Disease outcome in T1 glottic carcinoma

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Chapter 6

Clinical outcome of T1 glottic carcinoma since the introduction of laser surgery as a treatment option

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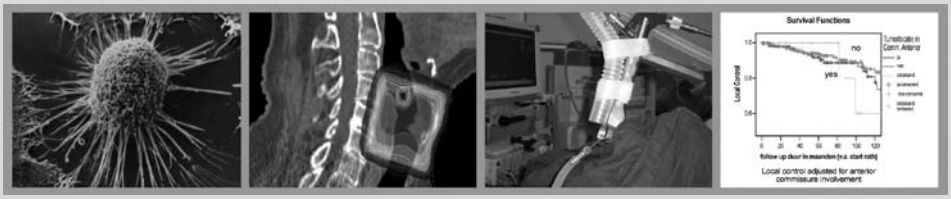

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Introduction

Radiotherapy and carbon dioxide endoscopic laser surgery (henceforth laser surgery) are both established treatment modalities for T1a glottic carcinoma. Both offer a high rate of cure, although direct comparison is complicated by the fact that studies on laser surgery are often based on selected lesions.

The average 5-year local control rate of radiotherapy for T1 glottic cancer in 17 large studies is 84% (range, 78% to 89%), with an average larynx preservation of 93%.(1–17) In these and other studies, there is insufficient evidence for an influence of T classification (T1a versus T1b) on local control. The impact of tumor size and/or extension (mainly toward the anterior commissure) is, however, still debated with studies finding evidence both for (3;7;18) and against (5;8;10;16;17;19) an influence on outcome.

For laser surgery, local control has typically been slightly higher, although many studies consist only of selected and often superficial midcord T1a lesions. The average 5-year rate of local control was 92% (range 88% to 94%), with an average larynx preservation of 98% in 10 such studies on selected T1a lesions. (20–29) Voice quality after laser resection of superficial, midcord T1a lesions is found to be good and often comparable to normal (30–33)

In 6 studies on unselected T1 lesions (T1a and T1b) treated with laser surgery, the average 5-year local control was 88% (range, 81% to 93%) and larynx preservation 98%. (29;34–38) For laser surgery, neither the influence of T classification nor anterior commissure invasion on local control is clear, with investigations of these factors currently limited to a few small studies. (26;29;37;39–41) The same is true for the influence of these factors on voice outcome. Although most surgeons would agree that larger and deeper lesions, and therefore larger resections, have significantly worse functional outcome, there is still only minimal protocolled, multidimensional data for how much worse this is. (42)

Although no randomized trial has been performed yet, from these retrospective data local control rates in selected T1a, and possibly even unselected T1 lesions, can be considered at least comparable with radiotherapy. Providing similar voice quality to radiotherapy (30;31;43;44) and the additional benefits of shorter treatment time, lower costs, and the possibility of repeated procedures, laser surgery is now the preferred treatment for superficial T1a midcord lesions according to Dutch National Guidelines and at our institution.

Laser surgery was introduced as a treatment option for superficial T1a midcord lesions at our institution in September 1996. The aim of this study was to evaluate treatment outcome for T1 glottic carcinoma for the 11-year period since its introduction. We also aimed to investigate the basis of treatment allocation to either laser surgery or radiotherapy in T1a lesions, as well as any potential difference in outcome for these 2 clinically defined groups.

Patients and Methods

The study cohort consisted of all patients diagnosed with T1 glottic carcinoma in the Leiden University Medical Center since the introduction of endoscopic CO2 laser surgery in September 1996. Information was collected from patient charts, hospital records, and the hospital-run oncological database. Patients in the database missing from follow-up for longer than 1 year were traced, and their current health status was established through charts and other hospital records.

