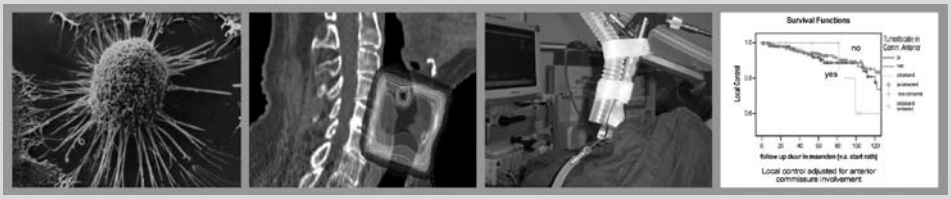
Disease outcome in T1 glottic carcinoma

Sjögren, E.V.

Chapter 10

The Dutch Larynx Survey

Report on the surgeon's perspective on indications for laser surgery in early states of glottic carcinoma



Introduction

Radiotherapy and (endoscopic) laser surgery are the two main treatment options in T1 glottic carcinoma. Treatment strategy depends on surgeon and patient preference and varies between countries, institutions and individual surgeons. The conclusion of a recent Cochrane analysis was that "there is currently insufficient evidence to guide management decisions on the most effective treatment" (1). In a survey of the members of the American Academy of Otolaryngology-Head and Neck Surgery, the lack of reliable comparative outcome analysis for the two treatment modalities was cited as the primary cause for the absence of coherent practice guidelines (2).

To answer the question whether laser surgery or radiotherapy is the superior treatment in early glottic carcinoma, work was begun in 2004 on designing a randomized controlled trial by a collaborating group of head and neck oncologists from Leiden and Rotterdam (A.P.M. Langeveld, R.J. Baatenburg de Jong, M.F. de Boer, J.D.F. Kerrebijn, P.C. Levendag). The trial would include patients with T1 glottic carcinoma, with local control and larynx preservation as primary outcomes. The trial protocol was further developed during the 7th joint FECS/AACR/ASCO workshop on Methods in Clinical Cancer Research in Flims, Switserland in June 2005 (E.V. Sjögren M.D.).

Unfortunately, during this workshop the sample size calculations showed that the study population needed was too large (see appendix 1 – sample size calculations). Judging from data from single modality studies, overall local control can be assumed to vary little between radiotherapy and laser surgery, even for unselected lesions. Establishing a difference of 2% in local control from 86% to 88% (see chapter 9, tables 9 and 10), apart from costing a total of 9028 patients, is not of clinical significance and was therefore not deemed relevant as a primary outcome. A difference of 6% in larynx preservation from 97% to 91%, although possibly relevant would require 251 patients per arm. With an average of 242 T1 glottic carcinomas diagnosed per year in the Netherlands (see chapter 2), and an expected accrual of 50% it would take 4.1 years to complete inclusion, and another 5 for follow-up to be completed. It is doubtful whether this accrual could be realized and if the data would still be relevant in 10 years time. We therefore conclude that a randomized controlled trial on laser versus radiotherapy in T1 glottic carcinoma with local control as primary outcome is neither attainable nor relevant, and that a trial with larynx preservation as primary outcome – although possibly relevant – is also not attainable.

Faced with this it was decided to take an alternative approach. Assuming equality of the treatment options, we turned to what we considered the second most important outcome parameter: voice. The patient self-evaluation of voice related disability was chosen as the primary outcome measure with the objective to detect a minimum clinically important difference, corresponding to 15 points on the Voice Handicap Index (VHI), between the

two treatment groups: laser surgery and radiotherapy, after two years follow-up. A prototype trial protocol requiring 70 patients in each arm was developed and presented at the NWHHT meeting in 2006. Although reactions were positive and there was national interest in pursuing the trial preparations, the following major hurdle presented itself. When asked whether they would be prepared to randomize T1 glottic carcinomas there was disunity among the head and neck surgeons present. After continued discussion it became apparent that there was no agreement on which lesions to include in such a trial. Two main concerns were voiced:
unwillingness to subject superficial, midcord T1a lesions to radiotherapy since excellent oncological and functional outcomes had been achieved with laser surgery in the period between 2004-2006.
the risk of poor voice quality when subjecting larger lesions involving the anterior commissure to laser surgery, for an uncertain gain in larynx preservation

Unbiased and adequate accrual are two desirable factors when running a large, multicenter trial. As both are jeopardized by lack of agreement on inclusion criteria it was decided to put further trial development on hold until more was known about the Dutch Head and Neck Surgeon's perspective on indications for laser surgery in T1 glottic carcinoma. For this purpose, a survey was developed.

