

Is There a Change in the Treatment of T1 Glottic Cancer After CO₂ Laser? A Comparative Study with Cold Steel

CO₂ Lazer Sonrası T1 Glottik Kanser Tedavisinde Değişiklik Var mı? Soğuk Bıçakla Karşılaştırma Çalışması

Original Investigation
Özgün Araştırma

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Abstract

Objective: Carbon dioxide (CO₂) laser provides high local control and disease-specific survival rates with minor morbidity and good quality of life in transoral cordectomy. We aimed to compare the oncological outcome and survival between cold steel and CO₂ laser in the treatment of early glottic cancer.

Methods: In this retrospective study, the participants were divided into two groups. The first group comprised patients who were operated upon between 2001 and 2007 using cold steel (group 1, n=38), and the second group comprised patients who were operated upon between 2008 and 2016 using CO₂ laser (group 2, n=88). Both groups were compared regarding age, gender, pathological grade, T stage, type of cordectomy, margin status, anterior commissure involvement, follow-up, locoregional recurrence, and disease-free survival (DFS).

Results: The overall survival rate and DFS were similar between the two groups (94.7% vs. 98.9% and 100% vs. 98.9%, respectively), and no association was

found between surgical margin positivity and local recurrence. However, a significant association between the presence of anterior commissure involvement and recurrence was found in all 126 patients (p=0.016). Local recurrence was significantly higher in the group 2 (p=0.024), but it did not affect overall survival and DFS in these patients (100% vs. 94.1%).

Conclusion: Although CO₂ laser excision is considered to be superior to cold steel regarding surgical time and bleeding control, the local recurrence rates were found to be higher with the laser than the cold steel. Thus, we argue that cases should be selected more carefully concerning the anterior commissure, depth of tumor invasion lateral to vocal muscle, difficulty at endoscopic exposure for lesions with anterior commissure involvement, and reliability of surgical margins at frozen sections.

Keywords: Glottic cancer, CO₂ laser, cold steel, survival, oncological results



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Öz

Amaç: Karbondioksit (CO₂) lazer, transoral kordektomide yüksek lokal kontrol ve hastaliksız sağkalım oranlarını beraberinde düşük morbidite ve iyi hayat kalitesi ile birlikte sağlamaktadır. Bu çalışmada erken evre glottik kanserlerde, soğuk bıçak ve CO₂ lazer kullanımının onkolojik sonuçlarını ve sağkalım sürelerini karşılaştırmayı amaçladık.

Yöntemler: Bu geriye dönük çalışmada, ilk grupta 2001-2007 yılları arasında soğuk bıçak kullanılarak opere edilen hastalarla (grup 1, n=38), ikinci grupta ise 2008-2016 yılları arasında CO₂ lazer kullanılarak opere edilen hastaların (grup 2, n=88) verileri karşılaştırıldı. Bu gruplar yaş, cinsiyet, patolojik evre, T evresi, kordektomi tipi, sınır durumu, ön komissür tutulumu, izlem, lokorejyonel nüks ve hastaliksız sağkalım açısından karşılaştırıldı.

Bulgular: Sağkalım ve hastaliksız sağkalım oranları gruplar arasında benzerdi (%94.7'ye %98.9 ve %100'e %98.9) ve bu değerlerin cerrahi sınır pozitifliği veya

lokal nüks ile ilişkisi tespit edilmedi. Hastaların tümü (126) ele alındığında sadece anterior komissür tutulumu ile nüks arasında anlamlı ilişki mevcuttu (p=0.016). Lokal nüks lazer grubunda anlamlı olarak fazlaydı (p=0.024) ancak bu durumun tümde sağkalım ve hastaliksız sağkalım oranlarını etkilemediği saptandı (%100'e %94.1).

Sonuç: CO₂ lazer cerrahisinin soğuk bıçağa cerrahi süre, kanama kontrolü gibi üstünlükleri olsa da; çalışmamızda soğuk bıçak kullanımına göre artmış lokal nüks oranları saptadık. Bu nedenle hasta seçiminde ön komissür tutulumu, tümörün lateralde vokal kasa olan invazyon derinliği, ön komissür tutulumu olan lezyonlarsa endoskopik görüş kısıtlılığı ve donuk kesitlerde cerrahi sınır güvenilirliği gibi konulara dikkat ederek hasta seçimi yapılması gerektiği yargısına vardık.

