

# Laser Surgery for Early Glottic Cancer

## Impact of Margin Status on Local Control and Organ Preservation

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**Objective:** To assess the impact of margin status on disease-free survival, overall survival, and organ preservation in early glottic cancer treated by endoscopic laser surgery.

**Design:** Prospective nonrandomized study.

**Setting:** Tertiary referral center.

**Patients:** A total of 274 patients with untreated (possibly biopsied) cTis, cT1a/b, cT2, cN0 glottic cancer; adequate exposure of the glottic region; no contraindications to general anesthesia; and the ability to give informed consent.

**Interventions:** European Laryngological Society laser cordectomy. Patients with negative margins ( $>1$  mm) were followed, patients with close margins ( $\leq 1$  mm) or 1 positive margin (tumor on margin) had another operation, and patients with more than 1 positive margin had postoperative radiotherapy. Median follow-up was 58 months.

**Main Outcome Measures:** Eight-year disease-free survival, 5-year overall survival, and organ preservation rate.

**Results:** Margins were negative in 180 patients, close in 40, and positive in 54. A second laser resection was performed in 36 of 94 patients with close or positive margins. Radiotherapy was administered to 36 patients. Patients with close or positive margins who did not undergo further treatment had a greater recurrence risk (hazard ratio, 2.53; 95% confidence interval, 0.97-6.59,  $P = .06$ ) than did those with negative margins, mainly owing to relapses in 5 of the 8 protocol breakers with positive margins not treated further. Eight-year relapse-free survival was 88.2%, 5-year overall survival was 90.9%, and the larynx was preserved in 97.1%.

**Conclusions:** Laser removal of early glottic cancer is oncologically adequate with margins greater than 1 mm from the tumor edge. Positive margins require further treatment; close margins may require further treatment depending on tumor characteristics.

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**A**N INVOLVED RESECTION margin in a head and neck malignant neoplasm is one of the most important factors affecting local recurrence.<sup>1-4</sup> Radical surgery, therefore, requires a wide margin of healthy tissue around the lesion. However, there is currently no consensus regarding how wide. In 2005, Meier et al<sup>5</sup> reported that most American Head and Neck Society members accept a clean margin as 5 mm on microscopic evaluation. However, this publication did not address laryngeal cancer. Batsakis<sup>6</sup> noted that for most authors, oral cavity, oropharynx, and hypopharynx cancers require wider margins than do those of the larynx. This may be reasonable because patients with T1-T2N0 squamous cell carcinoma of the vocal cord have local control and organ preservation rates that approach 90%<sup>7</sup> irrespective of treatment modality, which may be endoscopic laser surgery or radiotherapy (RT).

The few studies<sup>8-12</sup> that have addressed the impact of margin status on local control and disease-specific survival in vocal cord malignant neoplasms have provided contrasting results. In May 1999, we started a prospective nonrandomized study of patients referred to the European Institute of Oncology for early glottic squamous cell carcinoma biopsied elsewhere or coming to us directly with a suspicious lesion. Patients were generally treated with endoscopic surgery using a carbon dioxide laser. The aim of this study is to assess the impact of margin resection status on disease-free survival (DFS), overall survival, and organ preservation.

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## METHODS

### PATIENTS

Patients with a history of a vocal cord biopsy positive for squamous cell carcinoma or with a clinically suspicious lesion staged as early glottic cancer (cTis, cT1a, cT1b, T2) and with a

**Table 1. Patient and Tumor Characteristics Before Cordectomy in 274 Patients With Early Glottic Cancer**

Characteristic	Value
Age, median (range), y	65 (28-88)
Sex, No. (%)	
Male	250 (91.2)
Female	24 (8.8)
Previous cordectomy, No. (%)	3 (1.1)
Previous treatment, No. (%)	
None	86 (31.4)
Previous vocal cord biopsy	173 (63.1)
Positive for SCC	139 (50.7)
LIN I-III	22 (8.0)
Other	12 (4.4)
Cordal stripping	15 (5.5)
Clinical stage before cordectomy, No. (%)	
T0	2 (0.7)
Tis	22 (8.0)
T1a	220 (80.3)
T1b	10 (3.7)
T2	20 (7.3)
RT before cordectomy, No. (%)	0
Precordectomy anterior commissure involvement, No. (%)	
No	245 (89.4)
Yes	29 (10.6)

