Early glottic cancer

Single vocal cord irradiation: A competitive treatment strategy in early glottic cancer

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ABSTRACT

Introduction: The treatment of choice for early glottic cancer is still being debated; ultimately it relies on the functional outcome. This paper reports on a novel sparing 4D conformal technique for single vocal cord irradiation (SVCI).

Material and methods: The records of 164 T1a patients with SCC of the vocal cord, irradiated in the Erasmus MC between 2000 and 2008, were analyzed for local control and overall survival. The quality of life was determined by EORTC H&N35 questionnaires. Also the VHI (voice handicap index), and the TSH (thyroid stimulating hormone) blood levels, were established. On-line image guided SVCI, using cone beam CT or stereotactic radiation therapy (SRT) techniques, were developed.

Results: A LC rate at five-years of 93% and a VHI of 12.7 (0–63) was determined. It appeared feasible to irradiate one vocal cord within 1–2 mm accuracy. This way sparing of the contralateral (CL) vocal cord and CL normal tissues, could be achieved.

Conclusions: Given the accuracy (1–2 mm) and small volume disease (CTV limited to one vocal cord), for the use of stereotactic RT techniques SVCI with large fraction sizes is currently being investigated in clinic. It is argued that hypofractionated SVCI can be a competitive alternative to laser surgery.

Of all head and neck cancers (HNCs), approximately 30 percent originates from the larynx. In Europe, annually 52,000 patients are diagnosed with cancer of the larynx. Local control (LC) varies, depending on the subsite and/or extent of the disease (T-and N-stage). This paper analyzes patients with early glottic cancer (EGC), that is, as defined by the UICC/AJCC classification system, disease confined to one (T1a) true vocal cord [1]. Radiation therapy (RT) and carbon dioxide endoscopic laser surgery (LS) have both proven to be effective treatment modalities for T1a glottic cancers. A high cure rate is often cited using either one modality. A summary of the literature by Sjögren et al. [1,2] reported for T1 lesions treated with RT alone a LC rate at five-years of 84% (range 78–89%) and an average larynx preservation rate of 93%. Same author published in 2008 on 143 T1a lesions treated by RT (70) and LS (73); a local recurrence of 21% vs. 10% for RT and LS, respectively, was observed [2]. However, 16% of the LS group needed additional treatment consisting of LS (4%) and/or RT (11%). No significant difference in VHI was found for both treatment modalities [3]. Mendenhall and colleagues, reported in their review paper on T1 lesions treated by primary RT, local control rates of 85–94%.

Recently, Mendenhall [4] updated their own results on T1, T2 glottic cancer. A five-year LC rate of 94% was reported for T1a lesions. Also, of the 585 patients analyzed, ten (1.7%) experienced severe or fatal complications [4]. In a summary paper by Grant et al. [5], local control rates for transoral laser microsurgery (TLM) varied between 71% and 97% [6–20]. Cohen et al., in a meta-analysis of non-randomized studies comparing the VHI of patients receiving RT or LS, found the voice to be similar in both modalities (p = 0.1) [21]. Similarly, in the most detailed retrospective study published by Loughran et al. when using the full armamentarium of validated scoring systems for studying vocal performance no difference was observed [22]. With regard to the quality of voice in EGC; LS is in principle performed as a highly focussed treatment for a clinical target volume (CTV) located on one vocal cord, while in conventional RT, the radiation fields do not conform to the tumor volume per se but in fact both vocal cords are irradiated. Moreover, in a number of cases LS is still to be followed by EBRT of the larynx.

A comparative dosimetric analysis of vocal cord irradiation using different techniques, that is conventional (box technique) vs. IMRT of the larynx vs. single vocal cord irradiation, has recently been published by our group. This paper focuses on the comparison of the dose distribution in many of the normal tissues at risk, using either one of the aforementioned techniques. The reduction of potential side effects, such as pain, poor quality of voice, speech,
xerostomia, dysphagia, incidence of stroke or transient ischemic attack following radiation of the neck, and hypothyroidism, will be discussed. Given the fact that one is dealing with small volume disease (CTV [part of] one vocal cord), when using SRT techniques, the role of (hypo) fractionation can be analyzed. It is argued that single vocal cord irradiation by hypofractionation, considering the low probability of normal tissue side-effects, can be a future way to treat early (T1a) glottic cancers. Good local control rates, improvement of VHI, short overall treatment times and potential room for retreatment with preservation of the larynx, can be anticipated.

Materials and methods

The purpose of this paper is to report on treatment optimization when radiating T1a vocal cord lesions. As a base line observation, first the results from our own institution on LC, OS, quality of life (QoL) and voice handicap index (VHI) of EGC treated with conventional radiation therapy were analyzed. For a clinical review on LS, the reader is referred to the many papers on this issue reported in the literature. These data have been briefly summarized in the introduction section of this paper.

