

Clinical significance of granulation tissue after transoral laser microsurgery for glottic cancer

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Abstract

Background: Granulation tissue after transoral laser microsurgery can make it difficult to distinguish between normal healing and tumour recurrence.

Materials and methods: We carried out a retrospective analysis of 316 consecutive glottic carcinomas (T_{is}–T₃). Presence of granulation tissue at one and six months was correlated with demographic and clinical data, tumour and surgical characteristics, and tumour relapse.

Results: Granulation tissue appeared in 53.8 per cent of patients at month 1, resolving spontaneously in 41.8 per cent. Revision surgery was performed in 60.1 per cent and was effective in 41.1 per cent. At month 6, 14.9 per cent of patients presented with granulation tissue. In 74.5 per cent the tissue was surgically removed and was positive for malignancy in 62.9 per cent. Tumour relapse presented in 29.4 per cent with granulation tissue at month 1 and in 61.7 per cent at month 6 ($p = 0.000$). Granulation tissue at month 1 correlated with thyroid cartilage exposure and continued smoking. At month 6, granulation tissue correlated with thyroid cartilage exposure, the affected surgical margins and diabetes.

Conclusion: Granulation tissue after transoral laser microsurgery is frequent. When it persists at six months, revision surgery is formally recommended.

Key words: Laser Therapy; Granulation Tissue; Laryngeal Neoplasms; Wound Healing; carbon dioxide laser

Introduction

Transoral laser microsurgery is an accepted treatment option for upper aerodigestive tumours. Its positive oncological outcomes and functional results and the low incidence of complications have been reported by many authors.^{1–6} Currently, transoral laser microsurgery is the treatment of first choice for early laryngeal tumours at many European otolaryngology departments.

The healing process after transoral laser microsurgery is not well understood. Inflammation and fibrin accumulation are common during the early follow up. In some patients, granulation tissue formation may last for months. It has been reported that the heat effect of the laser may delay the healing process: compared to ‘cold’ surgical techniques, the risk of inflammation scars is increased and granulation may be expected.^{7–9} Scarring may result in vocal fold rigidity, although very good functional results have been reported.

To preserve as much function as possible, transoral laser microsurgery of the vocal folds is usually planned as a tailored resection, with very close

margins. Evaluation of definitive margins from the tumour specimen is not always easy. Presence of artefact secondary to electrocautery, uncertain margins due to shrinking of the specimen, or additional tissue ablation at the bedside after resection may make it difficult to interpret the pathology report. In this scenario, the presence of granulation tissue at follow up may be disconcerting for the surgeon, making it more difficult to distinguish between normal healing and residual/persistent disease. Some authors have advocated systematic revision surgery, while others have recommended a policy of wait and see.^{2,10,11} The latter is an accepted procedure when transoral laser microsurgery has been performed on the vocal folds, because the follow up with laryngoscopy or flexible endoscopy allows good visualisation of the area.

There is no consensus on how granulation tissue should be managed after transoral laser microsurgery. Michel *et al.*¹⁰ recommended systematic revision surgery 10 weeks after transoral laser microsurgery, when the margins were positive. Sigston *et al.*¹¹

concluded that routine re-excision or other additional treatment may not be necessary in early-stage glottic cancers, and that strict follow up was sufficient. Peretti *et al.*² carried out endoscopic re-excision in case of positive deep margins and strict follow up if superficial margins were involved.

The aim of our study was to analyse the clinical significance of granulation tissue after transoral laser microsurgery for glottic cancer. We studied the clinical, pathological and technical factors influencing the presence of granulation tissue and their correlation with tumour relapse.

Materials and methods

We evaluated all consecutive patients diagnosed with glottic cancer (T_{is}–T₃) and treated primarily with transoral laser microsurgery from 1997 to 2008 at a tertiary referral centre (Hospital Clínic, Barcelona, Spain). Exclusion criteria were previous radiation therapy or anterior commissure carcinoma of the larynx. The study was approved by the Ethics Committee of the Hospital Clínic, Barcelona.

For the laser resection, a Sharplan CO₂ laser (40 W) with the Sharplan 712 Acuspot or Digital AcuBlade (Lumenis Inc., Santa Clara, California, USA) micromanipulators was used. The power, spot size and depth of resection were set according to the preferences of the surgeon and the type and location of the tumour.

Except for very small resections, most patients were discharged with a broad-spectrum antibiotic and non-steroidal anti-inflammatory treatment for one week. When the thyroid cartilage was exposed or partially removed, two weeks of oral steroids were prescribed. The presence of granulation tissue was evaluated at months 1 and 6 after transoral laser microsurgery. We evaluated the correlations between granulation tissue and demographic and clinical data, tumour characteristics, technical aspects of surgery and tumour recurrence.

