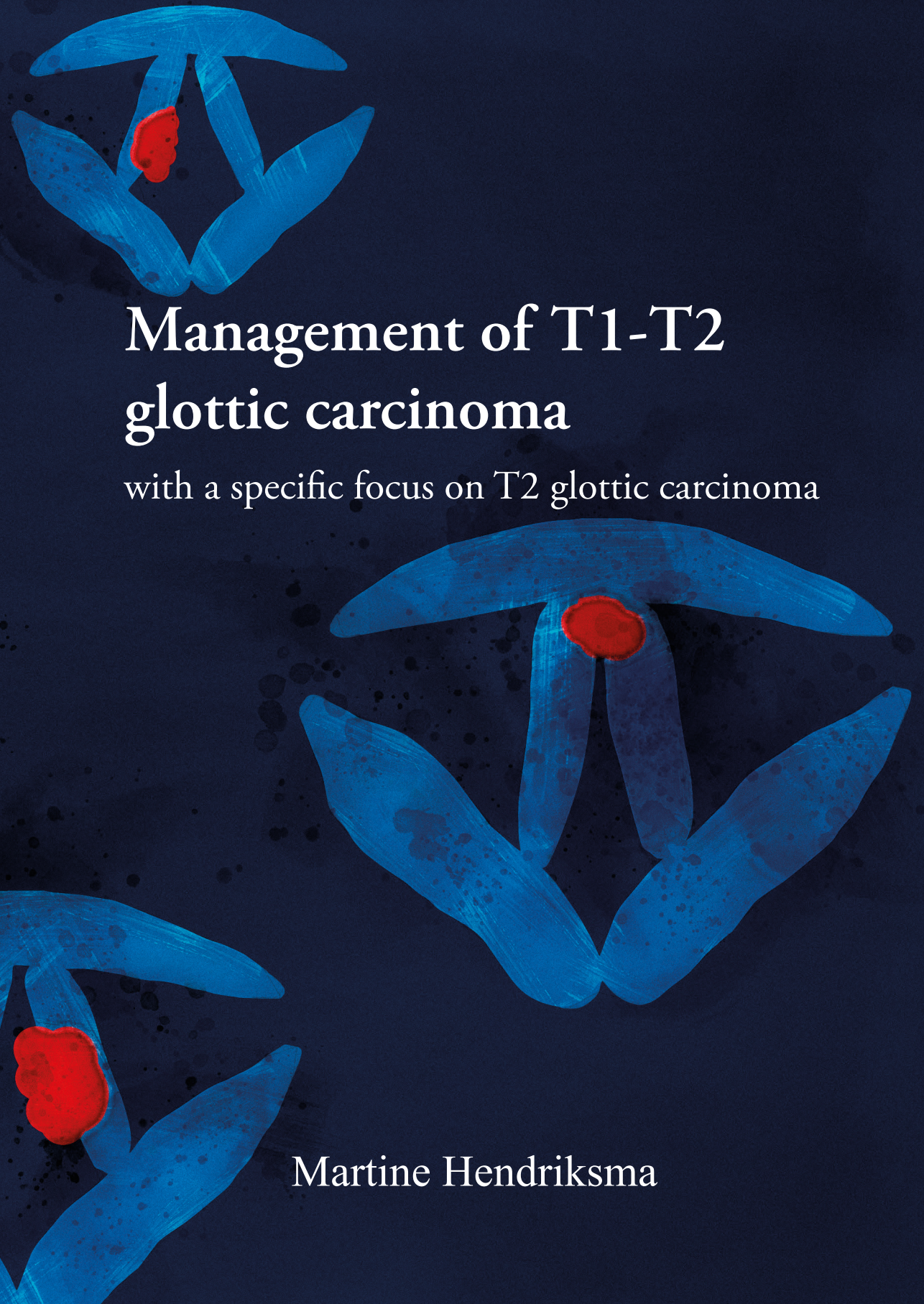

Management of T1-T2 glottic carcinoma

with a specific focus on T2 glottic carcinoma

Martine Hendriksma

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Promotor
Prof. dr. P.P.G. van Benthem

Copromotor
Dr. E.V. Sjögren

Leden promotiecommissie
Prof. dr. J.C. Jansen
Prof. dr. R.J. Baatenburg de Jong (Erasmus MC)
Prof. dr. R.P. Takes (RadboudUMC)
Dr. B.M. Verbist

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Chapter 1

General introduction and thesis outline

GENERAL INTRODUCTION AND THESIS OUTLINE

The topic of this dissertation is the comparison between the two main treatment modalities for early glottic carcinoma (Tis-T2), transoral CO_2 laser microsurgery (TOLMS) and radiotherapy, with a specific focus on T2 glottic carcinoma. This chapter will provide background information on early glottic carcinoma and the two main treatment modalities. Specific subjects such as aetiology, epidemiology, staging, history of the treatment modalities, the current guideline, and outcomes parameters are addressed. At the end of this chapter, the main aim and outline of this thesis will be discussed.

LARYNGEAL CANCER AND EARLY GLOTTIC CARCINOMA: THE AETIOLOGY, EPIDEMIOLOGY, AND STAGING

Next to cancer of the oral cavity, laryngeal cancer is the most common head and neck malignancy worldwide [1]. The most common type of laryngeal cancer is squamous cell carcinoma. These tumors develop from the squamous cells that form the epithelium of the larynx. The two most important etiological factors for developing laryngeal cancer are smoking and alcohol consumption [2]. Smoking is the major risk factor with alcohol consumption having an additional, synergetic effect [2, 3]. In addition, infection with the human papillomavirus (HPV), gastroesophageal reflux (GERD) as well as exposure to chemical, environmental, and industrial substances have been linked to the development of laryngeal cancer. The role of human papillomavirus is limited, estimated to cause approximately 5% of all laryngeal cancers [4–6]. This percentage is considered low compared to oropharyngeal cancer in which 22.5 to 45.9% of the tumors are HPV-related [5, 7]. The causal role of GERD on the development of laryngeal malignancies has not been fully elucidated, as studies show contradictory results [8, 9].

According to data released by the International Agency for Research on Cancer (IARC) in 2018, laryngeal cancer is the 21st most common type of cancer and the 19th leading cause of cancer-related deaths worldwide, with an estimated 177,422 new cases and 94,771 deaths globally in 2018 [1]. To put this into perspective, lung, breast, and skin cancer are the most common type of cancer worldwide with over 2 million new cases per year for each tumor type [1, 10, 11]. In 2017, 708 patients were diagnosed with laryngeal cancer in the Netherlands and 239 patients died due to laryngeal cancer that year [12]. In the last three decades, there has been a downward trend in the incidence of laryngeal cancer [13]. This is in line with the trend in smoking habits in the Netherlands, which shows a declining prevalence.

Laryngeal cancer can develop at all three subsites of the larynx; the supraglottis, glottis and the subglottis, with 66% of the tumors arising at the glottic subsite. At the time of diagnosis, the proportion of localized tumors (T1-2N0) is around 84%, of which 56% are T1 and 30% are T2

tumors [13, 14]. The rest of the tumors are staged as either stadium T3 or T4. Glottic tumors often present with persistent voice changes and hoarseness, which normally aids early diagnosis.

In December 2016, the Union for International Cancer Control (UICC) published the 8th edition of the tumor-node-metastasis (TNM) classification. The definition for Tis-T4 glottic cancer according to the 8th edition are shown in table 1 [15]. This classification defines tumor stage by anatomic disease extent by recording (i) the primary tumor side, (ii) regional node extent of the tumor and (iii) the absence or presence of metastases [16]. This thesis mainly focuses on tumors that arise at the glottic subsite and are staged as a T2 carcinoma. Since lymphatic spread of glottic carcinoma is rare and T2N+ is generally not considered as early disease, the focus has been narrowed further to tumors without regional lymph node involvement (N0).

Table 1. Definition of the TNM classification (Tis-T4) for glottic cancer

Tumor stage	Description of the tumor
Tis	Carcinoma in situ
T1	Tumor limited to vocal cords (may involve anterior or posterior commissure) with normal mobility T1a: tumor limited to one vocal fold T1b: tumor involves both vocal fold
T2	Tumor extends to supraglottic and/or subglottic and/or with impaired vocal fold mobility
T3	Tumor limited to larynx with vocal fold fixation and/or invades paraglottic space, and/or inner cortex of thyroid cartilage
T4a	Tumor invades through the outer cortex of the thyroid cartilage and/or invades the tissues beyond the larynx, e.g. trachea, soft tissue of the neck including deep/extrinsic muscle of the tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), strap muscle, thyroid, esophagus
T4b	Tumor invades prevertebral, encases carotid artery, or mediastinal structures

In the literature, T1 and T2 glottic carcinomas are often called 'early glottic carcinoma', however, there is no one clear definition of this entity. Most authors define early glottic cancer as tumors ranging from Tis to the T2N0-stage or as tumors ranging from T1 to T2N0-stage. For instance, Ferlito et al., in consultation with clinicians, pathologists, and biologists, defined early glottic carcinoma as an invasive carcinoma (microinvasive or superficial extending) that does not invade the vocal fold muscle or cartilage [17]. On the other hand, DeSanto and Olsen included carcinoma in situ in their definition and considered early glottic carcinoma to be a tumor staged as carcinoma in situ (Tis) or T1 carcinoma [18]. However, they recognized that not all T1 carcinomas behave the same [18]. Both aforementioned definitions are often used, and this difference has to be taken into account when comparing studies.

TREATMENT MODALITIES

The two main treatment modalities for early glottic carcinoma (here defined as Tis, T1 and T2) are surgical excision, most often performed with transoral CO_2 laser microsurgery (TOLMS), and radiotherapy. Open partial laryngectomy (OPL) is an alternative treatment option, however, this procedure is not routinely performed for early stage glottic carcinoma in the Netherlands and is therefore outside the scope of this thesis. A total laryngectomy (TL) is considered an ultimate salvage treatment in case of recurrent disease or extensive local disease or that cannot be adequately treated with another treatment modality.

History of treatment

In the early and mid-19th century, the idea of complete resection of a laryngeal tumor already existed [19], however, at that time this could not be easily realized due to the lack of anaesthetics, safe airway control, blood transfusion, and antibiotics. Despite these limitations, Theodore Billroth succeeded in performing the first laryngectomy in Vienna in 1873. The procedure was performed under local anaesthesia because the concept of anaesthesia by endotracheal intubation had not yet been developed [19–21]. Unfortunately, the patient died within seven months due to brain metastases [22, 23]. A few years later, the first laryngectomy with long-term survival was performed by Enrico Bottini in Turin in 1875 [19]. In this case, the indication was laryngeal sarcoma and after laryngectomy the patient survived for 15 years [22]. In the following years, most of the laryngectomies were disastrous, resulting in complications such as haemorrhage, sepsis, fistula formation, mediastinitis, pneumonia, and death [19]. In the late 19th century two physicians (Solis-Cohen and Gluck) developed techniques that separated the airway from the digestive tract by suturing the trachea directly to the cervical skin [19, 24]. With this technique, the mortality rate dropped by 50% in the early-20th century. Finally, in the mid-20th century, the modern TL came to be the treatment of choice for advanced laryngeal cancer (T3-T4), as it had become evident that in earlier stages of laryngeal cancer (T1-T2), curative treatment did not require removal of the entire larynx [19].

History of TOLMS

In 1886, Fraenkel was the first physician that performed a transoral resection of a glottic carcinoma [19, 25]. The development of transoral resections then stagnated during the early-20th century, until 1960 when Scalco et al. combined the operative microscope for otologic surgery with the Lynch suspension laryngoscope. This led to better visualization of smaller lesions, allowing more precise and more delicate surgery in a three-dimensional, stereoscopic field of vision [19, 26]. In 1965, the continuous CO2 laser was developed. Before this, a pulsed laser was used, although this laser demonstrated an explosive effect and the scattering of viable tumor cells [27]. A few years thereafter, in 1972, TOLMS was introduced by Strong and Jako when they attached the CO_2 laser to the surgical microscope [27]. Although TOLMS was first described in the United States of America, this technique was also further developed in

Europe by pioneers such as Steiner [28], Eckel [29] and others [30, 31]. They showed that the continuous CO2 laser could be used successfully to curatively treat early-stage laryngeal cancer. In 1992, Eckel reported four different categories of partial laser resections of the vocal folds and surrounding tissue (e.g. arytenoid or ventricular fold) [29], which became the basis of the classification system proposed by the European Laryngological Society (ELS) for resections at the glottic level in 2000. This classification system aims to provide more uniformity regarding the description of the extent and depth of different cordectomy procedures, and in turn to allow for a better comparison of postoperative results and better tools for teaching this technique. The ELS classification consist of eight different types of endoscopic cordectomies, categorized according to the extent of the resection (type I-IV and type Va-Vd) [32]. In 2007, the ELS proposed a revision for the classification since the first version did not include specific management for lesions originating from the anterior commissure [33]. To resolve this problem, they proposed a type VI cordectomy. The ELS classification is the most used classification system for endoscopic glottic resections today. The nine different resections according to the ELS are shown in table 2.

Table 2. European Laryngological Society classification of endoscopic cordectomies

Type of resection	Description of the resection
Type I	subepithelial cordectomy
Type II	subligamental cordectomy
Type III	transmuscular cordectomy
Type IV	total or complete cordectomy
Type Va	extended cordectomy encompassing the contralateral vocal fold
Type Vb	extended cordectomy encompassing the arytenoid
Type Vc	extended cordectomy encompassing the ventricular fold
Type Vd	extended cordectomy encompassing the subglottis to a distance of 1 cm
Type VI	anterior bilateral cordectomy and commissurectomy

Transoral CO_2 laser microsurgery has been used since 1996 at the Leiden University Medical Centre to treat early-stage glottic carcinoma. At first, the indication was confined to superficial T1a midcord tumors. In 2000, the Dutch guideline for laryngeal carcinoma declared TOLMS to be a good treatment option in these tumors, although radiotherapy remained the gold standard [34]. In the following years, there was a shift in the literature around the treatment modality for T1 glottic carcinoma from being centred on radiotherapy towards treatment with TOLMS. Studies investigating (long term) follow up after TOLMS reported high local control (80-100%), disease specific survival (85-100%), laryngeal preservation rates (90-100%) and equivalent voice outcome compared to radiotherapy. Furthermore, additional benefits such as shorter treatment time and lower costs were also reported with TOLMS. In the 2009 revision, the Dutch guideline for laryngeal carcinomas marked TOLMS as the preferred treatment for superficial T1a midcord tumors, requiring an ELS type I or type II resection [35]. The guideline for laryngeal carcinoma

in the Netherlands has not been updated since and is due to be revised. The literature has shown that more extended resections (ELS type III) with TOLMS result in good oncological and functional outcome and that TOLMS could be suitable for extended T1 and selected T2 tumors [36]. Furthermore, a study by van Loon et al. showed that most patients (96.0%) with extended T1 or limited T2 tumor prefer treatment by TOLMS over radiotherapy when given a choice, even when patients were counselled that their voice outcome would probably be worse after TOLMS [37]. The most common reason for choosing TOLMS over radiotherapy was shorter treatment time and having more treatment options in case of recurrence of disease. The authors concluded that optimizing future treatment options and practical considerations were more important to patients than primary functional outcomes (e.g. voice) [37]. TOLMS is widely acknowledged to be the preferred treatment in early glottic carcinoma in literature. In the Netherlands, physicians are relative conservative in the use of TOLMS as treatment modality compared to other countries, although TOLMS is used in early glottic cancer and selected intermediate-advanced lesions [38].

History of radiotherapy

The history of radiotherapy started in 1895 with the discovery of X-rays by Wilhelm Conrad Röntgen. Before completely understanding the physical properties and the biological behaviour of X-rays, they were already used by Emil Herman Grubbe in 1896 to treat a patient with breast cancer [39]. In the same year, Becquerel and Curie started to study the phenomenon of radioactivity in depth and investigated the natural source of radiation [40]. In 1919, Coutard designed fractionated external radiotherapy for larynx and hypopharynx tumors. Between 1920 and 1926 these tumors were one of the first deep-seated tumors to be cured by radiotherapy at the Curie Foundation in Paris. Unfortunately, this was at the expense of healthy tissue [41, 42]. The duration of treatment depended on the dimensions of the tumor; small lesions were treated in 15 days, whereas larger tumors were treated in 35 to 40 days [43, 44]. At 2 years post-radiotherapy, the local cure rate for laryngeal cancer was 32% [43]. In 1923, Ledoux introduced an option of internal radiation, by making a fenestration into the thyroid cartilage to allow radium needles to be placed into the tumor [44]. In 1928, this technique was further modified by Finzi and Harmer who placed radium needles on intact laryngeal perichondrium, rather than piercing it, to prevent destruction of healthy tissue [45]. However, this approach was not widely adopted due to the lack of reproducibility of this method [44]. In the mid-20th century, opinions on the indication of radiotherapy and surgery shifted between countries. For instance, Lederman, at the Royal Marsden Hospital in London, recommended primary radiotherapy in early cases when the tumor was limited to its region without fixation or lymph node involvement [46]. Surgery was recommended after failure of radiotherapy or in more advanced tumors. In so called 'early cases', where tumors were limited to the site of origin, 80% of the patients survived for five or more years [46]. One eighth of these patients underwent either partial or total laryngectomy because of radiation failure [46]. On the contrary, Fletcher, at Anderson Hospital and Tumor Institute in Houston, United States of America), recommended partial laryngectomy in early tumors.

These early cases tumors were defined as tumors limited to the middle third of the vocal cords or tumors with minimally involvement of the anterior commissure [41]. In cases where a total laryngectomy was required, radiation therapy was considered as alternative treatment. In the following decades, the methods in radiation therapy continued to improve. This led to the start of a more cooperative treatment planning by the late 1980s. The newer generation of radiation oncologists appreciated the more safe and efficient modern laryngeal surgery (e.g. TOLMS) and at that same time surgeons recognised the value of modern radiation techniques [19]. Despite all this, until today, the discussion remains which treatment modality is preferable for early laryngeal malignancies with regard to both oncological and functional outcomes. In the Netherlands, radiotherapy is still favoured over TOLMS in extended T1 and T2 glottic carcinoma according to the official national guideline, although it has not been updated since 2009 and is therefore due to be revised.

Difference between TOLMS and radiotherapy

As briefly highlighted before, both treatment modalities have advantages and disadvantages. The most important advantage of TOLMS as a primary treatment strategy is preservation of further treatment options in case of recurrent disease. After primary treatment with radiotherapy, it is more difficult to achieve radical resections with TOLMS and re-irradiation is usually not feasible. This leads to a higher laryngeal preservation rate among patients with early glottic carcinoma treated with TOLMS as a primary modality [47–52]. Additional advantages of TOLMS are shorter treatment time, limited postoperative morbidity, fewer long-term complications, and reduced costs [3, 53–56]. Disadvantages of TOLMS are that it requires general anaesthesia and that it may not be possible to achieve adequate exposure. Furthermore, in large resections (ELS type III-VI), which may be necessary for extended T1 or selected T2 lesions, it is widely assumed that the voice outcome will be worse after TOLMS than after radiotherapy [57–61]. However, comparative data for TOLMS and radiotherapy to back up this assumption are very limited and need further investigation. Finally, a limitation of TOLMS is that, despite its minimally invasive characteristic, it can lead to close or positive margins, which subsequently can necessitate a second-look procedure and possible a re-resection. The advantages of radiotherapy are related to the disadvantages of TOLMS. Radiotherapy does not require general anaesthesia and may provide a better voice outcome than TOLMS. However, it is more time-consuming as treatment duration is 5-6 weeks. Additionally, radiotherapy is more expensive than TOLMS [62]. Other disadvantages of radiotherapy included the possibility of acute or chronic complications which occur in 0-18% and 1-9% of patients, respectively [63]. Possible acute complications include skin erythema, skin desquamation, mucositis, dysphagia, and laryngeal oedema. Possible chronic complications are hypothyroidism, cerebrovascular events, laryngeal chondronecrosis leading to dysphagia and a compromised airway. Both acute and chronic complications after TOLMS are rare and occur in 1-5% or 1-2% of patients, respectively [63–66]. Possible acute complications after TOLMS include subcutaneous emphysema caused by accidental laser beam penetration

through the cricothyroid membrane and postoperative haemorrhage [67–70]. Possible chronic complications are persistent dysphagia and aspiration with possible pneumonia [71–75]. However, these chronic complications are mostly seen after larger resections (ELS type IV-VI) or in larger tumors (T3-T4) [71, 72].

OUTCOME PARAMETERS

Oncological outcomes

Early glottic carcinoma is a highly curable disease with good oncological outcomes. Different outcome measures are overall survival, local control, disease-specific survival, and laryngeal preservation. For T1 and T2 tumors, the local control rates after TOLMS or radiotherapy are comparable [76, 77]. Hence, laryngeal preservation and disease-specific survival are the most important outcomes for comparing the two treatment modalities. To further improve oncological outcomes and to predict success versus failure after TOLMS or radiotherapy, it is important to determine prognostic factors. This information could help enhance outcomes by facilitating the identification of patients most likely to benefit one of the two treatment modalities. Two prognostic factors that remain a topic of discussion with inconsistent results reported in literature are (i) involvement of the anterior commissure and (ii) impact of surgical margins status.

Functional outcomes

In addition to oncological outcomes, functional outcomes are also an important factor when choosing a primary treatment modality for early glottic carcinoma. Relevant functional outcomes reported in the literature are voice outcomes (voice quality, voice function, and voice performance), swallowing outcomes, airway preservation, and quality of life. In early glottic carcinoma, voice outcome is the most investigated parameter. Both TOLMS and radiotherapy affect the voice to some extent and since early glottic carcinoma is a highly curable disease, voice outcome is a major concern, as patients will generally live with the handicap the treatment causes long-term. To what extent the voice will be affected depends on different factors, such as patient (e.g. age, sex), tumor (e.g. involvement in anterior commissure, mobility), and treatment factors (e.g. total dose of radiotherapy, surgical margins after TOLMS) [78]. Functional outcomes after treatment for larger tumors (T2) are often worse compared to smaller tumors (T1), regardless of the treatment modality [71]. Direct comparison of functional outcomes between the two main treatment modalities remains difficult because of heterogeneity of studies and the wide range in outcome parameters studied. Additionally, whereas lesions treated with surgery are classified according to resection size, lesions treated with radiotherapy are very seldom stratified resulting in a mismatch of study groups that can affect both oncological and functional comparisons.

AIM AND OUTLINE OF THIS THESIS

While the use of TOLMS is expanding, radiotherapy is still the treatment modality of choice for extended T1 and T2 glottic carcinoma in the Netherlands. The discussion on the best treatment modality with regards to both oncological and functional outcomes is ongoing. This thesis tackles several issues regarding the treatment of early glottic carcinoma (Tis-T2), with a specific focus on T2 glottic carcinoma to contribute to the ongoing discussion: what is the role of TOLMS in T2 glottic carcinoma? As the use of TOLMS in these lesions is still limited in the Netherlands this thesis will act as a basis to explore whether this can be expanded.

Therefore, the specific aims of this thesis are:

1. To review the published literature on oncological and functional outcomes in T2 glottic carcinoma after treatment with TOLMS or radiotherapy (chapter 2)
2. To summarise the published literature on prognostic factors in patients with early glottic carcinoma (Tis-T2) treated with TOLMS or with radiotherapy, focusing on the involvement of the anterior commissure (chapter 3)
3. To assess the impact of surgical margin status on local disease control in patients with primary early glottic squamous cell carcinoma (Tis-T2) after treatment with TOLMS (chapter 4)
4. To evaluate long-term (2 years) quality of life and voice outcomes in patients with extended T1 and limited T2 glottic carcinoma treated with TOLMS (chapter 5)
5. To evaluate the survival outcomes in patients that received primary radiotherapy for T2N0 glottic carcinoma and to identify prognostic factors of local recurrence (chapter 6)
6. To assess long-term (>2 years) functional outcomes in patients with T2 glottic carcinoma treated with radiotherapy (chapter 7)

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Chapter 2

Oncological and functional outcomes of patients treated with transoral CO_2 laser microsurgery or radiotherapy for T2 glottic carcinoma: a systematic review of the literature

Martine Hendriksma
Bas J. Heijnen
Elisabeth V. Sjögren

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ABSTRACT

Purpose of review

To give an overview of the laryngeal preservation and functional outcomes of patients treated with transoral CO_2 laser microsurgery (TLM) or radiotherapy for T2 glottic carcinoma. This information supports physicians and patients in treatment counselling and choices.

Recent findings

A recent systematic review showed that local control rates at 5-year did not differ between radiotherapy and TLM for T2 glottic tumours. However, there is a lack of comparative data on laryngeal preservation as well as functional outcomes in T2 glottic carcinoma.

Summary

Laryngeal preservation for T2 tumours in this review is higher for patients treated primarily with TLM (88.8vs. 79.0%). It is important to differentiate between tumours with normal and impaired mobility (T2a andT2b) because the latter showed poorer prognosis for both TLM and radiotherapy. Involvement of the anterior commissure does not result in significantly lower oncological results, if adequately staged and treated. More studies are needed to support these data and to compare the functional outcomes between TLM and radiotherapy for T2 glottic carcinoma.

INTRODUCTION

Early glottic carcinoma (Tis-T2) is a highly treatable disease with either transoral CO_2 laser microsurgery (TLM) or radiotherapy and there is still much debate which modality is preferable for both oncological and functional outcomes. The latest Cochrane review showed that there is no formal proof that one treatment is more efficient than the other [1].

Both treatment modalities have advantages and disadvantages. One of the most important advantages of TLM as a primary strategy is the preservation of all treatment options in case of recurrent disease. Patients who have been initially treated with radiotherapy cannot be reirradiated and although TLM can be performed after radiotherapy the indication is limited. In line with this, several studies have indicated that patients with T1a tumours treated with TLM had a significantly higher laryngeal preservation than patients treated with radiotherapy [2–4]. Also, it has been shown that practical considerations and future options (such as preserving the larynx in case of recurrent disease) can be more important for patients with early glottic carcinoma than primary functional outcomes [5].

In addition to oncological outcomes, functional outcomes – such as voice, swallowing, and quality of life (QoL) are also important factors when choosing a primary treatment [6] with emphasis being put mostly on voice outcome. Several studies have shown that for Tis-T1a lesions requiring limited subepithelial or subligamental resections voice outcome after TLM is comparable with that of radiotherapy [7–10]. However, voice outcome for larger lesions requiring larger resections is poorer than for smaller lesions [11–18] and there is insufficient comparative data to radiotherapy to draw a conclusion.

So, although there are several comparative studies on the relative benefits of these two treatments in T1a glottic carcinoma there is little comparative data for T2 tumours. Recently, a systematic review concluded that there is no significant difference in the 5-year local control between radiotherapy and TLM for T2 glottic tumours [19]. However, to our knowledge, there is no review data on laryngeal preservation and functional outcomes after TLM and radiotherapy for patients with T2 tumours. As T2 glottic carcinoma remains a highly treatable disease with relatively high survival rates, larynx preservation is one of the primary outcomes both from the oncological and functional point of view. In our experience, ultimate larynx preservation vs. primary functional is the key issue when treatment options are discussed with patients. Therefore, the objective of this systematic review was to compare laryngeal preservation and functional outcomes for patients with T2 glottic carcinoma treated with either TLM or radiotherapy.

METHOD

A systematic search was performed on 6 September 2017 in PubMed, Embase, Web of Science, and Cochrane Library. The search strategy consisted of the following keywords: early glottic cancer, TLM/ radiotherapy, and functional/oncologic outcomes between January 2000 and September 2017. For these keywords, all synonyms were used.

Data extraction and inclusion criteria

Two independent reviewers (M.H. and B.J.H.) screened all papers on title and abstract, with the following inclusion criteria: patients with glottic squamous cell carcinoma staged as a pathologic T2N0 tumour and treated with either TLM or radiotherapy within a common time period. Excluded were: studies with reporting on recurrent cases, studies where outcome on T2 tumours was not extractable, papers not in English and studies reporting less than 10 patients. Full text of the included studies was independently reviewed with the extraction of oncological outcomes (laryngeal preservation, overall survival, disease-specific survival, and local control at 5-years calculated with a Kaplan–Meier or Cox regression method) or functional outcomes (voice outcome, QoL, or swallowing outcome). Primary outcomes were abstracted separately for T2a and T2b glottic tumours, if such information was available. During the extraction of oncologic data, papers that did not include laryngeal preservation were excluded. Subsequently, studies were assessed on the level of evidence according to level A, B, or C rating scale [20]. After the full-text screening, all the remaining papers were checked for relevant citations.

Statistical analysis

Prior to the review, no statistical analyses were planned. The perspective was that no randomized controlled trials were available and that studies showed heterogeneity instead of homogeneous groups. Therefore, only simple weighted averages of data were calculated.

