

LARYNGOLOGY

# Long-term impact of smoking cessation on new glottic cancer events in patients with early glottic cancer

## *Effetti a lungo termine dell'abolizione del fumo di sigaretta sull'insorgenza di nuovi eventi oncologici laringei, in pazienti trattati per tumori glottici in stadio iniziale*

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### SUMMARY

**Objective.** Patients with early glottic cancer sometimes exhibit new glottic cancer events after 5 years. This study aimed to analyse the patterns and risk factors of new glottic cancer events in patients with early glottic cancer 5 years after initial treatment.

**Methods.** In total, 209 patients were included in this study. Age, sex, T stage, anterior commissure involvement, smoking pattern and treatment modality were retrospectively analysed.

**Results.** The median follow-up was 91 (range, 60-266) months. The median time for the occurrence of new glottic cancer events was 97 (range, 61-199) months. New glottic cancer events occurred 5 years after initial treatment in 16 (7.6%) patients, among whom 12 (75.0%) had new glottic cancer event lesions overlapping with initial lesions. Smoking cessation after treatment was significantly correlated with fewer new glottic cancer events after 5 years.

**Conclusions.** New glottic cancer events occurring 5 years after initial treatment in patients with early glottic cancer are not negligible. In particular, if smoking is continued after treatment, these patients can experience new glottic cancer events even after 5 years.

**KEY WORDS:** laryngeal neoplasms, glottitis, recurrence, smoking cessation

### RIASSUNTO

**Obiettivo.** I pazienti con cancro glottico a basso stadio talvolta presentano nuovi tumori glottici dopo 5 anni. Questo studio ha lo scopo di analizzare i pattern e i fattori di rischio correlati con l'insorgenza di nuovi tumori glottici dopo 5 anni dal trattamento iniziale.

**Metodi.** In totale, 209 pazienti sono stati inclusi nello studio. L'età, il genere, lo stadio di T, il coinvolgimento della commissura anteriore, il fumo, e la modalità di trattamento sono stati analizzati retrospettivamente.

**Risultati.** Il follow-up mediano è stato di 91 mesi (range, 60-266). Il tempo medio di insorgenza di un nuovo cancro glottico è stato di 97 mesi (range, 61-199). I nuovi cancri della glottide si sono manifestati 5 anni dopo il trattamento iniziale in 16 (7,6%) pazienti; 12 (75,0%) tra questi presentavano lesioni sovrapponibili a quelle iniziali. La sospensione del fumo si è rivelata essere correlata in maniera statisticamente significativa con un minor rischio di nuovi tumori.

**Conclusioni.** La frequenza di nuovi tumori glottici a distanza di almeno 5 anni dal trattamento iniziale non è trascurabile. In particolare, se l'abitudine del fumo è continuata dopo il trattamento, questi pazienti possono mostrare nuovi tumori glottici anche dopo 5 anni.

**PAROLE CHIAVE:** neoplasie laringee, glottide, recidiva, cessazione del fumo

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## Introduction

Laryngeal cancer is one of the most common head and neck cancers. An estimated 13,560 new laryngeal cancer cases occurred in the United States in 2015, accounting for 3,640 deaths<sup>1</sup>. Among laryngeal cancers, glottic cancer refers to a malignancy of the true vocal cords and is the most common laryngeal cancer. Stage I (T1N0M0) and stage II (T2N0M0) glottic cancers are typically grouped together as early glottic cancer and are mostly treated as a single entity<sup>2</sup>. Standard treatments for early glottic cancer include transoral laser microsurgery (TLM) and radiotherapy (RT), both resulting in favourable oncologic outcomes<sup>3</sup>. The 5-year local control rates following TLM are reportedly 85-95% and 65-85% for patients with Stage I and II glottic cancers, respectively. Similarly, 5-year local control rates following RT are reportedly 85-95% and 60-80% for patients with Stage I and II glottic cancers, respectively<sup>4</sup>. Local control failure occurs mostly within 5 years of initial treatment in patients with early glottic cancer, regardless of whether they have undergone RT or TLM<sup>5-8</sup>. Therefore, clinical follow-up for these patients has been traditionally performed for 5 years after initial treatment.

