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Original Research Article

Second look, in primary site recurrence or second primary for T1 and T2 glottic cancer treated by CO_2 laser

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ABSTRACT

Background: Aim was to analyze the impact of second-look surgery in the surveillance of T1 and T2 glottic cancer treated with CO_2 laser.
Methods: Retrospective review of 98 patients treated between February 2005 and December 2022.
Results: Among 98 patients with early glottic cancer (T1/T2), 56 (57%) with suspected recurrence underwent a second-look surgery. Of all patients, 38 (38.77%) recurred 6 months after initial resection, 17 of which (45%) had a lesion in a different site from the primary. Of these 38 patients, 22 (58%) underwent laser surgery once, 12 (32%) underwent laser surgery twice, and 4 (10%) underwent laser surgery on three occasions during follow-up. The 5-year disease-free survival, 5-year survival, and larynx preservation rates were, respectively, 54%, 82%, and 90.8%.
Conclusions: Transoral resection is currently the first treatment option for early-stage glottic carcinoma because diagnosis and prompt treatment can be provided on an outpatient basis at the same time.

Keywords: Cancer, Larynx, Early stage, CO_2 Laser surgery, Organ preservation

INTRODUCTION

The development of transoral laser surgery in the treatment of early laryngeal cancer began in the 1960s with different laser systems. In 1970 Jako and Strong pioneered the use of CO_2 laser and described the results of transoral microsurgery for glottic cancer.[1,2] However, for many years radiotherapy was still considered the gold standard for treating early stages of laryngeal cancer. In Europe, particularly in Germany, laser surgery became the preferred treatment option in the 1990s.[3,4] In North America both radiotherapy and laser surgery are used as initial treatment. Even though the American society of clinical oncology now considers laser surgery as the first treatment option, in Latin America radiotherapy has not been replaced by laser surgery yet.[5] In Mexico, in our hospital, laser surgery started being used as first treatment option 17 years ago. More reports on the effectiveness of CO_2 laser as a one-time procedure have been published. However, the procedure can be repeated, if necessary, hence the term "second-look surgery". The literature describes instances where second-look surgery is indicated, e.g., the final histopathology report reveals positive margins, follow-up endoscopy shows recurrence,

or granulomas or synechiae form after treatment.[6-8] Due to field cancerization, the literature does not differentiate whether recurrences occur at the primary site or at a subsite different from the one previously treated (second primary). The present study aims to calculate the rate at which second-look surgery is performed on primary sites or other laryngeal subsites and to determine if survival and organ preservation are affected by this.

METHODS

This is a retrospective, cross-sectional, analytical study, in which we reviewed the medical records of 98 patients with stage I and II laryngeal cancer treated from February 2005 to December 2022. This study was reviewed, approved, and registered (#2021/0002) by the institutional review board. Patients treated only at our institution by suspension micro-laryngoscopy and CO_2 laser were included. Patients treated outside our institution or those who had previously received radiotherapy were excluded.

All cases of glottic squamous cell carcinoma in stages I and II that underwent suspension micro-laryngoscopy, cordectomy, and CO_2 laser surgery were examined to identify demographic characteristics, such as age and sex, symptoms, chronic comorbidities, TNM classification, and clinical stage.

All patients were followed every 3 months for the first year, every 4 months for the second year, and, finally, every 6 months until the fifth year. We performed office endoscopy as second-look surgery in patients with suspected larynx recurrence or, in some cases, with suspected granuloma since it can hide foci of carcinoma. We differentiated between primary site recurrence and second primary tumors at another laryngeal subsite.

Descriptive analysis was done using measures of central tendency. We used chi-square test for qualitative data, t-test for quantitative data, and Kaplan-Meier curves for survival plots. All data were analyzed using SPSS 25.

RESULTS

Characteristics such as age, sex, symptoms, comorbidities, TNM classification, and clinical stage of the 98 patients are shown in Table 1. Organ preservation was achieved in 89 cases (88.8%) despite recurrence. Outpatient surgery was performed in all cases; patients underwent surgery in the morning and were discharged later in the afternoon. They ate a normal diet and took painkillers. No patient suffered from bleeding or any other complication.

The flowchart shows the distribution of patients with no recurrence, primary site recurrence, and second primary tumors (Figure 1). Second-look surgery was performed once in 58%, twice in 32%, and on three occasions in 10% of these patients (Figure 1).

Table 1: Characteristics of the CO_2 laser group, n=98.