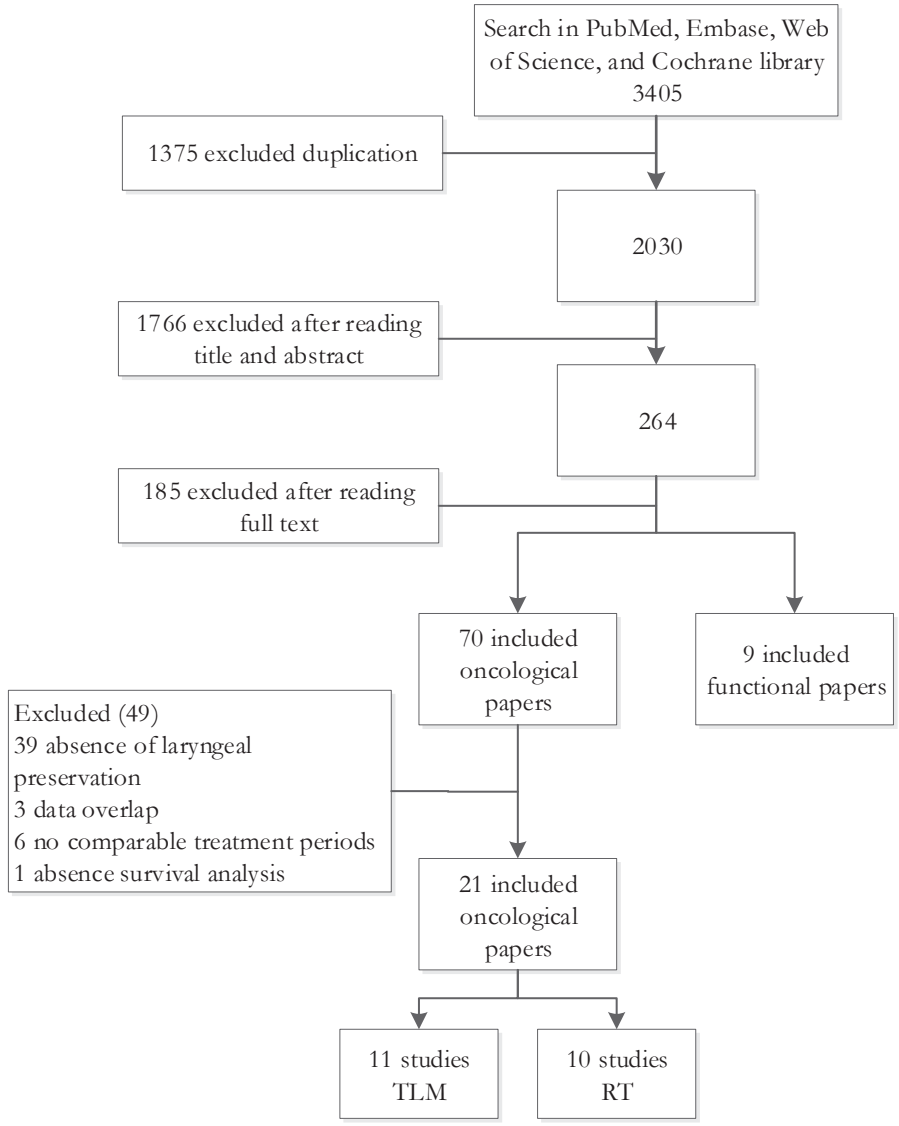
RESULTS

The results of the search are summarized in Figure 1. The initial search yielded 3405 papers. A total of 1375 duplicated were removed and 2030 papers were screened on title and abstract, of which 264 papers were reviewed on full text. Of these, 30 studies met the inclusion criteria, of which 21 with oncological outcomes and nine with functional outcomes. Hand searching for relevant citations did not result in additional papers.

Study characteristics

All 21 included studies were published in peerreviewed journals and had a level of evidence B [20]. No randomized controlled trials or comparatives studies were identified and only one prospective study was identified [21]. Eleven out of the selected 21 studies contained oncological

Figure 1. Flowchart of the present systematic review



Legend: date of search, September 6, 2017

outcomes of a total of 857 patients treated with TLM and 10 studies contained oncological outcomes of 437 patients treated with radiotherapy. In the majority of studies, both on TLM and radiotherapy, there was some selection of patients present. Large T2 tumours may not be suitable for an endoscopic approach and treatment must also be individualized according to patient preference. In four out of the 11 TLM studies [21–24], it was clear that the vast majority of the patients were treated with TLM. Although not directly specified in the other 7 studies, judging from the high number of patients it is very likely that TLM was the main treatment

modality in these studies as well. In two out of the 10 radiotherapy studies the strategy was clear. In one the vast majority of patients chose radiotherapy [25] and in the other patients were mostly treated with surgery (e.g. TLM or supracricoid partial laryngectomy) [26] with the remaining patients receiving radiotherapy. In seven studies, it was not clear what the treatment policy was.

Four out of the eleven TLM studies did not describe their management of the neck [22,27–29]. Depending on the study size and patient population neck dissection was performed in 0–15.7% of T2 patients. Postoperative radiotherapy was administered in 0% in five studies [24,28–31], 2.2% in one study [21], and 0% for T2a but 9.4% for T2b in one study [23]. One study did not give details on postoperative radiotherapy [27] and in three studies [22,32,33] the data could not be isolated for T2
tumours.

In the radiotherapy studies, different treatment strategies were applied. Total dose varied from 45 to 76.8Gy with a fraction size ranging from 1.2 to 2.4 Gy/session. Administration schedules also varied from once daily five times/week to twice daily six times/week. Seven out of 10 studies did not describe their management of the neck [25,34–39]. One study described that none of the patients received elective irradiation for neck lymph nodes [40]. In two studies, prophylactic irradiation was performed for neck lymph nodes [26,41].

Oncological outcomes

Tables 1 and 2 shows the oncological results of patients treated with either TLM or radiotherapy. The follow-up time varied and ranged from a minimum of 12 months to a median of 111 months. All studies reported on laryngeal preservation, 14 studies reported on overall survival, 13 studies reported on disease-specific survival and 17 studies reported on local control. Only two of the 25 studies reported T2a and T2b outcomes separately and only two studies reported results of only T2a tumours. Table 3 summarizes the weighted averages for the overall T2 tumours and for T2a and T2b tumours separately. Weighted averages for the overall T2 group for laryngeal preservation, overall survival, disease-specific survival, and local control at 5-years where 88.8, 69.2, 89.8, and 76.4% for TLM and 79.0, 82.9, 86.8, and 78.5% for radiotherapy, respectively (Table 3).

Functional outcomes

All nine included studies were published in peerreviewed journals and had a level of evidence B [20]. No randomized controlled trials, one comparatives, four prospective and three retrospective studies were identified. Two papers did not specify their study design. The nine functional outcome studies presented data outcomes of 504 patients. Two studies presented patients treated with radiotherapy, six patients treated with TLM and one study patients treated with either radiotherapy or TLM.

Table 1: Oncological outcomes of patients after treatment with TLM

First author	Study design	Treatment period	Treatment details	Patients	Follow-up (months)	Larynx preservation 5 years (%)	Overall survival 5 years (%)	Disease-specific survival 5 years (%)	Local control 5 years (%)
Ansarin [22]	RCS	1999-2013	TLM (ELS type I-VI)	90	Median 72	91.1		88	
Blanch [30]	RCS	1998-2008	TLM (NFS)	81*	Mean 45.4	73.2		79.2	59.3
Canis [23]	RCS	1979-2006	TLM (NFS)	T2a: 142	Median 96	93	72.2	93.2	83
				T2b: 127	Median 87	83	64.9	83.9	67.5
Day [31]	RCS	1995-2011	TLM (NFS)	17	Median 44.6	88	46	60	86
Eckel [21]	PCS	1987-1996	TLM (type II-IV)	93	Median 67	93.1	67.9	98.2	82
Hoffmann [27]	RCS	2001-2013	TLM (ELS type Va-VI)	12*	Mean 44.3	90.9	82.5	91.7	63.6
Lee [28]	RCS	1997-2011	TLM (ELS type I-VI)	11	Mean 69.4	90	68.2	90.9	81.8
Lucioni [29]	RCS	2000-2007	TLM (ELS type I-VI)	14	Mean 47.9	100	71.4	92.8	78.6
Peretti [33]	RCS	1998-2005	TLM (ELS type I-V)	109	Mean 84	95.1		98.3	85.6
Peretti [32]	RCS	2005-2010	TLM (ELS type V)	59	Minimum 18	84			76
Rödel [24]	RCS	1986-2004	TLM (NFS)	T2a: 102	Median 65				
				AC+ 64		89	80		76
				AC- 38		95	59		76

** only patients with involvement of the anterior commissure*

Abbreviations: AC+ = anterior commissure involvement; AC- = without anterior commissure involvement; ELS = European Laryngological Society; NFS = not further specified; PCS = prospective cohort study; RCS = retrospective cohort study

Table 2: Oncological outcomes of patients after treatment with RT

First author	Study design	Treatment period	Treatment details (Gy)	Patients	Follow-up (months)	Larynx preservation 5 years (%)	Overall survival 5 years (%)	Disease-specific-survival 5 years (%)	Local control 5 years (%)
Chen (34)	RCS	1983-2001	RT (63-72.8)	46	Minimum 12	63	64	70	
Dagan* (41)	RCS	1983-2002	RT (63-76.8)	T2a: 49	Median 85.2	82		93	82
				T2b: 31		77		89	70
Furusaka (35)	RCS	1981-2009	RT (66)	57	Median 111	60.4	88.5		
Gorphe (26)	RCS	2001-2012	RT (69)	T2a 34	NR	74.2	86.2		79.5
Harada (40)	RCS	1991-2010	RT (74.4)	35	Median 61	97	91		86
Motegi (36)	RCS	1999-2007	RT (64.8)	44	Median 74	95	91		77
Murakami (37)	RCS	1989-1998	RT (64-70)	27	Mean 75	92	81	100	83
Shor (38)	RCS	1986-1998	RT (60-66 SFX)	43	Median 58.8	92 AHFX			81 AHFX
			(55 AHFX)			80 SFX			80 SFX
Stoeckli (25)	RCS	2008-2012	RT (68-70.2)	30	Mean 70	77	78	88	67
Tateya (39)	RCS	1987-1998	RT (67.4) 1/day	20	Mean 80	60.3			
			(71.6) 2/day	21		95.2			

**ultimate local control with laryngeal preservation*

Abbreviations: AHFX = accelerated hypofractioned regimen; Gy = Gray; NFS = not further specified; RCS = retrospective cohort study; SFX = standard fractionation regimen;

Table 3: Weighted averages of the oncological outcomes for TLM and RT classified by tumour category

Tumour	Treatment	n	Larynx preservation 5 years (%)	n	Overall survival 5 years (%)	n	Disease-specific survival 5 years (%)	n	Local control 5 years (%)
T2	TLM	857	88.8	518	69.2	696	89.8	767	76.4
	RT	437	79.0	273	82.9	183	86.8	293	78.5
T2a	TLM	244	92.3	244	72.2	142	93.2	244	80.1
	RT	83	78.8	34	86.2	49	93	83	81.0
T2b	TLM	127	83.0	127	64.9	127	83.9	127	67.5
	RT	31	77.0	-	-	31	89.0	31	70

Table 4 summarizes functional outcomes and authors key findings. The follow-up time ranged from 4 to 66 months posttreatment. Two studies did not specify their follow-up time. Among them, seven studies reported on voice outcome, one on QoL and two on swallowing outcomes.

Owing to the heterogeneity in outcomes measures, a direct comparison between studies' outcomes was not appropriate and, therefore, we present the results as a descriptive narrative.

Voice outcome

Four studies reported Voice Handicap Index (VHI) scores of patients treated with either TLM or radiotherapy [42,43,47,49]. One of the studies reported only on the VHI physical subscores for patients treated with either radiotherapy or TLM. Owing to the differences in sample size, they did not perform a comparative analysis [49]. Another study found higher VHI scores among patients who had undergone type IV–V resections although they did not report the total scores. [43]. In one study on radiotherapy, the VHI improved after treatment for T2a tumours (23.8 points at 48 months) but not for T2b tumours (39.7 points) [42]. The fourth study included only patients with involvement of the anterior commissure treated with TLM (postoperative VHI 33.5 points) [46]. Two studies reported acoustic results after TLM or radiotherapy [43,48]. In one study, the fundamental frequency increased significantly after treatment with radiotherapy [48]. In the second study, resections for smaller tumours (type I–III for Tis-T1b) showed better results compared with larger resections (type IV–V) for T2 tumours [43]. Three papers reported aerodynamic results of patients treated with TLM or radiotherapy [44,46,48]. One study on radiotherapy concluded that the phonation time was shorter after treatment (15.08 s) [48]. One study on TLM concluded that the maximum phonation time was significantly shorter after treatment (8 s) [44]. The third study on radiotherapy concluded that the maximum phonation time was far below normal levels (3.2 s) [46]. Two studies reported on perceptual voice quality after treatment with TLM [45,46]. One study specifically on anterior commissure resections found moderate to severe dysphonia after treatment [46]. The other study found the range of dysphonia to be between normal and severe [45].

Table 4: Functional outcomes after treatment with either RT or TLM

First author	Study design	Treatment period	Treatment(s)	Patients	Topic	Follow-up	Measures used	Key findings / authors conclusions
Al-Mamgani (42)	PCS	2006-2011	RT (66-70Gy)	T2a: 209 T2b: 122	VO	4, 6 weeks; 3, 6, 12, 18, 24, 36, 48 months	VHI	T2b tumours have significantly worse VHI scores. T2b hardly improved after 48 months. T2a improved significantly and resulted in good VHI scores.
Bahannan (43)	NR	2000-2008	TLM (type IV-V)	10	VO	Postoperative, NFS	Acoustic analysis (F0, Jitter, NHR, Shimmer) VHI	Less favourable vocal outcomes were found after type IV-V resections in comparison with type I-III resection for Tis-T1 tumours.
Lester (47)	PCS	2002-2007	TLM (NFS)	12	VO	3, 12 months	Voice rating resultsAerodynamic analysis (MPT)	MPT deteriorated significantly with time, however subjective vocal rating improved significantly 12 months after treatment.
McClelland (48)	RCS	2002-2004	TLM (NFS)	8	VO	1 day-6 months	Perceptual voice analysis (Oats Russell Voice Profile)	Voices were rated as normal to severely impaired postoperatively.
Mendelsohn (44)	RCS	2005-2013	TLM (type Va-VI)	9 *	VO	4-6 months	Aerodynamic analysis (MPT, PQ) Perceptual voice analysis (GRBAS) VHI	Tumours involving the AC can be expected to demonstrate poorer functional outcomes. Voice outcomes measures demonstrated some level of handicap of vocal function, however with overall acceptable results.
Nasef (50)	PCS	2012-2015	TLM (type V)	40	S	1, 5, 10, 15, 90 days	MDADI VFS FEES	Fast and better swallowing outcomes, and reduced preoperative morbidity were observed after TLM than after vertical hemilaryngectomy.
Niedzielska (46)	NR	NR	RT (60-70Gy)	21	VO	1-3 years	Acoustic analysis (F0, Jitter, NHR, Shimmer) Aerodynamic analysis (PT)	For T2 patients the only significant increase was noted for the F0 parameter.
Remmelts (45)	RCS	2000-2008	RT (52.8 -70Gy) TLM (NFS)	38 2	VO	RT 66 months TLM 51months	VHI – physical subscale	Due to the differences in sample size, they did not perform a comparative analysis for this group.
Vilaseca(49)	PCS	2004-2006	TLM (NFS)	23	QoL	12 months	UW-QoL SF-12 v2 (MCS and PhCS)	Patients present with a very good QoL.

*Abbreviations: AC = anterior commissure; F0 = fundamental frequency; FEES = fiberoptic endocopic evaluation of swallowing; GRBAS = grade, roughness, breathiness, asthenia, strain; MCS = mental component score; Gy = Gray; MDADI = MD. Anderson Dysphagia Inventory; MPT = maximum phonation time; NFS = not further specified; NHR = noise to harmonic rate; NR = not reported; PhCS = physical component score; PCS = prospective cohort study; PQ = phonation quotient; PT = phonation time; QoL=Quality of Life; RCS = retrospective cohort study; S = Swallowing; SF-12, vs 2 = short form 12, version 2; UW-QOL = University of Washington Quality of Life Questionnaire; VFS = videofluorscopy ; VHI = voice handicap index; VO = Voice Outcome; * only patients with involvement of the anterior commissure*

Quality of life

One study reported on QoL after treatment with TLM using a validated instrument. Patients reported a good QoL postoperatively. Compared with preoperatively, postoperative QoL scores improved; however, this was not significant [50].

Swallowing outcomes

One study evaluated posttreatment swallowing using Functional Endoscopic Evaluation of Swallowing, Videofluoroscopy, and a validated questionnaire (MD Anderson Dysphagia Iventory) after treatment with TLM[45,47]. They found high mean and median score on the MD Anderson Dysphagia Iventory (overall and subdomains), indicating that patients had good swallowing functioning 1 week after TLM [47].

DISCUSSION

To our knowledge, this is the first systematic review presenting laryngeal preservation and functional outcomes in T2 glottic carcinoma. The results of this systematic review suggest that primary treatment with TLM results in higher laryngeal preservation than primary treatment with radiotherapy. Weighted averages of laryngeal preservation for patients treated with TLM at 5-year was 88.8 and 79.0% for patients treated with radiotherapy. Owing to the variety of measures, no conclusion could be drawn on functional outcomes.

Oncological outcomes

The weighted average for laryngeal preservation in glottic T2 in this review was 88.8%. Only two studies reported oncologic outcomes of T2a and T2b separately [23,41]. Other studies described the differences between impaired mobility and normal mobility of the vocal cord, but they did not describe the oncological outcomes separately [22,24,26,31–34,51–53]. Officially, the T2a and T2b categories are no longer part of the UICC or AJCC staging. However, it is important to realize that patients with impaired cord mobility, formerly staged as T2b tumours, have a poorer prognosis than patients with T2a tumours for both TLM [54,55] and radiotherapy [41,56]. It has even been argued that T2b tumours have a prognosis that more resembles T3 tumours [23,57]. This is in line with the results for the limited number of classified T2a and T2b tumours in this review in which T2a tumours show better oncological outcomes than T2b.

Two studies on TLM presented data exclusively on patients with T2 tumours with involvement of the anterior commissure [27,30]. Furthermore, three studies on TLM [29,32,33] and five studies on radiotherapy [25,26,34,37,38] statistically tested the involvement of the anterior commissure and all concluded that its involvement does not result in significantly lower oncological outcomes and was, therefore, not seen as a risk factor in TLM. However, studies do stress that accurate staging of the anterior commissure and adequate surgical techniques involving wide resection are imperative to successful treatment of these lesions [30,33].

Treatment details for patients treated with radiotherapy were well described. In contrast, patients treated with TLM were not. Only seven out of 11 studies described which resections were performed during surgery [21,22,28,29,32,58]. Among them, six studies classified their procedures according to the European Laryngological Society classification [59]. Only in two of these studies was the specific resection clarified for T2 glottic tumours [27,32]. In the other studies, several types of resections (type I–VI) were performed. Type I–III resections were mostly performed in studies where also Tis, T1a, and T1b tumours were included. Although it is not clearly stated, type I and II resections in these studies were presumably performed in smaller tumours (Tis-T1). For further studies, we suggest providing more detail on the type of resections performed/tumour stage. This will ensure that comparison between studies can be improved.

Four studies on radiotherapy matching the inclusion criteria were excluded because of a mismatch of the inclusion periods with the TLM studies. One of these studies [60] describes the largest published national population-based consecutive cohort of patients treated with primary radiotherapy for glottic squamous cell carcinoma to date. This study shows a continuous increase over time in laryngectomy-free survival. In the 1970s the 5-year laryngectomy-free survival was 41 vs. 57% in the time period between 2000 and 2011. The mean laryngectomy-free survival in this study was 48% [60]. This is lower than all other studies in this review. Owing to the large cohort of patients (n=1453), Lyhne et al. [60] would have had the most influence on the weighted average calculated in this review. The inclusion of this study would have changed the 5-year laryngeal preservation to 55.2% based on 1890 patients. Also, in the selection process, a number of other large studies on radiotherapy had to be excluded, as they did not specify the laryngeal preservation for T2 tumours.

Ultimate larynx preservation in this review includes salvage therapy, which differs between centers. It is important to realize that for both treatment modalities open partial laryngectomy (OPL) can be a salvage option and if part of the salvage strategy can help increase laryngeal preservation. OPL was employed in six out of 11 studies on TLM and in five of 10 studies on radiotherapy. It is not clear if in the other studies the technique was not available or no patient met the inclusion criteria for OPL.

Functional outcomes

A direct comparison between TLM and radiotherapy in nine studies of this review was not possible because of the heterogeneity of the outcome measures. Furthermore, objective parameters, like aerodynamic and acoustic ones, are difficult to compare, because of the absence of standard protocols, the wide range of values that can be considered in the normal range and the different computer programs used to register them, the distance between mouth and microphone, type of microphone, and recording devices used [61,62]. Also, unfortunately, we had to exclude several large studies who had grouped Tis-T1a-T1b and T2 tumours, where data on T2 tumours were

not extractable. All in all the data in this review are insufficient to draw any conclusions on the relative functional outcomes for TLM and radiotherapy in T2 glottic carcinoma.

The current study has some limitations. First, weighted averages for overall survival, disease-specific survival, and local control at 5-year could be biased as papers were selected specifically on 5-year laryngeal preservation which was the main objective of the study. However, a recent systematic review reporting on local control of T2 tumours treated with either TLM or radiotherapy showed similar local control outcome to ours 77.3 and 75.8%, respectively [19]. Therefore, we believe that our findings are reliable. Finally, there was heterogeneity in treatment details, treatment period, study design, and follow-up for both treatment modalities. This is, however unavoidable in such as study as this although we did try to limit this by selecting studies within the same time frame.

CONCLUSION

We conclude that there is evidence that patients with T2 tumours primarily treated with TLM have a higher laryngeal preservation than patients primarily treated with radiotherapy. This finding is in line with evidence for T1a glottic carcinoma. Although more studies are needed to confirm this, this finding is of added value when discussing treatment options with patients. More comparative studies are required to investigate which treatment option is superior in functional outcomes for T2 tumours.

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Chapter 3

Involvement of the anterior commissure in early glottic cancer (Tis-T2): a review of the literature

Martine Hendriksma
Elisabeth V. Sjögren

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ABSTRACT

Background

The impact of the anterior commissure (AC) involvement on prognosis in laryngeal cancer remains a topic of discussion with inconsistent results in the literature. This review examines AC involvement as a prognostic factor in patients with early glottic cancer (Tis–T2) treated with radiotherapy or transoral laser microsurgery (TLM).

Methods

A systematic literature search was performed. Due to the heterogeneity of the data, no meta-analysis was implemented. Weighted averages were calculated if the appropriate data were extractable.

Results

Thirty-four studies on radiotherapy and 23 on TLM fit the inclusion criteria. The majority of studies for both radiotherapy (67.7%) and TLM (75.0%) did not report a significant impact on oncological outcomes. Weighted averages were slightly lower in patients with AC involvement. The two studies that applied a more detailed classification showed a significant impact on the amount of AC involvement.

Conclusions

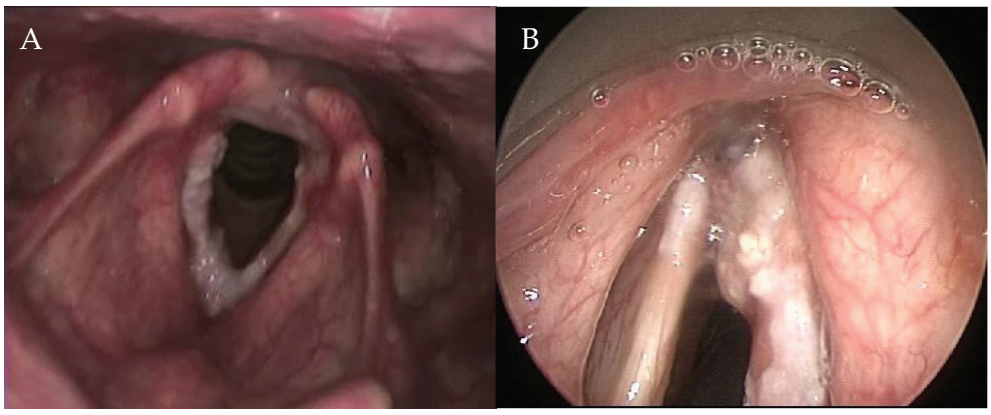
Binary variables (yes/no) for AC involvement lead to inconsistent results. Studies that use more detailed classifications of the AC show that there is a significant impact on the outcome. To further elucidate the role of the AC, detailed stratification of tumors involving the AC need to be investigated in further studies for both treatment modalities.

INTRODUCTION

Although it is widely acknowledged that the involvement of the anterior commissure (AC) in early glottic cancer (Tis–T2) can have negative impacts on outcomes, the extent of the impact remains a topic of discussion with inconsistent results reported in the literature. Some studies show a significant association between the AC and a higher recurrence rate, whereas others do not.

The AC is a complex anatomical subsite of the larynx, which encompasses different structures such as Broyles ligament, membranes, muscles, perichondrium, and the thyroid cartilage, and has a close relationship with the visceral structures surrounding it. Therefore, the AC has to be considered as a 3D structure and not as a point location (Figure 1). Rucci et al. defined the AC - on the basis of embryonic development - as the area of the glottis situated anteriorly between the vocal folds that extends in a vertical direction, both upwards and downwards [1]. It is rarely the site of origin of glottic cancer [1], but it is often involved in anterior lesions spreading from left to right, and from inferior to superior. Furthermore, due to its close proximity to the visceral spaces of the larynx (pre-epiglottic space, paraglottic space, and cricothyroid membrane), it has been argued that microscopic spread to these spaces may affect local control [2-4].

Figure 1. Extension in the anterior commissure. (A) Fiber endoscopic view during outpatient examination; (B) Endoscopic examination of the same patient in anesthesia



METHODS

Search

A systematic search was performed on 7 January 2019 on PubMed. The search strategy was conducted with a combination of the following keywords: laryngeal cancer, radiotherapy, and transoral laser microsurgery. For these keywords, all synonyms were used.

Inclusion Criteria and Data Extraction

For studies to be included, they had to be on adult patients with glottic squamous cell carcinoma staged as Tis, T1, or T2, treated with radiotherapy or TLM, to investigate the involvement of the AC as a prognostic factor, and be published between 1998 and 2018 in English. Also, a clear distinction had to be made, within the studies, between tumors that did and those that did not involve the AC to test this variable. Studies concerned with recurrent cases and studies reporting on less than 10 patients were excluded. Full-text versions of the included studies were reviewed for oncological outcomes. The primary endpoint was 5-year local control (LC) of tumors, with or without the involvement of the AC, calculated by the Kaplan-Meier or Cox regression method. Other oncological outcomes of interest were overall survival (OS), disease-specific survival (DSS), and laryngeal preservation (LP). During the extraction of data, papers that did not report LC were excluded. After the full-text screening, all papers were checked for relevant citations.

Statistical Analyses

Due to the heterogeneity of the data, no meta-analysis was performed. If data were extractable, weighted averages of the data were calculated for the separate tumor groups: T1, T2, and T1–T2.

