

# Reliability of Frozen Section Analysis in Transoral Laser Microsurgery of Upper Aerodigestive Tract Advanced Malignant Tumors

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## ABSTRACT

**Objective:** Transoral laser microsurgery (TLM) for endoscopic excision of head and neck cancers of the upper aerodigestive tract has become an accepted treatment modality. As in any excision of head and neck tumors, the persistence of tumor at the surgical margins influences the outcome. One of the frequent criticisms of endoscopic resection is that the laser use makes interpretation of the surgical margins difficult due to the thermal effect. The goal of this study is to assess the reliability of frozen section after laser excision in locally advanced tumors.

**Methods:** The charts of patients with T2 and T3 tumors, who underwent TLM between January 2000 and 2008, using the CO<sub>2</sub> laser AcuBlade system were reviewed. Frozen section margin results obtained during TLM were compared with margins after formalin fixation.

**Results:** Sixty-seven patients fulfilled the inclusion criteria. 20 had supraglottic tumors, 22 had oral cavity tumors, 13 had oropharyngeal tumors and 12 had hypopharyngeal tumors. Fifty-nine had no prior treatment, seven had prior radiation therapy and one had prior open surgery. The mean number of frozen margins per surgery was 4. Histological examination on the formalin-fixed tissue confirmed frozen section in 97% of the cases. In 3% of the frozen sections, the diagnosis of invasive carcinoma was missed. None of these patients had significant locoregional disease progression.

**Conclusion:** Frozen section analysis of margins is reliable during TLM when performed by an experienced team. It enables a one-stage approach reducing the need of a planned second procedure.

**Keywords:** Transoral laser microsurgery, Frozen section, Larynx, Pharynx, Surgical margins.

## INTRODUCTION

Since Jako, Strong and Vaughan introduced the CO<sub>2</sub> laser for endoscopic microsurgery of laryngeal carcinoma in the 1970s.<sup>1</sup> Transoral laser microsurgery (TLM) is now widely accepted for the treatment of early (T1-T2) and selected advanced oral, laryngeal and pharyngeal cancers.<sup>2</sup> As for open-neck procedures, the aim of TLM is to excise the tumor completely with histologically documented clear margins. However, the most reliable technique for assessing surgical margins is still controversial. Examination of surgical specimens resected with the CO<sub>2</sub> laser is considered difficult, and frozen section analysis is unreliable because of the thermal effect on the specimen.<sup>3</sup> Frozen section analysis is not a standard of care in surgical teams using TLM for upper aerodigestive tract tumors resection but it is used when intraoperative difficulties are encountered.<sup>4</sup>

Our objective is to report our experience on the reliability of frozen section and its results compared to paraffin section when used systematically in TLM-assisted procedures,

especially in advanced nonglottic tumors where achieving clear margins might be more difficult than T1 and/or glottis tumors.

## MATERIALS AND METHODS

We retrospectively reviewed the charts of patients treated in our department by TLM, between 2000 and 2008. We obtained the approval of the Medical Ethics Committee in our institution to perform this study. Procedures were performed by the two senior authors (MR/GL) using the AcuBlade system (Lumenis, Santa Clara, CA). The parameters of the AcuBlade system were a super-pulse mode with 10 watts power and a straight laser beam of 2 to 3 mm. Tumors were usually excised and removed *en bloc*. Only if *en bloc* resection was not possible, cuts through larger tumors were made and these tumors were resected in several pieces (piece-meal resection). When needed, electrocautery was used for hemostasis. Histological examination was performed by the two senior pathologists (MD/MCN).

We studied patients' demographics, T stage, type of surgical resection and the follow-up stressing on the necessity of performing resection surgery, the type of required later surgery (endoscopic/open surgery), and the 5-year survival. We recorded the number of frozen sections taken initially, the number of complementary margins due to positive first results or impossible readings. We compared the results of the frozen section with those of surgical margins after formalin fixation. The frozen section margins were taken on the surgical field, after resection of the lesions with macroscopically tumor free margins.

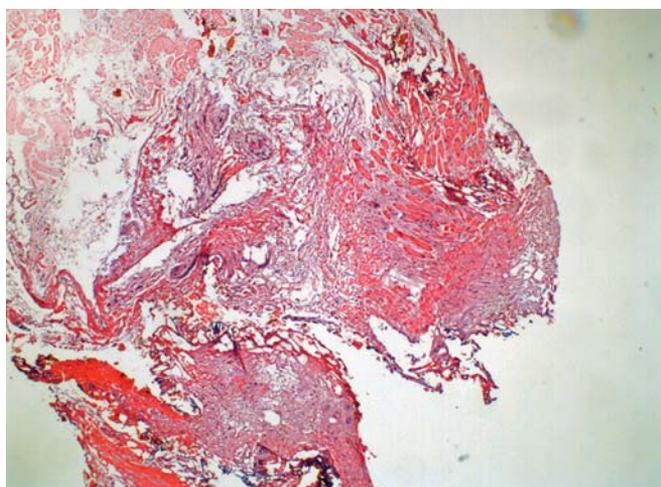
## RESULTS

A total number of 67 patients were included in the study. There were 48 men and 19 women, and a mean age of 61 years ranging from 43 to 83 years. About 59 patients had no prior treatment, seven had prior radiation therapy and one had prior open surgery. All patients had a biopsy prior to the surgical procedure to confirm the malignant nature of the lesion.