LC and survival using conventional radiotherapy of early glottic tumor

To analyze the LC rate and QoL results, all records of patients with SCC of the glottis were reviewed (Fig. 1); newly diagnosed carcinoma in situ (35 Tis), T1b lesions (38; both vocal cords) were excluded from the present analysis. The remaining patients with SCC of the true vocal cords (164 T1a) treated between 2000 and 2008 at our institute, were studied. All patients were simulated in supine position; for immobilization purposes a custom made head shell was manufactured. Lateral parallel-opposed wedged 6 MV photon beams, mean field size <36 cm² [6 × 6 cm²], with the iso-center placed at the center of the vocal cord lesion, were used. One fraction per day, fraction size of 2–2.3 Gy, was given five days per week, up to a total dose of 60–66 Gy. The dose was prescribed according to ICRU guidelines (with dose in the target varying between 95% and 107%) [23]. The absence of a lymphatic network and consequently the low incidence of nodal spread do not warrant elective nodal irradiation. Patients of the current series were analyzed for local control with or without salvage, and overall survival. Also, QoL using the EORTC H&N35 questionnaires, the quality of voice using the VHI (voice handicap index), and the thyroid function status (TSH [thyroid stimulating hormone] blood levels), were determined.

Intensity modulated radiotherapy for T1a early glottic cancers, single vocal cord irradiation technique

Ten patients with T1aN0M0 glottic carcinomas were previously treated at our institute by lateral P-O fields (box technique), and were retrospectively used for the current investigation. The conventional treatment plans were originally made using the CadPlan treatment planning system (Varian Medical Systems, Palo Alto, USA), and were regenerated in the XiO treatment planning system (V 4.33 Elekta-CMS Software), using heterogeneity corrections and a fast convolution superposition algorithm. In all planning CT scans (resolution 1 mm³) the clinical target volume (CTV, margin 3 mm) and the organs at risk (OARs) were delineated. The delineated structures were the vocal cords, arytenoids, swallowing muscle at the level of the vocal cords (inferior constrictor muscle, ICM), ipsi- and contra-lateral strap muscles, carotid arteries, thyroid gland, thyroid and cricoid cartilages, and the spinal cord. The cranial–caudal extensions of the contours of these OARs were at the level of the vertebra C2 and C7. IMRT and SVCI treatment planning was performed for an Elekta Synergy linear accelerator with 40 MLC leaf pairs and a leaf width at the isocenter of 4 mm (Elekta Beam ModulatorTM, Elekta Oncology Systems, Crawley, UK) at 6 MV. The minimum segment size allowed was 0.5 cm². The isocenter of the treatment was set to the center of one of the vocal cords. The radiation schedule proposed to be used in combination with the SVCI technique, is discussed in the next section.

Results and discussion

Laser surgery or radiotherapy

Carbon dioxide endoscopic LS is an established treatment technique for early glottic cancer. According to Sjögren et al. [2] LS was introduced in the Leiden University Medical Center, for T1a midcord lesions, in 1996. The results were summarized as follows; “T1a glottic carcinoma allocated to radiotherapy have a poorer outcome in terms of local control and laryngectomy free survival than do T1a patients selected for laser surgery”. Motta et al. [24] assessed the vocal function of patients who had undergone CO2 laser cordectomy. No functional compensation enabled the patients to achieve a voice quality comparable with that of controls. Vilaseca et al. [25] studied the voice quality after CO2 laser cordectomy. They concluded that the voice improved in almost 60% of the patients, returning to normal in 45%. Nunez et al. [26] analyzed functional outcome and self-evaluation of the voice of patients with T1 glottic carcinoma treated with endoscopic LS and RT. When comparing the VHI scores, this was in apparent favor for RT, in functional and emotional ratings as well as for the global scores. VHI scores of the T1a larynx cancer group after radiotherapy in our hospital has been listed in Table 1.

Despite the (sometimes contradictory) reports on post-treatment voice quality, it is mostly agreed upon that radiotherapy...
results in equal or even better voice quality post treatment as opposed to LS [3]. Moreover, even better outcomes are to be expected with the emerging more focused RT techniques (see below). Apart from this, the comparison of LS with conventional RT techniques is not really valid due to patient selection. For example, since patients treated for small, early lesions are exposed more commonly to LS and, therefore, a favorable outcome for this patient group is anticipated. This bias can only be overcome by the design of prospective randomized trials.