Method

Survey design

The survey was based on the ELS classification of laser resections, type I-VI which basically represent resections of increasing depth (3-4) (see appendix 2: ELS classification). For each resection type, 4 variations were specified representing extension of the resection. These variations were:
- resection limited to midcord
- resection including the midcord and the anterior commisure
- resection including the midcord and the vocal process
- resection including the midcord, vocal process and anterior commissure

Participants were then asked to consider whether they would perform the various resections on the basis of expected oncological results and on the basis of resulting voice outcome (possible voice dysfunction). Finally they were also asked if, given the particular type of resection, they would be prepared to sacrifice voice quality in the individual patient if this would mean lowering laryngectomy rate as a whole for the entire group. The questionnaire consisted of illustrations of the different resection types along with the related questions described above. For the full survey see appendix 3: Larynx Survey.

Survey distribution

The survey was distributed nationwide to all 8 Dutch Head and Neck Cancer Working groups (located in Amsterdam VU, Amsterdam AVL, Groningen, Leiden, Maastricht, Nijmegen, Rotterdam and Utrecht) between July and August 2007. The working groups were asked to consider the 19 different variations on the ELS type I-V resections and to indicate which resections they would be prepared to perform as a group.

Results

All 8 centers responded to the survey. The survey results are shown in table 1 and are summarized per resection type below.

Type I – subepithelial resections

All centers except one were prepared to perform all variations on type I resections. One center would not perform a type I resections of the anterior commissure on the basis of both oncological and voice related outcome. This center would however consider compromising voice quality in such resections if it would mean a decrease in laryngectomy rates.

Type II – subligamental resections

Six centers were prepared to perform all variations on type II resections. One center would not perform type II resections of the anterior commissure, and one center would not perform resections of the anterior commisure or the vocal process on the basis of both oncological and voice related outcome. Both would however consider compromising voice quality in such resections if it would mean a decrease in laryngectomy rates.

Type III – transmuscular resections

Only one center was prepared to perform all variations on type III resections. Four centers were prepared to perform midcord resections and resections of the vocal process but would not perform a resection of the anterior commissure, 3 on the basis of both oncological and voice related outcome and 1 on the basis of voice related outcome only. Two of these centers would consider compromising voice quality in such resections if it would mean a decrease in laryngectomy rates. Three centers would not perform type III resections at all, of which 2 for oncological reasons. Both centers would consider all type III resections if it would mean a decrease in laryngectomy rates. One center would not perform any type III resections for functional reasons and would not consider them even if it would prevent laryngectomies.

Type IV – total cordectomy

Only one center was prepared to perform a type IV resection if it did not include the anterior commissure. The 7 other centers would not perform type IV resections. In 3 of these

Table 1 | Response to questionnaire.

	Center 1			Center 2			Center 3			Center 4		
	oncol	**voic**	**TL**	**oncol**	**voic**	**TL**	**oncol**	**voic**	**TL**	**oncol**	**voic**	**TL**
Type I												
Type I midcord	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Type I + VC	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	yes	yes
Type I + PC	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Type I + VC+ PC	yes	yes	yes	no	no	yes	yes	yes	yes	yes	yes	yes
Type II												
Type II midcord	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Type II + VC	yes	yes	yes	no	no	yes	yes	yes	yes	yes	yes	yes
Type II + PC	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Type II + VC+ PC	yes	yes	yes	no	no	yes	yes	yes	yes	yes	yes	yes
Type III												
Type III midcord	yes	no	no	no	no	yes	yes	yes	yes	yes	yes	yes
Type III + VC	yes	no	no	no	no	yes	no	no	no	yes	yes	yes
Type III + PC	yes	no	no	no	no	yes	yes	yes	yes	yes	yes	yes
Type III + VC+ PC	yes	no	no	no	no	yes	no	no	no	yes	yes	yes
Type IV												
Type IV midcord	yes	no	no	no	no	no	yes*	no	no	no	no	no
Type IV + VC	yes	no	no	no	no	no	no	no	no	no	no	no
Type IV + PC	yes	no	no	no	no	no	yes	no	no	no	no	no
Type IV + VC+ PC	no	no	no	no	no	no	no	no	no	no	no	no
Type V en VI												
Extended supra	no	no	no	no	no	no	no	no	no	no	no	no
Extended sub	no	no	no	no	no	no	no	no	no	no	no	no
VC	no	no	no	no	no	no	no	no	no	no	no	no

* in a trial situation

Center 5			Center 6			Center 7			Center 8		
oncol	voic	TL	oncol	voic	TL	oncol	voic	TL	oncol	voice	TL
yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
no	no	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
no	no	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
no	no	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
no	no	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
no	no	yes	no	no	no	yes	no	yes	no	no	no
no	no	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
no	no	yes	no	no	no	yes	no	yes	no	no	no
no	no	yes	yes	yes	yes	yes	no	yes	yes	no	yes
no	no	yes	no	no	no	yes	no	yes	no	no	no
no	no	no	yes	yes	yes	yes	no	yes	no	no	no
no	no	no	no	no	no	yes	no	yes	no	no	no
no	no	no	yes	yes	yes	yes	no	yes	no	no	no
no	no	no	yes	yes	yes	yes	no	yes	no	no	no
no	yes	yes	no	no	no	yes	no	yes	no	no	no

centers the reason was oncological outcome. Three centers considered a type IV resection oncologically justified if it did not include the anterior commissure, but would not perform it for functional reasons. One center considered all type IV resections oncologically justified but again would not perform them for functional reasons.