Abbreviations: LIN I-III, laryngeal intraepithelial neoplasia grade I-II-III; RT, radiotherapy; SCC, squamous cell carcinoma.

clinically negative neck (cN0) were candidates. Specific eligibility criteria were (1) early glottic cancer (cTis, cT1a, cT1b, T2) with cN0, (2) adequate exposure of the glottic region, (3) no contraindications to general anesthesia, (4) willingness to participate in the study, (5) the ability to understand and the willingness to sign a written informed consent document, and (6) no previous surgery or RT for laryngeal cancer with curative intent.

Between January 1, 1999, and October 31, 2005, 318 patients with early glottic cancer were treated at the Head and Neck Surgery Division of the European Institute of Oncology. Of these patients, 44 were excluded because of previous treatment: 38 for RT to the larynx and 6 for previous open neck surgery. A total of 274 eligible patients (250 men and 24 women) were included in the study. The mean patient age was 65 years (range, 28-88 years) (**Table 1**). Patients recruited in the early period (1999-2002) had their cancers reclassified according to the latest International Union Against Cancer classification.<sup>13</sup>

### PREOPERATIVE, THERAPEUTIC, AND FOLLOW-UP PROCEDURES

The therapeutic protocol, its risks and benefits, and possible alternative treatments were discussed with the patient before obtaining informed consent. Preoperative evaluation included physical examination, routine blood tests, chest radiography, flexible endoscopy, and videolaryngostroboscopy. Computed tomography of the neck using contrast was performed for a bulky lesion at the anterior commissure, when the tumor extended to the laryngeal ventricle was not assessable by outpatient endoscopy, and when deeper infiltration of the vocal muscle was suspected. Intraoperative diagnostic procedures included visual evaluation using rigid endoscopes with 0° and 70° angles of view, with examination of both vocal cords to assess vocal cord rigidity, depth of infiltration, and tumor mass mobility.

All the surgical procedures were performed under general anesthesia with patients intubated using a laser-safe endotracheal tube (Laser-Flex; Mallinckrodt, Hazelwood, Missouri). A 25-W carbon dioxide laser (Martin, Tuttlingen, Germany) with a beam spot diameter of 150 µm was used for surgery. The laser was used in superpulse continuous mode, with output power set to 0.8 to 4.7 W. To obtain greater distance between the resection margin and the margin of a macroscopically visible lesion, irrespective of lesion location, the excision included the arytenoid vocal process, the anterior commissure on the medial line, all the mucosa of the floor of the ventricle, and the mucosa of the lower face of the vocal cord. Depending on preoperative and intraoperative findings, the deep resection margin could include the vocal ligament, the medial portion of the vocal muscle, and the entire vocal muscle, and it could even extend to the internal perichondrium of the thyroid cartilage. If necessary, the excision was extended to other adjacent structures (false vocal cord, anterior commissure, and contralateral vocal cord). In no case was intraoperative biopsy performed. The type of cordectomy (European Laryngological Society<sup>14</sup>) was as follows:

Type I (mucosa) in patients with superficial suspicious lesions without previous biopsy and normal vocal wave on laryngostroboscopic examination.

Type II (mucosa plus vocal ligament) in patients previously treated with vocal cord stripping and with no macroscopic evidence of disease or abnormal vocal wave on laryngostroboscopic examination.

Type III (mucosa, vocal ligament, medial portion of vocal muscle) in patients who had undergone diagnostic cordal punch biopsy or in patients with a macroscopically evident well-circumscribed lesion limited to the free border of the vocal cord.