Although most studies have examined 5-year local control rates<sup>9-16</sup>, some new glottic cancer events have been observed after more than 5 years following initial treatment in patients with early glottic cancer without recurrence during the first 5 years. Some studies have examined such cases, but have only described the overall long-term rates and showed decreasing Kaplan-Meier curves without focusing on lesions occurring beyond 5 years after initial treatment<sup>17-19</sup>. New cancer lesions occurring after 5 years are considered secondary primary cancers rather than recurrences. Therefore, studies on secondary primary cancers after glottic cancer usually include oral, pharyngeal, oesophageal and lung cancers<sup>20,21</sup>. However, we have recently encountered new glottic cancer events around the initial glottic cancer lesions 5 years after the initial treatment of early glottic cancer. To the best of our knowledge, new glottic cancer events after 5 years of initial treatment in patients with early glottic cancer have not been sufficiently researched. Therefore, this study aimed to analyse the prognostic factors and patterns of new glottic cancer events at 5 years after initial treatment in patients with early glottic cancer without recurrence during the first 5 years.

## Materials and methods

### *Patients*

We included 330 patients diagnosed with early glottic cancer who had undergone single treatment modality (TLM or RT) at our hospital between January 1994 and May 2014.

Of the 330 patients, 121 were excluded – 48 reported recurrences within 5 years after the initial treatment, 51 were lost to follow-up over 5 years after the initial treatment, and 22 received RT after TLM because of close resection margins. Finally, 209 patients with early glottic cancer without recurrence within 5 years were enrolled. Follow-up was regularly performed – 1 month after treatment completion, every 2 months in the first year and every 6 months for 5 years using laryngoscopy at every visit. Neck computed tomography was performed annually. Thereafter, follow-up was performed annually using only laryngoscopy at every visit. New glottic cancer events were recorded during follow-up visits.

Various clinical factors, including age, sex, T stage, anterior commissure involvement, smoking history and treatment modality, were analysed. The 8<sup>th</sup> edition of the American Joint Committee on Cancer staging manual was used for staging<sup>22</sup>. This manual defines T1 tumours as tumours confined to a unilateral vocal fold (T1a) or bilateral vocal folds (T1b) and T2 tumours as tumours extending to the supraglottis or subglottis with or without impaired vocal fold mobility. We also defined stage I (T1N0M0) and stage II (T2N0M0) glottic cancers as early glottic cancer.

### *Statistical analysis*

The clinical data were summarised as means for continuous variables and numbers for categorical variables. Continuous variables were compared using independent t-test. Nominal and ordinal categorical variables were compared using chi-square test, Fisher's exact test, and linear-by-linear association. The cumulative probability of new glottic cancer events was calculated using Kaplan-Meier analysis and compared using log-rank test. Univariable analysis of new glottic cancer events was performed using Cox regression. For all analyses, *P*-values of < 0.05 were considered to indicate significance. SPSS software (ver. 22.0; SPSS, Chicago, IL, USA) was used for statistical analyses.

## Results

The following patient characteristics were analysed: age, sex, T stage, anterior commissure involvement, smoking history and treatment modality (Tab. I). The median follow-up period was 91 (range, 60-266) months. However, the follow-up periods were not sufficient for many patients (166/209, 79.4%) at the time of analysis. Of the 124 patients in the smoking cessation success group, 101 were not continuously followed. Among the 85 patients in the smoking cessation failure group, 65 were not continuously followed.

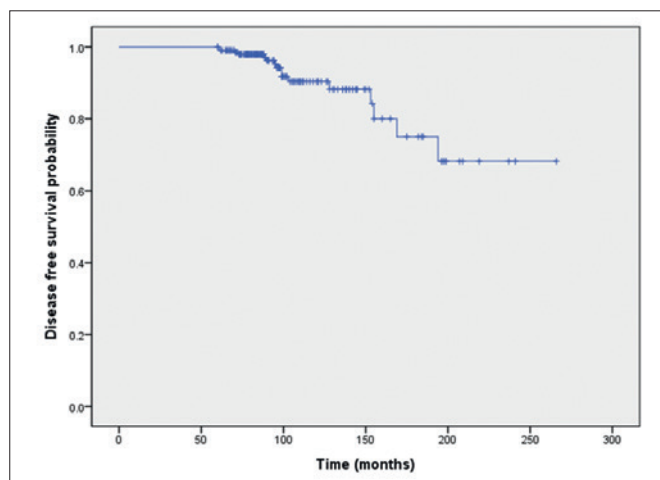
Of the 209 patients, 16 experienced new glottic cancer events at more than 5 years after the initial treatment. The