Variables	Laser group, N (%)
Age (in years)	63.97, min/max 30-91
	Mean 63.78
	Standard deviation 12.06
Sex	
Male	91 (92.9)
Female	7 (7.1)
Symptoms	
Dysphonia	97 (99)
Dysphonia + dyspnea	1 (1)
Concomitant diseases	
None	63 (64.3)
Diabetes	8 (8.2)
Hypertension	17 (17.3)
Dyslipidemia	1 (1.0)
Diabetes + hypertension	7 (7.1)
Hypertension + dyslipidemia	1 (1.0)
Obesity	1 (1.0)
T stage	
Tis	3 (3.1)
T1a	50 (51)
T1b	16 (16.3)
T2	29 (29.6)
Clinical stage	
0	3 (3.1)
I	67 (68.4)
II	28 (28.6)
Recurrence	
Yes (primary and second primary)	38 (38.8)
No	60 (61.2)
Status	
Alive without disease	84 (85.7)
Alive with disease	7 (7.1)
Dead without disease	1 (1)
Dead with disease	6 (6.1)
Status	
Alive	84 (85.7)
Dead	14 (14.3)
Organ preservation	
Larynx preservation	87 (88.8)
Total laryngectomy	11 (11.2)

Table 2 summarizes the clinical characteristics, symptoms, comorbidities, TNM classification, clinical stage, and treatment of patients with primary site recurrence or second primary tumors. Treatment modalities are also shown in Table 2. There was no significant difference among groups regarding organ preservation (laryngectomy). Following single or multiple recurrences, organ preservation was achieved in 76.2% of patients with primary site recurrence and in 64.7% of those with the second primary tumors (p=0.438).

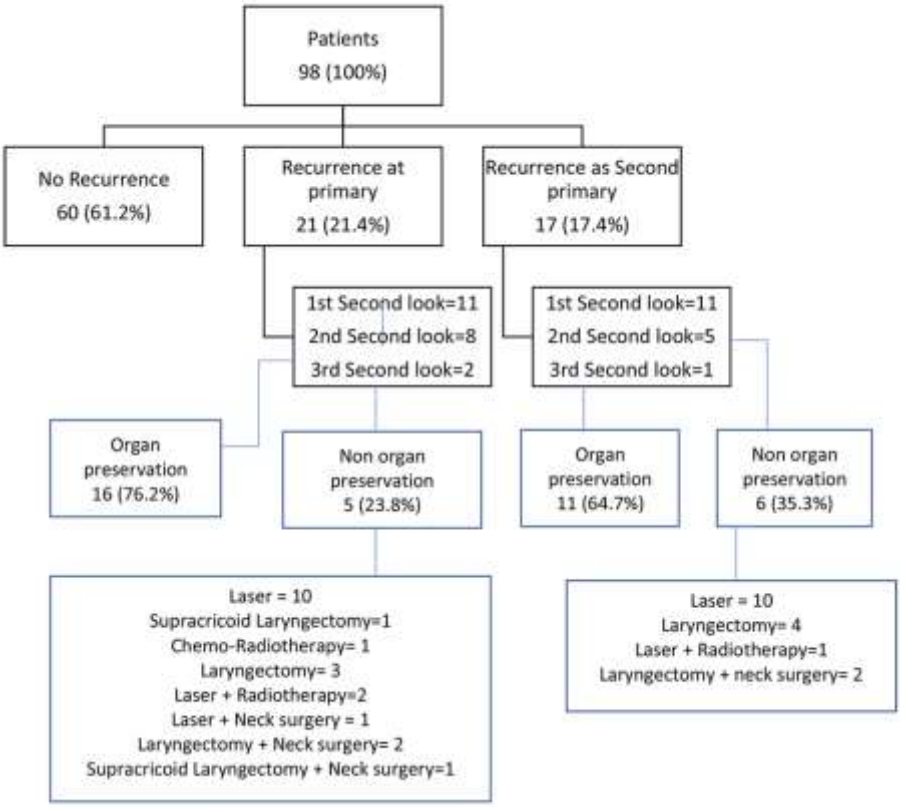

Figure 1: Flow diagram that show the distribution according to recurrence presentation.