Type IV (mucosa, ligament, vocal muscle) in patients with a macroscopically evident lesion extending to the anterior commissure or infiltrating deeper tissues (eg, the vocal muscle).

Type V (mucosa, ligament, vocal muscle, internal thyroid perichondrium) in patients with clear macroscopic presence of disease in the anterior commissure, the vocal muscle, and the floor of the Morgani ventricle.

In all cases, including enlarged cordectomies (types III-V), the specimens were removed en bloc. Each specimen was oriented and mounted whole on a sponge support to prevent tissue retraction. The margins were identified and marked with ink. Fixation in 10% buffered formalin followed. Five-micrometer-thick serial sections were obtained and were stained using hematoxylin-eosin for pathologic examination. All the margins were assessed, and the distances between tumor and specimen margins were measured. Negative margins had more than 1 mm between margin and tumor, close margins had 1 mm or less between margin and tumor, and positive margins had tumor on an examined margin.

For patients with negative margins, clinical evaluations (including flexible laryngoscopy, videostroboscopy, or both) were performed every 3 months in the first year, every 4 to 6 months during the second year, and annually for the next 3 years. Patients with close margins or a precancerous lesion (mild to moderate laryngeal intraepithelial neoplasia) were assessed every month for 6 months, every 2 months for the next 6 months, every 3 months for the next year, and annually for the next 3 years. Patients with 1 positive margin were scheduled for another operation (laser endoscopy), and if the new resection margins were free, they were followed as free-margin patients. Patients with 2 or more positive margins, a positive margin after a second operation, or T2-3 tumor with paraglottic space involvement were scheduled for RT.

**Table 2. Subsequent Treatments According to Margin Status (After Initial Cordectomy) in 274 Patients With Early Glottic Cancer**

Margin Status	No Repeated Operation		Second Laser Excision		Total
	No RT	RT	No RT	RT	
True negative	175	5	0	0	180
False positive (1 margin)	2	5	16	1	24
True positive (>1 margin)	6	13	10	1	30
Close	22	10	7	1	40
<b>Total</b>	<b>205</b>	<b>33</b>	<b>33</b>	<b>3</b>	<b>274</b>

Abbreviation: RT, radiotherapy.

## STATISTICAL METHODS

Patient characteristics are represented as frequencies and percentages for categorical variables and as medians and ranges for continuous variables. Disease-free survival was the time from surgery to recurrence or last follow-up. Survival probabilities across time were estimated using the Kaplan-Meier method,<sup>15</sup> and significant differences in subgroups were assessed using the univariate log-rank test.<sup>16</sup> The effect of margin status on the recurrence rate was assessed using a multivariate Cox proportional hazards regression model.<sup>17</sup> To ensure stable estimates, the number of possible predictors was determined by the number of reported events,<sup>18</sup> with a minimum of 5 events required per putative predictor. Putative predictors included in each multivariate model were age, sex, precordectomy anterior commissure involvement, type of cordectomy, tumor grade, and margin status. Because not all the patients followed the predetermined protocol (see the "Results" section), the margin variable was defined by 3 characteristics: margin status, whether a new laser resection was performed, and whether adjuvant RT was given. The margin categories were true negative (negative on specimen, no second surgery, and RT not given), false positive (positive margin but negative after a second operation [RT not given]), true positive (positive margin, still positive after a second operation [RT given]), close (RT+) (no second operation, RT given), and close (no RT) (no second operation, RT not given) (**Table 2**). The statistical analysis was performed using SAS for Windows version 8.2 (SAS Institute Inc, Cary, North Carolina).

