma up until January 2008. From it we conclude that there is little difference in local control for T1 glottic carcinoma, even in unselected lesions, between the two modalities radiotherapy and laser. However, these are overall outcomes. Proper stratification for tumor size/extension is not yet possible due to the inadequacy of the current staging systems. Prognostic factors influencing outcome of both modalities remain uncertain. There are some indications that laser surgery has the advantage in terms of ultimate larynx preservation, both in superficial and in more extended lesions. Dysphonia after treatment for superficial T1a glottic carcinomas is usually mild and there is little or no difference in overall voice quality in comparative studies. As seen in our own study (chapter 8), the grade of dysphonia as rated by trained listeners in auditory-perceptual analysis does not correspond to the amount of voice handicap reported by the patient, which is often mild, even after extended resections. There is need for more comparative data on voice outcome in extended T1 lesions / resections.

Chapter 10 reports on a national survey performed in all Dutch Head and Neck cancer working groups to gain insight into the surgeon's perspective on indications for laser surgery in glottic carcinoma. Two types of excisions were found to be plausible candidates for extending the current indications for laser surgery: superficial bilateral resections (type I and II) and deeper unilateral resections (type III). The survey also showed that being prepared to perform a certain resection outside of protocol is not automatically the same as being prepared to randomize all such lesions in a trial setting. This became apparent when the results of the survey were presented at the NWHHT research meeting in December 2007. The general feeling at this meeting was that surgeons are still apprehensive about compromising voice quality in more extensive resections. Until more evidence of oncological and functional results becomes available they consider laser surgery to be an alternative therapy in all lesions but superficial midcord T1a carcinomas, to be reserved for selected cases after careful consultation with the patient. Recruiting patients for a randomized trial therefore seems unlikely to be successful in the Netherlands at this moment. We refer to the last section of this thesis "recommendations for further research" for our proposal on how to resolve this situation.

General conclusion

During the "life-time" of this thesis we have seen a shift in the literature and expert opinion around T1 glottic carcinoma from being centered on results of radiotherapy and hunting for its prognostic factors towards the possible merits of laser surgery in these lesions. Laser surgery in the Netherlands has gone from being an alternative treatment for pioneers to an accepted and even recommended treatment modality in superficial T1a midcord carcinomas. In fact, after reviewing the current literature in 2007, the advisory board of the Dutch Cooperative Group on Head and Neck Cancer (NWHHT) changed the guideline from labeling laser surgery as an alternative treatment to being "the treatment of choice" for these lesions. Their decision was based on single modality studies having established both radiotherapy and laser surgery as effective treatments. Additionally, a few retrospective comparative cohort studies had been published, including one with a matched historical control group which is included in this thesis (see chapter 8), which showed that voice quality after laser and radiotherapy could be considered comparable for superficial T1a glottic caricioma. Although no formal decision analysis was performed, all reviewed outcomes being equal, a treatment strategy with laser surgery as primary modality was judged superior on the grounds that it is quicker, cheaper and on the assumption that the possibility of salvage treatment with additional resections or radiotherapy will eventually lead to more larynxes being saved. While the research reported on in this thesis supports the Dutch guideline in the choice of laser surgery as primary treatment modality in superficial midcord T1a lesions, it also identifies some issues that have a bearing on possible approaches to therapy and decision making processes in more extended T1 lesions. The remaining part of this chapter will focus on these unresolved issues as well as explore the implications, opportunities and strategies for future research.

Remaining issues in the treatment of T1 glottic carcinoma

The treatment dilemma in extended T1 lesions

The balance for the treatment of superficial T1a lesions has now definitely swung in favor of laser surgery. For more extended T1 lesions (50% of all T1 lesions in our series in chapter 6), radiotherapy is still the gold standard. The question as to the optimal treatment strategy in these lesions still remains. Using the same argument as in smaller lesions, local control being equal, more larynxes should theoretically be saved by implementing laser surgery as a primary treatment modality in this group as well. The problem is that – contrary to T1a midcord glottic carcinoma – there is insufficient evidence to compare local control and larynx preservation for the two treatment modalities in extended lesions. Furthermore, laser surgery is also widely assumed to have a major impact on functionality, i.e. voice quality and performance, in extended lesions. The fact that there is still little data to either confirm or refute this assumption is creating a "catch 22" situa-

tion. Surgeons are understandably unwilling to subject patients to a possibly severe functional handicap by performing extended laser resections – in the anterior commissure or deep into the vocalis muscle – on the theory of saving an unknown number of larynxes, when a very satisfactory "gold standard" is available in radiotherapy. This in turn means that the much needed data to resolve this issue is slow to emerge.