Staging and treatment allocation

Disease in all patients was staged by direct laryngoscopy; all patients had biopsy-proven squamous cell carcinoma. For reasons of voice preservation, at our institution laser surgery is performed only on T1a lesions when it is estimated that a sufficient margin can be obtained within the affected fold by either a subligamental or subepithelial resection (type I and II cordectomy according to European Laryngological Society [ELS] classification), (45;46) that does not extend into the anterior commissure. The final decision to perform laser surgery is therefore made during direct laryngoscopy. The surgical technique consists of an en bloc resection with sampling of margins when deemed necessary. T1a lesions not considered suitable for laser surgery are routinely treated with radiotherapy. This is in accordance with the current Dutch national guideline recommendations. Radiotherapy schedules are also based on Dutch national guidelines and consisted of 30 x 2 Gy, 5 times a week to a total dose of 60 Gy during the first part of the study period. After revision of the guidelines in 2000, it was changed to 25 x 2.4 Gy, 5 times a week to a total of 60 Gy.

Statistical analysis

Treatment outcome is presented in terms of cumulative incidence and 5 year outcome statistics for local control and larynx preservation (Kaplan–Meier). The impact of age, sex, and T classification (T1a vs T1b) was tested in univariate analysis (log rank). We also tested the effect of allocated treatment option (laser vs radiotherapy) on local control and larynx preservation in all patients and in T1a patients separately, realizing that this allocation was not random but based largely on, and therefore biased by, tumor size and extension. This was done to investigate whether these 2 clinically defined groups of T1a carcinoma, created through the advent of laser surgery, have comparable outcome.

Results

From the time of the first endoscopic CO2 laser procedure for T1 glottic carcinoma in September 1996 until August 2007, 189 patients were diagnosed with T1 glottic carcinoma at our center. Eight patients were excluded from the study because they had been diagnosed and treated within the last year and therefore had a follow-up time of less than 12 months, leaving 181 patients, of whom 143 (79%) had T1a lesions and 38 (21%) had T1b lesions. Patient characteristics are shown in Table 1. Of the patients with T1a lesions, 51% (n=73) were considered suitable for laser surgery and 49% (n=70) were considered unsuitable, and were thus treated with radiotherapy.

Table 1 | Baseline characteristics.

Parameter	Total, n=181	T1a RT n=70	T1a laser n=73	T1b* n=38
mean age (years)	70	70	70	70
range age (years)	33 - 95	33 - 89	37 - 89	46 - 95
Gender, no. of patients				
male	165	67	65	34
female	15	3	8	4
mean FU all patients (months)	57	58	57	54
range FU all patients (months)	13-121	6-118	7-117	2 - 121
mean FU living patients (months)	60	60	58	66

Abbreviations: RT, radiotherapy; FU, follow-up

* T1b 37 RT (95%) and 2 laser (5%)

Table 2 shows the reasons listed in patient charts for not allocating patients to laser surgery. Thirty six of the 38 T1b lesions (95%) were treated with radiotherapy. Overall mean follow-up time was 57 and 60 months, if only living patients were considered. Because information on all living patients was successfully retrieved, no patients were considered lost to follow-up. There was no difference in the baseline characteristics (age, sex, or follow-up time) between the treatment modalities.

Table 3 illustrates the treatment outcome by T classification and primary treatment modality. Tumor-positive resection margins necessitated additional therapy in 12 of 73 (16%) patients treated with laser surgery, consisting of a re-resection in 4 of 73 (5%) cases and radiotherapy in 8 of 73 (11%) cases.
Overall, 28 of 181 patients (15%) developed a recurrence. The number of recurrences was almost identical for the T1a (22 of 143, 15%) and T1b group (6 of 38, 16%). However, within the T1a group, the number of recurrences was more than twice as high in patients treated with radiotherapy (15 of 70, 21%), compared with patients treated with laser surgery (7 of 73, 10%). Treatment types for the recurrences are listed in Table 3. In the T1a radiotherapy group, 14% of patients underwent a total laryngectomy versus 8% in

Table 2 | Reasons listed for not allocating T1a patients to laser surgery.