## RESULTS

In 30 of 274 patients (10.9%), 8 with positive margins and 22 with close margins, the predetermined protocol in terms of follow-up, a repeated operation, or RT was not adhered to. Reasons for protocol deviation were that patients refused further treatment or their clinical condition contraindicated such treatment. All the patients were included in the analyses. The pathologic results were as follows: pT0 in 43 of the 188 patients (22.9%) who had undergone previous excisional biopsy, pTis in 36 of 274 patients (13.1%), pT1a in 114 of 274 (41.6%), pT1b in 35 of 274 (12.8%), pT2 in 37 of 274 (13.5%), and pT3 (paraglottic space invasion) in 9 of 274 (3.3%). Margins were disease free in 180 of 274 patients (65.7%), close in 40 (14.6%), and positive in 54 (19.7%). One margin was positive in 24 patients (8.8%), and more than 1 margin was positive in 30 (10.9%) (**Table 3**). Of the 180 patients with disease-free margins, no further treatment was given in 175; in the remaining 5, at stage pT2-pT3, adjuvant RT was given in accord with our policy.

**Table 3. Type of Cordectomy, Pathologic Stage, and Margin Status in 274 Patients With Early Glottic Cancer**

Characteristic	Patients, No. (%)
Type of cordectomy	
I	17 (6.2)
II	80 (29.2)
III	104 (38.0)
IV	24 (8.8)
V	49 (17.9)
Pathologic stage	
T0	43 (22.9) <sup>a</sup>
Tis	36 (13.1)
T1a	114 (41.6)
T1b	35 (12.8)
T2	37 (13.5)
T3	9 (3.3)
Margin status	
Negative	180 (65.7)
Close	40 (14.6)
Positive (1 margin)	24 (8.8)
Positive (>1 margin)	30 (10.9)

<sup>a</sup>In the 188 patients with a previous biopsy.

Of the 94 patients with positive or close margins, 28 received postoperative RT and 36 underwent a second laser resection. In 3 of 36 patients, histologic examination after second laser resection revealed a positive margin (true positive), and they were given adjuvant RT. In the remaining 33 patients, there was no evidence of residual disease on the second specimen (false positive), and they were followed-up according to the normal postoperative protocol. Adjuvant RT was given to 36 patients (13.1%) (Table 2).

Of the 188 patients with histologic diagnosis of vocal cord squamous cell carcinoma after incisional biopsy elsewhere, 114 (60.6%) had clinical staging performed elsewhere that did not correspond with pathologic staging after endoscopic laser surgery, and in 43 of 188 of these cases (22.9%) we found no evidence of residual malignant neoplasia (ypT0), as noted in a previous publication.<sup>19</sup> The remaining 86 patients had a clinical diagnosis of carcinoma without biopsy.

Of the 54 patients with positive margins, 24 had 1 and 30 had more than 1 positive margin. In 4 of the 24 patients, the deep margin was involved: 2 of these underwent repeated surgery and the other 2 had RT. In the other 20 of 24 patients with 1-margin involvement, the margin was not deep: 4 received adjuvant RT, 14 under-

went a second laser resection, and 2 received no further treatment. Of the 30 patients with more than 1 positive margin, 19 had deep margin involvement: 4 underwent a second operation, 12 received RT, 1 received a new laser resection and RT, and 2 received no further treatment. In the remaining 11 patients with more than 1 margin involvement, the deep margin was not involved: 7 underwent another resection, 1 received RT, and 3 received no further treatment. Thus, 8 of 54 patients with positive margins received no additional treatment (contrary to the protocol), 18 received RT, 26 underwent a second operation, and 2 underwent repeated operation and RT. Of the 7 of 54 patients with positive margins who relapsed, 1 received no further treatment, 2 underwent another operation, 3 received total laryngectomy, and 1 received subtotal laryngectomy. Furthermore, of the 23 patients with a positive deep margin, 6 underwent another operation, 14 received RT (1 of whom had a recurrence), 1 underwent another operation and RT, and

2 received no further treatment (1 of whom had a recurrence). Of the 20 patients at stage cT2, 1 was classified as such because of vocal cord hypomobility and the others because of local extent of disease.

