

Title:

Local recurrence and metachronous multiple cancers after transoral non-robotic surgery for pharyngeal and laryngeal squamous cell carcinoma: a retrospective multicenter study.

Running title: Local recurrence and metachronous multiple cancers after transoral non-robotic surgery.

Authors:

Koji Ushiro, M.D.<sup>a</sup>, Yoshiki Watanabe, M.D.<sup>b</sup>, Yo Kishimoto, M.D., Ph.D.<sup>c</sup>, Yoshitaka Kawai, M.D., Ph.D.<sup>c</sup>, Shintaro Fujimura, M.D., Ph.D.<sup>c</sup>, Ryo Asato, M.D.<sup>a</sup>, Takashi Tsujimura, M.D.<sup>d</sup>, Ryusuke Hori, M.D., Ph.D.<sup>efj</sup>, Yohei Kumabe, M.D.<sup>g</sup>, Kaori Yasuda, M.D.<sup>g</sup>, Hisanobu Tamaki, M.D.<sup>h</sup>, Takehiro Iki, M.D., Ph.D.<sup>h</sup>, Yoshiharu Kitani, M.D., Ph.D.<sup>i</sup>, Keisuke Kurata, M.D.<sup>i</sup>, Tsuyoshi Kojima, M.D., Ph.D.<sup>cj</sup>, Kuniaki Takata, M.D.<sup>j</sup>, Shinpei Kada, M.D., Ph.D.<sup>k</sup>, Shinji Takebayashi, M.D., Ph.D.<sup>l</sup>, Shogo Shinohara, M.D., Ph.D.<sup>m</sup>, Kiyomi Hamaguchi, M.D., Ph.D.<sup>cm</sup>, Masakazu Miyazaki, M.D.<sup>n</sup>, Tadashi Ikenaga, M.D.<sup>n</sup>, Toshiki Maetani, M.D., Ph.D.<sup>o</sup>, Hiroyuki Harada, M.D.<sup>o</sup>, Tomoyuki Haji, M.D., Ph.D.<sup>h</sup>, Koichi Omori, M.D., Ph.D.<sup>c</sup>

Affiliation:

<sup>a</sup> Department of Otolaryngology – Head & Neck Surgery, National Hospital Organization Kyoto Medical Center, Kyoto, Japan

<sup>b</sup> Department of Otolaryngology – Head & Neck Surgery, Japanese Red Cross Osaka Hospital, Osaka, Japan

<sup>c</sup> Department of Otolaryngology – Head & Neck Surgery, Kyoto university Graduate

School of Medicine, Kyoto, Japan

<sup>d</sup> Department of Otolaryngology, Japanese Red Cross Wakayama Medical Center, Wakayama, Japan

<sup>e</sup> Department of Otolaryngology - Head and Neck Surgery, University of Occupational and Environmental Health, Kitakyushu, Japan

<sup>f</sup> Department of Otolaryngology – Head & Neck Surgery, Fujita Health University, Toyoake, Japan

<sup>g</sup> Department of Otolaryngology – Head & Neck Surgery, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki, Japan

<sup>h</sup> Department of Otolaryngology – Head & Neck Surgery, Kurashiki Central Hospital, Kurashiki, Japan

<sup>i</sup> Department of Otolaryngology – Head & Neck Surgery, Shizuoka General Hospital, Shizuoka, Japan

<sup>j</sup> Department of Otolaryngology – Head & Neck Surgery, Tenri Hospital, Tenri, Japan

<sup>k</sup> Department of Otolaryngology – Head & Neck Surgery, Japanese Red Cross Otsu Hospital, Otsu, Japan

<sup>l</sup> Department of Otolaryngology – Head & Neck Surgery, Shiga General Hospital, Moriyama, Japan

<sup>m</sup> Department of Otolaryngology – Head & Neck Surgery, Kobe City Medical Center General Hospital, Kobe, Japan

<sup>n</sup> Department of Otolaryngology – Head & Neck Surgery, Nara Prefecture General Medical Center, Nara, Japan

<sup>o</sup> Department of Otolaryngology – Head & Neck Surgery, Medical Research Institute, Kitano Hospital, Osaka, Japan

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Corresponding author:

Koji Ushiro

Department of Otolaryngology – Head & Neck Surgery, National Hospital Organization

Kyoto Medical Center

1-1 Mukaihata-cho, Fukakusa, Fushimi-ku, Kyoto

612-8555, JAPAN

TEL +81-75-641-9161

FAX +81-75-643-4325

Email; [k\\_ushiro@ent.kuhp.kyoto-u.ac.jp](mailto:k_ushiro@ent.kuhp.kyoto-u.ac.jp)

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## Abstract

**Background:** Late laryngo-pharyngeal cancers after transoral surgery include not only local recurrences but also metachronous multiple cancers.