RESULTS

Search

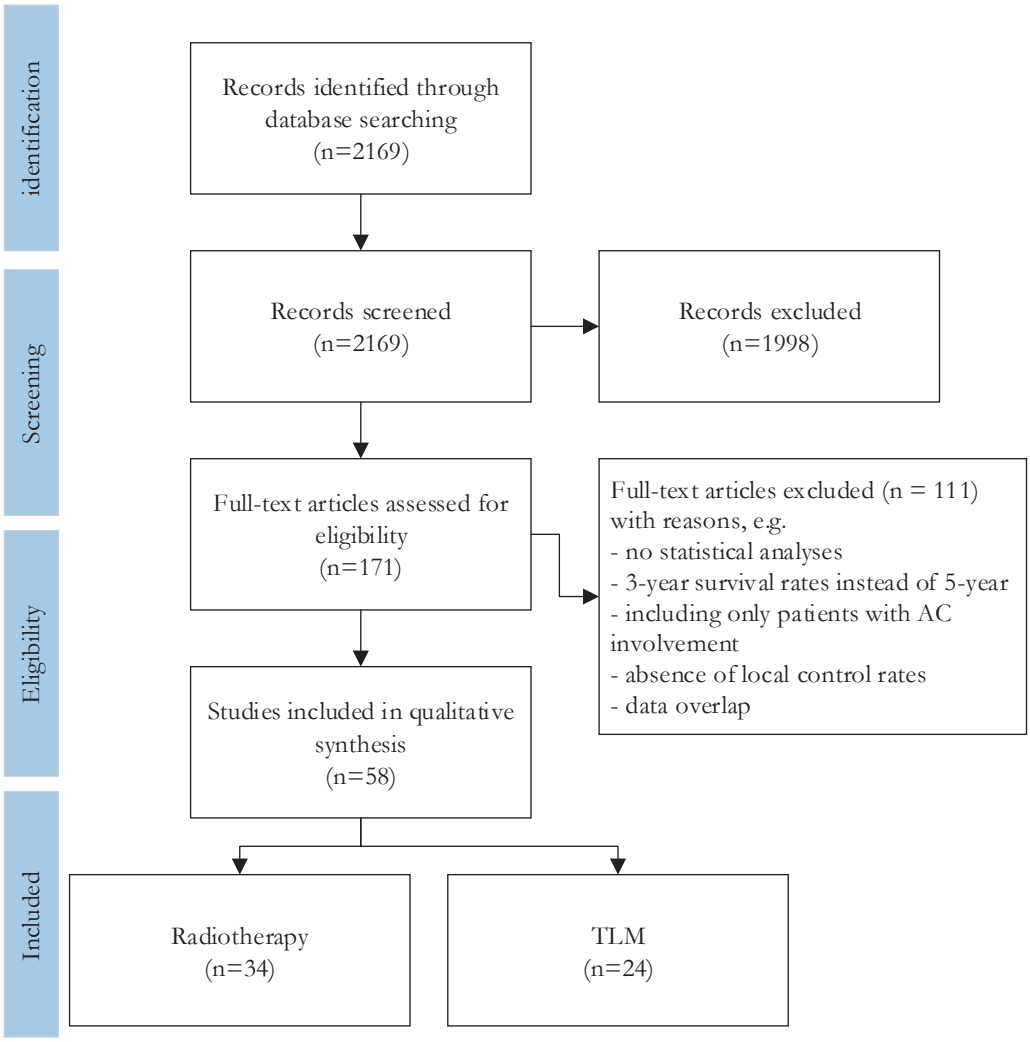
The results of the search are summarized in Figure 2. The initial literature search yielded 2169 citations, of which the title and abstract were screened. This identified 171 publications that underwent a full-text review. Of these, 34 publications on radiotherapy and 24 on TLM met the inclusion criteria. Reference cross-checking did not identify additional papers.

Study Characteristics

All 58 studies included in this review were published in peer-reviewed journals. Only one prospective randomized study, which was on radiation therapy, was identified [5]. All other publications had a level of evidence classified as B [6]. Most of the studies reported outcomes for early glottic cancer, grouping Tis–T2 tumors together, with only a few studies focusing on T1 or T2 tumors separately. The 34 radiotherapy studies included 9656 patients, of which 3930 patients (40.7%) had involvement of the AC. The 24 TLM studies included 3958 patients, of which 1169 patients (29.5%) had involvement of the AC.

In the radiotherapy studies, different treatment protocols were applied, and different techniques were used (conventional, accelerated, hyperfractionated, hypofractionated, and intensity-modulated radiation therapy), with doses varying between 60 and 78 Gy. Administration schedules varied from once daily, five times per week to twice daily, six times per week. Some studies applied elective neck irradiation, and some administrated a bolus in patients with AC

Figure 2. Flow diagram illustrating the searching and selection procedure



Abbreviations: AC = anterior commissure, TLM = transoral laser microsurgery

involvement. In 14 studies (41.2%) LC rates were not presented for the AC separately [7-20]. These studies only presented p-values, hazard ratios (HR), or odds ratios.

Most studies on TLM classified resections according to the European Laryngological Society (ELS) classification system [21,22]. Two studies [23,24] performed resections according to the principles proposed by Steiner and Ambrosch [25], and in three studies, the resections were not further specified [26-28]. In six studies (25.0%), LC rates were not presented for the AC separately [26,29-33].

Table 1. Oncological outcomes of patients after treatment with radiotherapy for involvement with or without the AC

First author and year	Treatment period	Treatment details	Tumor	Patients	Follow-up (in months)	5-year local control (%)	5-year overall survival (%)	5-year disease specific survival (%)	5-year laryngeal preservation (%)
Al-Mamgani 2014 [7]	1985-2011	Intended dose 66 Gy <'97 conventional >'98 accelerated	T1	AC+ 214 AC- 335	Median 93	OR = 1.1 p=0.646			
Al-Mamgani 2013 [34]	1985-2011	Intended dose 66 Gy <'97 conventional >'98 accelerated	T1-T2	AC+ 553 AC- 497	Median 90	AC+ 84 AC- 86 OR 1.1 p=0.091			
Berwouts 2016 [8]	2007-2011	IMRT: T1: 63 Gy T2: 67.5 Gy Conv RT T1: 66 Gy T2: 70 Gy	T1-T2	IMRT AC+ 7 AC- 33 Conv RT AC+ 11 AC- 70	IMRT: Median 45.6 Conv RT: Median 108	IMRT: p=0.22 Conv RT: p=0.62	IMRT: p=0.60 Conv RT: p=0.98	IMRT: p=0.64 Conv RT: p=0.27	
Bignardi 2004 [13]	1980-1988	63 Gy hyperfraction-ated	T2	AC+ 33 AC- 27	Median 117.6	HR 0.48 p=0.12			
Bron 2001 [35]	1983-1996	median 70 Gy	T1-T2	AC+ 43 AC- 38	Median 59	AC+ 66 AC- 90 p=0.009		AC+ 88 AC- 100 p=NS	
Cellai 2005 [36]	1970-1999	<61 Gy 82 61-65 Gy 352 >65 Gy 397	T1	AC+ 282 AC- 549	Mean 111.6	AC+ 78 AC- 87 p=0.001			
Cheah 2009 [37]	1993-2001	50 Gy	T1	AC+ 22 AC- 77	Median 84	AC+ 78 AC- 90 HR 2.17			
Chen 2003 [38]	1983-2001	T1: median 66 Gy T2: median 70 Gy	T1-T2	T1 AC+ 33 T1 AC- 55 T2 AC+ 29 T2 AC-17	Range 12-120	T1: 55 vs. 90 p=0.0035 T2: 54 vs. 70 p=0.74 MVA: RR 3.8 p=0.020		T1 p=0.0366	
Chera 2010 [14]	1964-2006	median 63 Gy	T1-T2	AC+ 369 AC- 216	Median 147	p=0.342			
Chung 2017 [15]	2006-2012	median 65.25 Gy	Tis-T2	AC+ 52 AC- 112	Median 77.7	HR 1.67 p=0.197			
Frata 2005 [39]	1970-1999	<61 Gy 33 61-65 Gy 83 >65 Gy 140	T2	AC+ 145 AC- 111	Mean 90	AC+ 69 AC-77 p=0.1			

First author and year	Treatment period	Treatment details	Tumor	Patients	Follow-up (in months)	5-year local control (%)	5-year overall survival (%)	5-year disease specific survival (%)	5-year laryngeal preservation (%)
Garden 2003 [40]	1970-1998	median 70 Gy	T2	AC+ 156 AC- 74	Median 82	AC+ 70 AC- 75 p=0.59			
Gowda 2003 [41]	1989-1997	total dose 50-52.5 Gy	T1	AC+ 50 AC- 150	Median 70	AC+ 89 AC- 94 p=0.47			
Gultekin 2012 [42]	1998-2007	median 64.4 Gy	T1	AC+ 31 AC- 152	Median 63	AC+ 79 AC- 82 p=0.65	AC+ 78 AC-92 p=0.16	AC+ 81 AC- 92 p=0.16	
Harada 2015 [16]	1999-2010	Hyperfractionated T1a: median 66 Gy T1b: median 70 Gy	T1-T2	AC+ 50 AC- 65	Median 61	UVA p=0.25			
Jin 2002 [43]	1958-1994	median 68.0 Gy	T1	AC+ 70 AC- 168	Median 127	AC+ 70.5 AC- 87.1 p=0.003 HR 2.00 p=0.024	AC+ 79.4 AC- 86.0 p=0.32		
Jones 2010 [17]	1987-2006	T1 median 63 Gy T2 median 74.4 Gy	T1-T2	AC+ 70 AC- 48	Median 69.6	NS			
Khan 2012 [18]	1986-2006	median 68.2 Gy	T1-T2	AC+ 71 AC- 52	Mean 67.2	UVA p=0.0505 MVA p=0.094			
Laskar 2012 [44]	1975-2000	Hypofractionated 50-62.5 Gy	T1	AC+ 228 AC- 414	Median 62	AC+ 86.3 AC- 90.3 p=0.367			
Lim 2015 [45]	1981-2010	median 66 Gy	T1-T2	AC+ 56 AC-166	Mean 85.2	AC+ 75.7 AC- 91.9 p<0.001 MVA HR 3.37 p=0.001			
Matsumoto 2016 [19]	2007-2014	maximum total dose 63.0-70 Gy	T1-T2	AC+ 13 AC- 30	Median 33	UVA 0.085 MVA HR 4.97 p=0.023			
Mendenhall 2001 [20]	1964-1998	median 63 Gy	T1-T2	AC+ 328 AC- 191	Median 118.4	MVA p=0.350	p=0.224	p=0.293	
Murakami 2005 [46]	1989-1998	T1a 60-66 Gy T1b-T2 64-70 Gy	T1-2	AC+ 59 AC- 71	Mean 75	AC+ 74 AC- 78 p=0.668			
Nozaki 2000 [47]	1985-1997	range 60-70 Gy	T1	AC+ 14 AC- 50	Not mentioned	AC+ 58 AC- 89 p<0.05			
Raitola 2000 [9]	1970-1991	range 45-70 Gy	T1-T2	AC+ 19 AC- 57	Median 82.8	HR 3.8 p=0.004 MVA = NS		HR 3.0 (0.9-9.9) p=0.0706	

Table 1 (continues from previous page). Oncological outcomes of patients after treatment with radiotherapy for involvement with or without the AC

First author and year	Treatment period	Treatment details	Tumor	Patients	Follow-up (in months)	5-year local control (%)	5-year overall survival (%)	5-year disease specific survival (%)	5-year laryngeal preservation (%)
Robert 2017 [48]	1987-2015	mean 66.5 Gy	T1-T2	AC+ 45 AC-213	Median 50	AC+ 84 AC- 88 p=0.382			
Sjogren 2009 [49]	1982-1993	median 60 Gy	T1	AC+ 106 AC-210	Median 70	AC+ 85 AC- 87 p=0.38			
Smee 2010 [10]	1967-2006	median 60 Gy	Tis-T2	AC+ 127 AC- 395	Median 91.2	UVA p=0.016 MVA p=0.040		UVA = 0.019 MVA 0.050 (SE 0.303)	
Sommat 2017 [11]	2000-2012	median 63.0 Gy	T1	AC+ 62 AC- 37	Median 58.8	HR 2.36 p=0.274			
Thairat 2004 [12]	1975-2001	median 66 Gy	Tis-T2	AC+ 37 AC- 118	Median 66	HR 1.1 p=0.73			
Tong 2011 [50]	1983-2005	55-68 Gy	T1	AC+ 197 AC- 236	Median 126	AC+ 86 AC- 95 p=0.004 MVA HR 2.34 p=0.011			
Warde 1998 [51]	1981-1989	50 Gy	T1-T2	AC+ 261 AC- 474	Median 81.6	AC+ 75 AC- 85 p=0.0005 MVA NS			
Yamazaki 2006 [5]	1993-2001	56.25-63 Gy	T1	AC+ 26 AC-154	Median 64	OR 0.25 p=0.25			
Zouhair 2004 [52]	1983-2000	median 70 Gy	T1-T2	AC+ 61 AC- 61	Median 85	AC+ 73 AC- 94 p=0.002 MVA RR 0.42 p=0.001			

Abbreviations: AC + = anterior commissure involvement, AC- = no anterior commissure involvement, AC0: no involvement of the anterior commissure, AC1 = involvement of the anterior commissure subsite on only one side of the midline, AC2 = involvement of the anterior commissure subsite that crosses the midline on only part of the longitudinal extension of this subsite, AC3 = involvement of the whole anterior commissure subsite on both sides across the midline, Conv RT = Conventional radiotherapy, Gy = Gray, HZ = hazard ratio, IMRT = Intensity Modulated Radiation Therapy, MVA = multivariate analysis, NS = not significant, OR = odds ratio, RR = Relative Risk, RT = radiothearpy, SE = Standard Error, UVA = univariate analysis.

Table 2. Oncological outcomes of patients after treatment with TLM for involvement with or without the AC

First author and year	Treatment period	Treatment details	Tumor	Patients	Follow-up (in months)	5-year local control (%)	5-year overall survival (%)	5-year disease specific survival (%)	5-year laryngeal preservation (%)
Ansarin 2017 [53]	1999-2013	TLM (ELS I-VI)	Tis-T3	AC+ 102 AC- 483	Median 72	AC+ 79.4 AC - 86.7 p=0.04 MVA HR 1.29 p=0.38		AC- 96.0 AC+ 87.2 p=0.004	p=0.12
Carta 2018 [54]	1993-2005 and 2010-2016	TLM (ELS I-VI)	Tis-T2	AC+ 105 AC-156 AC0 156 AC1 31 AC2 65 AC3 9	Median 51.6	AC+ 89.7 AC- 93.9 p=0.205 AC0 93.9 AC1.96.2 AC2 89.3 AC3 74.1 p=0.044	AC+ 78.6 AC- 89.5 NS	AC+ 98.4 AC- 100 NS	AC+ 95.3 AC- 99.1 p=0.08 AC0 99.1 AC1.100 AC2 96.1 AC3 71.1 p<0.0001
Chang 2017 [55]	2003-2009	TLM (ELS I-VI)	Tis-T3	AC+ 34 AC- 59	Median 35	AC+ 74 AC- 95 p=0.007 MVA NS			
Chone 2007 [56]	1998-2003	TLM (ELS I-III)	T1-T2	AC+ 24 AC- 24	Mean 44	AC+ 79 AC- 96 p=0.08			AC+ 96 AC- 100 p=0.50
Fang 2013 [57]	2004-2011	TLM (ELS I-VI)	T1-T2	AC+ 45 AC- 28	Median 33	AC+ 83 AC- 85 p=0.906			
Gallet 2017 [29]	2001-2010	TLM (ELS III-IV)	Tis-T2	AC+ 49 AC- 44	Median 75.6	UVA OR 3.4 p=0.021 MVA = NS			
Hakeem 2013 [26]	2000-2011	TLM (nfs)	T1-T2	AC+ 61 AC- 235	Mean 49	p=0.0001	AC+ 90.2 AC- 86.4 p=0.642	AC+ 95.1 AC- 91.5 p=0.642	AC+ 95.01 AC- 93.2 p=0.287
Hartl 2007 [30]	1994-2006	TLM (ELS I-V)	Tis-T1	AC+ 8 AC- 79	Median 46	p=0.16			
Hoffmann 2016a [58]	2001-2011	TLM (I-VI)	Tis-T2	AC+ 75 AC- 126	Mean 50.82	AC+ 54.6 AC- 79.8 p=0.004	AC+ 76.9 AC- 88.5 p=0.29	AC+ 90.8 AC- 99.0 p=.03	AC+ 91.9 AC- 100 p=0.0003

Table 2 (continues from previous page). Oncological outcomes of patients after treatment with TLM for involvement with or without the AC

First author and year	Treatment period	Treatment details	Tumor	Patients	Follow-up (in months)	5-year local control (%)	5-year overall survival (%)	5-year disease specific survival (%)	5-year laryngeal preservation (%)
Hoffmann 2016b [59]	2001-2013	TLM (Va-VI)	Tis-T2	AC1 29 AC2 17 AC3 50	Mean 44.3	AC1 71.6 AC2 87.5 AC3 50.8 p=0.04	NS	NS	NS
Hsin 2009 [27]	1999-2008	TLM (nfs)	Tis-T2	AC+ 18 AC- 30	Median 36.5	AC+ 74 AC- 71 p=0.90			
Ledda 2006 [60]	1993-2001	TLM (ELS I-V)	Tis-T2	AC+ 22 AC- 81	Mean 70.8	AC+ 87.5 AC- 96.5 p=0.6			
Lee 2013 [61]	1997-2011	TLM (ELS I-VI)	T1-T2	AC+ 33 AC- 85	Mean 69.4	AC+ 80.9 AC- 91.1 p=0.583	AC+ 88.7 AC- 91.6 p=.883		
Mortuaire 2006 [33]	1990-2000	TLM (ELS I-V)	Tis-T2	AC+ 22 AC- 88	Median 42	UVA NS			
Peretti 2000 [62]	1987-1994	TLM (I-V)	Tis-T2	AC+ 40 AC- 98	Mean 76	AC+72 AC- 86 p=0.2			
Peretti 2001 [63]	1995-1997	TLM (I-V)	Tis-T1	AC+ 12 AC- 76	Mean 43	AC+ 83 AC- 87 p=0.7			
Peretti 2010 [3]	1988-2005	TLM (ELS I-V)	Tis-T1	AC+ 84 AC- 391	Mean 84	AC+ 100 AC-99.2 p=0.44		AC+ 100 AC- 98.9 p=0.27	AC+ 98.8 AC- 98.1 p=0.57
Peretti 2013 [64]	2005-2010	TLM (ELS Type V)	T2-T3	AC+ 4 AC- 85	Minimal 18	AC+ 59 AC- 62 NS			AC+ 96 AC- 75 NS
Rodel 2009 [28]	1986-2004	TLM (nfs)	T1-T2	T1a AC+55 T1a AC-237 T1b AC+34 T1b AC-16 T2 AC+64 T2 AC-38	Median 65	T1a: 73 vs. 89 p=0.06 T1b: 68 vs. 86 p=0.32 T2: 76 vs. 7	T1a: 85 vs. 87 T1b: 93 vs. 72 T2: 80 vs. 59 NS		T1a: 95 vs. 98 T1b: 88 vs. 100 T2: 89 vs. 95 no p-value

First author and year	Treatment period	Treatment details	Tumor	Patients	Follow-up (in months)	5-year local control (%)	5-year overall survival (%)	5-year disease specific survival (%)	5-year laryngeal preservation (%)
Rucci 2010 [31]	2003-2007	TLM (ELS I-V)	Tis-T1	AC0 48 AC1 20 AC2 13 AC3 0	Mean 24.2	UVA p=0.0119 MVA OR 5.14 p=0.036			
Sachse 2009 [65]	1995-2005	TLM (ELS II-Va)	T1	AC+ 14 AC- 32	Median 36	AC+ 42 AC- 87 NS	AC+ 67 AC- 100		
Son 2018 [32]	2009-2014	TLM (ELS I-VI)	T1-T2	AC+ 25 AC- 48	Median 44	HR 3.45 p=0.030 MVA 1.03 p=.964	1.96 p=0.412		
Steiner 2004 [23]	1986-1996	TLM (proposal by Steiner)	T1-T2	T1a AC+28 T1a AC-130 T1b AC+16 T1b AC-14 T2 AC+45 T2 AC-30	Median 63.9	T1a: 84 vs. 90 T1b: 73 vs. 92 T2: 79 vs. 74 all p-value > 0.05	T1a: 87 vs. 86 T1b: 100 vs. 70 T2: 80 vs. 56 no p-value		T1a: 93 vs. 99 T1b: 88 vs. 100 T2: 93 vs. 97 no p-value
Wolber 2017 [24]	1992-2002	TLM (proposal by Steiner)	T1-T2	AC+ 21 AC-28	Mean 62.0	AC+ 57.1 AC- 92.9 p<.01	AC+ 90.5 AC- 96.4 p=.39		

Abbreviations: AC + = anterior commissure involvement, AC- = no anterior commissure involvement, AC0 = no involvement of the anterior commissure, AC1 = involvement of the anterior commissure subsite on only one side of the midline, AC2 = involvement of the anterior commissure subsite that crosses the midline on only part of the longitudinal extension of this subsite, AC3 = involvement of the whole anterior commissure subsite on both sides across the midline, ELS = European Laryngology Society, HZ = hazard ratio, MVA = multivariate analysis, nfs = not further specified, NS = not significant, OR = odds ratio, TLM = transoral laser microsurgery, UVA = univariate analysis.

In both the radiotherapy and TLM studies, the follow-up time varied. In radiotherapy studies, the follow-up time ranged between a median of 33 and 147 months, and in TLM studies follow-up time ranged between a mean of 24.2 and 84 months. Characteristics of the included studies are presented in Table 1 for radiotherapy and in Table 2 for TLM.

Local Control

In 23 out of 34 (67.6%) studies in the radiotherapy group, AC involvement did not have a significant impact on LC [5,7-9,11,13-18,20,34,39,40-42,44,46,48,49,51], and in 10 studies (29.4%), it did have a significant impact [10,19,35-37,43,45,47,50,52]. One study (2.9%) concluded that the AC was a predictive factor for LC in T1 tumors, but not in T2 tumors [38]. In the TLM studies, 18 out of 24 (75.0%) studies did not identify the AC involvement as a significant factor for LC [3,23,27,29,30,32,33,53,55,56-58,60-65], and two studies (8.3%) did [24,26]. One study (4.3%) concluded that the involvement of the AC was a predictive factor for LC in T1a tumors, although this was not the case in T1b or T2 tumors [28]. Three studies (12.5%) presented a more detailed classification of the AC involvement and concluded that the AC involvement had a significant impact on the AC [31,54,59]. One of these studies showed that in its binary approach (yes/no), the AC involvement did not have a significant impact on the AC, whereas it did in its more detailed classification [54].

Table 3 summarizes the weighted averages for the different tumor stages (T1, T2, T1–T2). Nineteen radiotherapy (55.8%) studies and 9 TLM (37.5%) studies could be included in the weighted averages. In T2 tumors treated with TLM, patients with involvement of the AC had a slightly higher 5-year LC rate than patients without involvement of the AC. In all the other groups, tumors with involvement of the AC resulted in a lower 5-year LC rate.

Table 3. Weighted averages for 5-year local control classified by tumor group

		n	T1	n	T2	n	T1-T2
Radiotherapy	AC+	1033	82.2	330	68.2	1140	78.2
	AC-	2064	89.1	202	75.7	1592	86.8
TLM	AC+	147	70.1	109	77.2	123	77.3
	AC-	429	89.1	68	75.1	165	91.1

Overall Survival, Disease Specific Survival, and Larynx Preservation

Four of the radiotherapy studies (11.8%) presented the 5-year OS [8,20,42,43]. The involvement of the AC did not have a statistically significant impact on any of these studies. Seven studies (20.6%) presented the 5-year DSS [8-10,16,20,35,38]. In two of these, the involvement of the AC had a statistically significant impact [10,38]. None of the radiotherapy studies presented the 5-year LP rates.

Ten of the TLM studies (41.7%) presented the 5-year OS [23,24,26,28,32,54,58,59,61,65]. The involvement of the AC had a statistically significant impact for one of these for patients with T1b and T2 tumors, but not for T1a tumors [23]. In seven studies, no significant impact was found [24,26,28,32,58,59,61], and in two studies, the impact on OS was not reported [23,54]. Six studies (25.0%) presented the 5-year DSS. Two of these studies showed a statistically significant impact of AC involvement on DSS [53,58], and three studies did not [3,26,59]. In one study, the impact of the AC was not reported [54]. Ten studies (41.7%) presented the 5-year LP rate. Six studies did not show a statistically significant impact of AC involvement on laryngeal preservation [3,26,53,56,59,64], whereas one study did [58]. In two studies, the impact of AC involvement on LP was not reported [23,28]. One study presented a binary approach (yes/no) as well as a more detailed classification. The first showed no significant impact on the AC, whereas the latest identified a significant impact on the involvement of the AC related to the amount of involvement of the AC [54].

DISCUSSION

Both radiotherapy and TLM are well–established treatment modalities for early glottic cancer involving the AC. Although it is widely acknowledged that involvement of the AC can have a negative impact on outcome, results reported in the literature on the impact of AC involvement have been inconsistent. In this review, we found that most studies - both for radiotherapy and TLM - do not report a significant impact of AC involvement on LC, OS, DSS, and LP.

Although the results and the manner of reporting in the included studies were too heterogeneous to perform a formal meta-analysis, we did calculate weighted averages for T1 and T2 tumors separately and for T1-T2 tumors together from the papers that provided 5-year LC rates for the tumors with or without the involvement of the AC. On this basis, only 19 radiotherapy (55.9%) studies and 9 TLM (37.5%) studies could be included in the weighted averages. These weighted averages showed that the involvement of the AC leads to a slightly higher recurrence rate after treatment with both RT and TLM. However, as stated, this is no formal meta-analysis, and, therefore, no definite conclusions can be drawn from these calculations. The varying results in the literature can be explained by variations in the clinical definition of the AC area, and in the detail of the clinical, endoscopic, and radiologic evaluation of the lesion in the preoperative setting, the distinctive features and limitations of each therapeutic modality, the biological behavior of the tumor, and variations in the rigor of the follow-up policy. Due to these factors, combined with the complicated anatomy of the AC, the involvement of this subsite may very well be too complex to be included as a simple binary variable (yes/no) as it is in most publications. To try to draw some conclusions from the existing literature, it is, therefore, necessary to take a closer look at the data of individual publications and at the definition of involvement of the AC. In 1996, Rucci et al. proposed a new staging system of the anterior commissure, as there was no consideration of the AC involvement

in the T stage of the TNM classification (Union for International Cancer Control-American Joint Committee on Cancer [66,67]). Rucci et al. classified the AC into four subgroups: AC0: patients without any involvement of the AC region; AC1: patients with involvement of the AC region on only one side of the midline, AC2: patients with involvement of the AC region that crosses the midline on only one part of the longitudinal extension of this region; AC3: patients with involvement of the whole AC region, on both sides of the midline [67]. They found that LC was significantly lower with the increase of the AC classification. They concluded that this AC classification was more reflective of prognosis than the TNM classification [67]. Since then, to our knowledge, every study utilizing this, or a similar classification of AC involvement into subgroups, has found a prognostic impact of increasing levels of AC involvement, with wider involvement leading to lower rates of LC or LP. Carta et al. did not show a statistically significant difference in LC rates between involvement and no involvement of the AC in patients with Tis–T2 tumors; however, they did find a statistically significant lower 5-year recurrence-free survival in the AC3 group when using Rucci et al.'s classification system. The AC3 group also showed a statistically lower 5-year LP rate [54]. Hoffmann et al. also found a significant difference in the 5-year disease-free survival in the AC3 group. However, they did not find a significant difference between the AC groups in terms of LP or DSS [59].

Recently, another classification was proposed by Piazza et al. [68]. They stratified six isoprognostic zones in early-intermediate tumors (T1–T3) treated with TLM according to the location and the extent of the tumor, describing different growth patterns and possible pathways of recurrence, and defined the role and limits of TLM as a single treatment modality. They concluded that the vertical extension across the AC leads to a decreased LC rate and lower LP rates in patients treated with TLM and that this location - with or without the involvement of the pre-epiglottic space (PES) - should be considered as a risk factor for TLM [68].

The classification of Piazza et al. regarding the AC is in line with earlier publications differentiating between the horizontal and vertical extension of the tumor [68]. In a recent review, Peretti et al. highlighted the importance of differentiating between tumors of the vocal cord affecting the AC in the horizontal plane against the vertical plane [69]. They defined several requirements when treating tumors involving the AC with TLM, such as complete exposure of the tumor, proper assessment tools with a suitable diagnostic workup, and having an experienced surgeon performing the procedure on this subsite of the larynx [69,70]. This is also suggested by the study of Vilaseca et al. [71], which investigated the impact on the AC involvement in patients with T1–T4a that were treated with TLM. They found that AC involvement was an independent factor for local recurrence. Half of their patients with recurrence were finally salvaged with TLM alone, suggesting that surgical experience could have played a role in local recurrence as a large proportion of patients were still amenable to TLM [71]. Tumors involving the AC and growing in the vertical plane are more difficult to expose due to a narrow angle, and the v-shaped

configuration of the thyroid cartilage [54]. Difficult or incomplete surgical exposure has a tendency toward incomplete resection [61], which can subsequently lead to a higher recurrence rate. Several authors argue that tumors with vertical extension to the supra– and/or subglottic areas have a higher risk of local failure due to their narrow relationship with, and therefore the risk of (minor)spread into, the underlying visceral spaces [2,3].

To the best of our knowledge, no studies that treated patients with radiotherapy have used detailed stratification of the involvement of the AC. Therefore, although AC involvement, particularly in the vertical plane, may be a risk factor in TLM, it may well be the same for other treatment modalities. More studies are needed to investigate these factors in other treatment modalities to ascertain the relative benefits of different approaches.

LIMITATIONS

The main limitation of this review is the heterogeneity of the studies that were included with regard to factors such as the clinical definition of the AC area, diagnostic protocols, and treatment protocols. Also, the majority of studies could not be included in the calculation of the weighted averages, as they did not present LC rates for patients with or without AC separately. Therefore, the weighted averages that were calculated should be interpreted with caution.

