Prognostic Value of Surgical Margins in Early-Stage Laryngeal Cancer Treated by Transoral Laser CO₂ Microsurgery

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Abstract

Transoral Laser CO₂ Microsurgery is an established mode of treatment for early glottic carcinomas. However, there are doubts in the literature with regard to histologic margin assessment following laser resection, as well as the prognostic significance of margin's status. We assess the prognostic significance of histopathologic margins status following surgical treatment of early laryngeal cancer with TLM.

A retrospective study was conducted at an academic tertiary center. The files of all cases that underwent primary laser microsurgical treatment for T1 glottic cancer within a two-year period were included in the study. Focus was given on oncologic outcomes with regard to tumor margin status on permanent histology.

Among 36 patients treated with curative intent by transoral laser resection for T1a, and T1b lesions, clear histologic borders were achieved in 24 cases. Undetermined or suspicious margins were reported in 12 cases. These cases were either followed up closely or re-operated upon depending on the surgeon's level of clinical suspicion. Oncologic outcomes were found to be comparable among groups, as rates of local control and organ preservation were 100% for cases with free margins, and similarly for those with initially undetermined or suspicious margins.

Therefore, it is suggested that in cases where the surgeon is confident with the outcome of CO₂ laser microsurgery, a “watch and wait” philosophy may be considered as an acceptable option even in cases where surgical margins are labeled undetermined or suspicious on pathology.

INTRODUCTION

Transoral CO₂ Laser Microsurgery (TLM) is an established mode of treatment for early glottic carcinomas, and widely accepted even for more advanced laryngeal lesions. It provides favorable oncological results in terms of local control, survival and functional preservation, minimal morbidity, while it is a cost-effective alternative to radiotherapy and open surgical procedures [1-3].

Whenever surgical management is selected for the treatment of cancer and no matter which type of surgery is used, the significance of achieving tumor-free surgical margins cannot be overstressed. It has been widely accepted that complete excision of a tumor at the primary site is essential in order to ensure local control [4,5]. Therefore, the aim of any oncologic procedure with therapeutic intent should be histologically confirmed disease-free margins [6,7].

Despite the above, the prognostic value of surgical margins in the treatment of laryngeal cancer with the use of TLM has not been consistently shown in the literature. In fact, an inconsistency has been previously noted between histopathology and clinical outcome in cases where surgical margins are assessed as suspicious or undetermined following TLM [8-10]. A favorable prognostic outcome has been reported even in cases where negative margins had not been clearly justified on pathology. In light of such findings, a watch and wait strategy or selective second look surgery for suspicious margins may be considered as reasonable alternatives, at least in situations where the surgeon feels confident with the clinical outcome of the excision [9,10]. Consequently, this study aims to assess the prognostic significance of undetermined or suspicious surgical margins in cases of early glottic cancer treated with TLM.

MATERIALS AND METHODS

A retrospective study was conducted at an academic tertiary center (Department of Otorhinolaryngology, Head and Neck Surgery, University of Crete School of Medicine, Heraklion, Greece). Relevant approval from the institutional review board of the hospital was obtained. The files of all patients who underwent primary TLM for T1a and T1b glottic cancer between September 2010 and September 2012 were reviewed. Patients with insufficient data, histology other than squamous cell carcinoma, and patients with second primary tumor at the time of diagnosis...
were excluded. All pathology reports were reviewed and staging was conducted in accord with the 2010 American Joint Committee on Cancer (AJCC) and Union Internationale Centre Cancer (UICC) classification [11]; T term indicates primary tumor staging. For glottic carcinomas, T1 is defined as tumor limited to true vocal cords without mobility impairment. Additionally, T1a lesions are limited to one vocal cord, whereas T1b lesions involve both true cords.

In this institution, laser surgery for laryngeal carcinomas is typically performed under general anesthesia, using suspension laryngoscopy, and a CO₂ laser device (Sharplan®), coupled to an operative microscope (Zeiss®, Oberkochen, Germany). Low to medium power rate of 4.0 - 5.5W in continuous mode is typically selected. Smaller lesions are removed en block and larger lesions in piecemeal fashion according to established techniques [1].

Following initial excision and according to the status of surgical margins as labeled in the pathology report, patients were divided into two groups: group 1 included cases in which negative histologic margins had been obtained; group 2 included cases with suspicious borders or undetermined margins after initial surgery. All pathology reports corresponded to permanent histology solely, as frozen section histology is not routinely performed for cases undergoing TLM in this institution.