According to age, patients were divided into younger (<65) and older (≥65) age groups.¹² Clinical variables that were considered important during the healing process were diabetes mellitus and tobacco use. Patients were divided into non-smokers (never smoked or had not smoked during the last five years), current smokers until surgery, and persistent smokers after surgery.

Variables related to tumour characteristics and the technical aspects of the surgery included TNM cancer staging (size or extent of the primary tumour (T), whether cancer cells have spread to nearby lymph nodes (N) and whether metastasis (M) has occurred),¹³ difficulty in exposing the tumour during surgery, thyroid cartilage exposure, thyroid cartilage invasion by the tumour, satisfactory resection according to the surgeon, and surgical margins. After consulting the pathology and surgery reports, the margin was classified as free, uncertain (less than 2 mm from the tumour or when the tissue was insufficient or

carbonised by CO₂ laser) or affected by the tumour. In a recent study, Blanch *et al.*¹⁴ reported no significant differences between free and uncertain margins in terms of oncological results. Accordingly, for the present analysis, specimens that were tumour free or uncertain in the histopathology report were considered negative, and those with affected margins were considered positive.

At month 1 of follow up, in cases with irregular granulation tissue, definitive positive margins, surgical uncertainty regarding a free-margin resection expressed by the surgeon or very poor function secondary to granulation, a surgical revision was performed. In the other cases, a policy of wait and see was initially adopted. Granulation tissue that persisted at the six-month follow up was surgically removed.

Statistical analysis

We analysed the data with SPSS for Windows version 18.0 (IBM Corporation, Armonk, New York, USA). Data are presented as mean ± standard deviation. We assessed the correlation between qualitative variables by means of a Pearson's chi-square test. We introduced significant variables into a logistic regression model (back-step Wald test) and we determined the independent risk factors of granulation tissue at one or six months. A *p* value < 0.05 was considered as statistically significant.

Results

From 1997 to 2008, 435 patients with glottic cancer were primarily treated with transoral laser microsurgery. We excluded 119 patients from the present analysis for involvement of the anterior commissure of the larynx (99), or loss to follow up (20). Finally, 316 patients were included in the present study. Two hundred and ninety-one (92.1 per cent) were men and 25 (7.9 per cent) were women, with a mean age of 64.6 ± 1.4 years (range, 20–90 years) at the time of surgery. The mean follow up was 59.6 ± 28.1 months (range, 6–166 months). Tumour relapse was evidenced in 68 patients (21.5 per cent) of the initial series.

Demographic and clinical data, tumour characteristics and technical aspects of the surgery are summarised in Tables I and II. The percentage of granulation tissue at months 1 and 6, together with its management, is described in Figure 1. At month 1, granulation tissue was present in 53.8 per cent of patients (170/316). A revision surgery of this granulation tissue was performed in 58.2 per cent of patients (99/170), obtaining a positive result for carcinoma in 39.4 per cent of them (39/99). At month 6, granulation tissue persisted in 14.9 per cent of patients (47/316), and was surgically removed in 74.5 per cent (35/47). Presence of malignancy was confirmed in 62.9 per cent of the surgically removed cases (22/35). Overall tumour recurrence occurred in 29.4 per cent (50/170) of patients with granulation tissue at month 1 and in 61.7 per cent (29/47) of patients with granulation

TABLE I
DEMOGRAPHIC AND CLINICAL DATA

	N (%)
Age	
<65 years	146 (46.2)
≥65 years	170 (53.8)
Smoker*	
Yes	196 (62.0)
No	117 (37.0)
Continued smoking after transoral laser microsurgery	
Yes	34 (10.8)
No	266 (84.2)
Unknown	16 (5)
Diabetes mellitus*	
Yes	35 (11.1)
No	278 (88)

*N/a = No data available for three patients

tissue at month 6. The follow up of patients who did not present with granulation tissue is also shown in Figure 1. Of those patients with no granulation tissue at month 1, 12.3 per cent (18/146) developed tumour recurrence within the follow-up period, while 14.5 per cent (39/269) of those who did not have granulation tissue at month 6 developed tumour recurrence.