**Table I.** General characteristics of participants (n = 209).

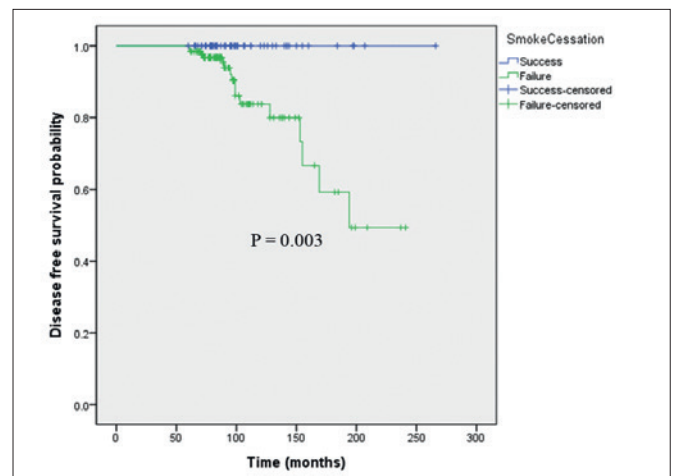
Variable	Total (n = 209)	New glottic cancer (-) (n = 193)	New glottic cancer (+) (n = 16)	P
Age (mean ± SD, years)	60.51 ± 7.94	60.24 ± 8.03	62.88 ± 6.93	0.210
<b>Sex</b>				
Male	201 (96.2%)	185 (92.0%)	16 (8.0%)	1.000
Female	8 (3.8%)	8 (100%)	0 (0%)	
<b>T stage</b>				0.538
T1a	93 (44.5%)	86 (92.5%)	7 (7.5%)	
T1b	73 (34.9%)	69 (94.5%)	4 (5.5%)	
T2	43 (20.6%)	38 (88.4%)	5 (11.6%)	
<b>AC involvement</b>				<b>0.089</b>
Yes	92 (38.9%)	88 (95.7%)	4 (4.3%)	
No	117 (61.1%)	105 (89.7%)	12 (10.3%)	
<b>Smoking cessation after treatment</b>				<b>0.003</b>
Success	124 (37.8%)	124 (100%)	0 (0.0%)	
Failure	85 (62.2%)	69 (81.2%)	16 (18.8%)	
<b>Treatment</b>				<b>0.670</b>
Transoral laser microsurgery	81 (38.8%)	74 (91.4%)	7 (8.6%)	
Radiotherapy	128 (61.2%)	119 (92.9%)	9 (7.1%)	

\*SD: standard deviation; AC: anterior commissure.

10-year disease-free survival rate was 90.7%. The median time for occurrence of new glottic cancer events was 97 (range, 61-199) months (Fig. 1). The disease-free survival rate was significantly higher in the smoking cessation success group after treatment than in the smoking cessation failure group (Fig. 2). Smoking cessation failure after treatment was significantly associated with the risk of new glottic cancer events at more than 5 years after initial treatment (Tab. II). No significant differences in second extra-glottic cancers [success, 4.1% (5/124) vs. failure, 8.2% (7/85);



**Figure 1.** Kaplan-Meier curve of new glottic cancer events.



**Figure 2.** Kaplan-Meier curve of new glottic cancer events according to smoking cessation.

$P = 0.19$ ] or Charlson comorbidity index scores (success, 1.3 vs failure, 1.9;  $P = 0.31$ ) were observed between the smoking cessation success and failure groups.

Of the 16 patients with new glottic cancer events, 10 were diagnosed based on changes in voice and 6 were diagnosed via follow-up laryngoscopy without definite symptoms. If the glottic anatomic extent of the initial and new glottic lesions overlapped, the cases were considered to be overlapping, otherwise the cases were considered to be non-

**Table II.** Univariate Cox regression model for new glottic cancer events occurring after 5 years in patients with early glottic cancer.

Variable	Univariate analysis		
	HR	95% CI	P
Age (< 65 yr/ ≥ 65 yr)	2.39	0.88-6.49	0.187
Sex (male/female)	0.04	0.43-9.35	0.575
T stage (T1/T2)	1.47	0.50-4.24	0.477
AC involvement (yes/no)	1.96	0.63-6.09	0.245
Smoking cessation after treatment (success/failure)	4.31	1.58-7.53	0.047
Treatment (RT/TLM)	1.91	0.69-5.31	0.214

\*HR: hazard ratio; CI: confidence interval; yr: years; AC: anterior commissure; RT: radiotherapy; TLM: transoral laser microsurgery.

overlapping. Further, 12 (75.0%) overlapping cases and 4 (25.0%) non-overlapping cases of new glottic cancer were observed. Among the overlapping cases, 5 (41.7%) were previously treated with TLM and 7 (58.3%) were previously treated with RT. Among the non-overlapping cases, 2 each (50%) were previously treated with TLM and RT. No significant differences in overlapping lesions were observed between the TLM and RT groups ( $P = 0.77$ ).