Anahtar kelimeler: Glottik kanser, CO₂ lazer, soğuk bıçak, sağkalım, onkolojik sonuç

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Introduction

Early glottic carcinoma involving only the true vocal cords has a very good prognosis if appropriate treatment with safe surgical margins is applied (1, 2). Endolaryngeal excision using cold steel has been reported to be useful in the management of early glottic carcinoma since 1920s, but it has gained more popularity after the advancement of laser technology coupled to operating microscope for laryngeal surgery (3, 4). In the last four decades, many studies have reported comparable oncological results, better preservation of laryngeal functions, less morbidity, and higher quality of life with endolaryngeal laser cordectomy than with open surgery (1, 2, 5-7).

At our department, we have used cold steel coupled with surgical microscope and telescopes in the treatment of early glottic carcinoma until 2007 with success, and since then, we have performed all endolaryngeal cordectomies using carbon dioxide (CO₂) laser (8). Despite reports favoring the use of laser in the treatment of glottic carcinoma (1, 2), we observed some problems regarding the intraoperative frozen section assessment of surgical margins. Since the CO₂ laser beam causes an acute thermal damage and severe coagulation in the tissues, the pathologists may sometimes encounter difficulty in deciding the safety of surgical margins. The histological effects of different surgical instruments, such as CO₂ laser, scalpel, and electrocautery, on oral mucosal incisions and tissue healing have been studied on animal models (9, 10). These studies indicated that CO₂ laser exerted the highest extent of epithelial damage lateral to wound edge and that the extent of collagen denaturation with scalpel was the lowest. Furthermore, scalpel usage was related with better wound healing, tissue re-epithelialization, and tensile strength but with worse hemostasis compared with laser (10, 11).

We should consider both the pros and cons of treatment options while dealing with any disease, especially malignancy. In this regard, CO₂ laser usage in the treatment of early glottic cancer has feasible advantages beside some minor adverse effects on tissue repair. Thus, we aimed to compare cold steel and CO₂ laser regarding the associated oncological outcome and survival and also to determine the relevance of surgical margins and local recurrence in the treatment of early glottic cancer.

Methods

This retrospective comparative study was conducted at the University of Uludağ, Department of Otorhinolaryngology and Head Neck Surgery on patients who underwent endolaryngeal cordectomy using either cold steel or CO₂ laser for T1 glottic carcinoma. The patients were classified into two groups according to the instrument used in cordectomy: the first group comprised patients operated upon between 2001 and 2007 using cold steel (group 1), and the second group comprised patients operated upon between 2008 and 2016 using CO₂ laser. The decision for endolaryngeal cordectomy was based on rigorous oncological principles, and cordectomy was performed by senior head and neck surgeons under general anesthesia. The exclusion criteria were as follows: (i) previous head and neck radiotherapy

or chemotherapy, (ii) inaccessible pre- or postoperative records, and (iii) previous laryngeal surgery at another hospital.

All the patients were evaluated using laryngeal flexible endoscopy and videolaryngostroboscopy at the outpatient clinic before surgery. The contrast-enhanced computed tomography of larynx was performed if the lesion involved the anterior commissure or laryngeal ventricle or if there was a suspicion of paraglottic invasion. Routine chest x-ray imaging was performed before surgery in each patient. Tumors were staged according to the criteria of 2010 edition of American Joint Committee on Cancer. The background information of all patients including age, gender, pathological grade, T category, type of cordectomy, margin status, anterior commissure involvement, follow-up time, need for adjunct treatment, locoregional recurrence, and disease-free survival (DFS) time were retrieved from patient files. Subsequently, the patient groups were compared according to the collected clinical data. This retrospective study was approved by the ethical committee of Uludağ University School of Medicine (approval number, 2017-4/12).