Reason for radiotherapy as first treatment	n*
Anterior commissure involvement or close proximity	26
Infraglottic involvement	11
Floor of ventricle involvement	9
Arytenoids involvement	5
Unclear margins of lesion	5
''Too large for laser''	4
''Not suitable for laser''	2
Severe dysplasia of contralateral vocal cord	2
Inadequate exposition	6
Contraindication for anesthesia	4
Unclear	4

*More than 1 reason listed for certain patients, therefore n>73.

Table 3 | Treatment outcome according to treatment modality.

	No. of patients (%)			
Parameter	**Total, n = 181**	**T1a RT, n = 70**	**T1a laser, n = 73**	**T1b*, n = 38**
Additional treatmenty	12 (7)	–	12 (16)	–
Radiotherapy	8 (4)	–	8 (11)	–
Laser re-excision	4 (2)	–	4 (5)	–
Recurrence	28 (15)	15 (21)	7 (10)	6 (16)
Total laryngectomy	13 (7)	10 (14)	–	3 (8)
Neck dissection only	1 (<1)	–	1 (1)	–
Laser excision	4 (2)	3 (4)	–	1 (3)
Radiotherapy	6 (3)	–	6 (8)	–
None	4 (2)	2 (3)	–	2 (5)
Deceased	38 (21)	14 (20)	12 (16)	12 (32)
Tumor-related	6 (3)	3 (4)	–	1 (3)
Other cause without tumor	28 (15)	8 (11)	11 (15)	11 (29)
Unknown cause	4 (2)	3 (4)	1 (1)	–

Abbreviation: RT, radiotherapy.
*T1b 36 RT (95%) and 2 laser (5%).
[y]Additional treatment due to irradical resection.

the T1b group and none in the T1a laser group, although in this group, 1 patient had to undergo a neck dissection for regional metastasis. In the T1a radiotherapy group, 2 recurrences were not treated, in one owing to the large extent of the regional recurrence, and in the other to distant metastasis. In the T1b group, 2 recurrences were also not treated, 1 because of additional distant metastasis, and the other because of synchronous end-stage lung cancer.

Thirty-eight of 181 patients (21%) had died at the time of analysis. The number of deaths was twice as high in the T1b group (32%) as in the T1a group (laser 16% and radiotherapy 19%). However, of the 6 tumor-related deaths, there was no difference in incidence between the T1a (3%) and T1b tumors (3%). Details of tumor-related deaths are shown in Table 4.

Table 4 | Details of tumor-related deaths.

Tumor stage	Primary treatment	Recurrence	Salvage treatment	Survival after primary diagnosis, months
T1a	Laser	Regional	Neck dissection	31
T1a	RT	Locoregional	Laser	31
T1a	RT	Regional	None	6
T1a	RT	Regional and distant	None	30
T1b	RT	Local (and lung cancer)	None	3
T1b	RT	Distant	None	13

Abbreviation: RT, radiotherapy.

The 5-and 10-year overall survival, local control, larynx preservation rate, and disease-specific survival are shown in Table 5.

Table 5 | 5-and 10-year survival statistics for overall population (Kaplan–Meier).

Survival parameter	5-y, %	10-y, %
Overall survival	87	77
Local control	89	84
Larynx preservation	96	89
Disease specific survival	98	96

The results of univariate analysis are shown in Table 6. Age, sex, and T classification had no influence on outcome. The outcome was, however, poorer for patients allocated to radiotherapy compared with those allocated to laser surgery for both local control (79% vs 90%, p=0.06) and larynx preservation (86% vs 100%, p=0.002). This was also seen when T1a lesions were analyzed separately (local control 75% vs 89%, p=0.05 and larynx preservation 83% vs 100%, p=0.001).

Table 6 | Univariate analysis.