Median follow-up was 58 months (range, 7-104 months) in October 2007, when 243 patients (88.7%) were alive without disease; 1 (0.4%) was alive with local disease, 24 (8.8%) had died of other causes with no evidence of locoregional glottic disease, and 6 (2.2%) had died of laryngeal cancer. In 10 patients, a second primary tumor occurred, although all were alive (**Table 4**). The larynx was preserved in 266 patients (97.1%), with 8-year DFS of 88.2% (**Table 5** and the **Figure**) and 5-year overall survival of 90.9% (**Table 6**).

Of the 94 patients with positive or close margins, 33 with successful repeated operations (false positives) had 8-year DFS of 93.9%. In the 175 patients with negative margins, 8-year DFS was 89.3%.

In the 33 patients with positive or close margins who did not undergo another operation but who were given RT, DFS was 87.3%. In the 30 patients with positive or close margins who did not undergo another operation and were not given RT, DFS was 76.7% ( $P=.01$  compared with those given RT, multivariate analysis) (Table 5). There was local recurrence in 6 of the 8 patients with positive margins who received no further treatment (Table 5).

Overall, 28 patients (10.2%) experienced recurrences, local in 25 (9.1%) and regional in 3 (1.1%), which were treated as follows: endoscopic laser resection in 14 (5.1%), RT plus chemotherapy in 3 (1.1%), total laryngectomy in 8 (32%), RT plus chemotherapy in total laryngectomy in 8 (2.9%), and selective neck dissection plus RT in the 3 patients (1.1%) with regional recurrence (Table 4).

#### COMMENT

The DFS of the subgroup with what we considered to be free margins (>1 mm) was similar (actuarial survival,

**Table 4. Follow-up, Recurrences, and Recurrence Treatment in 274 Patients With Early Glottic Cancer**

Variable	Value
Follow-up duration, median (range), mo	58 (7-104)
Vital status, No. (%)	
Alive without disease	243 (88.7)
Alive with disease	1 (0.4)
Dead with disease	6 (2.2)
Dead without disease	24 (8.8)
Postcordectomy recurrence, No. (%)	
No recurrence	246 (89.8)
Recurrence	28 (10.2)
Treatment of recurrence, No. (%)	
Total laryngectomy	8 (2.9)
Endoscopic laser surgery	14 (5.1)
Neck dissection + RT	3 (1.1)
RT + chemotherapy	3 (1.1)
Time between surgery and recurrence, median (range), mo	12 (3-72)

Abbreviation: RT, radiotherapy.

**Table 5. Eight-Year DFS According to Margin Status in 274 Patients With Early Glottic Cancer**

	Patient, No.	Events, No. (%) <sup>a</sup>	Univariate Analysis		Multivariate Analysis <sup>c</sup>	
			8-y DFS, %	P Value <sup>b</sup>	HR (95% CI)	P Value
All patients	274	28	88.2	NA	NA	NA
Margins						
Negative	175	15 (8.6)	89.3	NA	NA	NA
False positive (repeated operation)	33	2 (6.1)	93.9	.054	0.53 (0.11-2.42) <sup>d</sup>	.41
Close (no repeated operation, RT) <sup>e</sup>	33	4 (12.1)	87.3	NA	0.58 (0.08-4.37) <sup>f</sup>	.60
Close (no repeated operation, no RT)	30	7 (23.3)	76.7	NA	8.28 (1.65-41.6) <sup>g,h</sup>	.01
True positive (repeated operation and RT)	3	0	0	NA	NA	NA

Abbreviations: CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; NA, not applicable; RT, radiotherapy.

<sup>a</sup>Events indicates patients with recurrence in 8 years of follow-up.

<sup>b</sup>Log-rank test.

<sup>c</sup>Includes the variables associated with relapse of disease on univariate analysis: precordectomy anterior commissure involvement and type of cordectomy, adjusted for pT.

<sup>d</sup>Reference: negative margins.

<sup>e</sup>Includes 5 patients with negative margins given RT.

<sup>f</sup>Reference: false positives.