After the induction of general anesthesia, we examined the larynx using 0° and 70° rigid laryngeal telescopes to assess the anterior commissure, subglottis, and ventricles prior to orotracheal intubation. Subsequently, the patient was intubated with a microlaryngeal tube (5-mm diameter). Endolaryngeal surgery was performed using surgical microscope and cold steel in group 1 and using CO₂ laser (Acupulse; Lumenis; Yokneam; Israel) coupled to microscope in group 2. The details of surgical techniques used for tumor resection have been mentioned in our previous study (8). Following resection, the safety of surgical margins [anterior, posterior, inferior, superior mucosal, and lateral (deep)] was evaluated by a pathologist using frozen sections. We performed additional resections at adjacent tissue until reaching safe margins, as confirmed by the pathologist. The surgical margins at frozen sections were prepared using cold steel to prevent any assessment bias or tissue artifacts. The surgery was completed after achieving surgical hemostasis in the field. No postoperative medications were ordered except corticosteroid injections, if necessary. We reported the extent of cordectomy in the surgical reports according to the classification of European Laryngological Society (12).

The patients were examined at 2nd and 4th postoperative weeks using endoscopy for the control of wound healing. In addition, oncological follow-ups were done at monthly intervals. We re-scheduled the patients for endoscopic examination and control biopsy under general anesthesia if there was suspicion of recurrence, if permanent pathological slides showed conflicting results, new granulation tissue, or synechia formation, and if inadequate exposure to vocal cords was observed in the outpatient setting.

Statistical analyses were performed using SPSS 20.0 and MedCalc v12.3.0 (SPSS Inc., IBM, USA). Continuous and discrete variables were presented as median (minimum–maximum) and n (%). Pearson's X², Kaplan–Meier, and Fisher's exact tests were performed for between-group comparisons. Significance was set at p<0.05.

Results

Group 1 comprised 38 patients (37 males, 1 female) aged 41-75 (median, 60) years; group 2 comprised 88 patients (85 males, 3 females) aged 38-82 (median, 65) years in group 2. The two groups were similar regarding age and follow-up duration. T categories and cordectomy types performed in both groups are shown in Table 1. There was a significant difference between the groups regarding the cordectomy types ($p=0.046$), which indicated that a higher number of patients underwent type 1 cordectomy in the cold steel group (15.8%) than in the laser group (4.5%); conversely, a higher number of patients underwent type 4 and 5 cordectomies in the latter group (42%) than

Table 1. Demographic and clinical findings comparing two patient groups

| | Group 1 | Group 2 | P |
|-------------------------------------|------------|-------------|-------|
| Age (years; median) | 41-75 (60) | 38-82 (65) | |
| Follow-up (months; median) | 1-72 (24) | 4-86 (28.5) | |
| Cordectomy types | | | |
| Type 1 | 6 (16%) | 4 (5%) | 0.046 |
| Type 2 | 15 (39%) | 26 (29%) | |
| Type 3 | 7 (18%) | 21 (24%) | |
| Type 4 | - | 9 (10%) | |
| Type 5 | 10 (26%) | 28 (32%) | |
| T category | | | |
| Tis | 7 (18%) | 4 (5%) | 0.045 |
| T1a | 23 (60%) | 66 (75%) | |
| T1b | 8 (21%) | 18 (20%) | |
| Pathological diagnosis | | | |
| Carcinoma in situ | 7 (18%) | 7 (8%) | 0.259 |
| Microinvasive carcinoma | 3 (8%) | 9 (10%) | |
| Invasive carcinoma | 28 (74%) | 72 (82%) | |
| Positive surgical margin | 1/38 (3%) | 3/88 (3%) | 1.00 |
| Local recurrence | 2/38 (5%) | 17/88 (19%) | 0.024 |
| Recurrence after type 5a cordectomy | 2/10 (20%) | 6/28 (21%) | 1.00 |

Table 2. Clinical findings of patients with anterior commissure involvement in two patient groups

| | Group 1 | Group 2 | P |
|---------------------------------|---------|---------|------|
| Anterior commissure involvement | 8/38 | 40/88 | 0.01 |
| Local recurrence | 1/8 | 15/40 | 0.24 |
| Organ preservation | 8/8 | 39/40 | 1.00 |
| Overall survival | 100% | 97.5% | 1.00 |
| Disease-specific survival | 100% | 97.5% | 1.00 |

in the former group (26.3%). Positive surgical margins were reported in three patients at permanent sections, although all frozen sections were free of cancer in group 2. Among these three patients, one underwent postoperative radiotherapy, one underwent supracricoid partial laryngectomy, and the remaining one underwent revision endolaryngeal surgery to achieve a safe margin. Regarding the definitive margin status, there was no difference between the two groups ($p=1.00$, Fisher's exact test); furthermore, the pathological diagnosis was similar between the two groups ($p=0.259$, Fisher's exact test).