Twenty patients had supraglottic tumors, 35 had oral cavity or oropharyngeal tumors and 12 had hypopharyngeal tumors. All the patients had either T2 or T3 tumors.

In the supraglottic tumors group, 65% of the lesions were located on the epiglottis, 20% on the ventricular folds, and 15% on the aryepiglottic folds. In the oropharyngeal-oral cavity group, 49% had lingual tumors, 37% had tonsil tumors, 12% had tumors of the velum and 2% had a retromolar trigone tumor. In the hypopharyngeal tumors group, all the patients had piriform sinus tumors.

The mean number of initial frozen section per patient was 4 with a range between 1 and 8. An example of the quality of frozen section specimens is shown in Figure 1. Most of the patients (73.5%) did not require additional frozen sections. The other 26.5% required between 1 and 6 additional frozen sections because of positive margins or coagulated samples. The mean



**Fig. 1:** Example of morphological aspects of frozen sections (light power field), realized during surgery, after a careful orientation of the specimen for freezing. Despite the tissue alterations linked to thermal effect of laser or to freezing, histological status of margins can be reliably assessed

number of total frozen section per patient was 5 ranging between 2 and 11. Frozen section was concordant with histological assessment of margins after specimens were formalin-fixed and paraffin embedded, in 97% of the patients. In two patients there was a discrepancy between the results of frozen section and routine histological examination. It was a moderate dysplasia on frozen sections that was classified as severe dysplasia on routine examination. These patients are still alive with no evidence of disease at 36 months, one of them underwent a total laryngectomy at 48 months, and the other patient (a previously irradiated patient) underwent endoscopic resection because of positive routine histological margins on the tongue. The negative predictive value of frozen section in our series is 97%.

26.5% of the patients had peroperative extension of the surgery due to positive frozen section results. 88% did not require additional surgery or adjuvant radiation therapy. For the eight other patients, endoscopic resection was performed in four and open resection in four patients. Organ preservation was possible in 94% of patients. The 5-years survival rate is 84%.<sup>78-90</sup> Survival was estimated using Kaplan-Meier method<sup>5</sup> performed by SPSS 15.0 statistical software (SPSS Inc., Chicago III).

## DISCUSSION

Transoral laser microsurgery is now accepted as a reliable treatment modality for early oral, pharyngeal and laryngeal cancers (T1-T2) and even for selected advanced cases.<sup>6</sup> TLM has equal local control rates as well as organ preservation rates compared to those of open surgery and superior to those of radiotherapy.<sup>7-10</sup> TLM enables tumor resection with less perioperative morbidity and long-term complications.<sup>11</sup> It is cost effective.<sup>11</sup> The classification of some types of endoscopic resections has been standardized by the European Laryngological Society (ELS)<sup>12,13</sup> making the treatment strategies and reports more consistent. Regardless of the mode of resection (open/endoscopic), obtaining negative surgical margins at the time of resection is critical for adequate local tumor control. In a study published by Crespo et al<sup>14</sup> on the role of margin status in recurrence after CO<sub>2</sub> laser endoscopic resection of early glottic cancer, local recurrence was observed in 37.5% of patients with positive additional margins on permanent section but 0% recurred when additional surgical margins were negative on permanent section.

Iro<sup>15</sup> expressed the opinion that revision surgery is mandatory if final histologic analysis revealed positive margins. He demonstrated, in a large retrospective analysis, that unresected positive margins were associated with poor prognosis. This negative effect of positive surgical margins on outcome could not be ameliorated by adjuvant radiotherapy. This finding was confirmed by the work of Jackel et al on 1,467 patients with upper aerodigestive tract tumors.<sup>4</sup>

In a previous article, we demonstrated that the zone of thermal damage from AcuBlade system was limited to 20 µm

beyond the area of tissue vaporization.<sup>16</sup> Therefore, the use of the AcuBlade system, which has minimal thermal damage beyond the zone of ablation, enabled accurate frozen section analysis. In addition, when evaluating margins with frozen section we do not have the problem of tissue fixation that induces a shrinking of > 30% and makes the studying of the margins inaccurate.<sup>17</sup>

However, because freezing tissues result in histologic changes that can make the determination of squamous cell cancer difficult, frozen sections are deteriorated by the action of cooling and we wanted to see if frozen section interpretation was reliable and correlated well with the interpretation of routine histological examination. The correlation was 97%. When the frozen section margins revealed persistence of tumor at the edge of resection, as was identified in 26.5% of our cases, we were able to enlarge the resection during the same procedure precluding a second endoscopic resection under general anesthesia and all potential psychological inconvenience for patients. The time required for frozen section analysis of the resected margins was approximately 30 minutes depending on the number of margins studied.

The reliability of frozen section analysis depends on the surgeon's precision and pathologists' experience. The surgeon is responsible for what is submitted to the pathologist and how it is presented. It is necessary to mark the resection margins on the specimens with needles to facilitate orientation for the pathologist. This marking is even more important when a specimen is taken from the depth of the wound, and thus lacks an epithelial surface that might help the pathologist to orientate.

The drawbacks of frozen section analysis are as follows. It is time consuming for the histologist and not well reimbursed. Freezing of tissue might diminish the quality of the specimen that will be examined later with routine histological preparation. However, this does not appear to have significant impact since our survival data are similar to other series published in the literature.

## CONCLUSION

Frozen section is a reliable, cost-effective method to assess surgical margins reducing the need for systematic second look surgeries in TLM. The negative predictive value of frozen section analysis in TLM of upper aerodigestive tract malignant tumors is 97%.

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