<sup>g</sup>Reference: close or positive margins with RT.

<sup>h</sup>Compared with negative margins: HR, 2.53; 95% CI, 0.97-6.59;  $P=.06$ .

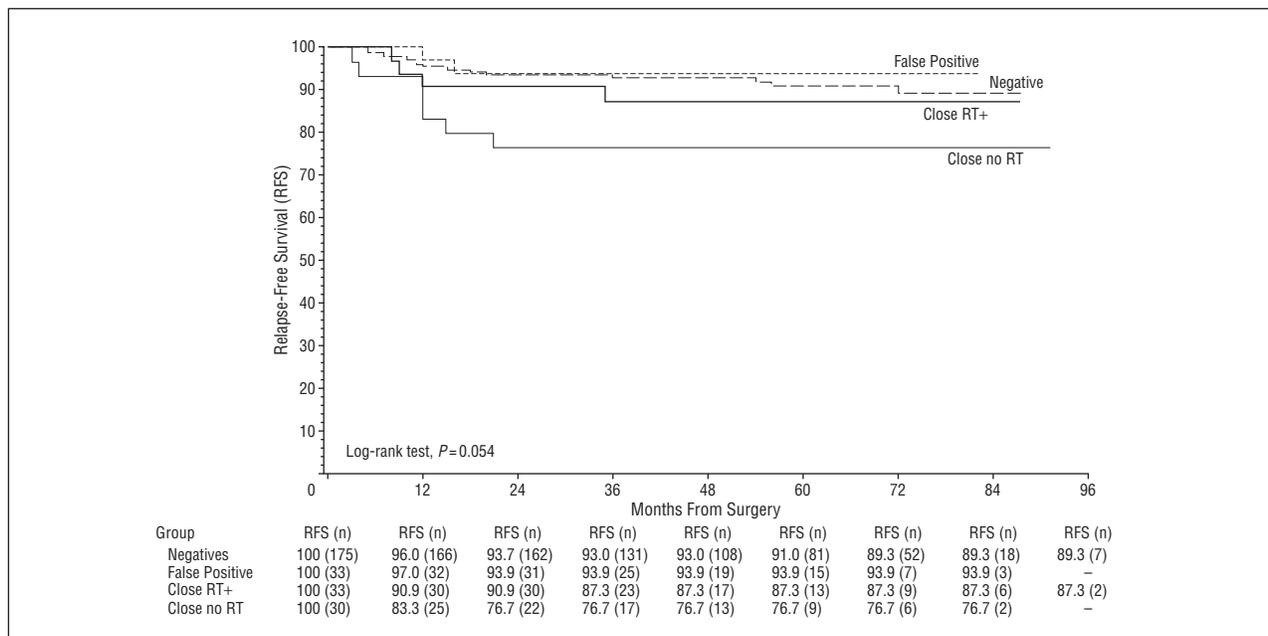


Figure. Kaplan-Meier disease-free survival (DFS) according to margin status. RT indicates radiotherapy.

Table 6. 5-Year Overall Survival (OS) According to Margin Status in 274 Patients With Early Glottic Cancer

	Patients, No.	Univariate Analysis			Multivariate Analysis <sup>c</sup>	
		Events, No. (%) <sup>a</sup>	5-y OS, %	P Value <sup>b</sup>	HR (95% CI)	P Value
All patients	274	18	90.9	NA	NA	NA
Margins						
Negative	175	4 (2.3)	96.8	NA	1 [Reference]	NA
False positive (repeated operation)	33	2 (6.1)	89.0	<.001	3.21 (0.52-19.57)	.21
Close (no repeated operation, RT) <sup>d</sup>	33	4 (12.1)	84.3	NA	2.69 (0.44-16.45)	NA
Close (no repeated operation, no RT)	30	7 (23.3)	67.1	NA	8.97 (2.18-36.89)	.28
True-positive (repeated operation, RT)	3	1 (33.3)	NA	NA	NA	.002

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not applicable; OS, overall survival; RT, radiotherapy.