In addition to a localized tumor growth confined to one or both vocal cords, geometrically complex tumors could also be treated with RT using IMRT techniques and still achieve excellent normal tissue sparing. These include tumors involving the anterior commissure (AC) which are most often not amenable for LS. Moreover, for T2 tumors extending into the sub- or supra-glottic regions, so far insufficient data with regard to LS are available.

**Single vocal cord irradiation (SVCI) with IMRT**

In the Erasmus Medical Center a study was undertaken by Osman et al. on the feasibility of unilateral vocal cord irradiation (SVCI) for T1a lesions. The concept was to see whether unilateral vocal cord irradiation could reliably be re-produced on a daily basis (i.e. in case of fractionated RT). In 2008, our first study was published showing that the intra-fraction movement of the vocal cords was small and not prohibitive for executing such a delicate treatment technique [27]. A second publication dealt with the adequacy of daily on-line re-positioning [28]. A subsequent paper showed the superiority of IMRT as opposed to lateral P-O irradiation techniques with regard to normal tissue involvement [29].

**Risk of ischemic vascular side effects after neck irradiation**

In recent years attention has increasingly been devoted to vascular effects when radiation is the treatment of choice for a primary cancer in the head & neck region [30,31]. RT of the head and neck is found to be a significant risk factor for carotid artery stenosis. In a paper by Brown et al. [30], an incidence of 18% carotid artery stenosis in the ipsilateral irradiated neck vs. 7% in the contralateral non-irradiated neck was reported. Lateral P-O portals include in part the carotid arteries; consequently, since one of the causes of stroke is carotid artery stenosis. Stroke could be considered as a typical side effect associated with irradiation of the head and neck. According to Dorrestein et al. [32], the overall risk of strokes after RT was significantly increased compared to the general population. Rosenthal et al. [31] concluded from a literature survey that 50 Gy could be considered the approximate threshold dose for vascular (i.e. carotid arteries) damage in the neck after post-irradiation. Consequently, treatment options for previously irradiated patients (with conventional RT methods) are potentially limited due to increased risk for carotid injury. In our planning study using SVCI techniques with IMRT, no part of the carotid arteries received doses as high as 50 Gy (see mean and maximum dose received by the carotid arteries Table 2). Therefore, this might allow for re-irradiation of these tumors. In conclusion, additional treatment options for recurrent tumors or second primary tumors in the upper aerodigestive track are another benefit for using IMRT. These tumors are usually salvaged with surgery with very generous surgical margins (e.g. by laryngectomy), obviously negating the effect on the QoL of these patients.

**Hypothyroidism**

Hypothyroidism remains an underreported and often under-appreciated late sequel of RT or thyroid surgery [33].

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**Table 1**

<table>
<thead>
<tr>
<th>VHI-total, mean (range)</th>
<th>12.7 (0–63)</th>
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<tbody>
<tr>
<td>VHI-F, mean (range)</td>
<td>3.4 (02–0)</td>
</tr>
<tr>
<td>VHI-E, mean (range)</td>
<td>2.7 (0–21)</td>
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<tr>
<td>VHI-P, mean (range)</td>
<td>6.5 (0–25)</td>
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**Table 2**