CONCLUSIONS

This review shows that the use of a binary variable (yes/no) for the involvement of the AC leads to conflicting results due to variability in definition, work-up, and treatment parameters of the AC area. However, weighted averages indicate that LC may be lower in tumors with involvement than tumors without involvement in the AC. Furthermore, all studies that use specific, detailed classifications of the AC show that there is a significant impact on outcome related to the amount of involvement of the AC. All in all, these findings point to a negative impact of AC involvement that may not be evident in simple binary (yes/no) studies of AC involvement. To further elucidate the role of the AC, detailed stratification of tumors involving the AC should be applied in future studies. To the best of our knowledge, no studies of patients treated with radiotherapy have used detailed stratification of the involvement of the AC. Therefore, to further elucidate the impact of AC involvement in these patients, stratifications need to be employed in these populations as well.

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Chapter 4

Evaluation of surgical margin status in patients with early glottic cancer (Tis-T2) treated with transoral CO_2 laser microsurgery

Martine Hendriksma
Marc W. Montagne
Ton P. M. Langeveld
Maud Veselic
Peter Paul G. van Benthem
Elisabeth V. Sjögren

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ABSTRACT

Purpose

To assess the impact of surgical margins status on local control in patients with primary early glottic (Tis-T2) squamous cell carcinoma after treatment with transoral CO_2 laser microsurgery (TLM) and to assess the significance of additional wound bed biopsies.

Methods

Patients with Tis-T2 tumours treated with TLM type I–III resections according to the European Laryngological Society classification between 2009 and 2013 were included in retrospective analysis. Recurrence rate was determined in patients with free versus non-free specimen margins and wound biopsies. Five-year survival rates were determined using the Kaplan–Meier method. Prognostic impact of pT-category, resection margin status, tumour differentiation, wound bed biopsy status, and number of biopsies on local control (LC) were tested with the log-rank test.

Results

Eighty-four patients were included in the analysis. Positive margins were seen in 68 patients (81.0%). Margin status after TLM did not significantly influence LC ($p = 0.489$), however, additional wound bed biopsies were significantly associated with lower LC ($p = 0.009$). Five-year LC, disease-specific survival, overall survival and laryngeal preservation were 78.6, 78.0, 98.6 and 100%, respectively.

Conclusions

Additional wound bed biopsies can help predict local recurrence in patients treated with TLM for early glottic carcinoma. We propose that there is enough evidence to support a wait-and-see policy in patients with positive specimen margins and negative wound bed biopsies. For patients with positive wound bed biopsies, further treatment is warranted.

INTRODUCTION

Early glottic cancer (Tis-T2) is a highly treatable disease with high local control rates (LC), for treatment with either transoral CO_2 laser microsurgery (TLM) or radiotherapy (RT). Several studies did not identify significant differences in local control between TLM and RT for Tis-T2 tumours [1-6].

To assess elimination of cancerous cells after TLM, pathologic evaluation of the surgical specimen is common practice. The aim in early glottic carcinoma is to perform a narrow margin resection in order to preserve as much tissue as possible to maximize preservation of laryngeal functions [7-9]. The surgical margins ideally should be free of neoplastic cells, with a layer of healthy cells surrounding the excised tumour.

It is commonly acknowledged that the assessment and interpretation of surgical margins in TLM have some issues. First of all the use of laser leads to the evaporation of tissue and charring of the specimen thus demolishing the actual surgical margin by approximately 0.05–0.5 mm [8, 10, 11]. Therefore, it is not uncommon to find close or positive margins during final pathology examination [7, 12]. Currently, literature still shows no clear definition of negative, close or positive surgical margins [13] and recommendations for free margins vary from 0.5 to 2 mm [7, 8, 10, 11, 14-17]. Moreover, controversy remains over the interpretation of surgical margins because of difficulties with orientation after piecemealing, the small size of the specimens, tissue retraction as a result of thermal energy on elastic fibres, thermal damage, and charring. Furthermore, fixation of tissue induces shrinkage, which also has to be taken into account on pathologic evaluation.

In literature, some studies conclude that positive margins have a negative impact on oncological outcome [14, 18, 19, 20] and patients should thus be retreated. However, others conclude that positive margins have no influence on local control [8, 10, 11, 16]. Therefore, the best management of close or positive margins has not been clearly determined [13] although it has been shown that mandatory retreatment could lead to unnecessary additional treatment in up to 84% of these patients [11]. Therefore, a wait-and-see policy could also be considered appropriate restricting the number of needless procedures performed [10]. According to the latest ELS recommendation for follow-up of laryngeal cancer, a second-look microsurgery is however mandatory in cases of positive surgical margins [21]. Nonetheless, some authors suggest that a second-look is not required in all patients and propose that with experience and good clinical judgement a philosophy of watch and wait is also appropriate [22]. Therefore, the role of second-look microsurgery is still debatable.

Other techniques that can be used to improve surgical margins assessment are frozen section analysis, optical and molecular imaging techniques of which narrow-band imaging (NBI) is the

most widely implemented, and wound bed biopsies. Frozen section analysis is a reliable, cost-effective method preventing routine second-look procedures [7, 23], although it does require extra operating time for every patient. Furthermore, intraoperative NBI can help in better defining surgical margins and reduce positive surgical margins, although this technique is only helpful for the mucosal plane [24, 25]. For the past years, in an attempt to obtain more certainty about the radicality of our resections while not extending operating time, we have used additional wound bed biopsies in our institution to guide further management. Therefore, the objective of this study was to assess the impact of surgical margins status on local control in patients with primary early glottic (Tis-T2) squamous cell carcinoma (SCC) after treatment with TLM and to assess the significance of wound bed biopsies.

MATERIAL AND METHODS

Records of all patients treated for early glottic cancer (Tis-T2) at the Leiden University Medical Centre (LUMC) between January 2009 and December 2013 were retrieved. Early glottic cancer was defined as tumour stage Tis, T1a, T1b or T2 with a fully mobile vocal fold without lymph node involvement or metastasis (N0M0) at the start of treatment. The medical charts of these patients were retrospectively assessed and patients receiving TLM with a curative intent were included. Patients with previous laryngeal cancer or other treatments were excluded. Data on patient demographics, pathologic T-category, follow-up, additional treatments and patient outcomes were collected. Pathology reports were assessed for: status of the resection margin, tumour differentiation, additional wound bed biopsy status, and number of biopsies.

Before TLM, all but 15 patients were staged by endoscopy and had biopsy-proven SCC. Two patients had frozen section analysis during their first endoscopy and thirteen patients were clinically suspicious. All these patients had TLM in the same session. TLM was carried out under general anaesthesia using a Sharplan laser with a digital acublade micromanipulator typically set in continuous or continuous superpulse mode. In most cases, the tumour was first transected to assess the depth of tumour invasion and then resected in two pieces. Resections varied from type I to type III of the European Laryngological Society (ELS) classification, as during the study period tumours requiring larger resections were treated by RT according to Dutch guidelines. Tumour specimens were pinned on a piece of cork and were sent to the pathologist for histological examination accompanied by descriptive drawings. In most cases standard practice was followed and additional wound bed biopsies were taken and contained separately. Typically, the wound bed biopsies were taken at five different points: four at the edges of the tumour ground and one deep biopsy in the middle of the tumour ground. If surgeons found it necessary, extra biopsies could be taken.

For the sake of this study pathological specimens and pathology reports were reviewed by the pathologist (MV). We defined surgical margin status as follows: not free if SCC or severe dysplasia was found in the margins, free if no SCC or severe dysplasia was found in the margins or not assessable if the assessment was impossible due to artefacts made either during or after surgery. We defined the wound bed biopsy status as follows: a positive biopsy was defined as one or more biopsies containing SCC or severe dysplasia; negative biopsies contained no SCC or severe dysplasia tissue, but could contain mild or moderate dysplasia; not taken meant that in that operation, no wound bed biopsies were taken.

Generally, the patients were discharged on the same day of surgery. All patients were followed according to protocol with flexible fiberoptic laryngoscopy scheduled every 2 months in the first year and with decreasing frequency afterwards until 5 years. In case of positive margins or wound biopsies, a second-look procedure or re-resection could be planned or regular follow-up was scheduled depending largely on the surgeon's clinical evaluation of the procedure.

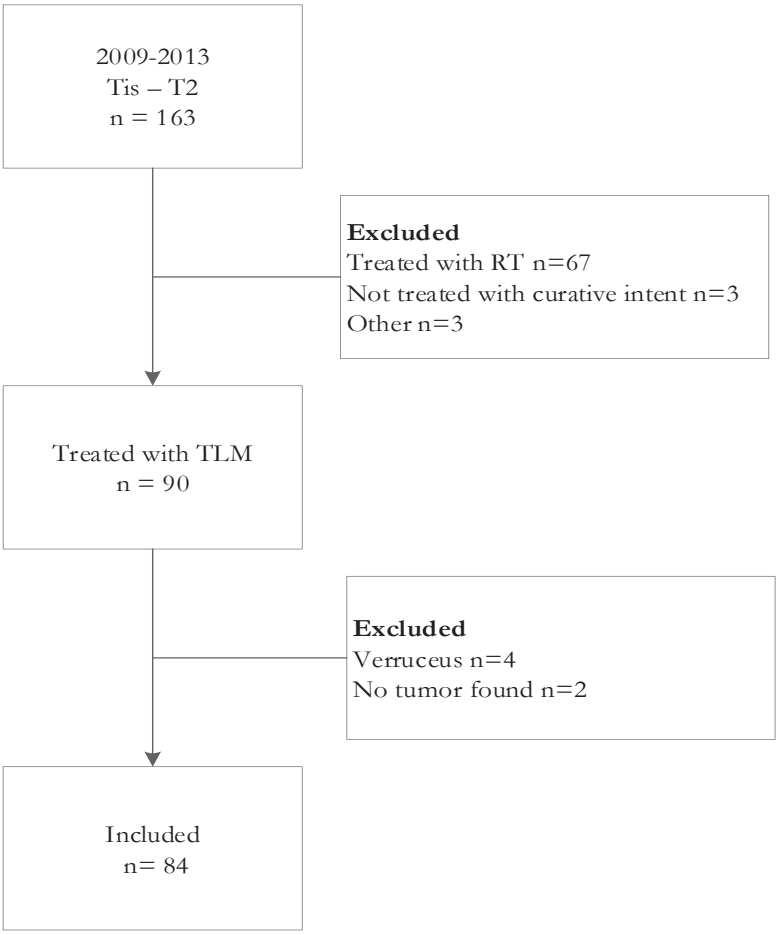
Statistical methods

Statistical analysis was performed with SPSS version 23.0 (Armonk, NY: IBM Corp.). Categorical variables were described using frequency and percentages. Means and standard deviations were reported for descriptive statistics. The entry point was the date of TLM. The endpoint for local control (LC) was the date of the first local recurrence. The endpoint for disease-specific survival (DSS) was the date of death, due to laryngeal cancer. Patients who died of unrelated or unknown causes were considered as without recurrence at the date of death. The endpoint for overall survival (OS) was to the date of death (all causes) or last follow-up. The endpoint for laryngeal preservation (LP) was the date of laryngectomy. Observations were censored at 60 months. Median follow-up was calculated with the reverse Kaplan–Meier method and given with the 95% CI. Survival analysis was performed with the Kaplan–Meier method to calculate LC, DSS, OS, and LP. The prognostic value of five categorical variables (pT-category, resection margin, tumour differentiation, additional wound bed biopsy results, and biopsy count) on local control was tested by univariate analysis with the log-rank test. For the pT-category, T1a and T1b are grouped, because the group with T1b tumours was too small. A p-value of < 0.05 was considered statically significant.

RESULTS

Between 2009 and 2013, 163 consecutive patients suffering from early glottic carcinoma (Tis-T2N0M0) with mobile vocal folds, were treated with either TLM or RT at our centre. Of these, 90 cases were primarily treated with TLM with curative intent. The remaining 73 patients were excluded; 67 of them were primarily treated with radiotherapy, 3 received TLM but without curative intent (debulking as part of overall curative treatment), 1 patient had microlaryngeal surgery without laser, and 1 patient had a laryngectomy performed because of a history of

Figure 1. Flow-diagram



Abbreviations: RT = radiotherapy, TLM = transoral laser microsurgery

another primary glottic carcinoma treated with RT. Finally, one patient underwent laser surgery in spite of the protocol suggesting laryngectomy, in an attempt to preserve the larynx. This patient had a history of RT for oropharyngeal cancer, and the lesion normally would have been considered too advanced for TLM. Eventually, cancer recurred with laryngectomy as a result after all. Out of the 90 patients treated with curative intent with TLM, 4 cases were excluded on the basis of histology (verrucous carcinoma) and in 2 cases no malignancy was found. Eighty-four cases were therefore included in this study (Figure 1). One patient developed a second primary early glottic carcinoma (stage T1a on the contralateral vocal fold) in the timespan of this study and was therefore included twice. Patients' demographics are listed in Table 1. Median follow-up was 53.0 months (95% CI 50.3–55.7 months). Three patients were lost to follow-up after

Table 1. Baseline characteristics

Characteristics	No. of cases (%) Total = 84 (100%)
Mean age at surgery (SD)	68.7 (9.3)
Sex	
Male	75 (89.3)
Female	9 (10.7)
Pathologic T category	
Tis	19 (22.6)
T1a	45 (53.5)
T1b	5 (6.0)
T2	15 (17.9)
Surgical margin status	
Not Free	68 (81.0)
Free	16 (19.0)
Wound bed biopsies	
Positive	12 (14.3)
Negative	55 (65.4)
Not taken	17 (20.2)

40.3 months and one patient moved after 51 months and had regular follow-up elsewhere. All patients had assessable surgical margins.

Surgical margins

The surgical margins were negative in 16 patients (19.0%). None of these patients underwent further treatment. Two patients with negative surgical margins (12.5%) developed local recurrence. Surgical margins were positive in 68 patients (81.0%). In this group, 12 patients (17.6%) had second-look microsurgery with re-excision. Only 3 patients (25.0%) showed evidence of persistent carcinoma after this re-excision. None of the patients were treated with RT because of positive margins. Overall, 14 patients with positive margins (20.6%) developed a local recurrence (Table 1).

Wound bed biopsies

In 67 patients additional wound bed biopsies were taken, with a mean of 4.3 (SD 3.2) biopsies per person. In 17 patients (20.2%) no additional wound bed biopsies were taken. The wound bed biopsies were negative in 55 patients (82.1%) (Table 1). Seven patients (12.7%) with negative wound biopsies developed a recurrence. The wound bed biopsies were positive in 12 patients (17.9%). All these patients had both mucosal and deep biopsies, of which in 11 patients superficial biopsies were positive and in 1 patient a deep biopsy was positive. Four of these patients underwent re-excision without showing evidence of residual disease. None of the patients with positive wound bed biopsies were treated with RT. Overall, 5 patients (41.7%) with

positive wound bed biopsies developed local recurrence of whom 2 had undergone a re-resection. In the patients without additional wound bed biopsies, 4 patients developed recurrent disease (23.5%). In patients of this group with re-resections, 2 patients (50%) developed recurrent disease nonetheless.

Survival

During follow-up, 16 patients developed a local recurrence (19.0%), after a median of 5.0 months (95% CI 2.4–7.6 months). Five patients (31.3%) were treated with TLM again, 8 patients (50.0%) received RT, 2 patients (12.5%) received TLM plus RT and 1 patient (6.3%) required a total laryngectomy, but refused this treatment and was therefore treated with supportive care. Three patients developed a second local recurrence after a median of 9 months (95% CI 0.0–20.2 months). Two of them were once more treated with TLM and the other patient received RT. No patients developed metastasis or regional lymph nodes. During follow-up, 22 patients (26.2%) died, 21 due to unrelated causes with no evidence of locoregional glottic disease and one due to laryngeal cancer. This was the patient who refused to undergo laryngectomy. The larynx was therefore preserved in all the 84 patients (100%).

The 5-year LC, OS, DSS and LP are 78.6, 78.0, 98.6, and 100%, respectively. In univariate analysis, positive wound bed biopsy was the only factor with significant impact on local control with a lower rate of local control for patients with wound bed biopsies positive for SCC (50 vs 88.2%, p = 0.009) (Table 2; Figure 2). Resection margin status had no impact on local control (76.9 vs 85.9%, p = 0.469) (Table 2). The three other variables (pT-category, tumour differentiation, and number of biopsies) also had no impact on local control (Table 2).

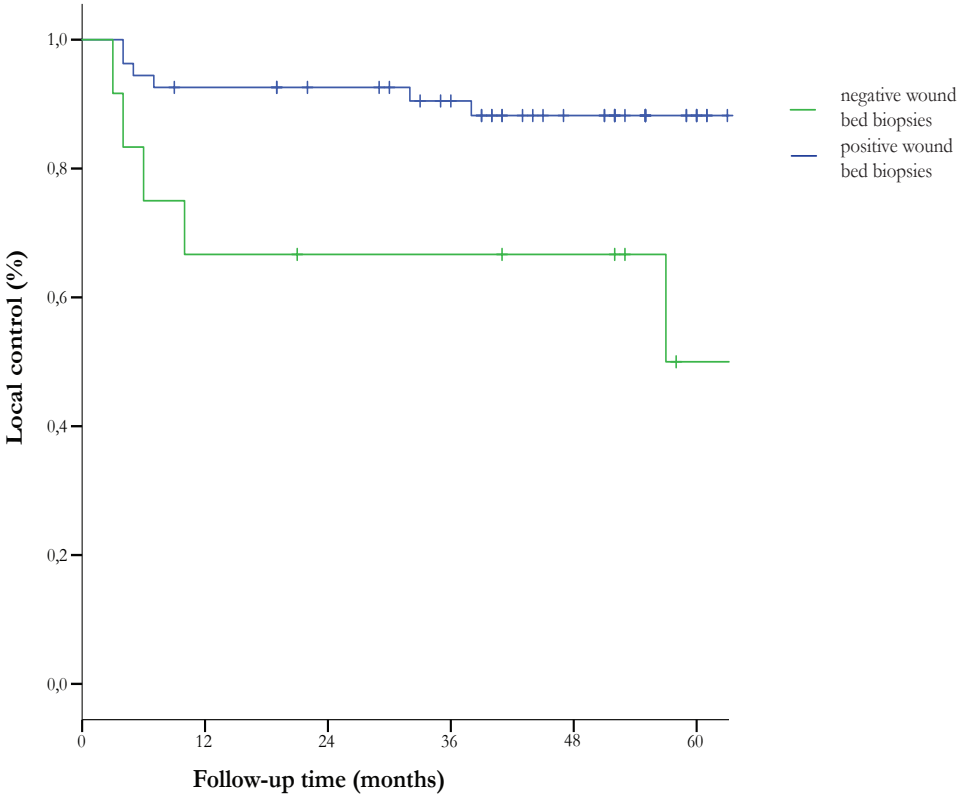
Table 2. Univariate survival analysis for prognostic factors on local control

Variable	No. of patients	5-year local control (%)	p-value*
Pathologic T category			.543
Tis	19	78.9	
T1	50	80.4	
T2	15	70.0	
Resection margin			.489
Not free	68	76.9	
Free	16	85.9	
Tumor differentiation			.654
Poor	7	77.6	
Moderate	34	80.9	
Good	28	71.4	
Biopsy count			.323
≤ 5	49	73.8	
≥ 6	35	84.5	

Variable	No. of patients	5-year local control (%)	p-value*
Additional wound bed biopsies			.009
Negative	54	88.2	
Positive	12	50.0	
Biopsy count			.323
≤ 5	49	73.8	
≥ 6	35	84.5	

** Calculated with the log-rank test*

Figure 2. Kaplan Meier curve for local control in relation to wound bed biopsies



DISCUSSION

The objective of this study was to assess the impact of surgical margins and wound bed biopsies on local control in patients with early glottic cancer (Tis-T2) after treatment with TLM. In this study, margin status after TLM did not significantly influence local control. However, we found that when additional biopsies of the wound bed were positive for SCC, local control was significantly lower in these patients.

Studies on the role of surgical margins in predicting local control after TLM in early glottic carcinoma vary greatly in their recommendations. While some authors recommend re-treatment once positive margins are found [14, 26], other authors agree on the statement that instead of solely assessing margin status, the surgeon's clinical judgment should be incorporated [10, 22, 27].

Perioperative evaluation of the radicality of the procedure by an experienced surgeon is considered an essential factor in decision-making by them. Sigston et al. [11] advocated a 'wait and see' policy, to avoid a large number of unnecessary procedures, pointing out that because of the readily accessible location of glottic cancers, qualitative visual follow-up is adequate for monitoring patients with early lesions. In moderately advanced lesions, however, periodical imaging should be added for early detection of submucosal recurrence [28]. Moreover, as the glottic area reveals symptoms earlier than other areas, enabling earlier detection by patients themselves they will visit their physicians outside the protocol if they experience symptoms. Later authors have also adopted this point of view [10, 22, 29]. In line with these aforementioned arguments, if following a wait-and-see policy, it is necessary to have compliant patients who will be available for follow-up by rigid or flexible endoscopy with stroboscopy combined with additional imaging techniques, such as narrow-band imaging. However, the ELS recommends second-look microsurgery in case of positive margins at histopathological assessment [21].

In our experience, however, there are some issues with routine second-look procedures. Firstly, during the healing stage of the vocal fold which takes up to 3 months evaluation is often compounded by wound debris, granuloma formation, and vulnerable mucosa. Once the mucosa is healed, in our experience flexible laryngoscopy with modern chip-on-tip cameras and now additional tools such as NBI closely matches the information gained during direct endoscopy. Palpation is missed, but in our experience, this is not entirely reliable and it is doubtful if a small submucosal residue will be detected at such an early stage. Also, in moderately advanced carcinomas where submucosal recurrence is more frequent imaging should be the primary modality for early detection or recurrences. Secondly, routine second-look procedures for positive surgical margin would lead to a significant number of unnecessary procedures under general anaesthesia, particularly in a population that is often affected by comorbidities. Therefore, based

on our results and aforementioned arguments, we prefer a wait-and-see policy in case of positive surgical margins, with second-look procedures only on a case-by-case basis, depending on the surgeon's evaluation of the procedure and possible healing abnormalities of the vocal fold and to add periodical imaging for early detection of submucosal recurrence in extended resections (type III or more) or on indication.

Since the surgical margins are carbonized after TLM, it is difficult to distinguish between positive and suspicious margins and in contrast to other studies we grouped suspicious and positive margins together and reported them as not free. This approach has also been reported by several other authors [30, 31]. The handling of surgical margins should be taken into consideration when comparing results with literature because the definition of positive and negative surgical margins varies between studies. Remarkably, 81.0% of the surgical margins were positive (or suspicious) in this study, while in the literature the rate of suspicious or positive margins on final examination ranged from 6 to 50% [12]. There may be several explanations for this. Although all specimens were reviewed for this study, they were scored in a binary way (positive or suspicions versus clearly negative). This binary scoring could be one of the reasons that we present higher percentages of (possibly) positive margins.

Another reason could be that in the earlier years of the study some tumours were operated with a wider spot diameter (0.7 mm). In addition to the well-known problems of shrinkage and carbonization this could have further eroded the margin without compromising the radicality of the resection. Furthermore, we cannot exclude a local variation in evaluation protocol having led to this result, and finally we cannot exclude that the pathologist reviewing the samples may have been the particularly meticulous knowing that the results would be analysed for a study. Despite the high rate of positive margins, our data are in line with the literature, showing that positive margins have no impact on local control [8, 10, 11, 16].

To our knowledge, additional wound bed biopsies are not commonly performed. Some authors rightfully claim that sampling error can occur leading to false-negative results [16, 32]. However, seeing the results of this study, it is our opinion that although not a guarantee of a radical resection wound bed biopsies can help distinguish those patients at risk for recurrent disease whilst significantly lowering the number of unnecessary procedures that would result from routine re-resections of positive surgical margins.

To the best of our knowledge, there are only a few studies that have performed peroperative additional biopsies [17, 19]. In contrast with our study, Charbonnier et al. carried out additional biopsies when margins were clinically suspicious during the procedure. However, these biopsies were not routine and they also grouped positive additional biopsies with positive margins. Therefore, the prognostic value of their additional biopsies was not independently analysed

[19]. Manola et al. performed wound bed biopsies but again, only when the margins were macroscopically positive or uncertain. In our study, additional biopsies were the best predictor of local control. However, not in all patients, additional biopsies were performed.

The 5-year LC for Tis, T1, and T2 in our study was 78.9, 80.4, and 70.0%, respectively. These rates are comparable with large series in literature, although the 5-year LC for T1 tumours is in the lower range [33]. A detailed analysis of our local control rates showed that the higher percentage of recurrence is related to a learning curve. The proportion of recurrences for the two senior laryngologists performing 92.9% of the procedures was 15.4%. The remaining 7.1% of procedures were performed by various less experienced surgeons and had a recurrence rate of 66.6% which had some impact on our overall 5-year rate of local control.

This study, therefore, confirms earlier reports of the importance of the learning curve in TLM [34, 35]. In addition, not all patients with positive wound bed biopsies underwent a re-excision. It also seems that although no evidence of persistent carcinoma was found, the re-excisions were not always extensive enough. With this knowledge, we now perform more extensive re-resections in patients with positive wound bed biopsies. Our 5-year overall survival of 78.0% was slightly lower than in some other series in literature [26,36]. This combined with the fact that four patients were lost to follow-up may also have had some small impact on our rate of local control as there were fewer life years included in the analysis.

Most recurrences (75%) were found within the first year, pointing out the importance of extensive follow-up and extra level of awareness in the first year after surgery. The majority of the recurrences in our study were treated with TLM, RT or TLM and RT. No laryngectomies were performed in case of recurrent disease. The only patient in whom this was indicated refused to undergo further treatment. This shows that if follow-up is carried out efficiently and recurrent tumours are treated in time, laryngectomy rate is low. The 5-year DSS and LP were in accordance with literature [24].

Due to the retrospective study design, this study has some limitations. First, although it was standard protocol, not all patients had additional wound bed biopsies taken during surgery due to several reasons. In some cases, surgeons were relatively certain of free surgical margins based on clinical evaluation and in some cases, the tumour was suspect for laryngeal papilloma. In three cases no cause was mentioned.

In summary, this study shows that additional wound bed biopsies can help predict recurrence after TLM for early glottic carcinoma in which ELS type I–III resection are performed and can help identify those patients where additional treatment is indicated. Looking at literature and at our own results, there is evidence to support a ‘wait and see’ policy in patients with

positive surgical margins if the perioperative findings of an experienced surgeon as well as close follow-up are incorporated, although this conclusion has to be confirmed in additional studies in other, larger patients populations. This is further supported by the finding that treatment for recurrent disease in our population was highly successful and laryngectomy was indicated in only one patient (1.2%). For patients with positive wound bed biopsies, we strongly recommend considering additional treatment in the form of re-excision with TLM or RT as the chance of a recurrence is high (50%).

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Chapter 5

Quality of life and voice outcome of patients treated with transoral CO_2 laser microsurgery for early glottic carcinoma (T1-T2): a 2 year follow-up study

Martine Hendriksma
Ydje van Loon
W. Martin C. Klop
Marieke M. Hakkesteegt
Bas J. Heijnen
Ibtissam el Hasnaoui
Martin A. de Jong
Ton P.M. Langeveld
Peter Paul G. van Benthem
Rob J. Baatenburg de Jong
Elisabeth V. Sjögren

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ABSTRACT

Purpose

Longitudinal studies in laryngeal cancer can provide clinicians information about short-term and long-term functional outcomes, like quality of life (QoL) and voice outcome. This information is important when counseling patients or choosing a primary treatment modality. The present study assessed long-term (2 years) QoL and voice outcome in patients with extended T1 and limited T2 glottic carcinoma treated with transoral CO_2 laser microsurgery (TLM) (unilateral type III or bilateral type II resections).

Methods

Three questionnaires were administered: the Voice Handicap Index (VHI), the European Organization for Research and Treatment of Cancer (EORTC) QoL questionnaire (QLQ)-C30, the EORTC QLQ-HN35. A perceptual voice evaluation at six different time points was conducted: preoperatively, and postoperatively at 6 weeks, 3 months, 6 months, 1 year, and 2 years. Fluctuations over time were investigated.

Results

Sixty-one patients were included in the analysis. Patients reported high-level functioning and low symptom scores 2 years postoperatively. Gender significantly affected the VHI scores at 2 years (mean VHI scores: female 8.7 vs. male, 23.9; $p = 0.023$). The major improvement in VHI scores was observed within the first 6 months. The tumor stage (T1a, T1b, and T2) significantly impacted the grade (mean scores at 2 years: 1.0, 1.9, and 1.7; $p = 0.001$). These scores stabilized at 6 months.

Conclusions

Patients show good long-term QoL with low symptom scores, a low voice handicap, and mild to moderate dysphonia, 2 years postoperatively. Scores stabilize at 6 months and provide a clear indication of status at 1 and 2 years.