Parameter	n	Local control		Larynx preservation	
		5-y rate	p-value	5-y rate	p-value
Age group					
<60 years	32	69%		82%	
60 -69 years	54	83%		90%	
70-79 years	68	88%		94%	
=>80 years	27	88%	0.41	100%	0.19
Gender					
male	166	83%		91%	
female	15	93%	0.45	100%	0.29
T classification					
T1a	143	82%		94%	
T1b	38	88%	0.94	91%	0.73
Therapy (total cohort)					
radiotherapy	106	79%		86%	
laser surgery	75	90%	0.06	100%	0.002
Therapy (T1a only)					
radiotherapy	70	75%		83%	
laser surgery	73	89%	0.05	100%	0.001

Discussion

Treatment allocation in T1 glottic carcinoma

In this study, we evaluated the treatment outcome of T1 glottic carcinoma since the introduction of laser surgery as a treatment option at our institution. Based on treatment allocation, our population breaks down into 3 categories: T1a lesions treated with laser surgery, T1a lesions treated with radiotherapy, and T1b lesions of which 95% were treated with radiotherapy. A crucial point when comparing the outcome for these categories is that treatment allocation is not random. It is based on Dutch national guidelines that recommend performing laser surgery only on T1a lesions, when a sufficient margin can be obtained within the affected fold; by either a subligamental or subepithelial resection that does not extend into the anterior commissure (type I and II cordectomy according to ELS classification). (45;46) Although achieving local control is paramount, the ability to perform a radical resection, while preserving adequate voice quality, has been an important consideration in treatment decision making and in the design of current guidelines. Although there is no consensus as to what constitutes adequate voice quality, Dutch National guidelines, based on the current literature, now consider the functional result of subepithelial and subligamental cordectomy (type I and II of the ELS classification) for

midcord T1a lesions good, and comparable to that of radiotherapy. (32;47;48) Deeper 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 of the ELS classification) are largely regarded as unsuitable for laser surgery, because poor voice quality is expected from these procedures. There is some protocolled, multidimensional evidence for this, although data are limited. (32;42;48) Although the surgeon can base his decision on the national guidelines, it is ultimately up to his or her expert opinion whether the type of cordectomy required for the radical resection of a particular lesion will result in acceptable voice quality or not. Stroboscopy, hydro-dissection, and cross-sectioning of the suspected lesion are methods that can help the surgeon in judging the depth of infiltration, but as of yet there is no standard protocol for evaluating the resectability of T1(a) carcinomas.

Outcome by treatment allocation

The 89% and 96% 5-year local control and larynx preservation rates for our total T1 population very closely match the average found in large series of T1 lesions treated with radiotherapy (see Introduction). The local control rate of 90% for T1a lesions selected for laser surgery is also in accordance with literature (see above). However, as many as half (49%) of the T1a lesions in our series were considered unsuitable for laser surgery and were treated with radiotherapy. The local control rate of 75% in these remaining T1a lesions, besides being lower than that for T1a lesions treated with laser surgery, is also decidedly in the lower ranges of what is achieved for (unselected) T1 glottic carcinoma treated with radiotherapy in literature (see above).

The same pattern was seen for the 5-year rates of larynx preservation, which was 83% in T1a lesions treated with radiotherapy versus 100% in T1a lesions treated with laser surgery. Although results from laser surgery proved excellent in this study, we have to take into account that 16% of laser-treated patients needed additional treatment consisting of a further laser resection in 4% and radiotherapy in 11%. The fact that overall disease-specific survival was 96% illustrates that T1 glottic carcinoma is a highly treatable disease, regardless of recurrence or treatment modality.

In summary, our results show that patients with T1a glottic carcinoma allocated to radiotherapy have a poorer outcome in terms of local control and laryngectomy-free survival than do T1a patients selected for laser surgery. Comparing outcomes for radiotherapy and laser surgery in this study is inherently biased, because the indications for the 2 treatment modalities are not equal. This is because the radiation group includes lesions that are larger and/or have extended spread (anterior commisure, vocal process, or deep layers of the vocal fold). Therefore, this comparison does not evaluate the efficacy and benefit of radiation versus laser surgery, but it does shows that these 2 clinically defined groups of T1a carcinoma, created through the advent of laser surgery, do not have comparable outcome, which is most likely because of the difference in tumor size and/or extension.