## Discussion

Among the 209 patients included in this study, 16 experienced new glottic cancer events at 5 years after initial treatment for early glottic cancer without recurrence within the first 5 years. Moreover, the glottic anatomic extent of the initial and new glottic lesions overlapped in many cases. Smoking cessation failure after treatment was a significant risk factor related to new glottic cancer events occurring beyond 5 years.

Some studies have investigated new glottic cancer events beyond 5 years in patients with early glottic cancer; however, these studies have not specifically reported the number of new glottic cancer events occurring beyond 5 years. These studies have only described the overall long-term rate and showed decreasing Kaplan-Meier curves after 5 years during follow-up. Moreover, they have analysed patients with early glottic cancer treated with only TLM<sup>17,18</sup>. Our data showed that treatment modality was not an independent predictor of new glottic cancer events occurring 5 years after the initial treatment. This result was similar to that of previous studies indicating that TLM and RT are equally effective for treatment of early glottic cancer<sup>6,9</sup>. In contrast to previous studies<sup>1,2,14,15,18,19</sup>, T stage and anterior commissure involvement were not found to be significant prognostic factors for new glottic cancer events occurring 5 years after the initial treatment in the present study. This difference may be attributed to our study design, which was aimed to reduce bias; we excluded patients with recurrence within 5 years after the initial treatment and patients with

out follow-up beyond 5 years after the initial treatment. Therefore, accurate comparisons between the results of this study and those of the previous studies may be difficult.

To the best of our knowledge, this is the first report demonstrating that continued smoking is related to new glottic cancer events at more than 5 years after the initial treatment for early glottic cancer. Smoking is the main risk factor for head and neck cancer development. However, smoking cessation is a difficult process for patients with this disease. Chan et al. reported that 45% of patients with head and neck cancer continue to smoke after cancer diagnosis, and patients willing to quit smoking after disease onset often fail to do so<sup>23</sup>. A systematic review revealed that smoking cessation in patients with head and neck cancer is associated with improved overall survival, recurrence rates and second primary tumours<sup>24</sup>. However, it is somewhat surprising that patients who continue smoking develop new glottic cancer events even 5 years after the treatment of early glottic cancer, which usually shows relatively good prognosis. This suggests that even patients with early glottic cancer require continual education about smoking cessation during follow-up.

We believe that some new glottic cancer events may be secondary primary malignancies or late recurrences. The classic criteria for defining second primary malignancy proposed by Warren and Gates are as follows: 1) histological confirmation of malignancy in both the index and secondary tumours; 2) anatomical separation of the two malignancies by normal mucosa; and 3) exclusion of the possibility of the second primary malignancy being a metastasis from the index tumour<sup>25</sup>. Some new glottic cancer events were somewhat inconsistent with the second criterion. The glottic anatomic extent of the initial and new glottic lesions overlapped in many new glottic cancer events (12/16, 75.0%). The concept of late recurrence has often been used in breast cancer and typically refers to those events occurring ≥ 5 years after diagnosis<sup>26</sup>. However, confirmation of late recurrence requires molecular analysis, which was not performed in this study. If the molecular patterns of initial

and new glottic lesions are identical, it may suggest late recurrences<sup>27,28</sup>.

One of the strengths of this study was the substantially long follow-up of our patients, with the longest being 266 months. Most studies on early glottic cancer only report 5-year follow-up. Therefore, our study offers a new perspective. Nevertheless, there are limitations to this study that must be acknowledged. The retrospective nature of this single-centre study might limit the generalisability of our findings. In addition, even if all patients were followed up for > 5 years after initial treatment, many were not continuously followed until the time of analysis. Future studies should include a large sample size, ensure longer follow-up duration without follow-up loss and adopt a prospective design to confirm our findings. Furthermore, loss-of-heterozygosity analysis or genetic tests should be performed to distinguish late recurrence from second primary malignancy.

## Conclusions

Although early glottic cancer is known to have a relatively good prognosis, new glottic cancer events can occur even after 5 years. Therefore, patients with early glottic cancer may be recommended to undergo laryngoscopic follow-up 5 years after initial treatment if their voices get worse or if they continue smoking. Furthermore, medical staff should provide sufficient information about the negative effects of smoking to all patients.

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## Conflict of interest statement

The authors declare no conflict of interest.

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## Author contributions

Conception and design: M-SK, T-KK. Analysis and interpretation of the data: M-SK, H-GW, M-WS, T-K K. Drafting of the article: M-SK. Critical revision of the article for important intellectual content: T-KK. Final approval of the article: M-SK, T-KK. Administrative, technical, or logistic support: H-GW, M-WS.

## Ethical consideration

This study was reviewed and approved by the institutional

review board (SNUH IRB No.1509-044-702). The need for informed consent was waived because of the retrospective nature of this analysis.

The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.

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