INTRODUCTION

Early glottic carcinoma (Tis-T2) can be treated effectively with radiotherapy or transoral CO_2 laser microsurgery (TLM). According to the Dutch Guidelines for laryngeal carcinoma, TLM is the advocated treatment for superficial midcord T1a glottic carcinoma, and radiotherapy is indicated for more extended T1 and T2 glottic carcinomas [1]. Studies have shown that both therapies provided good, comparable oncological results [2-4], but some studies show superior laryngeal preservation after TLM [5-8]. There is less data on the functional outcomes of these treatment modalities, such as quality of life (QoL) and voice outcome, particularly in patients with T2 glottic carcinoma [7]. The lack of these data often prohibits adequate comparisons of modalities in patient counseling.

Although oncological results play a highly significant role in selecting the treatment modality, functional outcomes are also important when determining the patient's treatment preferences. Each treatment modality has different side effects, and patients may have different preferences regarding the trade-offs. Therefore, treatment decisions for early glottic carcinoma should be based on both oncological and functional outcomes including patients' preferences.

Several studies have investigated QoL in patients with early glottic carcinoma after treatment with radiotherapy or TLM [9-13]. Most have reported good postoperative QoL scores that were either the same or better than preoperative scores. A questionnaire that is often used and has a well-proven method to measure QoL in cancer patients is the European Organization for Research and Treatment of Cancer (EORTC) QoL questionnaire (QLQ)-C30, which is a general questionnaire. This can be complemented with the specific head and neck cancer module, the EORTC QLQ-HN35. Both questionnaires ask the patient to rate their problems associated with their tumor and subsequent treatment and to reflect on their QoL. Voice outcome has also been studied in early glottic carcinoma after treatment with either radiotherapy or TLM. These studies showed that voice outcome improved significantly postoperatively after the treatment of Tis-T1a tumors (radiotherapy and TLM) or after limited resections (types I–II) (TLM) [12, 14, 15].

When the voice changes, it often affects patient's self-perception, as well as how others perceive their voice. Although many acoustic and aerodynamic parameters can be determined, these perceptive changes, such as dysphonia in the form of hoarseness or breathiness and an increase in vocal effort, are often the most fundamental to the patients and their surroundings. Therefore, measures of voice outcome that are often used in the clinical setting are self-assessment tools such as the Voice Handicap Index (VHI) and perceptual evaluation tools, such as the GRBAS rating scale.

Both QoL and voice outcomes may vary, mainly depending on the timing of the evaluation [16].

Most prospective studies have reported preoperative and 3- to 12-month postoperative functional outcomes; in contrast, cross-sectional studies have only reported postoperative results, with large variations in time frames. The advantage of longitudinal studies is that they can assess changes over time and determine when a stable condition is achieved. This information can support clinicians in counseling patients about their long-term expectations, an essential component of a well-informed treatment decision. In light of these findings, and due to the lack of long-term functional outcome data, the present study aimed to (1) assess long-term (2-year) results of QoL and voice outcome in patients treated with TLM for extended T1 and limited T2 glottic tumors and (2) investigate fluctuations over time, based on prospectively collected data.

METHODS AND MATERIALS

Patients

From December 2009 to March 2015, this non-randomized, prospective, longitudinal outcome study was conducted at the University Cancer Center, Leiden, The Hague, the Erasmus Medical Center, and The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital in The Netherlands. Included patients were those with extended T1N0 and limited T2N0 glottic carcinomas, which would require a unilateral transmuscular resection [European Laryngological Society (ELS) classification [17] type III] or a bilateral subligamental resection (type II), if treated surgically. All patients with lesions that met these criteria were offered a treatment choice between TLM and radiotherapy. Patients made their choice after comprehensive counseling (described elsewhere in detail by van Loon et al. [18]). After stroboscopy, the definite tumor stage was determined endoscopically under general anesthesia. Patients that met the inclusion criteria after endoscopy were enrolled in the study at that time. In case of T1b tumors, some procedures were staged to prevent web formation. The QoL and voice outcome were assessed with patient self-report questionnaires and perceptual voice analyses conducted at various time points during follow-up. The study was approved by the local Medical Ethics Committees at all three hospitals. Informed consent was obtained from all patients before inclusion into the study.

Questionnaires

We implemented three self-administered, validated questionnaires: the VHI-30 [19], the EORTC QLQ-C30 version 3 [20], and the EORTC QLQ-HN35 [21]. Each was assessed at six different time points: preoperatively, and postoperatively, at 6 weeks, 3 months, 6 months, 1 year, and 2 years. Patients were asked to complete the questionnaires unaided during their visit to the outpatient clinic.

Voice Handicap Index

The Dutch version of the VHI is a validated 30-item questionnaire. It measures the psychosocial effects of voice impairments in daily life. Patients score each item by selecting a response from a

five-point Likert scale, which ranges from 0 to 4 (0 = never, 4 = always). The sum of scores results in a total VHI score, which ranges from 0 to 120. A higher score indicates a worse voice-related outcome [19, 22]. A difference of ten points or more has been shown to be clinically relevant [23].

EORTC QLQ-C30

The EORTC-QLQ-C30 evaluates health-related QoL for the general population of patients with cancer. This questionnaire comprises 30 questions that address patient function and symptomatology over the preceding week. The questionnaire includes a global health status scale, five functional scales (physical, role, emotional, cognitive, and social), three multi-item symptom scales (fatigue, pain, and nausea and vomiting), and six single items that assess additional symptoms in patients with cancer (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Patients score each item by selecting a response from a four-point Likert scale from 1 (not at all) to 4 (very much), except for the global health status, which is scored from 1 (very poor) to 7 (excellent). These scores are transformed to a scale of 0–100. A higher score represents a higher (better) level of functioning or a higher (worse) level of symptoms [20]. A difference of ten points has been shown to be clinically relevant [24, 25].

EORTC QLQ-HN35

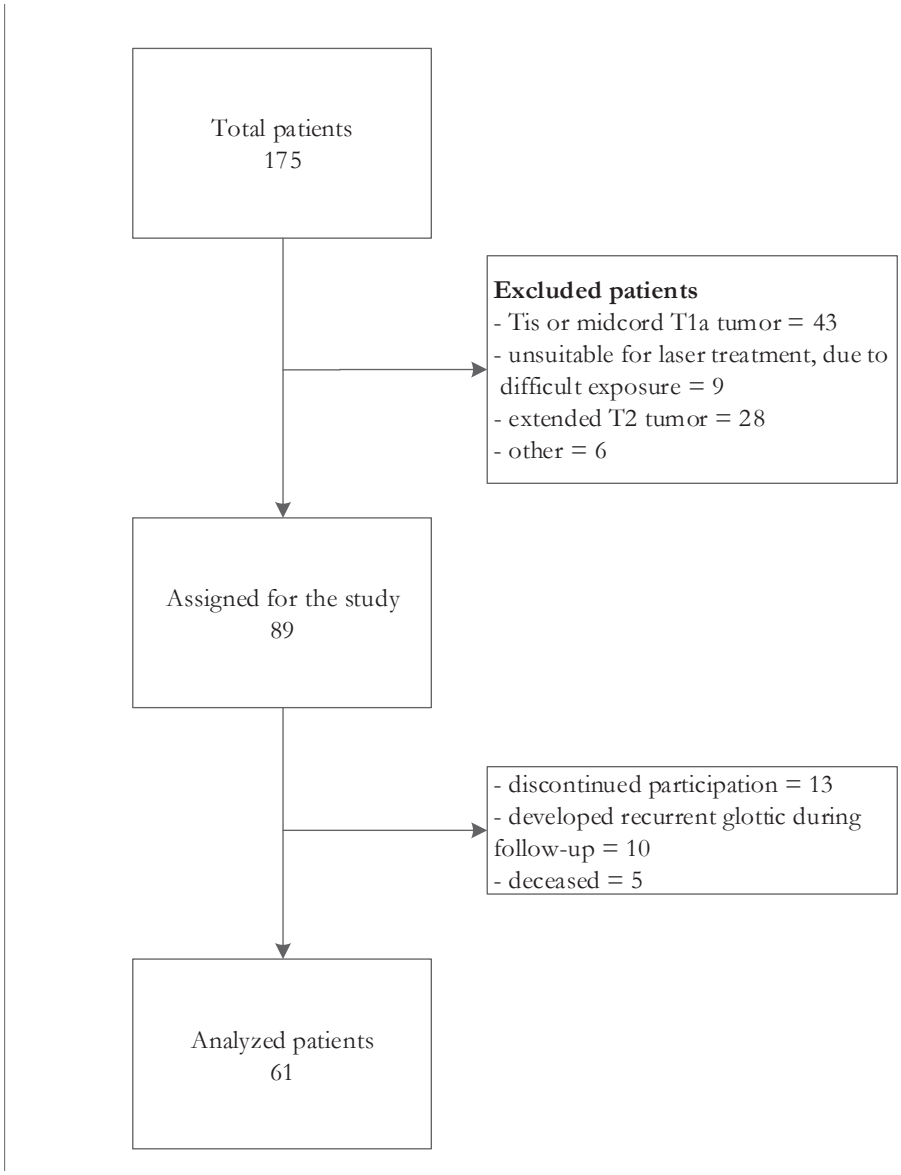
The EORTC QLQ-HN35 evaluates health-related QoL for patients with head and neck cancer. It is often used to complement the EORTC QLQ-C30. This questionnaire contains 35 questions that address symptoms and side effects of treatment, social function, and body image/sexuality. The questionnaire incorporates 7 multi-item scales: pain, swallowing, senses (taste and smell), speech, social eating, social contact, and sexuality; and 11 single items: teeth, opening mouth, dry mouth, sticky saliva, coughing, feeling ill, use of analgesics, nutritional supplements, feeding tube, weight loss, and weight gain. Each item is evaluated by selecting a response from a four-point Likert scale, the same as the scales used for the EORTC QLQ-C30. The final scores are transformed to a scale of 0–100. A higher score represents more severe problems or symptoms [21, 26]. A change of ten points has been shown to be clinically relevant [26].

Perceptual evaluation and voice recording

Perceptual evaluation was performed with the GRBAS rating scale on a 30-s running speech sample. Recordings were acquired at a sampling frequency of 44.1 kHz with a dual microphone headset recorder (Alphatron Medical Systems) and a Beyer dynamic microphone, in a noise-free environment. The speech sample consisted of a standard, phonetically balanced Dutch text, “80 dappere fietsers” [80 brave cyclists]. The GRBAS rating scale consisted of five scales (grade, roughness, breathiness, asthenia, and strain), of which only the grade of dysphonia was rated because it reflects the overall degree of hoarseness or the severity of the voice abnormality [27]. Each sample was scored on a scale of 0 (normal voice) to 3 (severe dysphonic voice), and a higher

score represented a more dysphonic voice [28]. A panel of four experienced listeners consisting of three speech–language pathologist and one ENT surgeon/laryngologist, all specialized in both oncological and benign voice pathology and treatment (B.J.H., M.M.H., V.A.H. vdK., E.V.S.),and blinded to all data scored the grade of dysphonia. In those cases where the experts rated the voice differently, consensus was reached through re-evaluation of the speech sample and discussion. The interrater reliability of our experts was of 0.91 (95% CI 0.89–0.93).

Figure 1. Flow diagram of patients selection for the study



Statistical methods

Statistical analyses were performed with SPSS version 23.0 (IBM Corp, Armonk, NY, USA). Assumptions of normality were assessed. The effect of time on the different questionnaires was assessed with the linear mixed model analysis; the model was adjusted for four possible confounders: gender, tumor stage, type of resection (unilateral type III vs. bilateral type II), and involvement of the anterior commissure (AC; no involvement vs. unilateral or bilateral involvement). Additionally, the least significant difference (LSD) post hoc test was used to adjust for multiple comparisons. The linear mixed model method was chosen, since it applies a correction for missing data. This correction is based on the observed data, and it uses all available information, without the need to censure an entire set of patient data, when one or more data points are missing or the need for imputation of measurements [29]. A p value of 0.05 was considered statistically significant.

RESULTS

Patients

One hundred and seventy-five patients with suspected or proven extended T1 and limited T2 glottic tumors were identified as candidates for the study. Of these, 89 were suitable for inclusion, based on endoscopy. Of these, 13 patients were lost to follow-up or discontinued participation in the first 3 months of the study. During the 2 years of follow-up, five patients died, due to unrelated causes, and ten patients developed recurrent disease. Thus, the final cohort comprised 61 patients for analysis (Figure 1). The baseline characteristics of these patients are presented in Table 1.

Table 1. Baseline characteristics

Characteristics	Number of patients (%) Total = 61 (100%)
Mean age at surgery, y (SD)	67.6 (8.90)
Gender	
Male	51 (83.6)
Female	10 (16.4)
Tumor stage	
T1a	29 (47.5)
T1b	19 (31.1)
T2	13 (21.3)
Resection (ELS classification)	
type III	38 (62.3)
type II bilateral	23 (37.7)
AC involvement	
No	12 (19.7)
Unilateral	26 (42.6)
Bilateral	23 (37.7)

Abbreviations; AC: anterior commissure, ELS: European Laryngological Society, SD: standard deviation, y: year

Table 2. Voice handicap index and perceptual evaluation results

Groups	Pre Mean	6 weeks Mean (Δ)	3 months Mean (Δ)	6 months Mean (Δ)	1 year Mean (Δ)	2 year Mean (Δ)	p-value
Voice Handicap Index							
Overall (n=61)	30.5	30.7 (0.23)	27.0 (-3.5)	23.3 (-7.2)	23.8 (-6.7)	21.8 (-8.7)	0.003
Male (n=51)	31.8	33.1 (1.3)	28.8 (-3.0)	25.7 (-6.0)	24.8 (-6.9)	23.9 (-7.9)	<0.001
Female (n=10)	24.0	18.5 (5.5)	17.8 (-6.2)	10.4 (13.6)	18.9 (-5.1)	8.7 (-15.3)	0.111
Perceptual evaluation - grade							
Overall (n=61)	1.5	1.9 (0.41)	1.6 (0.11)	1.4 (-0.11)	1.3 (-0.20)	1.4 (-0.05)	<0.001
T1a (n=29)	1.3	1.6 (0.32)	1.2 (-0.09)	1.1 (-0.17)	1.1 (-0.19)	1.0 (-0.29)	0.027
T1b (n=19)	1.8	2.4 (0.69)	2.1 (0.34)	1.7 (-0.08)	1.7 (-0.03)	1.9 (-0.15)	0.003
T2 (n=13)	1.7	1.9 (0.23)	1.8 (0.08)	1.6 (-0.07)	1.3 (-0.39)	1.7 (-0.01)	0.198
Male (n=51)	1.5	2.0 (0.48)	1.6 (0.11)	1.4 (-0.10)	1.4 (-0.12)	1.5 (-0.03)	<0.001
Female (n=10)	1.6	1.6 (0.01)	1.5 (-0.12)	1.4 (-0.22)	1.0 (-0.58)	1.4 (-0.25)	0.481

Pre = Preoperative, Δ = difference between preoperative and the indicated follow-up time

Table 3. Quality of life scores on the EORTC QLQ-C30

EORTC QLQ-C30 item	Pre Mean	6 weeks Mean	3 months Mean	6 months Mean	1 year Mean	2 year Mean	p-value
Global Health							
Global health status	77	81	83	81	81	81	0.047
Functional scales							
Physical functioning	95	95	94	94	93	94	0.190
Role functioning	95	96	94	94	95	97	0.635
Emotional functioning	72	85	85	87	88	90	<0.001
Cognitive functioning	89	91	89	92	91	88	0.362
Social functioning	92	93	95	96	95	95	0.402
Symptom scales							
Fatigue	20	15	14	15	17	12	0.118
Nausea and vomiting	1	1	2	3	3	3	0.329
Pain	6	7	3	4	7	5	0.173
Dyspnea	17	15	18	20	19	15	0.509
Insomnia	20	15	12	13	11	9	0.025
Appetite loss	5	2	4	5	3	4	0.857
Constipation	5	3	3	3	2	3	0.678
Diarrhea	4	6	4	2	5	3	0.429
Financial Difficulties	6	4	3	3	2	3	0.262

Pre = Preoperative

Voice Handicap Index

The mean VHI score improved significantly over time, ranging from 30.5 preoperatively to 21.8 at 2 years (Δ8.7, p = 0.003,). However, according to our definition, this improvement did not qualify as clinically relevant. The major improvement in the VHI score occurred within the first 6 months (Δ7.2). Thereafter, only small additional improvements were noted between 6 months and the 2-year follow-up. Gender was the only variable that significantly affected the VHI score; the difference in mean VHI scores was 11.6 points (p = 0.023) between male and female patients. The difference in mean VHI score per time point between male and female patients was 7.8 points (p = 0.204) preoperative, 14.6 points (p = 0.025) at 6 weeks, 11.0 points (p = 0.090) at 3 months, 15.4 points at 6 months (p = 0.018), 5.9 points (p = 0.346) at 1 year, and 15.1 (p = 0.039) points at 2 years. At 2 years, females showed a lower (normalized) VHI score and a larger improvement (Δ15.3) than males. Additionally, unlike the improvement observed in male patients, the improvement in the mean VHI score in female patients was clinically relevant (Table 2).

Table 4. Quality of life scores on the EORTC QLQ-HN35

EORTC QLQ-HN35 item	Pre Mean	6 weeks Mean	3 months Mean	6 months Mean	1 year Mean	2 year Mean	p-value
Symptom scales							
Pain	8	5	5	6	6	4	0.029
Swallowing	3	3	2	2	4	3	0.863
Senses problems	5	5	3	4	5	4	0.855
Speech problems (male)	38	31	20	18	13	14	<0.001
Speech problems (female)	20	15	10	10	10	7	0.691
Trouble with social eating	2	2	2	2	2	2	0.970
Trouble with social contact	4	4	2	3	4	4	0.269
Less sexuality	14	15	17	15	18	17	0.905
Teeth	9	3	9	8	6	8	0.329
Opening mouth	3	2	2	2	5	2	0.220
Dry mouth	18	13	17	19	15	9	0.079
Sticky Saliva (male)	15	16	12	10	15	13	0.363
Sticky Saliva (female)	0	4	0	5	4	0	0.963
Coughing	28	21	21	22	16	13	0.002
Felt ill	10	7	5	5	8	8	0.459
Pain killers	13	8	10	7	12	11	0.333
Nutritional supplements	1	2	1	0	4	0	0.169
Feeding tube	0	0	0	1	0	0	0.451
Weight loss	9	7	1	5	4	9	0.037
Weight gain	5	19	19	23	17	7	<0.001

Pre = Preoperative

EORTC QLQ-C30

Patients showed good global health status preoperatively and the improvement in global health status over time was only borderline significant. It increased from 77 preoperatively to 81 at 2 years postoperatively ($\Delta 4$, $p = 0.047$). However, this improvement did not qualify as clinically relevant. The results of the different functional scales showed that patients reported high levels of functioning. In all five scales, scores ranged from 88 to 97 points after 2 years. One of these scales—the emotional functioning scale—showed a significant and clinically relevant improvement ($\Delta 18$; $p < 0.001$), compared to preoperative values. The results of the symptom scales showed that patients also reported high levels of functioning on all items during the 2-year follow-up. The most common complaints were fatigue, dyspnea, and insomnia; scores ranged between 9 and 15 points. Only the change in insomnia showed a significant and clinically relevant improvement compared to preoperative values ($\Delta 11$; $p < 0.025$) (Table 3).

EORTC QLQ-HN35

The symptom scales showed low symptom scores at 2 years after treatment. As seen in the VHI questionnaire, gender had a significant effect on two items. Females had significantly lower mean scores than males on speech problems (10.6 points difference; $p = 0.037$) and sticky saliva (11.8 points difference; $p = 0.039$). At 2 years postoperatively, most complaints were about speech problems (male patients), sexuality, sticky saliva (male patients), coughing, and the use of painkillers; the scores for these items ranged between 11 and 17 points. Nevertheless, compared to preoperative values, both speech problems ($\Delta 24$, $p < 0.001$) and coughing ($\Delta 15$, $p = 0.002$) showed significant and clinically relevant improvements at 2 years. Pain also showed a significant improvement ($\Delta 4$; $p = 0.02$), but this improvement did not qualify as clinically relevant. The improvement in speech problems among female patients was clinically relevant, but the change was not significant ($\Delta 13$, $p = 0.691$) (Table 4).

Perceptual evaluation

The grade fluctuated significantly over time, and at 2 years, the pre- and postoperative values were similar ($p < 0.001$). Initial deterioration was observed at 6 weeks. Thereafter, recovery was noted, and the grade stabilized between the 3- and 6-month time points. The tumor stage (T1a, T1b, and T2) had a significant impact on the grade ($p = 0.001$). Patients with T1a tumors had significantly better end scores than patients with T1b tumors (difference in means: 0.76, $p < 0.001$) and patients with T2 tumors (difference in means: 0.49, $p = 0.031$). We found no significant difference between patients with T1b and T2 tumors (difference in means: 0.27, $p = 0.256$). At 2 years, the grade declined compared to preoperative values only in patients with T1a tumors ($\Delta 0.29$; Table 2). Male and female patients did not have a mean difference in score (difference in means: 0.120, $p = 0.644$), although male patients fluctuated significantly over time ($p < 0.001$), whereas female patients did not ($p = 0.481$).

DISCUSSION

This prospective study investigated QoL and voice outcome for 2 years after TLM (unilateral type III resection or bilateral type II resection) in patients with early glottic carcinoma (extended T1 and limited T2). Our results indicate good overall QoL with low symptom scores. The voice outcome data showed slightly elevated VHI and grade scores. The VHI showed most improvement within the first 6 months. Interestingly, the VHI was significantly affected by gender; at 2 years after treatment, females showed scores within the normal range (8.7 points) and males showed slightly elevated scores (23.9 points). The grade score for dysphonia declined initially after surgery and showed most of the improvement or recovery within the first 6 months. The grade was significantly affected, not by gender but by tumor stage. At 2 years, the grade scores were between 1.0 (T1a) and 1.9 (T1b), which indicates mild (T1a) to moderate (T1b–T2) dysphonia. The final scores showed improvement for T1a tumors, but no change for T1b and T2 tumors, compared to preoperative grade scores.

This study is one of the first to find a significant effect of gender on the VHI questionnaire, although we could not confirm this in the perceptual evaluation. Both men and women showed improvements over time, but only female patients achieved clinically relevant improvements. However, most likely due to the small sample size of female patients, this improvement did not reach statistical significance. The female scores fluctuated over time, with an outlier score at 1 year. Therefore, in future studies with small groups, we recommend studying scores over time, rather than only evaluating two different time points. On the other hand, the improvement in male patients was statistically significant, but not clinically relevant. In contrast to these results, the study by van Gogh et al. reported no association between the VHI scores and gender, either in patients with voice impairments or in the population with normal glottic function [23]. However, in another study on patients with a variety of laryngeal diseases, Karlsen et al. found a correlation ($r = -0.17$, $p < 0.05$) between the VHI score and gender; female patients had lower scores than male patients [30]. This latter finding was consistent with our results, although no exact VHI scores were given in that study [30]. The difference in VHI improvement between males and females might be explained by the fact that women show postoperative fundamental frequencies within the normal female range, whereas male patients show postoperative fundamental frequencies that are higher than the normal male range (van Loon et al. [18]). Potentially, this characteristic could lead male patients to experience a larger change in their voice and therefore to be less satisfied. The potential impact of gender on voice outcome after TLM for glottic carcinoma must be confirmed in future studies in larger patient populations. Until then, these results should be interpreted with caution.

The finding that patients with T1a tumors had significantly better grade scores than patients with T1b and T2 tumors might be explained by the fact that a lower tumor stage requires a smaller

volume resection of the vocal cords [31, 32]. During the first 6 weeks, a temporary deterioration in grade was observed for tumors in all stages, followed by an initial recovery at 3 months. Between the 3rd and 6th months, the grade further improved and stabilized. This pattern was consistent with results reported in previous studies [33, 34]. At 2 years, only patients with T1a tumors showed significant improvements, compared to preoperative values.

After 6 months, only small changes in both the VHI and grade scores were observed. Therefore, improvements achieved at 6 months were indicative of the states achieved at 1 and 2 years postoperatively. Furthermore, the grade evaluations, showing mild to moderate dysphonia in both males and females, indicated that the voice did not return to normal levels after 2 years. This finding could be explained by the destructive effect of surgery on the vibratory layers of the vocal cord and the development of fibrosis. Interestingly however, the VHI did return to normal values for females and was only slightly elevated for males. This discrepancy between the VHI score and grade evaluation implies that there is a difference between what the patients experience and how experts rate their voices. This lack of correlation between the VHI questionnaire and the perceptual evaluation has been shown in other studies [12, 14, 35, 36]. A study by van Loon et al. investigated the time trade off in patients with laryngeal cancer and concluded that none of the patients who were treated with TLM was prepared to trade off years to live in perfect health. This shows that the perceived side effects (e.g., dysphonia) by patients are not substantial and that patients are able to cope well with their limitations in daily life [37]. QoL is a multidimensional construct; thus, it is best measured with an instrument that reports on multiple domains of functionality and well-being. Among the most widely used questionnaires in head and neck cancer research are those developed by the EORTC (QLQ-C30 and QLQ-HN35). These questionnaires have been used in many studies on patients with laryngeal cancer. However, they have been used in only a few studies on patients with early glottic cancer [10, 12, 16, 38, 39]. Three of these studies compared QoL in patients with early glottic cancer that were treated with either radiotherapy or TLM [10, 38, 39]. Two previous studies focused exclusively on patients that underwent TLM [12, 16]. The study of Hsin et al. prospectively investigated 62 patients with early glottic cancer (Tis-T2) that underwent TLM (ELS types I–VI) [16]. They demonstrated an immediate decline in QoL scores in the first few months, which recovered to baseline after 6 months, and then improved at 12 months, compared with preoperative scores. That finding is in contrast with findings in our study, because our patients did not report an immediate deterioration in QoL scores postoperatively. This difference might be explained by the fact that the previous study treated 15 patients (24%) with type IV–VI resections [16]; in contrast, we only treated patients with unilateral type III and bilateral type II resections.

Items on the QLQ-30 and QLQ-HN35 questionnaires have previously shown little differences in scores between men and women [40]. However, laryngeal cancer is less common in women than in men; thus, demonstrating differences between the sexes can be challenging, due to the

limited number of female patients. Several studies on either general populations or patients with laryngeal cancer have shown that women reported significantly worse QoL scores than men [41, 42, 43, 44]. In our study, the data did not confirm this gender difference. On the contrary, we found that men reported significantly more problems of speech and sticky saliva than women did on the QLQ-HN35 items.

On both questionnaires (QLQ-C30 and QLQ-HN35), we observed slightly elevated values (12–17 points) for fatigue, dyspnea, speech (male patients), sticky saliva (male patients), coughing, and sexuality after 2 years of follow-up. Compared to normative data from the general Dutch population, QLQ-C30 items (fatigue and dyspnea) that were less than 10 points different from the reference group [44] were not considered clinically relevant. In the literature, no study has reported normative data for the QLQ-HN35 questionnaire; therefore, the other slightly elevated items (speech problems, sticky saliva, coughing, and sexuality) could not be compared to a reference. One multinational study analyzed data on 293 patients with laryngeal cancer (stages I–IV). Although that study tested the reliability and validity of the head and neck cancer module, it did not report normative data. They included patients that were newly diagnosed, had recurrent disease or were disease free (1–3 years after treatment), and were primarily treated with radiotherapy [24]. Compared to those results, our patients reported fewer problems. This discrepancy might be explained by the fact that they included larger tumors than those we included, and their patients were treated primarily with radiotherapy. In the future, it would be interesting to generate normative data for the QLQ-HN35 module to enable comparisons with healthy individuals.

The strengths of this study is the prospective design and the duration of the follow-up. Due to the long-term follow-up, we were able to show that the results at 6 months and 1 year, which are more common time frames for these types of study, are representative for the long term. Our results have therefore been useful to us in counselling patients who undergo these specific resections on what to expect—both in terms of end results and the time frame within which these are achieved. The study had some limitations. First, due to the longitudinal nature of our study and the inclusion of patients from three different hospitals, we could not avoid missing data, despite the prospective study design. In addition, we did not collect data on patient comorbidities and smoking after treatment. This could be of relevance and interesting for further research. Second, we did not collect data on speech therapy. However, all patients were instructed by the speech–language pathologist in vocal hygiene after TLM. No patient received speech therapy before 3 months after surgery. After that, speech therapy was administered on a case-by-case basis. We acknowledge that speech therapy can improve the voice results, and therefore we advocate the collection of data on speech therapy in future studies as suggested by Heijnen et al. [45]. Third, the sample size of female patients was small. Therefore, the significant effects of gender on the VHI and QLQ-HN35 questionnaire must be confirmed in future studies with lager sample size.