Risk factors for granulation tissue

In the univariate analysis, the probability of granulation tissue in the first month was related to continuing smoking after transoral laser microsurgery ($p = 0.01$) and to thyroid cartilage exposure during surgery ($p = 0.028$), but not to group age ($p = 0.742$), past smoking ($p = 0.067$), diabetes ($p = 0.449$), primary tumour classification ($p = 0.143$), surgical exposure ($p = 0.40$), thyroid cartilage invasion ($p = 0.617$),

TABLE II
TUMOUR CHARACTERISTICS ACCORDING TO TUMOUR CLASSIFICATION¹³ AND TECHNICAL ASPECTS OF SURGERY

	N(%)
Primary tumour classification	
T _{1s} +T _{1a} + T _{1b}	233 (73.7)
T ₂	62 (19.6)
T ₃	21 (6.6)
Tumour exposure during surgery	
Good	276 (87.3)
Difficult	40 (12.7)
Thyroid cartilage exposure*	
Yes	62 (19.6)
No	251 (79.4)
Thyroid cartilage invasion	
Yes	8 (2.5)
No	308 (97.5)
Surgeon's tumour resection report	
Satisfactory	301 (95.3)
Uncertain	15 (4.7)
Surgical margins	
Negative or uncertain	286 (90.5)
Affected	30 (9.5)

*N/a = No data available for three patients

subjective impression of complete resection by the surgeon ($p = 0.971$) or surgical margins ($p = 0.474$).

The probability of granulation tissue at month 6 was related to primary tumour classification ($p = 0.028$), exposure of thyroid cartilage ($p = 0.000$) and surgical margins ($p = 0.014$), but not to group age ($p = 0.928$), past history of smoking ($p = 0.147$), persistent smoking ($p = 0.486$), diabetes ($p = 0.06$), surgical exposure ($p = 0.330$), thyroid cartilage invasion ($p = 0.068$), or surgeon's impression of complete resection ($p = 0.568$).

In the multivariate analysis, thyroid cartilage exposure during surgery and continued smoking after transoral laser microsurgery were independent risk factors for the appearance of granulations at month 1 ($p = 0.026$, 95 per cent confidence interval (CI): 1.086–3.593, and $p = 0.004$, 95 per cent CI: 0.287–0.794, respectively). Independent risk factors for the appearance of granulation tissue at month 6 were thyroid cartilage exposure during surgery ($p = 0.000$, 95 per cent CI: 2.321–9.142), diabetes ($p = 0.038$, 95 per cent CI: 1.056–6.351) and positive surgical margins ($p = 0.013$, 95 per cent CI: 1.278–8.148).

Discussion

Since the first descriptions of transoral laser microsurgery in the 1980s, its oncological efficacy in laryngeal cancer has been demonstrated and its indications have steadily expanded. The presence of granulation tissue after transoral laser microsurgery is common; it may require repeated revision surgeries and it may increase both costs and morbidity rates. There is no consensus on how to manage these situations.

Some authors have reported a delayed healing process after transoral laser microsurgery compared with 'cold' surgical techniques. Delayed abnormal healing is frequently observed, with the presence of granulation tissue, mucosal oedema, scars and the formation of synechiae. These findings have been attributed to the high temperatures used by the CO₂ laser during the resection.⁷⁻⁹ From an oncological point of view, discrimination between normal healing and tumour persistence or relapse may be difficult in the presence of granulation tissue.

To our knowledge, only Jeong *et al.*¹⁵ established the chronological evolution of healing after laser cordectomy and correlated its findings with the probability of tumour recurrence. The authors concluded that the laryngeal mucosa had stabilised after 100 days in 80.4 per cent of patients, and recurrences were observed in 33 per cent of patients with delayed healing (over 100 days). Therefore, they recommended a policy of wait and see for up to three months to avoid unnecessary biopsy.

Our results at month 1 corroborate those of Jeong *et al.*,¹⁵ confirming that the presence of granulation tissue is frequent (53.8 per cent). In our sample, granulation tissue spontaneously disappeared in 41.8 per cent of patients during the subsequent months. Tumour