<sup>a</sup>Events indicates patients with recurrence in 5 years of follow-up.

<sup>b</sup>Log-rank test.

<sup>c</sup>Includes the variables associated with relapse on univariate analysis: precordectomy anterior commissure involvement and type of cordectomy, adjusted for pT.

<sup>d</sup>Includes 5 patients with negative margins who received RT.

89.3% at 5 years) to that reported in other studies of early glottic cancer (80%-94%).<sup>20-22</sup> This finding supports our decision to consider the rather narrow margin of 1 mm as free. We based this decision on clinical experience that the modality of local spread in laryngeal cancer differs from that in other head and neck areas. The peculiarities of laryngeal embryologic development and the scarce glottic submucosal lymphatic network also suggest that the resection margins can be narrower than required in other head and neck cancers. The high magnification available in endoscopic laser equipment makes such narrow margins possible.

We found, however, that when the margins were positive, the incidence of local recurrence in this series was higher and DFS was lower (76.7% at 84 months) compared with those with free margins. Furthermore patients with close or positive margins who were given further treatment (another operation, adjuvant RT, or sometimes both) had DFS that did not differ significantly

from those with negative margins ( $P = .41$  for RT and  $P = .14$  for no RT). This contrasts with the finding that patients with close or positive margins who did not undergo a second resection and were not given RT had a greater risk of recurrence (hazard ratio, 2.53; 95% confidence interval, 0.97-6.59;  $P = .06$ ) than did patients with negative margins and an 8-fold greater risk of recurrence compared with those with positive or close margins treated with adjuvant RT (hazard ratio, 8.28; 95% confidence interval, 1.65-41.6;  $P = .01$ ) (Table 5). These findings indicate that if positive margins are found, additional treatment should always be given, in conformity with the existing policy at the European Institute of Oncology. There are few studies in the literature regarding the impact of resection margins in early glottic cancer treated by endoscopic laser surgery, and the area is one of controversy. For example, some studies<sup>8-10</sup> have found that positive or suspicious margins are unrelated to recurrence rate, whereas others<sup>11,12</sup> have reported that

local disease recurrence is significantly correlated with the presence of positive surgical margins.

Another implication of these results is that the wide macroscopic resection we practice is necessary, regardless of lesion size or anatomical location. This approach usually results in specimens that can be adequately examined for resection margins even after the specimen shrinkage that occurs during fixing.

In our experience, wide resection of the vocal cord mucosa does not negatively affect vocal outcome, although wide resection of the deep margin (muscle margin) or irregular sectioning of vocal muscle often produces poorer functional results. Functional outcomes in the present series are in line with those reported elsewhere, specifically, type IV and V cordectomies (in 63 patients) were associated with marked voice compromise, whereas type I to III cordectomies (211 patients) gave results similar to those obtained with RT.<sup>7</sup>

To conclude, the outcomes of this study are consistent with those of other published studies indicating that endoscopic laser surgery for early glottic cancer affords optimal oncologic radicality. Overall survival was 90.1% at 5 years, DFS at 8 years was 88.2%, and the organ preservation rate was 97.1%. These data further suggest that margins can be considered free if the distance to disease is at least 1 mm. However, if margins are positive, further treatment should always be given.

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**Author Contributions:** All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Ansarin, Calabrese, Giugliano, and Chiesa. *Acquisition of data:* Cattaneo, Massaro, Maffini, and Ostuni. *Analysis and interpretation of data:* Santoro. *Drafting of the manuscript:* Ansarin, Cattaneo, Massaro, and Maffini. *Critical revision of the manuscript for important intellectual content:* Ansarin, Santoro, Calabrese, Giugliano, Ostuni, and Chiesa. *Statistical analysis:* Ansarin and Santoro. *Administrative, technical, and material support:* Cattaneo and Massaro. *Study supervision:* Ansarin and Chiesa.

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