Fourth, in the QLQ-HN35 we found a slightly elevated score in the item sticky saliva. Normally, you may expect elevated scores for sticky saliva after the treatment with radiotherapy and not after the treatment with TLM. However, no explanation could be given by the authors as to why sticky saliva showed elevated scores. Therefore, it would be interesting to generate normative data for this questionnaire.

CONCLUSION

Based on our findings, we conclude that patients with extended T1 and limited T2 tumors treated with TLM (unilateral type III or bilateral type II) show good QoL with low symptom scores and slightly elevated voice outcome data, at 2 years after treatment. Most of the improvement is observed within 6 months, and this level of improvement provides a clear indication of the status at 1 and 2 years postoperatively. These findings are useful for guiding patients in clinical decision making.

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Chapter 6

Survival and prognostic factors for outcome after radiotherapy for T2 glottic carcinoma

Martine Hendriksma
Marc, A.P. van Ruler
Berit M. Verbist
Martin A. de Jong
Ton P.M. Langeveld
Peter Paul G. van Benthem
Elisabeth V. Sjögren

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ABSTRACT

Background

Local recurrence after radiotherapy for T2 glottic carcinoma remains an issue and identifying patients at risk for relapse is, therefore, important. This study aimed to assess the oncological outcomes and prognostic factors in a consecutive series of patients treated with radiotherapy for T2N0 glottic carcinoma.

Methods

Patients with T2N0 glottic carcinoma treated with radiotherapy were included in this retrospective study. Five- and ten-year local control (LC), overall survival (OS), disease-specific survival (DSS), and laryngeal preservation (LP) rates were calculated with the Kaplan–Meier method. The impact of prognostic variables was evaluated with the log-rank test.

Results

Ninety-four patients were included for analysis. LC, OS, DSS, and LP rates were 70.5, 63.7, 86.0, and 74.7%, respectively at five years and 65.8, 41.0, 75.6, and 72.4% at 10 years. In total, 46 scans were included in the analyses. Vertical involvement of the anterior commissure on imaging showed a significant impact on LC.

Conclusions

In accordance with previously described surgical risk factors, we identified vertical involvement of the anterior commissure on imaging as a prognostic factor for radiation failure.

INTRODUCTION

Laryngeal carcinoma is one of the most frequent types of head and neck cancer. In 2017, 708 patients were diagnosed with laryngeal carcinoma in the Netherlands. Around sixty-five percent of tumors arise from the glottic region [1], and of those, about 30% are diagnosed as T2-stage tumors [2]. The two main treatment modalities for T2 tumors are radiotherapy and transoral CO_2 laser microsurgery (TLM). Both treatments aim to achieve high cure rates and preserve organ function with an acceptable voice outcome. The Dutch guidelines on the treatment of laryngeal carcinoma advocates radiotherapy as the treatment of choice for T2 glottic carcinoma [3].

Currently, there is no definite proof that one treatment modality is more effective than the other [4]. Several studies have shown that both radiotherapy and TLM provide high, comparable local control (LC) rates for T2 glottic carcinoma [5]. However, a recent systematic review on T2 glottic carcinoma showed that, similar to findings for T1a glottic carcinoma [6–8], larynx preservation (LP) rates after primary treatment were higher with TLM than with radiotherapy [9]. Hence, determining prognostic factors could improve risk stratification in patients considered for radiotherapy in T2 glottic carcinoma. This information could help enhance outcomes by facilitating the identification of patients most likely to benefit from radiotherapy as opposed to surgical treatment.

The present retrospective study aimed to (1) evaluate survival outcomes in consecutive patients that received primary radiotherapy for T2N0 glottic carcinoma at our center and to compare these results to those in the current literature, as well as to (2) identify factors predictive for survival outcomes in this cohort. The ultimate goal of the study is to contribute to the ongoing evaluation of the comparative benefits of radiotherapy and TLM for patients with T2 glottic carcinoma.

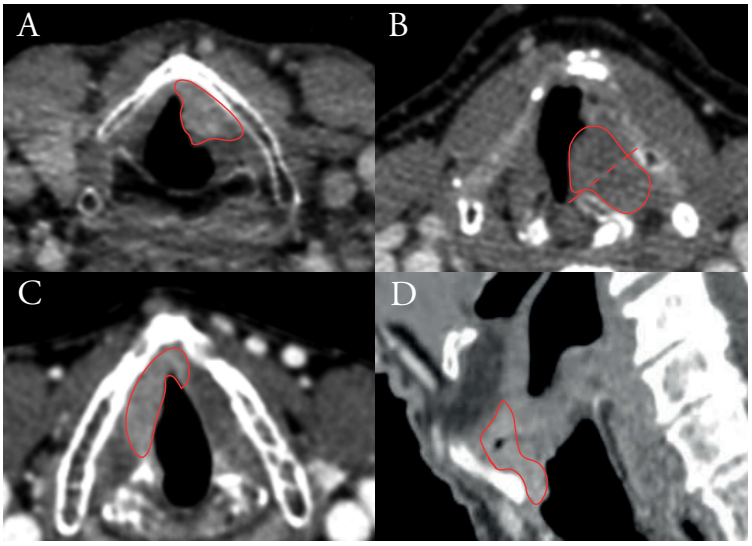
METHODS

Patients

We retrospectively reviewed the records of all patients diagnosed with T2N0 glottic squamous cell carcinoma that received primary treatment with radiotherapy at the University Cancer Centre Leiden—the Hague between 2000 and 2012. The cancer center has two locations, one in Leiden and one in the Hague, which use the same irradiation schemes/protocols. Patients were identified through the hospital oncological database, which registers the site and the stage of all patients with oncological tumors. We assessed the medical charts of these patients and collected data on the demographics, tumor characteristics, diagnostics, treatment details, follow-up, and patient outcomes. All available Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scans were reviewed by the radiologist (B.M.V.) and scored for several variables related

to tumor location: 1) superficial versus deep vocal fold muscle infiltration; 2) anterior versus posterior vocal fold muscle involvement defined by the relation of the tumor to the vertical plane tangential to the arytenoid vocal process and perpendicular to the ipsilateral thyroid lamina (henceforth: position relative to the M-line as defined by Succo et al. [10]); 3) horizontal involvement of the anterior commissure in the glottic plane; and 4) vertical involvement of the anterior commissure resulting from supraglottic and subglottic extension (Figure 1). If the tumors were not visible on CT or MRI, they were classified as superficial. In the patients where the original scans were not available for re-evaluation, radiological reports were reviewed to rule out paraglottic or pre-epiglottic space involvement or suspicious neck nodes. In three patients, imaging had not been performed. All these three patients had normal mobility of the vocal folds and N0 neck on ultrasound and were therefore included in the cohort. Acute and chronic radiotherapy toxicities were analyzed according to the Common Terminology Criteria for Adverse Events, version 4.0 (National Cancer Institute, Bethesda, USA). Patients were excluded if they had previous laryngeal cancer or received a primary treatment other than radiotherapy. The study was approved by the Leiden University Medical Center with approval number G17.098/SH/sh on 13th February 2018.

Figure 1. Examples of the four parameters scored in Computed Tomography and Magnetic Resonance Imaging scans.: A) deep infiltration of left glottic in the vocal fold muscle; B) tumor that is located both anterior and posterior of the M-line; C) horizontal involvement of the anterior commissure in the glottic plane; D) vertical involvement of the anterior commissure (supraglottic and infraglottic extension).



Follow-up

During radiotherapy, patients underwent a weekly clinical examination. After treatment, all patients were periodically evaluated, according to the protocol, with flexible fiberoptic laryngoscopy. Evaluations were scheduled every two months in the first year and with decreasing frequency until five years posttreatment. When a suspected lesion was detected during follow-up, a biopsy was performed.

Statistical analysis

Data analyses were performed with SPSS version 23.0 (IBM Corp., Armonk, NY, USA). The outcome parameters of the study were the five- and 10-year rates of LC, disease-specific survival (DSS), overall survival (OS), and LP. The median follow-up was calculated with the reverse Kaplan–Meier method. The Kaplan–Meier five- and 10-year survival curves were used to calculate LC, DSS, OS, and LP. The entry point was the start of radiotherapy. The endpoints were the date of the first local recurrence, for LC; the date of death due to laryngeal cancer, for DSS; the date of death of all causes, for OS; and the date of the laryngectomy, for LP. Th potential prognostic factors were evaluated with univariate analysis and the log-rank test. The following variables were tested in univariate models for LC, DSS, and LP: involvement of the anterior commissure, mobility of the vocal cords, tumor infiltration relative to the vocal fold muscle, tumor position relative to the M-line, horizontal and vertical involvement of the anterior commissure, type of radiotherapy (conventional versus intensity-modulated radiation therapy (IMRT)), elective lymph node irradiation, total dose, fraction size, and overall treatment time. Multivariate analysis using cox proportional hazard analysis was not performed due to insufficient sample size. Bonferroni correction was applied to correct for multiple testing (Bonferroni-corrected value of $p = 0.05/11 = 0.005$).

RESULTS

Patients and Treatment Characteristics

Between 2000 and 2012, 94 consecutive patients were treated with radiotherapy for cT2N0 glottic carcinoma. There were 82 male (87.2%) and 12 (12.8%) female patients. Mean age at diagnosis was 64.4 (range 32–84) years. Seventy-nine patients (84%) were treated with conventional radiotherapy, applied as a parallel-opposed bilateral field, generated with a 4–6 MV linear accelerator. Fifteen patients (16%) were treated with IMRT. The total dose ranged from 60.0–70.0 Gy (median 68.0 Gy); the dose per fraction ranged from 1.8 to 2.4 Gy (median 2.0 Gy). In total, 37 patients (39.4%) underwent elective lymph node irradiation, with a total dose range of 44.0 to 58.0 Gy (median 46.0 Gy). The overall treatment time ranged from 35 to 49 days (median 42.0 days).

Radiological Characteristics

In 50 patients, CT or MRI scans were available. Four scans were excluded because of movement

Table 1. Univariate analysis for impact on local control

Characteristics	No. of Patients (%)	5-Year Local Control (%)	*p*-value
Clinical characteristics (n = 94)			
Involvement AC			
Yes	61 (64.9)	68.1	0.597
No	33 (35.1)	74.8	
Mobility			
Normal	76 (80.9)	69.1	0.438
Impaired	18 (19.1)	77.4	
Radiological characteristics (n = 46)			
Tumor infiltration in VM			
Superficial	16 (34.8)	92.9	0.077
Deep	30 (65.2)	68.0	
Position relative to M-line			
Anterior	37 (82.2)	76.6	0.875
Posterior	1 (2.2)	100	
Both	7 (15.6)	71.4	
Horizontal involvement AC			
Yes	13 (28.3)	59.2	0.047
No	33 (71.7)	83.0	
Vertical involvement AC			
No	32 (71.1)	81.8	
Supraglottic	5 (11.1)	100	<0.0001
Subglottic	4 (8.9)	75.0	
Both	4 (8.9)	0.0	
Treatment characteristics (n = 94)			
Type of radiotherapy			
Normal	79 (84.0)	71.6	0.277
IMRT	15 (16.0)	65.2	
Elective neck irradiation			
Yes	37 (39.4)	68.6	0.827
No	57 (60.6)	72.0	
Total dose			
≤68 Gy	49 (52.1)	71.8	0.965
>68 Gy	45 (47.9)	69.1	
Fraction size			
≤2.0 Gy	84 (89.4)	71.0	0.770
>2.0 Gy	10 (10.6)	67.5	
Overall treatment time			
≤42 days	73 (77.7)	68.2	0.331
>42 days	21 (22.3)	79.0	

Abbreviations: AC= anterior commissure, Gy = gray, IMRT= intensity-modulated radiation therapy, VM = vocal fold muscle.

and streaking artifacts. In total, 46 scans were included for the analysis, of which 36 were CT (78.2%), and 10 were MRI (21.7%) scans. Of the 46 included scans, 31 were of good quality and 15 of moderate quality. The radiological characteristics are listed in Table 1.

Follow-up

Three patients (3.2%) were lost to follow-up at two months, five months, and six months, respectively. These three patients were clinically free of disease at the time of their last examination. The median follow-up was 106.0 months (95%CI: 80.3–131.7) (range 2–175 months).

Survival and Local Control

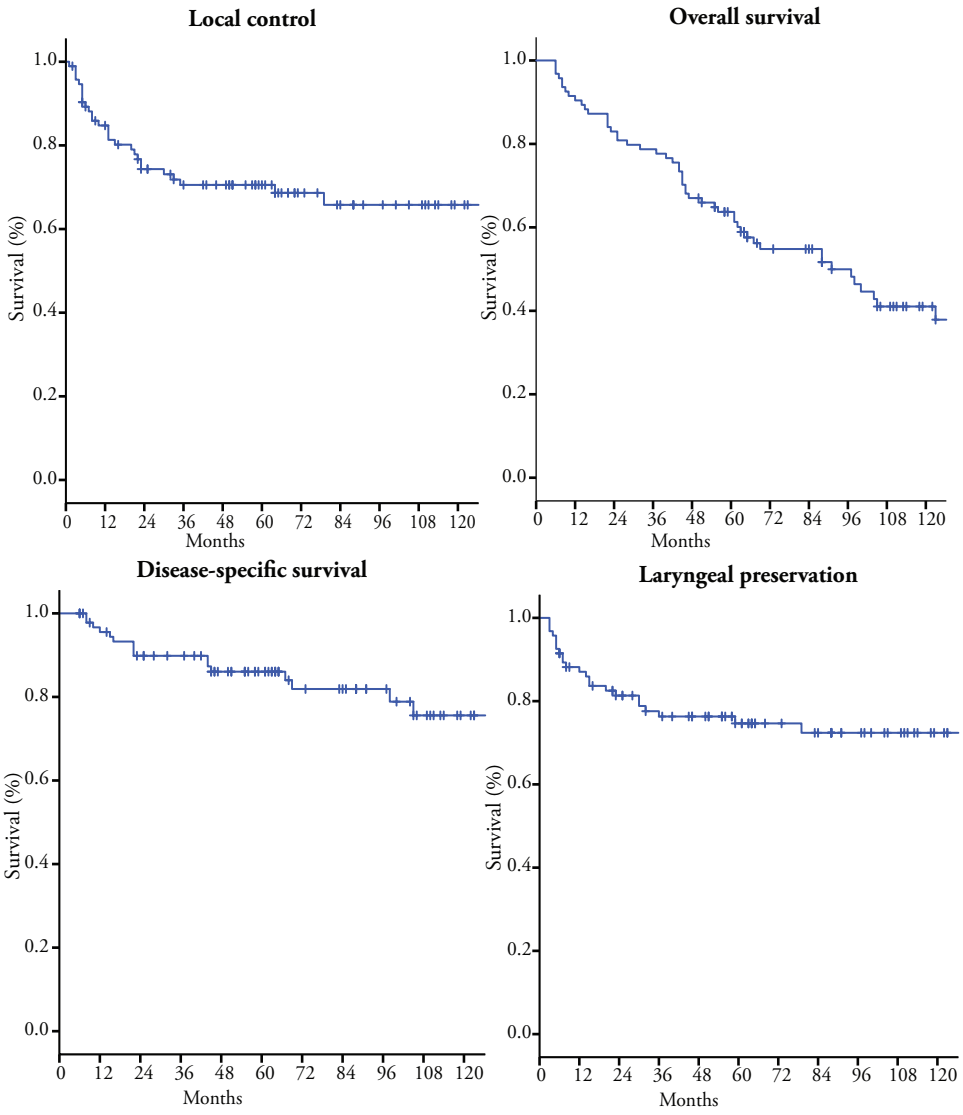
During follow-up, 28 patients (29.8%) developed local recurrence, after a median of 11.5 months (range 1–79 months). Of these, recurrence was detected within 24 months of treatment in 82.1%. The five- and 10-year LC rates were 70.5% and 65.8%, respectively (Table 2 and Figure 2).

Table 2. Five- and ten-year oncological outcomes.

Outcomes	5-year survival (%)	10-year survival (%)
Local control	70.5	65.8
Overall survival	63.7	41.0
Disease-specific survival	86.0	75.6
Laryngeal preservation	74.7	72.4

Salvage therapy consisted of TLM in three patients (10.7%); re-irradiation in two patients (7.1%); total laryngectomy with or without neck dissection, including radiation of the neck in 18 patients (67.9%), and partial laryngectomy in two patients (7.1%). Additionally, two patients (7.1%) required a total laryngectomy, but refused this, and therefore, received the best supportive care. None of our patients had neck failure without having a local recurrence. In six of the 28 patients (21%) that developed a local recurrence, positive neck nodes were identified. Two of the six patients had undergone elective neck irradiation during primary treatment, and four patients had not. Ten patients (35.7%) developed a second recurrence. Of these, two patients were treated by re-irradiation; two patients underwent a total laryngectomy with neck dissection; one patient underwent a total pharyngectomy and a gastric tube reconstruction with a pectoralis major muscle flap; two patients underwent surgical resection, one with and one without radiotherapy, due to stomal recurrence. Three patients did not have curative treatment, of which one patient underwent palliative chemotherapy, and two patients received the best supportive care. In total, 23 patients (24.5%) underwent a total laryngectomy due to recurrent disease. The five- and 10-year LP rates were 74.4% and 72.4%, respectively (Table 2 and Figure 2). During follow-up, 16 patients died due to laryngeal cancer (17.0%), and 38 patients (40.4%) died of unrelated causes. The five- and 10-year DSS rates were 86.0 and 75.6%, and the five- and 10-year OS rates were 63.7 and 41.0% (Table 2 and Figure 2). In the univariate analysis, one radiological variable

Figure 2. Oncological outcomes



(vertical involvement of the anterior commissure) showed a significant association with LC and one radiological variable (horizontal involvement) showed a trend towards lower LC (Table 1). All four patients with sub- and supraglottic extension in the anterior commissure developed recurrent disease, (five-year LC 0%). Horizontal involvement of the anterior commissure also showed a trend towards lower LP (p = 0.009), with a five-year LP of 59.2% in patients with horizontal anterior commissure involvement versus 90.1% in those without. Deep infiltration of the vocal muscle showed a trend towards lower DSS (p = 0.037) with a five-year DSS of 57.5% in patients with deep infiltration versus 79.2% in those with only superficial involvement and

a trend towards higher LC in patients with superficial tumor infiltration (p = 0.077) (Table 1). No other clinical or treatment-related variable showed any significant impact on the oncological outcomes.

Toxicity

No patient died due to toxicity from radiotherapy. Overall, thirteen patients (13.8%) reported grade 3 or grade 4 adverse events. Acute adverse events were reported in 10 patients: in one patient, radiotherapy was interrupted due to laryngeal edema, which required a tracheostomy (grade 4) and nine patients required a nasogastric feeding tube during radiation therapy for grade 3 dysphagia. Five patients (5.3%) had late complications (grades 2 and 4): two patients developed laryngeal necrosis for which they underwent a tracheostomy, and three patients required treatment for hypothyroidism.

DISCUSSION

*T*he objective of this retrospective study was to evaluate the five- and 10-year survival outcomes of patients primarily treated with radiotherapy for T2N0 glottic carcinoma and to identify prognostic factors associated with radiotherapy failure in these patients. Treatment with radiotherapy alone resulted in good outcomes rates at five- and 10-years for LC (70.5% and 65.8%), OS (63.7% and 41.0%), DSS (86.0% and 75.6%), and LP (74.7% and 72.4%). Despite the small numbers of available scans (n = 46), vertical anterior commissure involvement on imaging showed a significant impact on LC. No other patient, tumor, treatment, or radiological-related variable in our analysis had any significant impact on oncological outcomes.

Primary radiotherapy is a widely accepted treatment option for early glottic cancer. It is the advocated treatment in the Netherlands for extended T1a tumors and T2 tumors. In the literature, the five-year LC rate for T2 tumors ranges from 48 to 97.6%, with a weighted average of 75.81% [5]. These wide ranges probably reflect the heterogeneity of tumor extension and location found within the T2 stage [11]. This study showed five-year LC rates comparable to those reported in the literature. Our five-year OS and DSS rates were also comparable to those in the literature (ranges 53–91% and 69–100%, respectively) [12–28].

Only a few studies have reported 10-year oncological outcomes for T2 glottic carcinoma treated with radiotherapy. Khan et al. reported their 20-year experience of definitive radiotherapy for early glottic cancer. They divided T2 tumors into T2a (with mobile vocal folds) and T2b (without mobile vocal folds) types and showed LC rates of 87% and 56%, respectively. Their 10-year OS for T1–T2 tumors was 50% [29]. Chera et al. reported 10-year OS rates of 51% and 49% for T2a and T2b tumors, respectively [17]. Le et al. reported a 10-year OS of 63% for T2 tumors [30]. Frata et al. reported 10-year LC, OS, and DSS of 70%, 37%, and 85%, respectively [31]. These 10-year oncological outcomes are comparable with those found in this study.

Several retrospective studies have investigated prognostic factors for radiation failure in early glottic carcinoma. However, to date, little evidence has been published from randomized controlled trials or large prospective studies. Recently, a systematic review with a meta-analysis investigated 56 potential risk factors for radiation failure in early glottic carcinoma (T1–T2) [32]. Its results indicate that male gender, low hemoglobin level, anterior commissure involvement, tumor stage (T2 tumor), tumor size/volume, and poor differentiation/dedifferentiation could increase the probability of radiation failure. Several studies have focused on the involvement of the anterior commissure as a potential risk factor for radiation failure. Although it is widely acknowledged that the involvement of the anterior commissure can have a negative impact on the outcome, the extent of the impact remains a topic of discussion, with the results reported in literature being inconsistent. Some studies show an association between the anterior commissure involvement and LC [33–37], whereas others do not [12,22,27,29–31,38,39]. In our study, we found that the clinical, binary variable on anterior commissure involvement (yes/no) had no significant impact on oncological outcomes, whereas the vertical involvement of the anterior commissure on imaging showed a significant impact on LC. The varying results found in the literature can be explained by the variations in clinical definition of the anterior commissure area, variation in the detail of the clinical, endoscopic, and radiological evaluation of the lesion in the preoperative setting, the distinctive features, and limitation of each therapeutic modality, the biological behaviors of the tumor, and variations in the rigor of the follow-up policy [40]. These factors, combined with the complicated anatomy of the anterior commissure, the involvement of this subsite may very well be too complex to be included as a binary variable (yes/no) [40]. Therefore, the role of the anterior commissure in the risk of primary radiotherapy failure in patients with T2 glottic carcinoma remains unclear, and further studies are needed to elucidate the impact of this sublocalization on the outcome.

The inconsistency in the literature regarding the impact of anterior commissure involvement is also found in surgical series (TLM). Notably, T2 tumors with vertical anterior commissure extension (supracommissural and subcommissural) have a significantly lower LC and LP rate with TLM than other T2 subtypes [11,41,42]. Also, in T3 tumors, the involvement of the posterior part of the muscle, behind the so-called M-line, has been associated with a significantly lower LC, DSS, and OS rate in patients treated with open partial horizontal laryngectomies [10]. The higher risk of oncological failure in these areas is thought to be related to their proximity to some of the membranes and visceral spaces of the larynx such as the pre- and paraglottic space and the cricothyroid ligament.

To the best of our knowledge, this is the first study to investigate these surgical risk factors in a radiotherapy cohort. In accordance with the aforementioned surgical studies, we found a significant impact of vertical involvement of the anterior commissure on LC and a trend towards lower LC and LP in the horizontal involvement of the anterior commissure as classified

on imaging. Deep infiltration in the vocal fold muscle also showed a trend towards lower LC and DSS. Although these trends were not significant in this study, we view our findings as an indication that these parameters warrant further study. The number of patients in the different radiological categories was limited, especially in the case of the vertical anterior commissure involvement. In this subgroup, none of the patients with supraglottic extension in the anterior commissure developed a local recurrence versus 25% of patients with subglottic extension and 100% of patients with sub- and supraglottic extension. Currently, we have no evident explanation for this. However, it might be that the involvement of these sites carries increasing levels of risk. This theory has to be investigated in the future, prospective studies to extend the understanding of these variables. Therefore, these results have to be interpreted with caution.

To further improve LC rates in high-risk patients in T2 glottic carcinoma, chemoradiotherapy (CRT) might be considered. Several studies have investigated this treatment modality in T2 laryngeal cancer. They show that CRT is feasible, well-tolerated, and effective. Furthermore, they show promising LC rates between 91.5% and 100% [43–47]. However, the number of patients treated with CRT was low, and some studies also included T1 tumors. Three studies compared RT with CRT [45,48,49]. One of these studies concluded that CRT was not found to be effective for 21 patients with T2 glottic carcinoma [49]. However, the study of Akimoto et al. reported a significant difference in the five-year disease-free survival between RT alone and CRT (68% and 89%, respectively) [48]. The study by Bhateja et al. compared the outcome of patients with T2bN0 tumors treated with RT to that of patients with T2b-T3N0/N+ treated with CRT. They found that the T2bN0 tumors treated with RT alone showed a trend towards lower LC than the T2b-T3N0/N+ patients treated with CRT, even though the latter group includes higher stage tumors [45]. Thus, data suggest that applying concurrent chemoradiotherapy may be a reasonable strategy to improve LC in patients with high risk T2 glottic carcinoma, although risks and benefit have to be considered [45]. Therefore, a prospective randomized controlled trial is needed to evaluate risks and the improvement of LC in CRT in T2 glottic carcinoma.

We interpret our results as an important indication that tumor extension in the anterior commissure is a risk factor for reduced oncological control both in surgical and radiotherapy patients and that patients with tumors with these high-risk growth patterns require close surveillance, independently of treatment modality. Due to the retrospective nature of this data, the impact of subcategorization of T2 tumors according to these factors should be further studied in a prospective manner.

In the aforementioned surgical studies, the detailed classification of the type of anterior commissure involvement was obtained using a combination of clinical, radiological, and surgical information, whereas we based our classification on imaging. This was due to the retrospective nature of this study with which anterior commissure involvement could only be specified as a

binary variable (yes/no) and could not be further determined, whereas the imaging could be reevaluated specifically for this study. As stated earlier, the binary involvement of the anterior commissure based on our clinical information did not have a significant impact on LC. Additionally, we did not find a significant impact of the mobility of the vocal fold, whereas deep involvement demonstrated a trend towards increased LC. This suggests that a more specific classification of tumors in this area than is currently offered by the TNM classification system, may be necessary [41,42] and that incorporating imaging improves evaluation of tumor extent.

LIMITATIONS

This study has some limitations. First, the sample size was small, especially the numbers of scans that were available (n = 46). This means that our findings are based on a small number of observations. Larger studies are needed to confirm these preliminary findings. Also, the retrospective nature of the study meant that we would not obtain all the scans for reevaluation and had to rely on reports of the imaging for the confirmation of the tumor stage (T2N0). In addition, due to the retrospective design, it was not possible to include all the risk factors mentioned in the literature, due to a lack of available data and the low numbers of events.

CONCLUSION

This study shows good oncological outcomes for patients with T2 glottic carcinoma treated with radiotherapy at our center. In accordance with previously described subtypes of T2 glottic carcinoma and known surgical risk factors, we identified vertical involvement of the anterior commissure on imaging as a prognostic factor for radiation failure. Prospective studies are warranted to extend our understanding of tumor extension variables on imaging in all treatment modalities for glottic cancer.

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Chapter 7

Long term functional ouctome in T2 glottic carcinoma after radiotherapy

Martine Hendriksma
Bas J. Heijnen
Berit M. Verbist
Martin A. de Jong
Ton P. M. Langeveld
Peter Paul G. van Benthem
Elisabeth V. Sjögren

Submitted

ABSTRACT

Objective

To evaluate the long-term functional outcomes (voice outcome, quality of life, and swallowing performance) in patients that received primary radiotherapy for T2N0 glottic carcinoma, stratified for tumor extension.

Methods

A cross-sectional study was performed on patients that were treated with radiotherapy for T2N0 glottic carcinoma. Four questionnaires (Voice Handicap Index-30 (VHI-30), European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, EORTC QLQ-HN35, and M.D. Anderson Dysphagia Inventory (MDADI) were used to measure the different aspects of functional outcome. Furthermore, objective evaluation (acoustic and aerodynamic parameters) and perceptual evaluation (GRBAS) was performed.

Results

In total, 14 patients were included in this study. The median time between the start of radiotherapy and the time of assessment was 42 months [range 26-143]. Patients reported high-level functioning with low symptom scores, good swallowing function, and showed a median grade of dysphonia of 1.5. The median VHI-30 score was 17.5. The median VHI-30 score for tumors with superficial spread and deep infiltration into the vocal fold muscle (VM) were 8.0 and 23.5, respectively.

Conclusions

This study shows that patients with T2N0 glottic carcinoma treated with radiotherapy show good long-term QoL with low symptom scores, good swallowing functioning, and slightly elevated voice outcome parameters. Patients with tumors infiltrating the VM showed a trend towards higher VHI-30 scores. More studies are needed to investigate the functional outcomes after treatment for T2 glottic carcinoma.