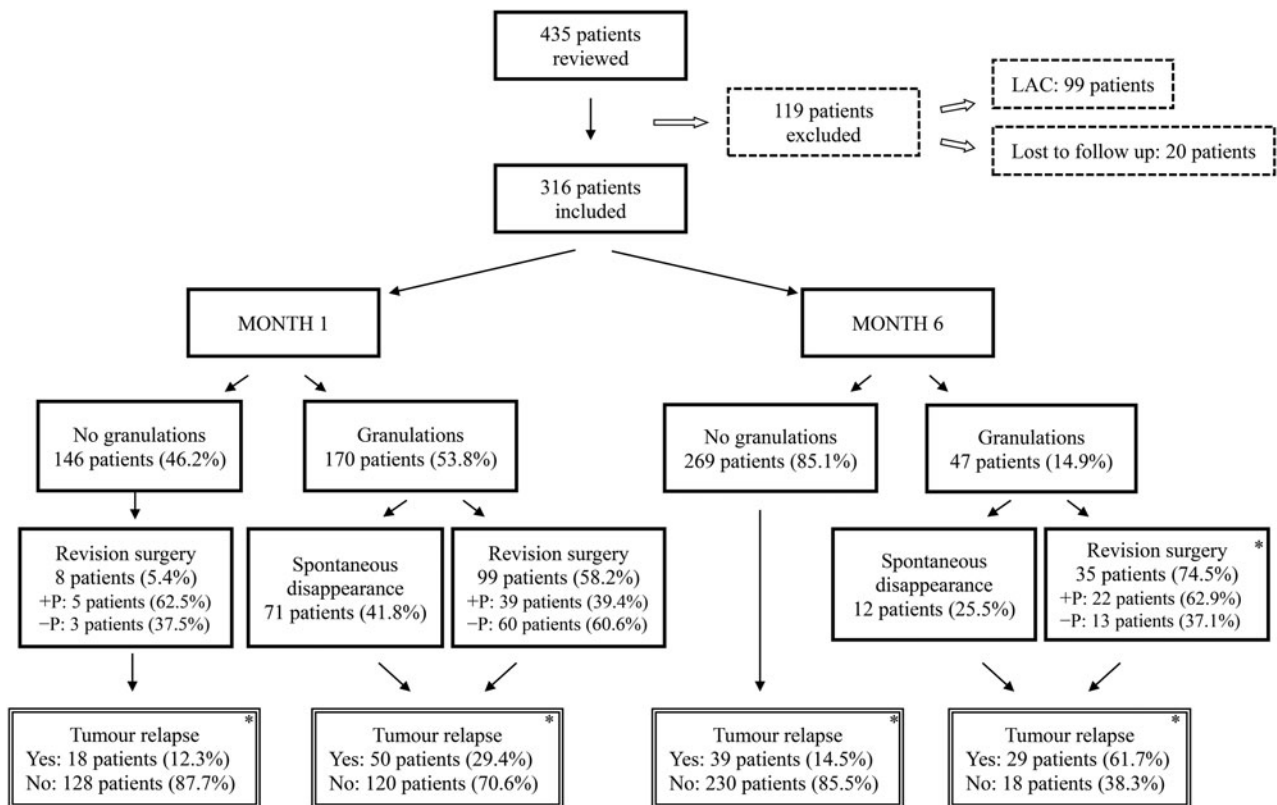


FIG. 1

Relationship between granulation tissue and tumour relapse. * = statistically significant values. LAC = laryngeal anterior commissure; +P = positive pathology report for carcinoma; -P = negative pathology report for carcinoma

relapse was recorded in 29 per cent of patients with persisting granulation tissue and in 21 per cent of the series as a whole. This suggests that in the case of potential routine revision surgery, the probability of negative histopathology would have been higher than 70 per cent; therefore, revision surgery would have been unnecessary in 7 out of 10 patients.

At month 6 we found an incidence of granulation tissue of 14.9 per cent. Its persistence over time was significantly associated with diabetes mellitus, thyroid cartilage exposure and affected surgical margins. Although the presence of granulation tissue at month 6 was not systematically related to tumour relapse, revision surgery was strongly recommended. The rate of tumour persistence in our study group with delayed healing was higher than in the study by Jeong *et al.*¹⁵ However, our sample included early and locally advanced tumours (T₁-T₃), while Jeong *et al.* analysed T₁ alone. The more advanced the tumours, and the more extended the resections, the longer the healing process was expected to take, which explains the longer period of 'wait and see' adopted at our centre.

Tumours growing in the laryngeal anterior commissure were excluded from our analysis because of their special clinical behaviour (i.e. unusually advanced stages at the moment of their diagnosis), and because of the high risk of recurrence. Resection of laryngeal anterior commissure tumours by means of transoral laser

microsurgery is considered controversial according to recent studies, and requires an experienced surgeon.¹⁶ Thus, in many otolaryngology departments, the standard surgical protocol for laryngeal anterior commissure tumours remains the external approach. Moreover, the resection technique adopted at our centre has been modified significantly over time,¹⁶ to improve oncological outcomes. We thought that the inclusion of laryngeal anterior commissure tumours would have interfered with the results and would have made the comparisons less accurate.