This treatment dilemma is illustrated in the patient case below. It is also reflected in the inconsistency of treatment strategies on international, institutional and even on the individual surgeon level. In a survey of the members of the American Academy of Otolaryngology-Head and Neck Surgery, the need for reliable comparative outcome analysis for the two treatment modalities was cited as the primary cause for lack of coherent practice guidelines (1). The conclusion of a recent Cochrane analysis was that "there is currently insufficient evidence to guide management decisions on the most effective treatment" (2).

Patient case

A 70-year-old patient has been histologically diagnosed with a glottic carcinoma at a district hospital and has been referred for treatment to the local Head and Neck oncological center. The pre-operative stroboscopy shows an evident tumor of the middle 1/3 of the right vocal fold and somewhat discolored mucosa of the anterior 1/3 into the anterior commissure. The Head and Neck surgeon is discussing the options with the patient:

H/N surgeon: "We know it's a malignant tumor of the vocal fold. We have a choice of two treatments: radiotherapy and laser surgery. We need to discuss the alternatives so that we know what to do during surgery tomorrow."
Patient: "What is the best option?"
H/N surgeon: "If the disease is limited to the middle of one vocal fold, both treatments will have a high chance of curing the disease and both will give a reasonable voice outcome. With laser surgery we can treat you immediately. Radiotherapy will mean 6 weeks of daily visits."
Patient: "I gather laser is the best option then. But is it limited to one vocal fold?"
H/N surgeon: "It may be, but I won't know for sure until tomorrow during the procedure."
Patient: "And what if it's not? What is the best option then?"
H/N surgeon: "We know radiotherapy will still have a good chance of curing the disease and indications are that laser surgery will do the same for a limited spread onto the other vocal fold which looks to be the case...."
Patient: "So I'll still have laser surgery then?"
H/N surgeon: "...however, your voice may be poorer than if you had radiotherapy."
Patient: "How much poorer?"
H/N surgeon: "We really don't know but it's probably still an acceptable voice."
Patient: "My voice is important to me. I think I'll have radiotherapy then, even if it is a 6 week treatment. At least my voice will be good and the cure rate will be good."

H/N surgeon thinking to herself: but if you have laser surgery, you can still be irradiated in the event of a recurrence. It may be worse for your voice but you will probably have less chance of losing your larynx. And we might possibly even be able to reconstruct your vocal fold....should I discuss this with the patient...I'd better not. Too much uncertainty. Radiotherapy is a safe bet.

Why is the evidence insufficient?

The preferred way to compare effectiveness of two treatments is in a randomized, controlled trial, to rule out selection bias and confounding by indication. Comparing two treatments on the basis of non-randomized follow-up studies is therefore not ideal. However, in the case of extended T1 lesions there are 3 major factors preventing a non-randomized comparison even if we were to accept the method as legitimate on the basis of "best available evidence". These factors are: (1) the uncertainty about relevant prognostic factors for disease outcome, (2) the limitations of the current staging system (TNM and ELS classification) and (3) the insufficient data on functional outcome (voice).

(1) Uncertainty over relevant prognostic factors

As discussed extensively in chapter 9, there is still much uncertainty over the relevance of various prognostic factors. The literature on radiotherapy contains numerous retrospective studies of large size with conflicting results. For laser surgery, studies are still focused on describing disease outcome with just a few reports containing formal univariate or multivariate analyses for prognostic factors. A crucial factor in this dilemma is tumor size / extension. Uncertainty over the weighted relevance of lateral spread such as into the anterior commissure, to the floor of the ventricle, the subglottis or the vocal process, as well as the depth of invasion has two major implications. (1) Comparing results for radiotherapy and laser surgery is impossible, except in large series from centers where there is a strong preference for one of the treatment modalities so that patients are consecutive. If this is the case it can be assumed that all variations of tumor extension are present in equal quantities. Such series are rare in laser surgery. (2) Results cannot be stratified according to prognostic factors to evaluate the true relative risks for the two treatment modalities.

(2) Limitations of the current staging system (TNM and ELS classification)

An effective staging system must provide consistent and accurate information for implementing appropriate treatment and predicting outcomes for a given tumor stage.
Through its crude handling of tumor size/extension, the TNM classification fails both requirements. Firstly, the T1a/T1b and T2 staging does not discriminate between those tumors most suitable for laser resections and those most suitable for radiotherapy and it thereby serves no purpose in the implementation of treatment. Secondly, in numerous studies the sub-stages T1a/T1b for T1 tumors have consistently proven non-prognostic

for local control in radiotherapy. Sub-staging into T1a and T1b has also not been proven prognostic in studies for laser surgery, although arguably these studies are far fewer and usually smaller. Intuitively the fact that the T1a/b sub-classification is not of prognostic value makes sense, as the distinction between the two sub-stages is based only on lateral spread and takes no account of the depth of invasion. Furthermore, it does not address anterior commissure involvement which can be present in both T1a and T1b tumors. Despite the failings of the TNM in this respect, there is evidence from alternative classifications that tumor extension within the T1 stage is related to outcome both for radiotherapy and laser surgery (see chapters 6 and 9). However, as these classifications vary from study to study there is not enough data to justify amendment of the TNM classification at this moment.