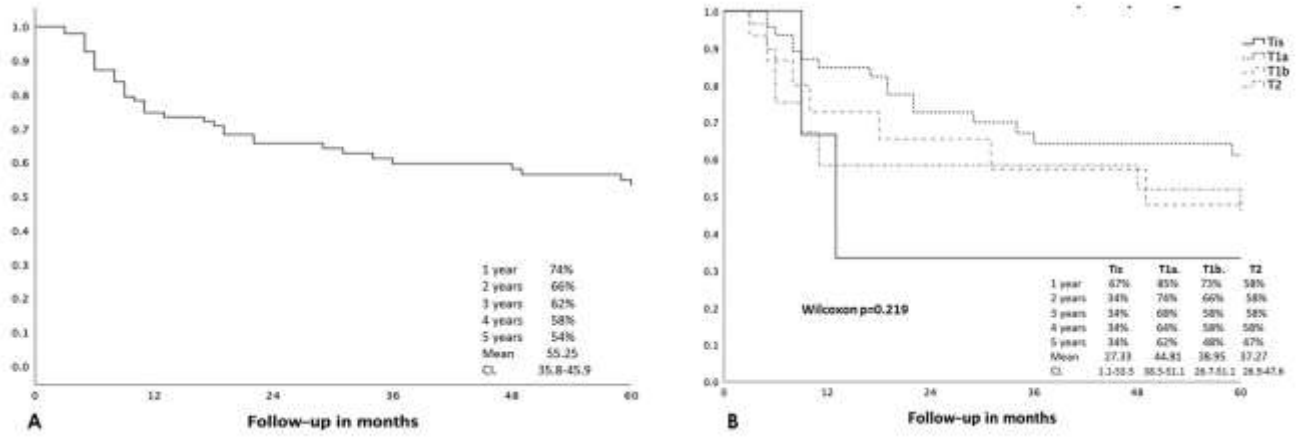

Figure 2: General disease-free survival, and disease-free survival in primary site recurrence or second primary tumor.

The disease-free survival rate suggests that recurrence peaks at 3 years (60%). From then on it remains stable for up to 10 years (53%) (Figure 2). We compared patients according to their type of recurrence, which has different biological behavior depending on whether it is a primary site recurrence or second primary tumor, and observed that disease-free survival was similar for up to 5 years (Figure 2).

The 5- and 10-year survival rates were 85% and 82%, respectively, which suggests that a large number of patients are cured (Figure 3). After comparing the sites of recurrence, we observed that patients with primary site recurrence had a lower survival rate, but it was not statistically significant, p=0.462 (Figure 4). We believe other factors affect lower survival rates because the cancer-specific survival rate was similar (85%) in both groups during the first 3 years. However, the 5- year survival rate was higher in the group of second primary tumors.

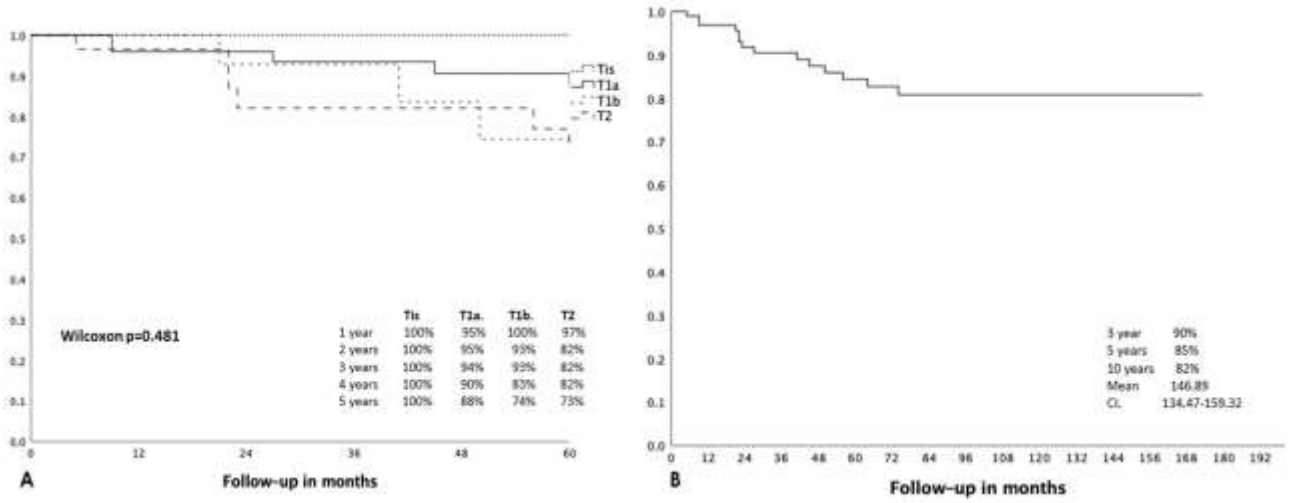

Figure 3: Overall survival and overall survival in primary site recurrence or second primary tumor.