The course of each case was assessed after the initial excision, and groups were compared for local, and regional disease control rates, as well as overall survival. Local disease control, reflecting the analysis of tumor recurrence in the primary site, was calculated from the date of surgery to the date of local recurrence diagnosis or date of last follow up. Overall survival, representing the total mortality rate of patients, was calculated as the percentage of patients alive for more than five years divided by the total number of patients. Typical follow up comprised of thorough clinical examination including flexible endoscopy, and was performed monthly for the first year, every two months for the second year, every three months for the third year, every four months for the fourth year, every six for the fifth and yearly thereafter. In addition, CT scans of the larynx and neck were performed twice a year for the first three years following surgery.

Additional data that was collected and placed in the database included organ preservation rate for each group. Microsoft Excel and SPSS Version 21 (SPSS Inn., Chicago, IL) were used for the analysis.

RESULTS AND DISCUSSION

Among 36 cases that met the inclusion criteria, 24 (67%) were men and 2 (6%) were women. Mean age in the study group was 63 years, ranging from 40 to 81 years. The male-to-female ratio was approximately 15:1. Most cases (28, 78%) presented with T1a lesions. Mean follow-up was 51.2 months, ranging from 36 to 62 months. Demographic data for all cases included in the study are listed in (Table 1).

Group 1, where clear surgical margins had been initially achieved included 24 (67%) patients. Five of these cases (20.8%) had T1b lesions and the rest T1a. Group 2, where surgical borders were assessed as undetermined or suspicious, comprised of 12 (34%) subjects, three with T1b lesions (25%), and the rest with T1a. All cases in group 1 were placed on regular follow up. Such follow up comprised of monthly evaluation in the outpatient clinic, and this typically included flexible laryngeal endoscopy. No local recurrences were observed in this group.

Among group 2 cases, two patients showed undetermined margins, while ten patients had suspicious margins. There were no cases with clearly positive margins. For both cases with undetermined margins a “watch and wait strategy” had been decided and they had been placed on follow up. No local or regional recurrences were observed. In four of the patients with suspicious margins, a second look procedure was performed within ten weeks after the initial procedure. In one case, the resection specimen was labeled as positive for residual tumor, while in three cases no evidence of residual tumor was found at the primary site. All of these cases were negative for local or regional recurrence on follow up. In the remaining six patients with suspicious margins, the surgeon was confident that resection of the lesion was complete and a “watch and wait” strategy had been followed. No local or regional recurrences were observed in these cases as well.

The final rate of local control, as well as organ preservation was 100% for patients with initially undetermined or suspicious margins, as well as for those with free histologic margins. The overall survival rate of early glottic cancer treated with TLM was 100% (Table 2).

Transoral CO₂ laser microsurgery was initiated in the treatment of early laryngeal carcinoma in the 1970s [12]. Since then, its indications have been expanded, and TLM is an established mode of treatment for early, and widely accepted even for more advanced, glottic carcinomas [13-15]. This approach allows early stage tumors to be completely removed with minimal functional cost for the vocal cords. In addition, it may offer favorable oncologic outcomes with relatively low morbidity and mortality [14,16].

We assessed the prognostic significance of tumor margins following laser resection of early glottic carcinomas. Patients undergoing TLM for T1 glottic cancer during a two-year period were retrospectively evaluated. According to the status of permanent histologic margins patients were divided in two groups. Disease course was followed for every group and oncologic outcomes were compared. Group 1 cases, with negative histologic margins, were typically managed with follow up. Cases with undetermined or suspicious margins (group 2) on histopathology were also managed with close follow up whenever the surgeon was confident that the initial excision was complete. In cases where residual disease had been suspected

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**Table 1: Demographic data of cases included in this series.**

<table>
<thead>
<tr>
<th>Disease classification</th>
<th>T1a</th>
<th>T1b</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td># of cases (rate)</td>
<td>28</td>
<td>8</td>
<td>36</td>
</tr>
<tr>
<td>Mean age in years (range)</td>
<td>61.2(40-86)</td>
<td>66.3(59-78)</td>
<td>63.1(40-86)</td>
</tr>
<tr>
<td>Male gender (rate)</td>
<td>26</td>
<td>8</td>
<td>34</td>
</tr>
<tr>
<td>Female gender (rate)</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviations: #: Number
It is common knowledge among surgeons that status of surgical margins has well defined and predictable patterns of spread and lends itself well to partial resections with minimal margins. Moreover, perhaps due to lack of lymphatic drainage in the glottic region, surgical achievement of wide margins in this area has not been associated with better local control, and has a negative effect on functional outcomes when organ preservation, and overall survival. Therefore, incomplete tumor resection should be managed with revision surgery or additional treatment modalities [19,20]. Consequently, the aim of every surgery with curative intent for glottic cancer should be to remove the tumor completely with histologically documented clear margins [4,5,21].