<table>
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<tr>
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<th>Dose (Gy)</th>
<th>SVCI with IMRT</th>
<th>BVCI with IMRT</th>
<th>PO clinical plans</th>
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</thead>
<tbody>
<tr>
<td>PTV</td>
<td>Mean ± SD</td>
<td>67 ± 1</td>
<td>67 ± 1</td>
<td>67 ± 1</td>
</tr>
<tr>
<td>CTV</td>
<td>Mean ± SD</td>
<td>67 ± 1</td>
<td>67 ± 1</td>
<td>67 ± 1</td>
</tr>
<tr>
<td>CL vocal cord</td>
<td>Mean ± SD</td>
<td>39 ± 8</td>
<td>(n.a.)</td>
<td>67 ± 1</td>
</tr>
<tr>
<td>IL arytenoid</td>
<td>Mean ± SD</td>
<td>64 ± 3</td>
<td>65 ± 1</td>
<td>66 ± 1</td>
</tr>
<tr>
<td>CL arytenoid</td>
<td>Mean ± SD</td>
<td>20 ± 8</td>
<td>66 ± 2</td>
<td>66 ± 1</td>
</tr>
<tr>
<td>ICM</td>
<td>Mean ± SD</td>
<td>28 ± 4</td>
<td>39 ± 5</td>
<td>61 ± 3</td>
</tr>
<tr>
<td>IL strap muscle</td>
<td>Mean ± SD</td>
<td>17 ± 2</td>
<td>18 ± 3</td>
<td>49 ± 8</td>
</tr>
<tr>
<td>CL strap muscle</td>
<td>Mean ± SD</td>
<td>9 ± 4</td>
<td>18 ± 3</td>
<td>49 ± 10</td>
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<tr>
<td>Thyroid gland</td>
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<td>3 ± 1</td>
<td>3 ± 1</td>
<td>17 ± 11</td>
</tr>
<tr>
<td>Thyroid gland</td>
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<td>10 ± 8</td>
<td>10 ± 9</td>
<td>15 ± 11</td>
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<tr>
<td>Thyroid cartilage</td>
<td>Mean ± SD</td>
<td>28 ± 5</td>
<td>38 ± 7</td>
<td>66 ± 1</td>
</tr>
<tr>
<td>Cricoid</td>
<td>Mean ± SD</td>
<td>22 ± 4</td>
<td>28 ± 4</td>
<td>61 ± 4</td>
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<td>Max ± SD</td>
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<td>31 ± 4</td>
<td>66 ± 3</td>
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<tr>
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<td>22 ± 10</td>
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**Fig. 2.** An example of typical dose volume histograms (DVH) comparing the dose received by the CTV (panel 1). Also depicted are the organs at risk when using conventional parallel opposed beam (dotted lines), and IMRT for single cord irradiation (solid lines), respectively.
recognition and suppletion with thyroid hormones may prevent the development of clinical symptoms of hypothyroidism. In the laboratory of the Erasmus MC, TSH normal values range from 0–4.3 mUnits. In the patients under investigation, a maximum of 6% had abnormal values of TSH (that is outside the normal range), see also Fig. 1. This low number is probably due to the anatomical position of the thyroid gland. Thus, a small dose is apparently to be received by the thyroid glands with normal anatomical positioning (see Table 2 in general). However, a simple TSH routine check in follow-up is still worthwhile for picking up these isolated cases (6%). A detailed analysis of hypothyroidism is beyond the scope of the present paper.

Radiotherapy for the management of early glottic tumors

A comparison of the dose received by the various structures from the different radiotherapy techniques is shown in Figs. 2 and 3. In Fig. 2 examples of typical dose-volume-histogram (DVH) comparisons are shown, illustrating the dose received by the vocal cords, arytenoids, inferior constrictor muscle (ICM), spinal cord, strap muscles, and the arytenoids when using lateral P-O wedged photon beams (dotted lines), and IMRT for a single vocal cord (solid lines). In the lateral P-O beam plans most of the structures receive the full dose as opposed to IMRT plans, where notable sparing of normal tissue is obtained (also see Table 2). Fig. 3 shows examples of three dose distributions; column (A) for SVC with IMRT for a T1a tumor on the right vocal cord. In addition, in column B, an example of a T1b–IMRT plan is shown for both vocal cords. Finally, column C, a typical dose distribution for lateral P-O beams is presented. At present accurate treatment techniques are available to apply highly focused radiation, e.g. with the use of cone beam CT and stereotactic radiation. Given the small target and the large amount of sparing of different normal tissues, apparently the CTV and PTV margin can be small and the benefit of hypofractionation becomes an issue. We have, therefore, proposed to start a clinical pilot study using five fractions of 8.5 Gy per fraction, with the dose prescribed to the 80% isodose line. Finally, we have not discussed the issue of costs per treatment modality since they differ substantially given the variations in health care providers (national guidelines) per country.

Conclusion

Treatment modalities of T1 vocal cord lesions differ substantially per institution. Many of the selection factors involved were evaluated in this study in order to arrive at the best treatment option. The analyzed selection factors were LC, OS, QoL, preservation of voice, potential for vascular side effects, and hypothyroidism. The weight given to each of the QoL factors and the potential side effects of LS will guide the preference for either LS or RT. The outcome in QoL and the preservation of voice have, in

Fig. 3. Transverse (top), coronal (middle), sagittal (bottom) slices showing typical dose distributions (iso-dose fill) obtained using IMRT for the right vocal cord (first column), IMRT for both vocal cords (second column), and P-O plans (third column).
general, favorably been reported for RT; this is despite the fact the RT involves a larger surface area than is the case with LS (i.e. two vocal cords in stead of one). Vascular side effects and hypothyroidism are not present when using LS. The risk for the occurrence of these side effects is, however, extremely small in the case of RT and can be further reduced by using advanced RT techniques, such as IMRT and SVCI. For good reasons (see paragraph before), it has been argued to start the clinical testing of the role of hypofractionation in these very small target volumes. Finally, of obvious advantage is the fact that RT is a non-invasive technique. However, in terms of evidence based medicine, randomized trials for the outcome of SVCI by IMRT techniques and LS are absent but are definitely needed in order to make a more balanced comparison for these competitive techniques.

Conflict of interest statement

No conflicts of interest.

Reference