Table 2: Characteristics of the recurrence group.

Variables	Recurrence group, n=38		P value
	At primary, n=21 (%)	As second primary, n=17 (%)	
Age (in years)	65 Min/max 52-81 years Mean 65.86 Standard deviation 9.835	64 Min/max 39-82 years Mean 64.59 Standard deviation 12.248	0.725
Sex			
Male	20 (95.2)	16 (94.1)	0.88
Female	1 (4.8)	1 (5.9)	
Symptoms			
Dysphonia	21 (100)	17 (100)	NA
Concomitant diseases			
None	16 (76.2)	12 (79.6)	0.432
Diabetes	2 (9.5)	0 (0)	
Hypertension	1 (4.8)	2 (11.8)	
Dyslipidemia	0 (2.6)	1 (5.9)	
Diabetes + hypertension	1 (4.8)	2 (11.8)	
Hypertension + dyslipidemia	1 (4.8)	0 (0)	
T stage			
Tis	1 (4.8)	1 (5.9)	0.381
T1a	9 (42.9)	7 (41.2)	
T1b	7 (9.5)	5 (29.4)	
T2	9 (42.9)	4 (23.5)	
Clinical stage			
0	1 (4.8)	1 (5.9)	0.458
I	11 (52.4)	12 (70.6)	
II	9 (42.9)	4 (23.5)	
Number of recurrences			
1	11 (52.4)	11 (64.7)	0.737
2	8 (38.1)	5 (29.4)	
3	2 (9.5)	1 (5.9)	
Recurrence site			
Same site	21 (55)	-	
Different site	-	17 (45)	
Recurrence treatment			
Laser	10 (47.6)	10 (58.8)	
Supracricoid laryngectomy	1 (4.8)	0 (0)	0.768

Continued.

Variables	Recurrence group, n=38		P value
Chemo-radiotherapy	1 (4.8)	0 (0)	
Laryngectomy	3 (14.3)	4 (23.5)	
Laser + radiotherapy	2 (9.5)	1 (5.9)	
Laser + neck surgery	1 (4.8)	0 (0)	
Laryngectomy + neck surgery	2 (9.5)	2 (11.8)	
Supracricoid laryngectomy + neck surgery	1 (4.8)	0 (0)	
Status			
Alive without disease	15 (71.4)	15 (88.2)	0.201
Alive with disease	3 (14.3)	1 (5.9)	
Dead without disease	0 (0)	1 (5.9)	
Dead with disease	3 (14.3)	0 (0)	
Status			
Alive	15 (71.4)	15 (88.2)	0.206
Dead	6 (28.6)	2 (11.8)	
Organ preservation			
Larynx preservation	16 (76.2)	11 (64.7)	0.438
Total laryngectomy	5 (23.8)	6 (35.3)	

DISCUSSION

The demographic characteristics of the patients in this study did not differ from what has been reported in the literature worldwide, with a mean age of 68 years and higher male prevalence (93.8%).[6-8]

Present series included patients with suspected recurrence who were candidates for second-look surgery. In our hospital second-look surgery is performed only during follow-up, and not as scheduled procedure. It is indicated for granuloma due to likelihood of hidden tumors, especially in the anterior commissure, as reported in 44% of cases.[8] Second-look surgery is also indicated for leukoplakia, erythroplakia/ obvious recurrence. Biopsies of such precancerous lesions reveal that 14% of them will recur and 6% will progress to cancer. Time to cancer progression is 4, 3, and 2 years for mild, moderate, and severe dysplasia, respectively.[9] Preuss et al described that persistent neck pain was associated with recurrence in upto 70% of cases and, therefore, should be considered highly suggestive of malignancy.[7] In our series, pain neck was not observed and voice changes remained the most indicative sign.

Ideal time to perform second-look surgery is controversial. A Spanish study by González-García et al recommends expectant management, that is, to perform second-look surgery until recurrence is suspected based on presentation of symptoms/ new lesion during follow-up and confirmed either by fiberoptic laryngoscopy/ endoscopy.[10] They did not define second-look surgery as such in cases where new endoscopic resection performed with no suspicion of lesions. Therefore, another strategy could be performing second-look surgery within 3-6 months after initial surgery or adopting watch-and-wait approach until lesion is suspected.