In group 1, two patients died due to secondary cancer of a different organ, and in group 2, one patient died due to primary cancer. Therefore, overall survival rate and DFS were 94.7% and 100%, respectively, in group 1, and both the overall survival rate and DFS were 98.9% in group 2. Local recurrence developed in two patients in the group 1, whereas recurrence was reported in 17 patients in the group 2. A statistically significant difference was found between the groups regarding local recurrence ($p=0.024$, Pearson's χ^2 test), but no difference was found when patients with type 5 cordectomy in both groups were compared separately ($p=1.000$, Fisher's exact test) (Table 1). In the cold steel group, both recurrences were at the anterior commissure that extends to the ventricular bands. The exact locations of local recurrence in the laser group ($n=17$) were as follows: the anterior commissure, eight patients; anterior 1/3rd of the vocal cord, three patients; both the ventricular band and vocal cord, four patients; posterior 1/3rd of the vocal cord, one patient; and opposite to the vocal cord, one patient. Two patients with recurrence in the group 1 were successfully salvaged by open partial laryngectomy, and 17 patients in the group 2 were successfully salvaged by either open partial laryngectomy ($n=6$), total laryngectomy ($n=1$), radiotherapy ($n=4$), or revision endolaryngeal cordectomy ($n=6$). One patient died during hospital stay due to postoperative complications of primary cancer. The organ preservation rate and DFS of patients with recurrence in groups 1 and 2 were 100% vs 94.1% and 100% vs 94.1%, respectively.

In the groups 1 and 2, control suspension microlaryngoscopy for a second look was required in 18 (47.4%) and 37 (42%) patients and was required for a third time in two and nine patients, respectively, with no statistically significant difference between groups ($p=0.580$). Eight patients in the group 1 and 40 in the group 2 had an anterior commissure involvement. Although there was a statistically significant difference between the groups regarding the anterior commissure involvement ($p=0.01$, there was no difference regarding the recurrence rate ($p=0.24$) between patients with anterior commissure involvement on intergroup analysis. In addition, there was no difference between the groups with anterior commissure involvement regarding overall survival and DFS ($p=1.000$) (Table 2).

Finally, we evaluated the presence of any association between recurrence and other variables such as pathological diagnosis, T category, type of cordectomy, surgical margin positivity, anterior commissure involvement, age, and follow-up duration in all 126

Table 3. Association between clinical variables and recurrence in all 126 patients

| | Recurrence (-) n=107 | Recurrence (+) n=19 | P |
|--------------------------------------|-------------------------|------------------------|-------|
| Corpectomy types | | | |
| Type 1 (n=11) | 9 | 2 | 0.082 |
| Type 2 (n=40) | 36 | 4 | |
| Type 3 (n=28) | 26 | 2 | |
| Type 4 (n=9) | 6 | 3 | |
| Type 5 (n=38) | 30 | 8 | |
| T category | | | |
| Tis (n=10) | 9 | 1 | 0.140 |
| T1a (n=90) | 79 | 11 | |
| T1b (n=26) | 19 | 7 | |
| Pathological diagnosis | | | |
| Carcinoma in situ (n=14) | 12 | 2 | 0.215 |
| Microinvasive carcinoma (n=12) | 11 | 1 | |
| Invasive carcinoma (n=100) | 84 | 16 | |
| Positive surgical margin | | | |
| Negative (n=122) | 104 | 18 | 0.295 |
| Positive (n=4) | 3 | 1 | |
| Anterior commissure involvement | | | |
| Negative (n=78) | 73 | 5 | 0.016 |
| Positive (n=48) | 34 | 14 | |
| Age (years) (median) | 38-82 (60) | 46-78 (64) | 0.412 |
| Follow-up duration (months) (median) | 1-78 (24) | 7-86 (31) | 0.644 |

patients. Overall, there was a significant difference only between the presence of anterior commissure involvement and recurrence ($p=0.016$) (Table 3). In regression analysis, the risk of recurrence was found to increase 3.56 times (HR 95%, 1.24:10.19) in the presence of anterior commissure involvement. In the laser group, this relation was also significant only for anterior commissure involvement and not others ($p=0.021$).