The evolvement of surgical treatment for T1 glottic carcinoma has drawn attention to the issue of tumor extension and the shortcomings of the TNM classification herein. Unable to accommodate the different types of resections being performed on T1/T2 glottic carcinomas in existing classifications the ELS introduced a new system in 2000 dividing resections into categories based on extension (type I-V), with a revised version adding a type IV in 2007 (see appendix 2: ELS classification) (3;4). The system is therefore founded on surgical planes and functional reasoning. It has proven suitable for its purpose although in practice the distinctions between the different types of resections may not be as clear as they are in theory. Contrary to the TNM classification, the ELS classification has proved of value for describing functional outcome after laser surgery. Several authors have found the degree of dysphonia proportional to the depth of tissue removed and thus to the type of resection performed (5-7). However, even the categories in the ELS classification are at times too general for this purpose. Superficial resections of the anterior commissure are classed as "type V" or "extended cordectomies", as are resections of the false vocal fold, the arytenoids and large bilateral resections. Although there is an official sub-classification for type V resections (type Va-Vd), it is seldom used.

Is the ELS classification then an appropriate substitution for the TNM classification in T1/T2 glottic carcinomas? Looking back to the requirements postulated at the beginning of section (2) this is unlikely. First of all the ELS classification is a classification of resection types and not of tumor extension. As such, the classification is by definition retrospective to the surgical procedure. Unfortunately, as of yet there is no consensus on how tumor depth should be determined prior to resection. Therefore, the value of the ELS classification for evaluating functional outcome after radiotherapy has not yet been established. Secondly, as the ELS classification has primarily been used to evaluate functional outcome there is as of yet insufficient evidence as to the independent prognostic potential for disease control of the different resection types. Thirdly, the system does not take into account the nodal status or distant disease, crucial to a complete staging system. For the ELS classification to be used as a true tumor staging system, consensus would have

to be reached on how to establish the depth of invasion prior to a surgical intervention. The independent prognostic potential of the separate categories would have to be validated and nodal and distant status would have to be incorporated. Therefore, although an improvement on the TNM staging system in certain aspects, the ELS classification may currently not be considered an adequate replacement. As discussed in section (1) on prognostic factors, the net effect of an inadequate staging system for tumor extension is that it prevents stratification and the assessment of confounding due to extension within individual studies. Furthermore, it decreases the external validity as results cannot be compared between studies or applied to clinically relevant subgroups. Outcome data are therefore currently inadequate for counseling and prognostication. These limitations are illustrated in the attempted literature review on disease and functional results for extended T1 lesions (appendix 4).

(3) Insufficient functional (voice) data

Literature on functional outcome is sparse and heavily affected by selection bias. Further problems are large variations in follow-up time as a consequence of retrospective design and small sample sizes due to the relative rarity of the disease and the laborious character of (multidimensional) voice research. In addition, voice analysis methods used lack uniformity, reliability and validity. The European Laryngological Society (ELS) concluded in 2001 that there is no single voice analysis method that adequately describes voice function and that the assessment of voice dysfunction thus needs to be multidimensional (8). However, the clinical relevance of the various parameters included in such multidimensional protocols is in many cases unclear. All of the above leads to poor validity and precision in literature on functional outcome. Furthermore, literature on functional results is heavily centered on voice outcome and other aspects of functionality such as swallowing and late side effects of radiotherapy are mostly ignored. Side effects of radiotherapy are usually described only briefly as mild with acute complaints of mucositis and dysphagia as well as laryngeal edema. Late side effects are argued to be rare by Cellai and Mendenhall (9;10) illustrated by the fact that a tracheotomy is necessary in less than 1% of cases of late damage. It is however important to point out that although rare, late damage in the form of tissue necrosis can have serious consequences and may even lead to a laryngectomy, as was the case for 3 patients in the study by Van der Voet (11). There is no data on how patients experiencing side-effects after radiotherapy value them. The same holds true for long-term effects of laser surgery. We therefore believe the current data with regard to functional outcome is insufficient and that more detailed information on other aspects than voice will become important as treating physicians try to establish the relative benefits of the two treatments.

Solution: wait for randomized trial data?