Following Steiner's technique, we perform resections by cutting through the tumor until surgical margins of healthy tissue are observed at depth, particularly in large tumors.[11] When margin status is uncertain, an intraoperative evaluation is requested, but this is not done regularly. In his study of 240 patients, Steiner reported 6 recurrences, 1 patient requiring total laryngectomy, and a survival rate of 100%.[12] In some instances, R0 resections are not achieved despite intraoperative evaluations. Preuss et al obtained R0 resections in only 53% of cases.[7] In R0 resections of the glottis the distance between the margin and tumor must be 1 mm.[13] Pathologists cannot define the margins when carbonization or thermal damage is caused by laser. Furthermore, the final analysis could show positive margins, especially in en-bloc resections since many surgeons still do not consider intratumoral resection as an option.

In 2003 Pearson et al were the first to assess the importance of second-look surgery.[14] They electively performed it in 87% (20/23) of patients with anterior commissure involvement, and found a recurrence rate of 12%. Anterior commissure involvement is one of the main indications for second-look surgery. The first prospective study to evaluate the effectiveness of second-look surgery was published in 2008. It included 29 patients with anterior commissure lesions and re-examined them 3 months after the initial surgery. Recurrences were detected up to 8 months after initial surgery in 25.9% of cases.[8,15] In the present series, 21.4% (21/98) of patients had primary site recurrence, a similar rate to what has been reported. However, we also observed recurrences at sites that had not been treated, and are considered as second primary tumors. We did not find a higher recurrence rate in the anterior commissure. If anterior commissure involvement is suspected, we perform a partial resection of the thyroid cartilage as described by Steiner (during my training with him).

Even though most of the studies reviewed considered positive margins as the main recurrence factor, Lee et al and Hartl et al revealed that there was no direct statistical relationship between margin status and recurrence.[16,17] We agree with their finding since intraoperative frozen section analysis for margin status is normally not feasible as it is expensive and time-consuming. Margin status is a controversial topic, but most surgeons who perform laser surgery rely on clinical margins during the procedure. Fang et al called into question the usefulness of this procedure and evaluated frozen section analysis as a predictor of recurrence and thus avoid a second-look surgery, which they considered of little benefit and expensive.[18] They found that the initial frozen section analysis was important factor for recurrence and predictor of survival. However, frozen sections are not always available for margin analysis. Moreover, their study was not comparative, and advantages of second-look surgery in examining and treating non-pathological effects of laser surgery were not taken into consideration.[19]

Prospective studies should distinguish between positive, close or suspicious, and negative margins. Carlos Chiesa et al found 70% of negative margins and 20% of suspicious margins. Second-look surgery was performed in 66% of cases with suspicious margins.[20] It is important to consider discrepancy between surgeon's clinical impression of margins, final histopathology report.[21-23]

Recurrence rates of 21%, 36.5% and 24%, have been described. In our series, we found a recurrence rate at the primary site of 21.4%; however, 17 (45%) patients developed lesions in sites different from the primary site.[6-8] These lesions should be considered second primary due to field cancerization. Patients with second primary tumors seemed to have a higher survival rate, but this difference was not observed when we compared it against specific-cancer survival at 3 years. However, at 5 years the survival rate is once again higher in patients with second primary tumors. We cannot provide an explanation for this since literature does not differentiate between primary site recurrence and recurrence at sites other than the primary. Total organ preservation was 88.8%. This rate was 71% after second-look surgery, which is similar to that reported in other studies.[6-8] The main limitation of the present study is that the treatments were done at different times; it will be important in the future to carry out paired comparative studies.

CONCLUSION

Transoral resection is currently the first treatment option for early-stage glottic carcinoma because diagnosis and prompt treatment can be provided on an outpatient basis at same time. T1 tumors are treated mainly by transoral endoscopic surgery because tumors need biopsy to receive treatment and Transoral surgery must be consider for diagnosis and treatment in the same time. T2 tumors must be treated by surgery or radiotherapy. T2 tumors treatment by surgery can be done in 1 day, radiotherapy needs that-patients comes many times to be treated.

Second-look surgery at our hospital is not performed regularly, only in cases of suspected recurrence with close patient monitoring. Radiotherapy must be considering only for T1 tumor in recurrence. It is worth differentiating between primary site recurrence and second primary tumors at other sites in larynx. Surgical margin assessment is still a topic of debate, but it should be performed using frozen sections, meanwhile, it is mostly operator dependent.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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