The World Health Organization considers individuals over the age of 65 as older adults.¹² We divided our population into 'older' and 'younger' according to this criterion, and evaluated whether age had a negative influence on the healing process. Many previous studies concluded that wound healing takes longer in healthy older adults but that it is nonetheless satisfactory.¹⁷⁻¹⁹ In our study, age had no influence on the appearance of granulation tissue.

According to some studies, tobacco use correlates with delayed post-operative wound healing, wound infection and tissue dehiscence by affecting the tissue microenvironment.^{17,20-23} In the case of the larynx, direct irritant action of cigarette smoke on the mucosa should be considered, as it has been demonstrated in other locations.²⁴ From this point of view, our results are in agreement with previous studies. Compared to non-smokers, current smokers at the time of transoral

laser microsurgery did not present a higher incidence of granulation tissue at months 1 and 6. In contrast, patients who persisted in smoking after transoral laser microsurgery presented a higher risk of granulation tissue at month 1, but not at month 6.

A common complication of diabetes is prolonged and incomplete wound healing.^{17,25,26} Eleven per cent of our patients presented with diabetes mellitus, while the normal prevalence in Spain ranges from 6.1 to 13.3 per cent.^{27,28} A significant correlation between diabetes and granulation tissue was found at month 6; however, the retrospective nature of our study does not allow us to draw any definitive conclusions. The type of diabetes and duration were not reported, and glycaemia levels and glycated haemoglobin were not prospectively monitored. Therefore, no correlation between glycaemia levels and wound healing can be established in our series.

Surgical exposure of the thyroid cartilage or removal of its perichondrium may cause a breakdown in the vascularisation of the subsequent cartilage, independently of additional heat damage with the laser. The results of our study confirm that cartilage exposure is an independent risk factor for abnormal healing at months 1 and 6. Thus, in cases in which thyroid cartilage has been exposed and tumour margins are negative, a longer follow-up period could be considered without increasing the risk of recurrence.

Surgical margins represent the most important factor for cancer recurrence, whatever the surgical technique used. Many authors have concluded that affected margins after transoral laser microsurgery are related to tumour relapse, and recommend revision surgery.^{2,10,29,30} Our findings corroborate these reports, since affected margins were related to the persistence of granulation tissue at month 6 after laser microsurgery. In contrast, positive margins did not correlate with granulation tissue during the first month. In our opinion, many factors play a key role during the first month of the healing process, including acute inflammation, local infection, vascularisation deficit and environmental irritants, even in the case of microscopic tumours. With time, the importance of acute factors diminishes and the presence of malignant cells may become more evident. This supports the policy of revision surgery when granulation tissue persists longer than expected.

To the best of our knowledge, this is the largest study in the literature evaluating the clinical significance of granulation tissue formation after transoral laser microsurgery in early and advanced glottic tumours. Our study includes a cohort of patients treated by different surgeons over a period of 10 years. Because of our increasing experience during this period, minor modifications in the resection technique have been implemented and may represent a limitation with regard to reaching objective conclusions. The increasing experience of the surgeons may also have had an impact on patient management and surgical outcomes, and

should not be underestimated. In fact, in the early stages of our use of transoral laser microsurgery many more revision surgeries were scheduled when granulation tissue formation was present to rule out tumour persistence.³¹ However, all patients were followed up by two experienced otolaryngologists (J-L B, I V) in accordance with the standard protocol of our department, and all variables were recorded prospectively in our database. From this point of view, the results of our analysis are quite homogeneous and may be of interest to surgeons using transoral laser microsurgery for the first time.

- **Presence of granulation tissue after transoral laser microsurgery for glottic carcinoma can make it difficult to distinguish between normal, but delayed, healing and tumour persistence**
- **Granulation tissue at month 1 after transoral laser microsurgery is frequent (more than 50 per cent of patients), especially if the thyroid cartilage was exposed during transoral laser microsurgery and the patient continued smoking**
- **Granulation tissue will spontaneously disappear in the 6 months following transoral laser microsurgery in nearly 50 per cent of patients**
- **Persistence of granulation tissue at month 6 is related to thyroid cartilage exposure, affected surgical margins and diabetes. In this situation, revision surgery should be performed due to the high risk of tumour persistence**

In conclusion, granulation tissue is frequent at month 1 after transoral laser microsurgery, especially if the thyroid cartilage was exposed during surgery and the patient continued smoking. Spontaneous disappearance of granulation tissue is to be expected in the following 6 months in around 50 per cent of cases. Persistence of granulation tissue at month 6 is related to thyroid cartilage exposure, affected surgical margins and diabetes. In this situation, revision surgery is mandatory because the risk of tumour persistence is higher. Further prospective studies are necessary to confirm the results of our study.

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