Should we then just accept the situation and postpone the refining of decision making until randomized trial data become available? Although a randomized trial will reduce selection bias and confounding, we believe there are several problems with this approach. Firstly, as we showed in our sample size calculations for a trial in unselected T1 lesions from chapter 2 and appendix 1, powering a randomized controlled trial with larynx preservation as outcome will potentially require a large number of patients whereby it becomes doubtful if adequate accrual will ever be possible. Furthermore, as seen in appendix 4, data on expected effect sizes for radiotherapy and laser in extended T1 lesions are still very limited and difficult to interpret due to inadequacies in the current staging systems. Unless these inadequacies are resolved, both the internal validity (calculations for the sample sizes needed) and the external validity (applicability) of trial data remain problematic. Treating physicians will not be able to individualize treatment information on disease or functional outcome to the degree needed for clinical counseling and prognostication. Lastly, as discussed in chapter 10, head and neck surgeons are currently not prepared to randomize patients on the grounds that the functional outcome of extended laser resections is too uncertain. As illustrated in the patient case above, there seems to be a deadlock situation.

Breaking the deadlock – phase I, II, III

To break the current deadlock it is helpful to think of the situation in terms of therapeutic cancer trial taxonomy. In cancer medicine, new therapies usually pass through a set trajectory of studies:

phase I: finding dose limiting toxicity
phase II: finding evidence of effect
phase III: determining efficacy by randomization (RCT)

Proceeding to the next level is only done when enough evidence has been found for the previous one. In laser surgery for extended lesions of glottic carcinoma, the functional impairment can be thought of as a "dose limiting toxicity". Therefore, although we have some evidence of effect from retrospective cohort studies, the lack of level I data in this case cannot be ignored. This is what is instinctively keeping surgeons from randomizing their patients. We therefore propose to take one step back to obtain more and better quality level I data before proceeding to randomization in a level III study.

Will we ever reach phase III – the randomized controlled trial?

In the ideal situation this would be so, but apart from the problem of identifying relevant subgroups within the T1 stage and the large sample sizes involved, the "dose limiting toxicity" of a more extended resection will play a crucial role in the feasibility of a trial. In other words: how far are patients and surgeons prepared to go in losing the voice to keep the larynx? As discussed above, in the case of superficial, midcord lesions the retrospective data from single modality cohort studies, coupled with circumstantial arguments have over time produced a treatment policy favoring laser surgery in these lesions despite the lack of RCT data. In fact, many would now argue that it has become unethical to randomize such a lesion to radiotherapy. The same may well happen in more extended lesions before data from a RCT have time to emerge.

Recommendations for further research

In our opinion, the ultimate goal of further research in this field should be to work towards a reliable comparison of the two treatment modalities for more extensive lesions of T1 glottic carcinoma: radiotherapy and laser. As we have seen from the complex trade-off between disease outcome and voice preservation discussed in this thesis, a comprehensive comparison must include not only measures of disease outcome such as larynx preservation (effectiveness) but also a measure for the functional outcome and how the patient values this outcome (utility). From this, we can then calculate the quality adjusted effectiveness for a certain strategy and compare it to the other. As a further step, costs can also be integrated into this equation. This procedure would result in a table like the example shown below from the seminal article "A clinician's guide to cost-effectiveness analysis" by Detsky and Naglie,1990 (12).

Table 1 | Costs, Effects, Utility and Benefits of Treating Patients with Disease X with two Alternative Strategies, Treatment A and Treatment B.

Strategy	Treatment Costs	Effectiveness (Life Expectancy)	Utility (Quality of Life)	Utility adjusted Life Expectancy	Benefits
Treatment A	$20 000	4.5 years	0.8	3.60 QUALY's*	$4000
Treatment B	$10 000	3.5 years	0.9	3.15 QUALY's*	$2000

* QUALY's = quality adjusted life-years

The implementation of this strategy for extended T1 glottic carcinoma seems simple enough: first define the relevant outcome measures for effectiveness and utility, and then input adequate data on these outcome measures in the table. However, from the discussion in the previous section it is evident that these data are currently not available. Considering the dilemmas examined in the same section, the recommendation of this thesis is that a research project be designed along the following lines:

We firstly propose the development of a tumor assessment protocol, not only for lateral extension but also for depth. Secondly, we propose thorough and systematic research to determine "toxicities" associated with laser and radiotherapy for T1-T2 glottic carcinoma, consisting not only of voice outcome, but other relevant factors such as swallowing and late effects of radiotherapy as well. We also propose that investigations into functional outcome be not only qualitative but also directed at determining utility for these patients. We advocate that these investigations concentrate on the resection types identified in the National Larynx Survey (see chapter 10) as the most likely candidates for extending laser indications: superficial bilateral resections (type I and II) and deeper unilateral resections (type III). Thirdly, as long as stratified randomized trial data for these lesions are not available, we propose that a systematic literature review is conducted to establish "best available evidence" for oncological results. A decision model based on the above information can then be designed to determine the "trade-off" between radiotherapy and laser surgery. Work on this project is currently underway.

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