INTRODUCTION

Radiotherapy is one of the two main treatment modalities for T2N0 glottic carcinoma yielding both high rates of local control and larynx preservation [1]. However, due to the high rates of disease control it is clear that outcome evaluation must include functional outcomes, as patients will generally live out their lives with the handicap the treatment causes. Multidimensional functional parameters such as quality of life, voice outcome (voice quality, voice function, and voice performance) and swallowing performance should be included in the appraisal of treatment results.

Whereas there is a sizeable amount of oncological outcome data available, functional outcomes after treatment for T2 glottic carcinoma with radiotherapy are sparse, especially in the long-term. Most studies have investigated T1 glottic carcinoma alone or grouped T1 and T2 tumors together such that data on T2 tumors is not extractable. The few studies that have reported functional outcomes after treatment with radiotherapy in T2 glottic carcinoma demonstrate an improvement in post-treatment voice, although parameters do not normalize [2–5]. Studies also show that radiotherapy can affect the functional outcome after a longer period of time, probably due to progressive fibrosis in the glottic tissue [6, 7]. However, the T2 stage in glottic carcinoma is a heterogenous group of tumors with varying extension - some have a large surface area without deep extension whereas others may have a smaller diameter but penetrate deep into the vocal fold muscle (VM). To our knowledge, so far only one study has reported outcomes according to tumor extension in T2 glottic carcinoma [5], which is of interest when comparing the outcomes of radiotherapy to those of defects created by surgical modalities. Therefore, the objective of this cross-sectional study was to evaluate the long-term functional outcomes in patients that received primary radiotherapy for T2N0 glottic carcinoma at our center between 2007 and 2016, stratified for tumor extension.

METHODS

Patients

Between January 2019 and April 2019, a cross-sectional study on functional outcomes after treatment for T2N0 glottic carcinoma was performed in the Leiden University Medical Center (LUMC). The target population of the study were patients with T2N0 glottic carcinoma that were treated with radiotherapy between January 2007 and December 2016. Exclusion criteria were: the inability to speak and read the Dutch language, treatment for recurrent disease, treatment for other head and neck tumors and the presence of any cognition conditions hampering compliance with the study (e.g. dementia). This study was approved by the Local Medical Ethics Committee (P18.150) in the LUMC and all patients signed informed consent before inclusion into the study.

Treatment details and radiology

Radiotherapy was applied with a linear accelerator using a 4-6 MV photon beam. For T2a tumors, the total dose ranged from 60 to 70 Gy (median 70 Gy), administered in 5 fractions, ranging between 2.0 and 2.4 Gy (median 2.4), per week for 6 weeks. For T2b tumors, the total dose consisted of 70 Gy, administered in 5 fractions of 2.0 Gy per week for 7 weeks. Additionally, patients with T2a received unilateral elective neck radiation therapy of level II, III, and IV consisting of a total dose ranging between 46.0 and 57.75 Gy (median 54.25 Gy). Patients with T2b tumors received bilateral elective neck radiation therapy of levels II, II and IV consisting of a total dose of 54.25 Gy administered in fractions of 1.55 Gy bilaterally. The field area was 6x6 cm. The upper limit was the hyoid bone, the lower limit the cricoid cartilage and the skin was the anterior border. Chronic complications were analyzed with the common terminology criteria for adverse events (CTCAE) version 5.0. All available preoperative Computed Tomography (CT) scans were reviewed by one radiologist (B.M.V.) and scored for superficial spread versus VM infiltration. If tumors were not visible on CT, they were classified as superficial.

Questionnaires

Four self-administrated questionnaires were implemented: the Voice Handicap Index-30 (VHI-30) [8], the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 [9], the EORTC QLQ-HN35 [10], and the M.D. Anderson Dysphagia Inventory [11]. Patients were asked to complete the questionnaires after the voice recording during their visit in the outpatient clinic.

Voice Handicap Index

The Dutch VHI is a validated questionnaire measuring voice problems in daily life [12]. It consists of 30 questions with three subscales (functional, emotional, and physical) and it is scored with a five-point Likert scale ranging between 0 (never) to 4 (always). Summarizing the score leads to a total score between 0 and 120, with 120 points indicating a maximal voice handicap. A total score of 15 points is taken to indicate voice problems in daily life [8, 12].

EORTC QLQ-C30

The Dutch EORTC QLQ-C30 is a validated questionnaire measuring the health-related QoL in patients with cancer [9]. It comprises 30 questions that address patient function and symptomatology over the preceding week. The questionnaire includes a global health scale, five functional scales (physical, role, emotional, cognitive, and social), three multi-item symptom scales, each containing multiple question on the items fatigue, pain, and nausea and vomiting and six single items, each containing one single question on the items dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties. All items are answered on a four-point Likert scale (1 = not at all, 4 = very much), expect for the global health status, which is score on a 7-point Likert scale (1 = very poor, 7 = excellent). Calculated scores range between 0 and

100. Depending on the item, a higher score can represent a higher (better) level of functional or a higher (worse) level of symptoms.

EORTC QLQ-HN35

The Dutch EORTC QLQ-HN35 is a validated questionnaire that evaluated the health related QoL specifically in head and neck cancer patients [10]. It consists of 35 question that address symptoms and side effects of treatment, social function, and body image/sexuality. The questionnaire incorporates 7 multi-items scales (pain, swallowing, senses (taste and smell), speech, social eating, social contact, and sexuality), and 11 single items (teeth, opening mouth, dry mouth, sticky saliva, coughing, feeling ill, use of analgesics, nutritional supplements, feeding tube, weight loss, and weight gain), that are answered on a four-point Likert scale. Calculated scores range between 0 and 100. A higher score represents more severe problems or symptoms.

MDADI

The Dutch MDADI is a validated questionnaire evaluating the impact of dysphagia on the QoL [13]. It comprises 20 questions that are answered on a five-point Likert scale ranging between 1 (strongly agree) and 5 (strongly disagree). Two questions are scored in the opposite direction, i.e. 1 (strongly disagree and) and 5 (strongly agree). The questionnaire is subdivided in a global score and three subscales (emotional, functional, and physical). A higher score indicates a higher functioning [11, 13].

Perceptual evaluation

Perceptual analysis was performed using the GRBAS-rating scale on a 30 second running speech sample [14]. The speech sample consisted of a standard phonetically balanced Dutch text "80 dappere fietsers" (80 brave cyclists). The GRBAS scale comprises 5 subscales (grade, roughness, breathiness, asthenia, and strain), of which only the grade was rated. A panel of two experienced speech-language pathologists (B.J.H and V.A.H. vdK) familiar with the GRBAS-system who were blinded to all data, conducted the perceptual evaluation. Each speech sample was scored from 0 (normal) to 3 (severely dysphonic); a higher score therefore indicates a more dysphonic voice [14].

Objective evaluation and voice recording

The voice recordings were made in a noise-free environment and were acquired at a sampling frequency of 44.1kHz with a dual microphone headset recorder (Alphatron Medical Systems) and a Byer dynamic microphone (type Opus 56, Germany). The voice parameters existed of aerodynamic parameters (maximum phonation time (MPT)) and acoustic parameters (dynamic range, fundamental frequency, percentage jitter, percentage shimmer and the harmonics to noise ratio (HNR)). The acoustic parameters were measured with PRAAT software for acoustic analyses [15]. The MPT was determined by measuring the duration of the substained /a/ at the

most comfortable pitch and loudness. The longest MPT from two attempts was taken as the representative MPT. Jitter, shimmer and HNR were measured on a stable 2-second mid-section of the sustained /a/. The dynamic range in decibels (dB) and the fundamental frequency in Hertz (Hz) were extracted from the patient's phonetogram recorded with the program Voice Range Profiler (VRP) (Alphatron, Rotterdam, the Netherlands, 2007).

Statistical analysis

Statistical analysis was performed using SPSS version 25.0 (IBM Corp. Released 20117. Armonk, NY, USA). First, descriptive statistics of the median with range were calculated for all different outcomes. Then, Spearman correlation coefficient were calculated between the grade and the other voice outcome parameters and between the time to assessment and the different voice outcome parameters. The VHI-30 score was compared between tumors with superficial spread and those with VM infiltration. To test this difference the Mann-Whitney U test was used.

RESULTS

Patients

In total, 68 patients were treated with radiotherapy for a T2N0 glottic carcinoma between 2007 and 2016. Forty patients were excluded: 5 patients due to the development of recurrent disease and 35 patients due to having deceased. In total, 28 patients were approached of which 14 agreed to participate in this study (response-rate 50.0%). Baseline characteristics are presented in table 1. The median time between the start of treatment and assessment was 42 months [range 26-143].

Voice Handicap Index

The median VHI-30 score was 17.5 with a range between 1 and 54 (table 2). Six out of the fourteen patients (42.9%) reported a VHI-30 score within the normal range (<15 points). The physical subscale showed the highest score with a median of 9.0 [0-22]. The emotional and physical subscales showed lower scores, 6.0 [0-16] and 2.0 [0-16], respectively. Patients with deep infiltration of the VM showed a higher VHI-30 score (median 23.5 [1-54]) than patients with superficial spread (median 8.0 [3-39]) . However, this result was not statistically significant (p=0.272).

EORTC QLQ-C30

Patients showed a good global health status with a median of 79 points at time of assessment (table 3). The results of the different functional scales also showed high levels of functioning, ranging between 87 and 100 points. The most registered complaints were fatigue (median 22 [0-78]) and insomnia (median 17 [0-100]).

EORTC QLQ-HN35

The symptom scale showed low symptom scores (table 4). After a median of 42 months the most registered complaints were dry mouth, (median 33 [0-100]), sticky saliva (median 33 [0-100]), coughing (median 33 [0-100]) and a decrease in sexuality (median 50 [0-100]). Notably, patients did not complain about speech problems in this questionnaire and the median score of 6 on this item is considered as low.

Table 1. Patient characteristics

Characteristics	No. of patients (%)
Total group	14 (100)
Sex	
Male	11 (78.6)
Female	3 (21.4)
Median age at RT [range]	64.0 [47-84]
Clinical characteristics	
Mobility	
Normal	12 (85.7)
Impaired	2 (14.3)
AC involvement	
Yes	5 (35.7)
No	9 (64.3)
Radiological characteristics	
Tumor extension	
Superficial spread	6 (42.9)
Deep infiltration in the VM	8 (57.1)

AC= anterior commissure, RT = Radiotherapy, VM = vocal fold muscle

Table 2. Median values for voice outcome parameters

Voice parameters	Total (n=14)
Voice Handicap Index	17.5 [1-54]
Superficial (n=6)	8.0 [3-39]
Deep (n=8)	23.5 [1-54]
Grade*	1.5 [0-3]
MPT (sec)	17.4 [4.7-34.3]
Dynamic range (dB)	36.0 [26-50]
Fundamental frequency (Hz)	
Male (n=11)	98 [86-181]
Female (n=3)	171 [147-194]
Jitter (%)	0.66 [0.30-3.50]
Shimmer (%)	5.5 [1.65-15.7]
HNR (dB)	17.5 [9.02-21.7]

dB = decibels, HNR = harmonics to noise ratio ,Hz = hertz, MPT = Maximum phonation time, sec = seconds

Table 3. Quality of life results according to the EORTC QLQ C30

EORTC QLQ-C30	Median [range]
Global Health	
Global health status	79 [42-100]
Functional scales	
Physical functioning	87 [53-100]
Role functioning	100 [67-100]
Emotional functioning	92 [59-100]
Cognitive func tioning	100 [67-100]
Social functioning	100 [17-100]
Symptom scales / items	
Fatigue	22 [0-78]
Nausea and vomiting	0 [0-33]
Pain	8 [0-50]
Dyspnea	0 [0-67]
Insomnia	17 [0-100]
Appetite loss	0 [0-100]
Constipation	0 [0-33]
Diarrhea	0 [0-100]
Financial Difficulties	0 [0-67]

Table 4. Quality of life results according to the EORT QLQ-HN35

EORTC QLQ-HN35	Median [range]
Symptom scales / items	
Pain	8 [0-25)
Swallowing	0 [0-42]
Senses problems	0 [0-50]
Speech problems	6 [0-56]
Trouble with social eating	0 [0-50]
Trouble with social contact	0 [0-33]
Less sexuality	50 [0-100]
Teeth	0 [0-67]
Opening mouth	0 [0-0]
Dry mouth	33 [0-100]
Sticky Saliva	33 [0-100]
Coughing	33 [0-100]
Felt ill	0 [0-67]
Pain killers	0 [0-67]
Nutritional supplements	0 [0-0]
Feeding tube	0 [0-0]
Weight loss	0 [0-100]
Weight gain	0 [0-67]

MDADI

The MDADI showed high functioning, with a median score of 95.0 [32-100] (maximum score 100) (table 5). In this questionnaire there was one outlier with a total score of 32. We cannot exclude the possibility that this was due to a misunderstanding of the instructions as all other questionnaires indicated a high level of functioning in this individual.

Table 5. Results on the impact of dysphagia on quality of life measured by MDADI

MDADI	Median [range]
Total score	95.0 [32.0-100]
Emotional subscore	90.0 [23.7-100]
Functional subscore	100 [28.0-100]
Physical subscore	95.0 [37.5-100]

Perceptual evaluation

The median grade of dysphonia was 1.5 with a range between 0 and 3 (table 2). In three patients (21.4%) the voice was scored as normal, in 4 patients (28.6%) as mildly dysphonic, in 6 patients (42.9%) as moderately dysphonic and one voice (7.15%) was rated as severely dysphonic. The grade was lower in the patients with deep infiltration (median 1.0 [range 0-2]) in the VM than in patients with superficial infiltration (median 2.0 [range 0-3]). However, this result was not statistically significant. No correlations were found between the grade and other voice parameters.

Acoustic and aerodynamic parameters

The median values for the different acoustic and aerodynamic parameters are shown in table 2. The median MPT was 17.4 seconds [range 4.7-34.23]. The voice in the patient with the lowest MPT (4.7 seconds), was so severely dysphonic that the VRP software was unable to analyze the voice parameters due to the irregularity of the signal. Also, the other acoustic parameters could not be analyzed in this patient. No correlations exist between time of assessment and the difference voice outcomes measures.

Toxicity

Treatment was not interrupted in any of the patients. In two patients (14.3%) a grade 3 acute adverse event was reported. One patient required a nasogastric feeding tube during treatment for grade 3 dysphagia and one patient required admission to the hospital and medication due to grade 3 dyspnea. Five patients reported late complications of hypothyroidism (35.7%), of which three were treated with medication. In the two other patients' treatment was not necessary.

DISCUSSION

In this cross-sectional study, we investigated long-term functional outcomes in patients with T2N0 glottic carcinoma treated with radiotherapy. Our results show good long-term results after a median follow-up of 42 months. In general, the VHI was slightly elevated, whereas the perceptual evaluation showed mild to moderate dysphonia. Quality of life scores indicate high functioning with low symptom scores and the swallowing function showed high functioning as well. Patients with infiltration of the VM showed a trend towards a higher voice handicap than those with superficial spread, however this was not statistically significant. No correlations were found between voice outcomes parameters and the time of assessment.

Only a few studies have presented long-term (> 24 months) functional outcomes after treatment with radiotherapy. Only two studies described acoustic and aerodynamic parameters after treatment with radiotherapy in T2N0 glottic carcinoma [2, 4]. The study of Niedzielska evaluated the phonatory function after 1-3 years in 11 male patients with T2N0 glottic [4]. Their voice outcome parameters (jitter, shimmer, fundamental frequency and MPT), were comparable with our results. The study of Argarwal et al. analyzed the voice quality (jitter, shimmer, and minimal intensity) before and after radiotherapy (between 3 and 6 months) in 50 patients, of which 17 patients had T2 glottic carcinoma [2]. We found similar scores for jitter, but higher scores for shimmer. This difference might be explained by the fact that they used other testing conditions than ours. A study by Remmelts et al. investigated the voice outcome with the physical subscale of the VHI-30 questionnaire [16]. They found a mean score of 9.9 (range 0-30) on this subscale in 38 patients with T2 glottic carcinoma, after a median time of 66 months. We found a similar score on this subscale after a median time of 42 months.

A study by Al-Mamgani et al. investigated the VHI in 223 patients with T1-T2 glottic carcinoma [5]. The VHI-30 score in patients treated for a T2a tumor after 36 and 48 months was 24.3 and 23.8, respectively. The mean score in T2b tumors after 36 and 48 months was 36.2 and 39.7, respectively, showing that tumors leading to impairment of vocal fold movement (T2b) had a higher voice handicap than tumors that did not. Compared to this both our study, and the study by Remmelts et al., showed lower VHI-index scores for patients with T2 tumors treated with radiotherapy. However, in line with Al-Mamgani et al. we did find a trend towards higher VHI-30 scores in patients with more deeply infiltrating tumors, which in our case was defined as tumors that infiltrated the VM. It is possible that our study was positively influenced by the small numbers of participants and the fact that our cohort consisted mainly of T2a tumors (n=12 (85.7%)). Even if seven (58.3%) of these T2a tumors had infiltration of the VM they still showed normal mobility. Therefore, T2b tumors with impaired mobility were underrepresented in our cohort. Looking at our results we hypothesize that patients with T2 glottic tumors infiltrating the VM may have poorer voice outcome, with T2b with fixated vocal folds having the poorest result.

This hypothesis will however have to be proven in larger studies. The study of Remmelts et al. did not describe the substage of T2 tumors, which officially are no longer part of the American Joint Committee on Cancer Staging [17], and only assessed the psychical subdomain of the VHI-30 [16]. It is not known whether this subdomain is representative of the total score of the VHI-30.

More data on functional outcomes of different subcategories of T2 tumors in radiotherapy is crucial for an adequate comparison of results to those of other treatment modalities. In surgical studies, for instance on transoral laser microsurgery (TOLMS), it has long been recognized that T2 glottic carcinomas are a heterogeneous group of lesions, requiring a variation of different types of resection, with varying functional and oncological outcomes [18]. Studies show that larger resection types as defined by the European Laryngological Society (ELS) (ELS type IV-VI resections) result in worse voice outcome, compared to superficial resection (ELS type I-III resections) [19, 20]. As the study by Al-Mamgani and our study indicate, comparing functional outcomes of these different resection to a simple mean or median score for an overall cohort of patients with T2 glottic tumors treated with radiotherapy is probably not adequate when determining the relative merits of the treatments and when counselling patients in therapy choice. Furthermore, it is our opinion that to harmonize outcome studies between modalities, the subcategorization of tumors and comparison between modalities should be based on clinical and radiological extension of the tumor in addition to mobility (T2a/T2b).

As for the quality of life, the EORTC QLQ-C30 questionnaire is designed as a general questionnaire for patients with cancer, whereas the head and neck module (EORTC QLQ-HN35) is designed for patients with head and neck cancer patients and thus more sensitive for specific toxicities and symptoms related to the treatment. To our knowledge, there are no studies that report results with these questionnaires for T2N0 glottic carcinoma specifically. Two studies that used the EORTC QLQ-C30 and HN35 questionnaires included both T1 and T2 glottic carcinoma and treated them with radiotherapy [21, 22], but did not report separately on the two categories. The study by Arias et al. investigated QoL in 59 patients, of which ten had T2 tumors. Their results showed almost similar elevated scores on the EORT QLQ-C30 compared with our results. On the EORTC QLQ-HN35 they showed the highest scores on the items dry mouth, stick saliva, coughing, use of painkiller and weight gain [22], where we reported the highest scores on less sexuality, dry mouth, sticky saliva and coughing. The study of Stoeckli et al. investigated QoL in 16 patients with T1 and T2 tumors. They did not specify how many patients had T2 tumors. This study also reported an elevated score for fatigue and insomnia on the EORTC QLQ-C030 and also showed the highest scores for dry mouth, sticky saliva and coughing [21], similar to our results. However, a comparison of our results with normative data from the general Dutch population on the EORTC QLQ-C30 questionnaire shows comparable scores, even on the elevated items (fatigue and insomnia) [23]. Therefore, the question remains if these elevated items on the long-term are related to the treatment or not? Unfortunately, no normative data

from the general Dutch population exists for the EORTC QLQ-HN35. Therefore, a comparison was made with a multinational study on 108 patients with newly diagnosed laryngeal cancer (stage I-IV) and 185 disease free patient after treatment for laryngeal cancer [24]. Elevated scores in our study are comparable with their combined scores (patients undergoing active treatment and disease free-patients), only the sexuality item is higher in our study.

Limitations

The study has some limitations. Firstly, the sample size was small and T2b tumors were underrepresented. As stated, this may have positively biased our results. Secondly, due to the cross-sectional study design, comparison between pre- and posttreatment was not possible. Also, not all patients were assessed at the same time-point postradiotherapy, although there was minimum follow-up of 26 months, that in our opinion represent a long-term follow-up.

CONCLUSION

Based on our findings, we conclude that patients with T2N0 glottic carcinoma treated with radiotherapy show overall good long-term QoL with low symptom scores and slightly elevated voice outcomes parameters, that do not return to normal values after a median of 42 months. Patients with tumors infiltrating the VM show a trend towards a higher voice handicap, which is supported by data in the literature. More studies are needed to investigate (long-term) functional outcomes after treatment for T2 glottic carcinoma; particularly to investigate the effect of tumor extension on functional outcomes after treatment with radiotherapy so as to allow for a meaningful comparison of results to those of other treatment modalities and for more accurate counselling of patients.

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Chapter 8

Conclusions and recommendation for further research

CONCLUSIONS AND RECOMMENDATIONS FOR FURTHER RESEARCH

INTRODUCTION

The work in this thesis tackles several issues regarding the treatment of early glottic cancer (Tis-T2), with a specific focus on T2 glottic carcinoma. The objective is to compare oncological and functional treatment outcomes between transoral CO2 laser microsurgery (TOLMS) and radiotherapy, as well as to investigate prognostic factors in both treatment modalities to support decision making in T2 glottic carcinoma. With this information, we try to answer our main question: what is the future role of TOLMS in patients with T2 glottic carcinoma in the Netherlands, where the use of TOLMS is currently limited in these patients. As such, this thesis will act as a platform for the investigation whether this can be expanded into these patients. In this chapter, the main findings and conclusions are presented, followed by remaining issues in the treatment of T2 glottic carcinoma and the recommendations for future research.

MAIN FINDINGS

Oncological outcomes

In **chapter 2**, we performed a systematic review to give an overview of the laryngeal preservation rate in patients with T2 glottic carcinoma primarily treated with TOLMS or radiotherapy. This study showed that primary treatment with TOLMS results in a higher laryngeal preservation rate than primary treatment with radiotherapy in T2 glottic carcinoma. The five-year laryngeal preservation rate after TOLMS and radiotherapy were 88.8 and 79.0%, respectively [1]. This indicates that the principle of a higher larynx preservation rate when using TOLMS as primary treatment modality, which has been described earlier in T1 glottic tumors [2–8], is also applicable in T2 lesions. In this study, we also found that T2a tumors showed better oncological outcomes than T2b tumors for both TOLMS and radiotherapy.

Chapter 4 is a retrospective cohort study in patients with Tis-T2 glottic carcinoma treated with TOLMS between 2009 and 2013, focusing on the five-year oncological outcomes. The five-year rates of local control, overall survival, disease-specific-survival, and laryngeal preservation were 78.6, 78.0, 98.6 and 100%, respectively. The local control rates for Tis, T1, and T2 were 78.9, 80.4 and 70.0%, respectively [9]. These rates were comparable with large series in the literature, although the five-year local control rate for T1 tumor is in the lower range [10] showing that results for TOLMS from larger clinics are attainable in our center. Extensive analysis showed that the lower local control in these tumors was related to the learning curve, which has been reported earlier in treatment with TOLMS [11, 12].

Chapter 6 is a retrospective cohort study in patients with T2 glottic carcinoma that were treated

with radiotherapy between 2000 and 2012 in which we investigated the five- and ten-year oncological outcomes. The local control, overall survival, disease-specific survival, and laryngeal preservation rates were 70.5. 63.7, 86.0, 74.7% at 5 years and 65.8, 41.0, 75.6, and 72.4% at ten years [13]. Our five- and ten-year survival rates were comparable with studies reported in the literature [14–32]. The five-year laryngeal preservation rate is also comparable with our review, reporting a laryngeal preservation rate of 79.0%. Although study design and time period differ between studies in this thesis, and recruitment has taken place in different hospitals, oncological outcomes between the different studies are comparable and correspond to the results reported in the literature, indicating that basing future treatment decisions on outcome data in literature is a valid strategy for our center.

Regarding oncological outcomes, we conclude from the studies above that the same principle of a higher larynx preservation when using TOLMS as primary treatment modality, which has been described earlier in T1 glottic tumors, is also applicable in T2 lesions. In addition, our findings show that the oncological outcome data in our center are in line with those of literature, indicating that results for TOLMS from larger clinics are attainable in our center and that basing future decisions on the outcome data in literature is a valid strategy for both TOLMS and radiotherapy.

Risk factors for oncological failure in TOLMS and radiotherapy

In **chapter 3,** we performed a systematic review that examined the involvement of the anterior commissure as a prognostic risk factor. We found that most studies – for both TOLMS and radiotherapy – do not report a significant impact of anterior commissure involvement on local control, overall survival, disease-specific survival, or laryngeal preservation. Weighted averages were slightly lower in patients with anterior commissure involvement than patients without involvement. Furthermore, the review showed that the use of binary variables (yes/no) for the involvement of the anterior commissure leads to conflicting results due to variability in definition, work-up, and treatment parameters of the anterior commissure area. Studies that used a more detailed classification for the anterior commissure involvement generally show a significant impact on the local control [33–36]. The impact in these studies is related to the degree of involvement of the anterior commissure. Therefore, our analysis of the data supports earlier publications that have called for a more detailed stratification for anterior commissure involvement [33, 34, 37].

In **chapter 6**, we investigated several clinical, treatment, and imaging-related variables in patients with T2 glottic carcinoma treated with radiotherapy. The four parameters that we reviewed on imaging were: 1) tumor infiltration in the vocal fold muscle (superficial versus deep infiltration); 2) horizontal involvement of the anterior commissure in the glottic plane; 3) vertical involvement over the anterior commissure (subglottic or/and supraglottic extension); and 4) tumor location related to the M-line, which is defined by the surgical plane tangential to the arytenoid vocal

process and perpendicular to the ipsilateral thyroid lamina (anterior versus posterior) [35]. These parameters have previously been shown to have an unfavorable prognosis in surgically treated patients and to the best of our knowledge have not been investigated in patients treated with radiotherapy [34, 38, 39]. In this chapter, we found that vertical anterior commissure involvement on imaging had a significant impact on local control. Horizontal involvement of the anterior commissure showed a trend towards lower local control and laryngeal preservation. Deep muscle infiltration into the vocal fold muscle on imaging showed a trend toward lower local control and disease-specific survival. No other patient, tumor or treatment-related variables in our analysis had any significant impact oncological outcomes [13].

In chapter 4, we found that in our patients with Tis-T2 tumors treated with European Laryngological Society (ELS) type I-III resections, positive surgical margins did not show an impact on local control and therefore mandatory retreatment is not necessary. However, we found that additional positive wound bed biopsies, routinely taken after ELS type I-III resection, were significantly associated with lower local control. Based on these results we suggest that there is enough evidence for a wait-and-see policy with close follow-up in patients with positive surgical margins and negative wound bed biopsies. For patients with positive wound bed biopsies, further treatment is warranted [9].

Regarding risk factors, we conclude that the use of a binary variable (yes/no) for the involvement of the anterior commissure leads to inconsistent results and that this parameter needs to be classified in more detail. When this is done, the anterior commissure shows a more consistent risk profile in which vertical involvement of the anterior commissure in particular is a prognostic factor both in patient treated TOLMS and radiotherapy. Furthermore, we find that there are indications that other surgical risk factors such as deep muscle involvement may be prognostic in patients treated with radiotherapy and should also be considered when designing treatment in these cohorts.

FUNCTIONAL OUTCOMES

A variety of studies has been performed for functional outcomes after treatment in T1 glottic carcinoma. However, the literature on functional outcomes after treatment for T2 glottic carcinoma is sparse. In **chapter 2**, we performed a systematic review to gain an overview of what is known about the functional outcomes after TOLMS and radiotherapy in T2 glottic carcinoma. However, a direct comparison between TOLMS and radiotherapy was not possible for several reasons including the heterogeneity of both tumor stages and outcome measures between the studies. Several larger studies had to be excluded for these reasons. Despite the fact that TOLMS is often considered more harmful to the voice – especially where more extended resections such as ELS IV-VI resection are concerned – no definite conclusions can be drawn regarding the relative

functional outcomes of the two modalities [40], and more comparative studies, matched for the extent of the tumor, are needed to investigate how the two treatment modalities really compare.