All patients were discharged the day after surgery. Oral intake of soft foods and liquids was allowed four hours after surgery. Antireflux treatment was ordered for patients who had laryngopharyngeal reflux symptoms. The perioperative complication rate was similar between the groups.

Discussion

Although transoral cordectomy using cold steel had been reported almost 90 years ago, it was almost completely replaced with the transoral laser excision in the last 30 years, with high

organ preservation and survival rates (1, 5, 13). In the last 20 years, CO₂ laser has been widely accepted because it offers the advantages such as better bleeding control, reusability for salvage surgery, and lesser morbidity with good quality of life compared with open external surgery (1, 2, 5). It also allows a precise removal of lesions with tiny and targeted surgical margins under microscopic guidance. The enhanced visualization in a bloodless surgical field encouraged surgeons to operate transorally on more extended tumors involving the anterior commissure, ventricular fold, supraglottis, or subglottis. This instrument enabled surgeons to excise more risky lesions with small surgical margins, and the early oncological results were promising. However, we argue that along with the benefits, laser technology carries the risk of underestimating or neglecting the depth and extent of the lesion. Another drawback of using the laser is the difficulty in pathological assessment of surgical margins, as the small-sized tissue excised during endolaryngeal cordectomy may contract *in vitro* and interfere with interpretation of safe surgical margins at frozen sections (14). Pathological assessment is technically more difficult with CO₂ laser as it may lead to some artifacts. It was argued that thermal coagulation and subsequent severe tissue damage may lead to these artifacts (10, 11). On the other hand, some others believe that frozen section assessment of surgical site after CO₂ laser is very reliable with high negative predictive value, especially when an acublade laser mode is preferred (15, 16). Thus, in the present study, to address our concerns regarding the reliability of surgical margins after CO₂ laser cordectomy, we decided to compare the oncological results, safety of surgical margins, and recurrence rates associated with CO₂ laser with our previous study results using cold steel in endolaryngeal cordectomy (8).

Anterior commissure involvement and presence of positive surgical margins are the two main factors determining the prognosis in T1 glottic cancers. However, the definition of a safe surgical margin in transoral laser surgery is still under debate. Many authors believe that excision of the tumor with at least 2-mm clean margins from the tumor edge is acceptable to achieve an oncologically safe result. Ansarin et al. (17) revealed that patients with a positive surgical margin or those with a close margin (≤ 1 mm) exhibited greater recurrence rates than those with a >1 mm safe margin. Similarly, in a study conducted by Crespo et al. (18), the presence of positive surgical margins at permanent sections in CO₂ laser cordectomy was significantly correlated with local recurrences. DFS and local control rate of patients with positive margins were found to be impaired in the study of Charbonnier et al. (14). They also pointed out the importance of vocal muscle involvement by tumor cells as a negative factor in prognosis. Mortuaire et al. (19) reported a similar finding that vocal muscle infiltration had a negative effect on DFS. On the contrary, some authors reported that surgical margin status did not have any significant effect on the oncological outcomes (20, 21). Michel et al. (20) revealed no difference in the overall or recurrence-free survival according to the resection margin histologic status after endoscopic laser cordectomy. In our study, three of 88 (3.4%) frozen sections

were misinterpreted as negative but confirmed to be positive in permanent pathology sections in the laser group. Among these three patients, one had a recurrent lesion that was successfully treated with open partial laryngectomy; one had close follow-up with no recurrence; and the remaining one underwent adjuvant radiotherapy. In the cold steel group, in one of 38 (2.6%) patients, the surgical margin was found to be positive in the permanent section, and the patient was treated with a second endolaryngeal excision. According to the definitive margin status, there was no difference between the cold steel and laser groups. The overall survival rate and DFS were similar between the two groups with no significant difference. In addition, we did not find any association between surgical margin positivity and local recurrence in all 126 patients.