With regard to TLM specifically, however, a somewhat different reality may exist. According to recent literature, an inconsistency is noted between clinical outcome and histopathology in cases where surgical margins have been judged as suspicious. It is well known that laser surgery may pose increased difficulties in order for pathologists to reliably assess the status of tumor resection borders [8-10,22]. Reasons for this discrepancy are related to the nature of the CO₂ laser itself including tissue contraction and evaporation, heat artifacts, orientation, and small size of samples. A carbonization zone of at least 0.3mm in the specimen should be taken into account when assessing tumor margins. Such difficulties often result in surgical margins falsely assessed as positive or undetermined on permanent histology. In this context, frozen section control may be recommended as an indicator for further resection after piecemeal excision of tumors [23]. Frozen section has proved to be a useful tool in order to evaluate margin status preventing second look surgeries in TLM for glottic cancer, when performed by an experienced team [24]. However, in this institution, and in many other centers, this method is not practical due to time, spatial, and even financial restraints that predominate in the operation room [8].

Recently, a philosophy of selective second look procedure or a “watch and wait” strategy have been favored in cases of discrepancy between a surgeon’s clinical impression, and histopathology regarding the completeness of resection [8-10]. It has been demonstrated that positive or suspicious margins in early glottic cancer may not be related to recurrence, and suspicious margins may be managed with close follow up. A previous study reported that compromised borders in T1a patients undergoing TLM were not a significant factor with regard to overall or recurrence-free survival [10]. In another study, no clear relationship was found between status of surgical margins and local recurrence rates [19]. In a large series of 595 patients, positive margins in early laryngeal cancer were not shown, even in specific correlation to head and neck cancer [17,18]. According to previous reports, patients with negative histologic margins at the end of surgical treatment have showed significantly better survival, and local control rates compared to patients with compromised borders [17,18]. The prognostic significance of negative margins is not lost even if multiple operations are necessary in order to achieve such margins [4,5]. Therefore, incomplete tumor resection should be managed with revision surgery or additional treatment modalities [19,20].

<table>
<thead>
<tr>
<th>Status of surgical margins</th>
<th>Rate of Local Control with Laser resection</th>
<th>Rate of Overall Survival</th>
<th>Rate of Organ Preservation</th>
<th>Number of Recurrences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (n=24)</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>None</td>
</tr>
<tr>
<td>Group 2 (n=12)</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviations: n: Number

In order to achieve negative margins during TLM different strategies have been proposed. Following initial excision, frozen section histology is typically performed in many institutes, and if results are positive, further resection is undertaken [16-18]. Other centers do not routinely rely on frozen sections; whenever residual disease is found on the resection borders of permanent histology, revision surgery is advocated. Alternatively, other forms of treatment or close follow-up may be considered as acceptable options in these situations [16-18].

It is common knowledge among surgeons that status of surgical margins significantly affects oncologic outcomes regardless of accompanying disease stage. A significant correlation between positive or uncertain margin status, and both loco regional as well as overall survival rate control have been previously
found to affect local control [24]. Other reports have suggested that undetermined or even positive borders in early glottic cancer may not affect oncologic outcomes in terms of local control, and five year overall or recurrence-free survival, whenever selective second look procedure or “watch and wait strategy” were adopted [25]. The present study seems to be in accordance with the prementioned literature.

CONCLUSIONS

It must be emphasized that when the surgeon’s clinical impression is used as a tool to decide the postoperative course after laser surgery in spite a given pathology report, experience might play a key role. In this series, out of four cases with suspicious labeled margins and clinical suspicion, residual disease was found in one patient after a second procedure. On the other hand, in six cases with suspicious margins and absence of clinical impression, no recurrences were noted on follow-up. As the level of experience and clinical expertise may vary, the efficacy to depict the so called “suspicious” cases and therefore overrule a histology report might change as well. It should also be noted that a rather high rate of suspicious histologic margins for T1 carcinomas was found in this series. Reasons for this finding are not clear to the authors. In addition, the small number of cases and the retrospective nature of the study may be regarded among the limitations of this report. In conclusion, it is suggested that in early laryngeal cancer, surgical margins should be interpreted based on the surgeon’s intraoperative impression. Whenever the surgeon is confident that resection borders are satisfactory and no further treatment is required, cases may be managed with close follow up, even if undetermined or suspicious margins are mentioned in the pathology report.

AUTHORS’ CONTRIBUTIONS

AK conceived of the study, participated in the design, and drafted the manuscript. MD collected data, performed the statistical analysis and assisted in drafting the manuscript. EP contributed in the collection of data. SV assisted in data collection and statistical analysis. GV designed the study and made important contributions to the final form of the manuscript. All authors read and approved the final form of the manuscript.

REFERENCES