Chapter 5 prospectively assessed the long-term voice outcome and quality of life (QoL) in patients with T1 and T2 tumors, which were treated with bilateral type II resection of unilateral type III resection, according to the ELS classification between 2009 and 2015. Furthermore, we determined timepoint after the procedure at which the voice outcome reached a stable condition. Our results showed that patients reported good QoL with a high level of functioning and limited symptoms two years after treatment with only a slight elevation in voice outcome scores compared to normal values. Patients with T1a tumors showed significantly better perceptual evaluation than patients with T1b and T2 tumors. Patient with T2 tumors showed similar perceptual scores pre- and post-operatively. Most of the improvements were observed within the first 6 months, and this level of improvement provides a clear indication of the status at 1 and 2 years postoperatively. In this study, we also found that male patients report higher voice handicap index scores, which was to the best of our knowledge not reported in other studies. The potential impact of gender on the voice handicap index should be investigated in further studies [41].

Chapter 7 cross-sectionally assessed the long-term functional outcomes (>24 months) in patients treated with radiotherapy for T2 glottic carcinoma between 2007 and 2016. In this study, we found that patients treated with radiotherapy showed good QoL with low symptoms scores, good swallowing function, slightly elevated VHI scores, and mild to moderate dysphonia. In this study, no correlation was found between worse voice outcome and the time of assessment. We also found that patients with tumor infiltrating the vocal fold muscle showed a trend towards higher voice handicap index than patients with superficial spread, which has been described in our studies, where patients with T2b tumors show poorer voice outcome. However, it is possible that our study was positively biased by the small numbers of participants and the fact that our cohort consisted mainly of T2a tumors.

Regarding functional outcomes, we conclude that patients with T2 glottic carcinoma treated with radiotherapy show good long-term functional outcomes. Patient with superficial tumor spread show a trend toward lower voice handicap index than patients with tumor infiltrating the vocal fold muscle. Compared with the scientific literature, our voice handicap index scores showed better (lower) results in these patients. An explanation for this could be that patients had more time to adapt to their current voice over a longer period of time, and therefore report less deviance than after a shorter period of time. Results could also have been positively biased by the low number of patients and the large number of superficial tumors. No other conclusion could be drawn on T2 glottic carcinoma, due to the heterogeneity of the studies and the different functional outcomes that are used. More research is needed to compare the two main treatment modalities in T2 glottic carcinoma.

GENERAL CONCLUSION

During recent decades, many studies have been performed in patients with early glottic cancer, which provide new insight into the two main treatment modalities, TOLMS and radiotherapy, and their outcomes. Building on these studies, this thesis aimed to contribute to this body of knowledge focusing on the following research questions: (i) What is the role of TOLMS in T2 glottic carcinoma in the Netherlands? (ii) Should more patients with T2 glottic carcinoma be treated with TOLMS?

Within this thesis, we found that (i) the laryngeal preservation rate for T2 glottic carcinoma is higher after primary treatment with TOLMS than after primary treatment with radiotherapy, and that this is higher for T2a than for T2b tumors for both treatment modalities; (ii) that the binary use (yes/no) for the involvement of the anterior commissure as a prognostic factor leads to inconsistent results, whereas studies with a more detailed classification of the anterior commissure show that there is a significant impact on oncological outcomes; (iii) that vertical involvement of the anterior commissure on imaging has a significant impact on local control not only in patients treated with TOLMS but also in patients receiving primary radiotherapy; and (iv) that patient with T2 glottic carcinoma treated with radiotherapy reported good long-term functional outcomes, although patients with tumors infiltrating the vocal fold muscle show a trend toward a higher degree of voice handicap than patients with tumor with only superficial spread.

IMPLICATIONS OF THESE FINDINGS

Firstly, from an oncological viewpoint, a higher laryngeal preservation rate after TOLMS means that expanding the current indications for TOLMS should be considered. The Dutch guideline for the treatment of laryngeal cancer has not been updated since 2009 and is currently undergoing revision. However, in the last version TOLMS was only recommended for T1a tumors, which require an ELS type I or type II resection [42]. Based on the work in this thesis and earlier work of our group in this area, from an oncological viewpoint [43, 44], we would advocate seriously considering TOLMS for the primary treatment of more extended T1a and selected T2 glottic carcinomas. The T2 stage in glottic carcinoma is a heterogeneous collection of tumor extensions leading to a wide range of local control and laryngeal preservation rates, and not all T2 tumors might be suitable for TOLMS. Several authors have stratified these tumors according to the location and the extension of the tumors and defined the role and limits of TOLMS as a treatment modality [34, 36]. Based on our results and in accordance with the studies previously mentioned, we would suggest that patients with tumors that have superficial supraglottic or infraglottic extension, horizontal involvement of the anterior commissure and deep infiltration into the vocal fold muscle can be treated with TOLMS with good oncological outcomes. However, it must be emphasized that there is a learning curve to the surgical technique and as we have

seen from our own data, an experienced surgeon is required to obtain the results as presented in larger series in literature [45, 46]. Tumors with vertical involvement of the anterior commissure lead to lower local control and laryngeal preservation in both TOLMS and radiotherapy due to the close relationship with the visceral compartments in this area. Therefore, in these cases, both treatment modalities are an option and decision making should incorporate the experience of the surgeon as well as careful consideration of the pros and cons of both techniques. In addition to the involvement of the anterior commissure, other factors play a role in oncological outcomes. We have found indications that known surgical risk factors, previously unstudied in patients undergoing radiotherapy, may play a significant role in these patients as well. Tumor extension within the T2 stage therefore needs close attention, not only in the surgical but also in both treatment groups for prognostic and counselling purposes.

Regarding the functional outcomes, we can expect the results in the patients with superficial subtypes of T2 tumors (superficial supraglottic or infraglottic extension and horizontal involvement of the anterior commissure) to be postive based on earlier studies as the resection will remain limited at the level of the vocal fold. In patients with deep infiltration into the vocal fold muscle, our findings show that there is insufficient stratified data to compare the two treatment modalities, and that therefore no definite conclusions can be drawn. However, our data also show that ELS type III resections are functionally well tolerated with low levels of voice handicap contrary to the once common conception in the Netherlands that these resections would lead to poor voice outcome [43]. Additionally, limited data from this thesis and earlier data [47] suggest that deep infiltration in the muscle may have a negative impact on voice outcome in patients treated with radiotherapy as well. The implications of these findings are that the benefits of TOLMS may still outweigh the drawbacks and that withholding these resections based on presumed functional adversity may be limiting not only patient choice but also patient outcome. The remaining part of this chapter will focus on remaining issues in T2 glottic carcinoma as well as the recommendations for further research.

REMAINING ISSUES IN THE TREATMENT OF T2 GLOTTIC CARCINOMA

As always, there are many areas in which the overall care for patients with head and neck cancer can be improved. Directly related to our line of research, one such area is that of assessment and classification of glottic carcinomas in general and T2 carcinomas specifically. Two issues within this area, insufficient stratification in outcome studies and insufficiencies in the current tumor staging system, are discussed below as they are of particular importance to future studies in this field.

Insufficient stratification in outcomes studies

The T2 stage consists of a collection of heterogenous tumors with regard to local extension and

prognosis [34, 36]. Already in 2005, Peretti et al. proposed a subclassification for the T2 stage based on the different extensions of the lesions within this stage and showed the impact of this subclassification on prognosis [36]. In 2018, Piazza et al. designed a more intricate 3D model for subcategorization of glottic tumors according to oncological outcomes [34]. Identifying the particular subtype based on the extension of a tumor on pretreatment imaging would allow for stratification within tumor stages in outcomes studies of different treatment modalities, and would in turn provide a more accurate comparison of both oncological and functional results. These improved outcomes would also make customization for evaluation and treatment of a specific tumor feasible [34].

Insufficiencies in the current tumor staging system

An effective staging system must provide consistent and accurate information for predicting outcomes for a given tumor stage and must be clear to interpret. The TNM classification does not fulfill these requirements and has not been substantially updated since 2002 for glottic tumors even though various new aspects have been highlighted in the last 18 years. For instance, the definition of the T1 versus T2 substage within the TNM classification can lead to inconsistencies. The depth of the lesions is not taken into consideration and is substituted with a clinical parameter – mobility of the vocal fold. As this is a subjective parameter, some take this to mean mobility of the arytenoid and not the membranous part of the vocal fold, whereas others consider even a slight decrease in membranous vocal fold movement due to bulkiness of the tumor to warrant an upstaging. However, a tumor that grows into the vocal fold muscle does not necessarily lead to impaired mobility and an exophytic tumor that seems to impair the vocal fold purely based on exophytic bulk can still be superficial. Although vocal fold mobility is a subjective parameter, several studies have highlighted that patients with impaired vocal fold mobility have a higher risk of recurrent disease than patients with normal mobility [15, 16, 23, 48–53]. It has even been argued that the outcomes of patients with impaired mobility are more comparable to T3 tumors [45]. This has led some clinicians, particularly surgeons, to shift to radiological parameters identifying high risk areas within the larynx that have been consistently associated with a decrease in tumor control (e.g. deep involvement into the vocal fold muscle, posterior involvement of the vocal fold muscle, vertical or horizontal involvement of the anterior commissure). Not making this distinction may lead to withholding of additional treatment for patients with poorer prognosis, which could impact their outcome. Such data could be used to revise the TNM classification to improve coherence and prognostic accuracy of staging. However, before this can be done these radiological risk factors from surgical studies need to be assessed for their prognostic value in other treatment modalities. Once high-risk patients can be better identified, there is still the question of the optimal treatment strategy for these patients.

RECOMMENDATIONS FOR FURTHER RESEARCH

Based on the findings in this thesis and on the remaining issues discussed above, we propose three different directions for further research that could contribute to the ongoing discussions on which patients would benefit most from TOLMS and which patients would most benefit from radiotherapy in T2 glottic carcinoma? Before giving these further recommendations, it is important to realize that no randomized controlled trials exist in patients with T2 glottic carcinoma. There has been one study that has aimed to compare TOLMS to radiotherapy in patients with early glottic cancer. However, this trial failed to recruit enough patients and closed without reaching their primary endpoints [54]. The main reasons for the failure of this study were that surgeons and recruiters did not all accept the primary outcome (locoregional recurrence) as a rationale for the study and both treatment modalities were considered equally successful, recruiters and patients focused on the pragmatics of the different study arms, favoring TOLMS rather than a longer treatment period with radiotherapy over radiotherapy [54], as well as the large number of patients needed due to the relatively high success rate of both treatments and the relatively small difference in outcome between them. Since then, no authors have attempted to start a randomized controlled trial and most evidence is based on retrospective studies supplemented by a few prospective series. A future randomized trial is unlikely to be initiated for the reasons discussed above.

1) Comparison between TOLMS and radiotherapy in T2 glottic carcinoma

In our opinion, the primary goal for further research in the line of this thesis is to work towards a reliable and therefore stratified comparison between functional outcomes after TOLMS and radiotherapy in the subtypes of T2 glottic carcinoma that are well treatable by TOLMS as described earlier. Comparing lesions that have been stratified for tumor extension before treatment will allow for a more accurate comparison of the functional outcomes. It will determine if voice results after TOLMS are indeed as bad as widely assumed in the Netherlands though not supported by earlier studies in this field. This will also help treating physicians weigh the pros and cons of both treatments with patients in a more evidence-based manner. Preparations for this study are underway.

2) Determine cross-treatment risk factors

Furthermore, in this thesis we find that there are indications that known surgical risk factors relating to tumor extension (e.g. deep involvement into the vocal fold muscle, posterior involvement of the vocal fold muscle, vertical or horizontal involvement of the anterior commissure) may be prognostic in patients treated with radiotherapy as well. Due to the limited sample size in our study, further research is needed to confirm this. If these factors prove to identify high-risk patients with a poorer prognosis for both TOLMS and (chemo)radiotherapy, then these factors may then be considered for the adaption of the TNM classification. This leads to the question of

how tumor extension in these risk areas is best visualized. Currently, CT is the mainstay in most centers for the assessment of submucosal tumor spread. However, MRI has been indicated to be more accurate in preoperative staging of T1-T2 glottic carcinoma than CT (MRI 80% accurate versus CT 70%) [55]. MRI can provide information that is currently beyond the capability of CT, although evaluation with MRI has some limitations such as the higher level of experience needed for the assessment and degradation of image quality related to motion artifacts in non-cooperative patients [56]. A great advantage is that next to identifying tumor extension into high risk areas, MRI can also better delineate tumor boundaries and therefore predict the extent of the resection that is needed during TOLMS [57]. This information can then subsequently be used in counseling with a patient during their clinical decision making as to the functional outcome of the required resection. Further data on the role of MRI in the work up of glottic cancer is therefore needed.

3) Other treatment options or adjuvant treatment in high-risk patients

To further improve local control rates in high-risk patients in T2 glottic carcinoma, other treatment modalities might be considered, such as chemoradiotherapy (CRT) or open partial horizonal laryngectomy (OPHL). CRT may be applied as a treatment strategy in patients with high-risk T2 tumors, such as vertical involvement of the anterior commissure, deep infiltration into the vocal fold muscle, and posterior muscle involvement, that initially would be treated with radiotherapy only [58]. Limited data suggests that chemoradiotherapy can further improve LC rates in high-risk patients and can preserve the larynx and function [59–63]. The role of OPHL as well as its oncological and functional outcomes has been well described [64] and we anticipate the indications in T2 glottic carcinoma will be limited in general and in the Dutch situation specifically [64], but further studies are need to determine the role of CRT for specific T2 glottic tumors.

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Chapter 9

Dutch summary / Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Het larynxcarcinoom is een zeldzame kankersoort. In Nederland worden per jaar ongeveer 700 patiënten gediagnosticeerd met het larynxcarcinoom. Zesenzestig procent van de larynxcarcinomen ontwikkelt zich op glottis niveau, waarop de focus ligt in dit proefschrift. Hiervan is 56% een T1 tumor, 30% een T2 tumor en de overige een T3 of T4 tumor. Het glottis larynxcarcinoom presenteert zich in de meeste gevallen met heesheid en wordt daarom vaak in een vroeg stadium gediagnostiseerd. De twee belangrijkste behandelmodaliteiten voor het T1 en T2 glottis larynxcarcinoom zijn laserchirurgie en radiotherapie. Volgens de Nederlandse richtlijn van het larynxcarcinoom uit 2009 is de aanbevolen behandeling voor een oppervlakkige 'midcord' T1 tumor laserchirurgie en voor de overige T1 tumoren en T2 tumoren radiotherapie. Uit recent onderzoek is gebleken dat ook de grotere T1 tumoren en kleine T2 tumoren in aanmerking kunnen komen voor laserchirurgie en dat als patiënten zelf een keuze mogen maken zij de voorkeur hebben voor laserchirurgie. In dit proefschrift wordt getracht de vraag te beantwoorden: Wat is de rol van laserchirurgie bij patiënten met een T2 glottis larynxcarcinoom in Nederland, waarbij het gebruik van laserchirurgie nu beperkt is?

In **hoofdstuk 1** wordt een algemene inleiding gegeven over het larynxcarcinoom. De twee belangrijkste behandelmodaliteiten worden besproken, alsmede hun ontwikkeling door de tijd en de belangrijkste voor- en nadelen van beide behandelingen. Daarnaast worden de twee hoofduitkomsten besproken: de oncologische en functionele uitkomsten. De oncologische uitkomsten bestaan uit lokale controle, totale overleving, ziekte-specifieke overleving en larynxpreservatie. De functionele uitkomsten bestaan uit stemuitkomsten (stemkwaliteit, stemfunctie, stemprestatie), slikfunctie en kwaliteit van leven. Aan het einde van dit hoofdstuk worden de doelstellingen van dit proefschrift besproken.

In **hoofdstuk 2** wordt een overzicht gegeven van de beschikbare literatuur met als belangrijkste uitkomst de larynxpreservatie na de behandeling met laserchirurgie of radiotherapie van het T2 glottis larynxcarcinoom. De 5-jaars larynxpreservatie van primaire behandeling met laserchirurgie en radiotherapie waren respectievelijk 88% en 79%. Daarnaast waren de oncologische uitkomsten voor beide behandelingen hoger voor T2a tumoren dan voor T2b tumoren. Deze resultaten geven aan dat er een hogere larynxpreservatie graad is na primaire behandeling met laserchirurgie, die ook eerder beschreven zijn in T1 glottis larynxcarcinoom. Ook werden de functionele resultaten vergeleken tussen laserchirurgie en radiotherapie bij patiënten met een T2 glottis larynxcarcinoom. Helaas kon geen goede vergelijking worden gemaakt vanwege de heterogeniteit van de uitkomstparameters die gebruikt zijn in de verschillende studies en doordat veel studies het T1 en T2 glottis larynxcarcinoom samen beschrijven in een groep.

In **hoofdstuk 3** wordt door middel van een systematische review de betrokkenheid van de voorste commissuur als prognostische risicofactor besproken. De voorste commissuur is een

complex anatomisch gebied in de larynx. In de meeste studies, voor zowel laserchirurgie (75%) als radiotherapie (67,7%), werd geen significante impact gerapporteerd van de betrokkenheid van de voorste commissuur voor de verschillende oncologische uitkomsten. De gewogen gemiddelden waren in beide behandelingen iets lager voor patiënten met betrokkenheid van de voorste commissuur versus patiënten zonder betrokkenheid. Daarnaast vonden we dat het gebruik van binaire variabelen (ja/nee) voor de betrokkenheid van de voorste commissuur leidt tot tegenstrijdige resultaten. Studies die gebruik maakten van een meer gedetailleerde classificatie van de voorste commissuur, laten over het algemeen een significante invloed zien op lokale controle. De impact in deze studies is gerelateerd aan de mate van betrokkenheid van de voorste commissuur. Onze resultaten ondersteunen daarom gegevens van eerdere publicaties waarin werd opgeroepen tot een meer gedetailleerde stratificatie voor de betrokkenheid van de voorste commissuur en het advies is dit dan ook toe te passen, hetgeen door anderen wordt benadrukt in de literatuur.

Hoofdstuk 4 is een retrospectieve cohortstudie bij patiënten met een Tis-T2 glottis larynxcarcinoom die werden behandeld met laserchirurgie, met type I-III resecties, gedefinieerd door de European Laryngological Society (ELS). In deze studie werd er gekeken naar de 5-jaars oncologische uitkomsten en de impact van chirurgische marges en wondbed biopten op de 5-jaars lokale controle. De lokale controle, totale overleving, ziekte-specifieke overleving en larynxpreservatie na 5 jaar waren 78,6, 78,0, 98,6 en 100% voor de gehele studiepopulatie. De lokale controle percentages voor Tis, T1 en T2 waren 78,9, 80,4 en 70,0%. Deze uitkomsten zijn vergelijkbaar met grotere series in de literatuur, hoewel de 5-jaars lokale controle voor T1-tumoren in het lagere bereik ligt. Uitgebreide analyse toonde aan dat de lagere lokale controle in deze tumoren gerelateerd was aan de leercurve, die eerder gemeld is bij de behandeling met laserchirurgie. Daarnaast werd gevonden dat positieve chirurgische marges geen invloed hadden op lokale controle. We vonden echter dat wondbedbiopten, routinematig genomen na laserchirurgie resecties, significant geassocieerd waren met een lagere lokale controle. Op basis van deze resultaten kan gesuggereerd worden dat er voldoende bewijs is voor een afwachtend beleid met nauwgezette follow-up na positieve chirurgische marges en negatieve wondbedbiopten. Voor patiënten met positieve wondbedbiopten is verdere behandeling gerechtvaardigd.

Hoofdstuk 5 is een prospectieve cohortstudie die de lange termijn stemuitkomsten en de kwaliteit van leven beschrijft van patiënten met een uitgebreidere T1 tumor (groter dan midcord) en kleine T2 tumor, die behandeld zijn met een bilaterale type II en unilaterale type III resectie, gedefinieerd volgens de ELS. De patiënten behandeld met deze resecties rapporteren een goede kwaliteit van leven en hebben een licht tot matige dysfone stem na 2 jaar. Daarnaast laten de functionele uitkomsten in de eerste 6 maanden de grootste verbetering zien en is dit een goede voorspelling voor de resultaten op 1 en 2 jaar postoperatief.

In **hoofdstuk 6** zijn de oncologische uitkomsten en prognostische factoren onderzocht bij patiënten met een T2 glottis larynxcarcinoom die behandeld zijn met radiotherapie. De lokale controle, totale overleving, ziekte-specifieke overleving en larynxpreservatie na 5 jaar waren 70.5, 63.7, 86.0 en 74,7% en na 10 jaar 65.8, 41.0, 75.6 en 72.4%. Deze oncologische uitkomsten zijn vergelijkbaar met de resultaten die gevonden waren in andere studies. Er werden drie soorten prognostische factoren onderzocht: klinisch, behandel en radiologisch gerelateerde factoren. De klinisch en behandel gerelateerde factoren lieten geen significante invloed zien op de oncologische uitkomsten. Een van de radiologische factoren, de verticale betrokkenheid van de voorste commissuur op beeldvorming had een significante invloed op de lokale controle. Horizontale betrokkenheid van de voorste commissuur op beeldvorming toonde een trend naar lagere lokale controle en larynxpreservatie. Diepe spierinfiltratie in de stemband op beeldvorming toonde ook een trend naar lagere lokale controle en ziekte-specifieke overleving.

In **hoofdstuk 7** worden de lange termijn resultaten (≥24 maanden) van patiënten met een T2 glottis larynxcarcinoom besproken die zijn behandeld met radiotherapie. Patiënten rapporteerden op de lange termijn over het algemeen een goede kwaliteit van leven en goede slikfunctie en vertoonden licht tot matige stemafwijkingen, na een mediaan van 42 maanden. In de studie werd geen correlatie gevonden tussen slechtere stemuitkomsten en het tijdstip van beoordeling. Patiënten met diepe spierinfiltratie in de stemband, gescoord met behulp van CT en MRI, vertoonden een trend naar hogere stemhandicap dan patiënten met oppervlakkige verspreiding over de stemband.

In **hoofdstuk 8** worden de bevindingen uit de hoofdstukken 2 tot en met 7 samengevat en de conclusies van dit proefschrift weergegeven. Binnen dit proefschrift wordt geconcludeerd dat (i) de larynxpreservatiegraad voor T2 glottis larynxcarcinoom hoger is na primaire behandeling met laserchirurgie dan na primaire behandeling met radiotherapie, en dat dit hoger is voor T2a dan voor T2b-tumoren voor beide behandelingsmodaliteiten; (ii) dat het binaire gebruik (ja/nee) voor de betrokkenheid van de voorste commissuur als prognostische factor tot inconsistente resultaten leidt, terwijl studies met een meer gedetailleerde classificatie van de voorste commissuur laten zien dat er een significante impact is op de oncologische uitkomsten; (iii) dat verticale betrokkenheid van de voorste commissuur bij beeldvorming een significante invloed heeft op de lokale controle, niet alleen bij patiënten die met laserchirurgie worden behandeld, maar ook bij patiënten die primaire radiotherapie krijgen; en (iv) dat patiënten met T2 glottis larynxcarcinoom behandeld met radiotherapie goede functionele resultaten op lange termijn rapporteerden, hoewel patiënten met tumoren die de stembandspier infiltreren een trend vertonen naar een hogere mate van stemhandicap dan patiënten met een tumor met alleen oppervlakkige verspreiding. Ten slotte worden de verdere implicaties van de gevonden resultaten besproken en suggesties gedaan voor toekomstig onderzoek op dit gebied.

Appendix A

Abbreviations
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ABBREVIATIONS

AC	Anterior commissure
AC+	Anterior commissure involvement
AC-	No anterior commissure involvement
AC0	No involvement of the anterior commissure
AC1	Involvement of the anterior commissure on only one side of the midline
AC2	Involvement of the anterior commissure subsite that crosses the midline on only part of the longitudinal extension of this subsite
AC3	Involvement of the whole anterior commissure subsite on both sides across the midline
AHFX	Accelerated hypofractioned regimen
Conv RT	Conventional radiotherapy
CRT	Chemoradiotherapy
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
dB	Decibels
DSS	Disease specific survival
ELS	European Laryngological Society
ENT	Ear, Nose and Throat
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, the core questionnaire
EORTC QLQ-HN35	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Head and Neck cancer module
F	Female
F0	Fundamental frequency
FEES	Fiberoptic endoscopic evaluation of swallowing
GERD	Gastroesophageal reflux
GRBAS	Grade, roughness, breathiness, asthenia and strain
Gy	Gray
HNR	Harmonic to noise ratio
HPV	Human papillomavirus
HZ	Hazard ratio
Hz	Hertz
IARC	International Agency for Research on Cancer
IMRT	Intensity Modulated Radiation Therapy
LC	Local control
LP	Laryngeal preservation
LSD	Least significant difference
LUMC	Leiden University Medical Centre
M	Male
MCS	Mental component score

MDADI	M.D. Anderson Dysphagia Inventory
MPT	Maximum phonation time
MRI	Magnetic Resonance Imaging
MVA	Multivariate analysis
N	Number
NFS	Not further specified
NHR	Noise to harmonic ratio
NS	Not significant
OPHL	Open partial horizontal laryngectomy
OPL	Open partial laryngectomy
OR	Odds ratio
OS	Overall survival
PCS	Prospective cohort study
PhCS	Physical component score
PQ	Phonation quotient
Pre	Preoperative
PT	Phonation time
QoL	Quality of life
RCS	Retrospective cohort study
RR	Relative risk
RT	Radiotherapy
S	Swallowing
SCC	Squamous cell carcinoma
SD	Standard deviation
SE	Standard Error
Sec	Seconds
SF-12 vs 2	Short form 12, version 2
SFX	Standard fractionation regimen
Tis	Carcinoma in situ
TL	Total laryngectomy
TLM	Transoral CO_2 laser microsurgery
TNM	Tumor-node-metastasis
TOLMS	Transoral CO_2 laser microsurgery
UICC	Union for International Cancer Control
UVA	Univariate analysis
UW-QOL	University of Washington Quality of Life Questionnaire
VFS	Videofluoroscopy
VHI	Voice Handicap Index
VM	Vocal fold muscle
VO	Voice outcome

LIST OF CONTRIBUTING AUTHORS

R.J. Baatenburg de Jong, MD, PhD
Department of Otorhinolaryngology and Head & Neck Surgery, Erasmus MC Cancer Institute

P.P.G van Benthem, MD, PhD
Department of Otorhinolaryngology and Head & Neck Surgery, Leiden University Medical Center

M.M. Hakkesteegt, PhD
Department of Otorhinolaryngology and Head & Neck Surgery, Erasmus MC Cancer Institute

I. el Hasnaoui, BSc
Department of Otorhinolaryngology and Head & Neck Surgery, Leiden University Medical Center

B.J Heijnen, MSc, PhD
Department of Otorhinolaryngology and Head & Neck Surgery, Leiden University Medical Center

M.A. de Jong, MD
Department of Radiation Oncology, Leiden University Medical Center

W.M.C. Klop, MD, PhD
Department of Head & Neck Surgery, Netherlands Cancer Institute/Antoni van Leeuwenhoek

A.P.M. Langeveld, MD, PhD
Department of Otorhinolaryngology and Head & Neck Surgery, Leiden University Medical Center

Y. van Loon, MD, MSc
Department of Otorhinolaryngology and Head & Neck Surgery, Leiden University Medical Center

M.W. Montagne, MD
Department of Otorhinolaryngology and Head & Neck Surgery, Leiden University Medical Center

M.A.P. van Ruler, MD
Department of Radiation Oncology, Haaglanden Medical Center

E.V. Sjögren, MD, PhD
Department of Otorhinolaryngology and Head & Neck Surgery, Leiden University Medical Center

B.M. Verbist, MD, PhD
Department of Radiology, Leiden University Medical Center

M. Veselic, MD, PhD
Department of Pathology, Leiden University Medical Center

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ABOUT THE AUTHOR

Martine Hendriksma was born on 14 October 1990, in 's-Hertogenbosch, the Netherlands. In 2008, she graduated her secondary education (VWO) at Maurick College, Vught. In 2009, Martine started her study Medicine at Utrecht University. During her studies she was an active member in several student boards. In 2013, she did a clinical rotation in the Tygerberg hospital at the Stellenbosch University, South Afrika. During her studies she started with research at the department of Otorhinolaryngology, Head & Neck surgery at the UMCU. In 2016, Martine obtained her medical master's degree. After graduation, she started with research at the Otorhinolaryngology Head & Neck department at the LUMC. After nine months, she was given the opportunity to continue her research as a PhD candidate, under supervision of P.P.G van Benthem, MD, PhD and E.V. Sjögren, MD, PhD, resulting in this thesis. In October 2019, she has started her residency in Otorhinolaryngology and Head & Neck Surgery at the LUMC. Martine currently lives in the Hague with Willem van Leeuwen, whom she married to in June 2021.

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