More interestingly, the outcome for our irradiated T1a patients is also poorer than the average outcome reported for (unselected) T1 patients treated with radiotherapy in the literature (see above). The past results of stratification analysis for the influence of tumor size on the results of radiotherapy have been contradictory, possibly because there has been no standard way of defining tumor size. However, these findings support earlier reports that found a significant influence of tumor size and/or extension on outcome in T1 glottic carcinoma. (3;7;10;14) To our knowledge, there are no studies to which we can compare our results or verify our findings, in regard to this specific irradiated T1a patient group.

This means that treatment allocation which is based on expert opinion and the guidelines discussed above, and designed to select T1a lesions suitable for laser surgery on the basis of voice preservation, is at the same time identifying an especially disadvantageous subgroup of T1a lesions in terms of local control and larynx preservation after radiotherapy. However, except from being considered unsuitable for laser surgery, it is unclear what precisely the defining characteristics of these lesions are. As stated, one might suspect that possible submucosal spread to the subglottis, into the ventricle or to the deeper layers of the vocalis muscle, maybe bordering on a T2 stage, is responsible for the decrease in local control. Also, spread into the anterior commissure may account for more recurrences, although this factor is still controversial in literature. The reasons that we inventoried for not allocating patients to laser surgery in our patient group included spread, not only into the anterior commissure but also into the floor of the ventricle, maximal infraglottic spread (5 mm), and arytenoid involvement, as well as lack of exposure and contra-indications for general anesthesia (Table 2).

Implications of the findings

These findings raise 2 questions. The first question is whether the current TNM staging system for early stages of glottic carcinoma is sufficient. For T1 lesions, it is based only on the involvement of one (T1a) or both vocal cords (T1b), ignoring both the involvement of the anterior commissure and the depth of infiltration. An effective staging system must provide consistent and accurate information for predicting outcomes for a given tumor stage and for implementing appropriate treatment.

However, tumor classification (T1a vs T1b) was not a prognostic factor for outcome of radiotherapy (see Background). Our findings further support this, as the outcome for the irradiated T1a tumors was poorer than that for T1b in this study. The value of T classification as a prognostic factor in lesions treated only with laser surgery is still unclear. Furthermore, our data suggest that there may be a group of lesions that are at a relatively high risk for local recurrence and laryngectomy after radiotherapy, ''hidden'' within the T1a category, which is not sufficiently identified by current staging methods. At the moment, this group is best described as ''not suitable for laser.'' Finally, our data also show that T classification is also inadequate for use in the allocation of treatment, as only 50% of our T1a lesions were treated by radiotherapy. Insufficiencies in a staging system

that cause discrepancies in outcome result in a lack of reliable comparative data on oncological and functional outcome in the early stages of glottic carcinoma.
The second question is whether laser surgery would be a more effective treatment option, at least in some T1a patients now being treated with radiotherapy. If so, and the risk of undergoing a laryngectomy would be reduced by extending the current limits of resections, then surgeons and patients may be willing to compromise on voice quality. However, as this question confronts us with 3 unknown parameters, namely:
- detailed knowledge of the defining features of these T1a carcinomas,
- and therefore the oncological result of laser surgery,
- and the postoperative voice quality it would produce in these patients,
a stand-off situation is created. Surgeons are reluctant to proceed to more extensive resections, instead opting for radiotherapy in the belief that this will produce similar oncological results with better voice quality.
To resolve this situation, a number of issues need to be addressed. First, the poorer outcome for larger tumors and/or tumors with unfavorable extension allocated to radiotherapy should be taken into account during patient counseling. Second, there is a need for detailed, protocolled description of the defining features of T1a tumors during endoscopy, so that tumors not suitable for laser can be better characterized and outcome can be measured for specific subcategories of T1a lesions. Finally, there is a need for detailed and multidimensional protocolled description of post-operative voice quality in patients treated with laser resections extending beyond the current guidelines. Thus, we obtain a clear picture of what type of voice quality can be expected, if indications were expanded. Eventually, this will lead to further refinement of treatment strategies for early stages of glottic carcinoma.

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