Type V – extended cordectomy

As for extended type V and VI resections, only three centers were prepared to perform some sort of variation on these resections. All other centers considered them unjustified, because of both oncological and voice outcome.

Discussion

The current Dutch guideline considers laser surgery the treatment of choice for superficial T1a midcord lesions requiring a type I or II resection. The results of this survey show that the majority of centers (6 out of 8) are prepared to perform variations on these resections, including resection of tissue in the anterior commissure and on the vocal process. This indicates a general willingness to at least consider extensions of the current guideline to include superficial bilateral lesions. As for deeper bilateral resections (type III) only one center was prepared to perform these at this moment in time, although some centers would consider them if it proved to reduce laryngectomy rates compared to the standard treatment with radiotherapy. However, within the type III resections we can identify a pivot point for 50% of the centers. Three centers were not prepared to compromise voice outcome by performing type III resections including the anterior commissure (i.e. bilateral) and one center was not prepared to perform them at all, even if it would mean a decrease in overall laryngectomy rates. From this we conclude that for these centers this currently represents the turning-point at which the poor voice outcome, possibly even aphonia, for the patients as a group does not justify saving the larynx in certain individuals. Also, in larger resections aspiration may also become a problem. No center was prepared to perform bilateral type IV resections. Deep bilateral resections involving the vocalis muscle therefore do not seem to form the next step in extending the indications for laser resections.

In the case of unilateral resections, the results show that 5 out of 8 centers are prepared to perform a transmuscular (type III) resection as long as it does not include the anterior commissure. Only one center would perform a total cordectomy (not including the anterior commissure). Both would however consider compromising voice quality in such resections if it would mean a decrease in laryngectomy rates, although 3 other centers considered it oncologically, but not functionally justified. In line with these data, most centers (n=5) would not consider an extended supraglottic resection (type V) as this would mostly involve a type IV resection of the vocal fold.

From the background data and from the survey in this chapter we conclude firstly that in the event of renewed plans for a randomized controlled trial in T1 glottic carinoma, careful consideration would have to be given as to what would constitute a meaningful primary outcome parameter other than local control or larynx preservation, as the sample size needed to adequately power a trial for these outcomes is not attainable in the Netherlands, even in a nationwide trial. Secondly, a randomized controlled trial in T1 glottic carcinoma should not include superficial T1a midcord lesions as laser surgery has already been labeled the treatment of choice in these lesions (see chapter 1). Thirdly, the two types of excisions that most centers would consider performing outside protocol are superficial bilateral resections (type I and II) and deeper unilateral resections (type III). However, data on expected effect sizes for radiotherapy and laser in extended T1 lesions are still very limited. Also, the fact that these two resections, although clinically relevant, do not correspond to existing categories in either the TNM or the ELS classifications makes what little data there is difficult to interpret. A brief summary is presented in appendix 4 – review of extended T1 lesions.

Despite these results it must be added that the survey also revealed some discrepancy among centers as to what is considered an oncologically safe resection, especially when the anterior commissure is involved. Also, 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 attitude at this meeting was that surgeons are still apprehensive about compromising voice outcome in more extensive resections. Until more data on oncological and voice outcome become available, laser surgery will generally be considered as an alternative therapy in all lesions but superficial midcord carcinomas, to be reserved for selected cases after careful consultation with the patient. The accrual for a randomized trial at this moment, at least in the Netherlands, therefore seems unlikely to succeed. We refer to the last section of this thesis "recommendations for further research" for our proposal on how to resolve this situation.

References

1. Dey P, Arnold D, Wight R, MacKenzie K, Kelly C, Wilson J. Radiotherapy versus open surgery versus endolaryngeal surgery (with or without laser) for early laryngeal squamous cell cancer. Cochrane.Database.Syst. Rev. 2002;CD002027.
2. DiNardo LJ, Kaylie DM, Isaacson J. Current treatment practices for early laryngeal carcinoma. Otolaryngol. Head Neck Surg. 1999;120:30-7.
3. Remacle M, Eckel HE, Antonelli A, Brasnu D, Chevalier D, Friedrich G et al. Endoscopic cordectomy. A proposal for a classification by the Working Committee, European Laryngological Society. Eur.Arch. Otorhinolaryngol. 2000;257:227-31.
4. Remacle M, Van Haverbeke C, Eckel H, Bradley P, Chevalier D, Djukic V et al. Proposal for revision of the European Laryngological Society classification of endoscopic cordectomies. Eur.Arch.Otorhinolaryngol. 2007;264:499-504.