There is almost no debate on the association between anterior commissure involvement and worse prognosis in patients undergoing endolaryngeal cordectomy. Most authors have a consensus that such patients have a low DFS and overall survival and, thus, need to be treated more carefully concerning larger surgical margins. Mendelsohn et al. (22) reported 5/30 (16.7%) recurrence rate in their study with a group of patients who underwent CO₂ laser cordectomy involving anterior commissure. The overall organ preservation rate was 28/30 (93.3%) in that study. They pointed out that tumors arising from the anterior commissure had a more widespread oncologic mutational change. Thus, subclinically involved peripheral margins at this location are more prone to local recurrences. In their study, Rödel et al. (23) revealed a negative impact of anterior commissure involvement on local disease control in T1 glottic lesions. Edizer and Cansız (24) also found a higher risk of local recurrence if the tumor involved the anterior commissure in transoral laser surgery for glottic cancers. Similarly, Chone et al. (25) reported a higher rate of local recurrence (21%) in patients with anterior commissure involvement compared with those without involvement (4%), but without statistical significance. Initial anterior commissure involvement was indicated to increase the risk of local recurrence regardless of the surgical approach, either external or transoral laser, in a study conducted by Sachse et al. (26). All the above-mentioned studies evaluated the local recurrence in patients with or without anterior commissure involvement who underwent endolaryngeal laser surgery. In our study, we also found that overall, anterior commissure involvement was significantly associated with local recurrence; however, there was no difference between the two groups with anterior commissure involvement regarding local recurrence, DFS, and overall survival. This may be due to less number of patients with anterior commissure involvement in the cold steel group and elaborate patient selection regarding the extent of lesion with cold steel use.

In this study, we realized that after CO₂ laser, there was a significant increase in the percentage of lesions with anterior commissure involvement that were excised via transoral route [group 1: 21% (8/38) vs group 2: 45% (40/88)]. We assumed that this may be due to very meticulous selection of low-risk lesions before laser with the concerns of bleeding at surgical site, difficulty of exposure, prolonged surgical time, and greater sacrifice of

healthy surrounding tissue. However, after laser, surgeons feel more comfortable, safer, and somehow extremely self-confident with this powerful instrument. This may be a drawback in some circumstances as one may underestimate the extension or the depth of tumor and enforce to excise all the lesions via an endolaryngeal approach. In this study, anterior commissure involvement was reported in 40 patients at permanent pathology report in the laser group; however, we performed type 5 cordectomies in only 28 patients among group 2 in the first surgery. This indicates that we probably misdiagnosed or underestimated the extent of primary lesion and applied inappropriate cordectomy type. The local recurrence rate was higher in the laser group than in the cold steel group [19% (17/88) vs (5% or 2/38)]. We argued that this difference may be due to a higher percentage of patients with anterior commissure involvement in the laser group or due to artifacts caused by the thermal effect of laser that makes the assessment of surgical margins difficult at frozen sections if used in a continuous-wave mode (27). Whatever the reason, fortunately with successful salvage treatment modalities, we achieved very good and similar organ preservation and DFS rates in patients with local recurrences in both groups.

Conclusion

We can achieve very good local control and high DFS with transoral CO₂ laser cordectomy in glottic tumors. Unfortunately, the tumors involving the anterior commissure exhibit worse prognosis irrespective of the surgical approach. Although CO₂ laser excision is considered to be superior to cold steel regarding surgical time, bleeding control, precise and targeted incisions, and small surgical margins in the literature, we found an increased local recurrence rate compared with that in our previous study with cold steel. Thus, we argue that cases should be selected more carefully regarding the anterior commissure involvement and more attention should be paid to reliability of surgical margins at frozen sections. CO₂ laser provides oncologic outcomes similar to cold steel in the treatment of T1 glottic cancers and is a very useful instrument considering the additional benefits it offers.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Uludağ University School of Medicine (2017-4/12).

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