**Methods:** We compared clinical information, surgical outcomes, and late laryngo-pharyngeal cancers in patients who underwent transoral nonrobotic surgery for laryngo-pharyngeal squamous cell carcinoma without lymph node metastases between 2015 and 2021 in a multicenter retrospective study.

**Results:** Four hundred and fifty-seven patients were included. Positive surgical margins were found in 121 patients (26.5%). Twenty-two patients (4.8%) received additional treatment. Positive horizontal margins of invasive carcinoma ( $p = 0.003$ ) and positive horizontal margins of carcinoma in situ only ( $p = 0.032$ ) were independent risk factors for local recurrence, and prior radiotherapy ( $p = 0.001$ ) for metachronous multiple cancers. Local control was significantly worse without additional treatment ( $p = 0.049$ ), but there was no significant difference in survival.

**Conclusions:** Patients with positive margins had an increased frequency of local recurrence, but salvage therapy was effective.

## Introduction

Surgery, radiotherapy (RT), chemotherapy, or a combination of these have been selected

as the treatment of choice for laryngopharyngeal squamous cell carcinoma (LPSCC). Radiotherapy has played a central role in non-surgical treatment, and altered fractionation regimens or the addition of chemotherapy have been used to improve survival<sup>1)2)</sup>. However, it has been pointed out that these intensified treatments cause a significant increase in treatment-related adverse events such as mucositis, xerostomia, and long-term dysphagia<sup>3)</sup>. In recent years, transoral surgery (TOS), a minimally invasive surgery, has been widely reported as an alternative treatment to chemoradiotherapy (CRT) to prevent these adverse events. TOS includes endoscopic laryngo-pharyngeal surgery (ELPS)<sup>4)</sup> and transoral videolaryngoscopic surgery (TOVS)<sup>5)</sup>, which have been developed and widely used in Japan, and transoral robotic surgery (TORS)<sup>6)</sup>, which has recently spread worldwide. However, TOS is a minimally invasive procedure with minimal resection in a relatively narrow surgical field, and resection with an adequate safety margin may be difficult to achieve. Therefore, adjuvant treatment may be performed considering the risk of local recurrence due to inadequate surgical margin, but the indication for adjuvant treatment after TOS has not been well studied so far. In addition, synchronous and metachronous multiple cancers are known to occur at a relatively high rate in LPSCC, and this is known as “field cancerization”<sup>7)</sup>. Late laryngo-pharyngeal cancers after initial TOS include not only local recurrences but also metachronous multiple cancers, which may have different effects on survival. Therefore, we conducted a multicenter retrospective study of factors influencing late laryngo-pharyngeal cancers and survival in patients who underwent non-robotic TOS, which has been performed mainly in Japan up to date, with the aim of contributing to treatment decisions after TOS.

## Materials and Methods

The study was conducted by the Kyoto University Hospital and Affiliated Facilities Head and Neck Clinical Oncology Group (Kyoto-HNOG), includes a total of 13 tertiary care hospitals belong, and Fujita Health University Hospital. A retrospective chart review was performed of patients who underwent non-robotic TOS for laryngo-pharyngeal cancer with curative intent between 2015 and 2021. Patients with recurrence after initial treatment were also included if surgery was performed with curative intent. Patients who underwent surgery for diagnostic purposes and those who remained in debulking with gross residual tumor were excluded. The eligibility criteria were patients with primary lesions in the oropharynx, hypopharynx, or supraglottis, pathologically diagnosed squamous cell carcinoma, and no evidence of cervical lymph node metastasis. Exclusion criteria were T4 cases in the 8th edition of the AJCC/UICC TNM staging system, patients requiring additional open surgery for primary tumor resection or reconstruction with free or local flaps, patients receiving preoperative treatment, and patients with prior TOS for LPSCC.

This study includes different methods of non-robotic TOS. The surgical field of view was secured by FK-WO retractor (Olympus Medical Systems, Tokyo, Japan), curved rigid laryngoscope (Nagashima Medical Instrument Company, Ltd., Tokyo, Japan), straight rigid laryngoscopes including the Weerda-type distending laryngoscope (Karl Storz, Tuttlingen, Germany), or other types of mouth gags such as Crowe-Davis or Dingman retractor. The surgical field was visualized using a flexible gastrointestinal endoscope, a conventional rigid endoscope, a flexible endoscope that can be angled in four directions such as Endoeye flex (Olympus Medical Systems), or a microscope. When neck dissection was indicated, it was performed as a concurrent or staged procedure, depending on the philosophy and surgical practice of the institution. In addition,

postoperative adjuvant therapy was not standardized and was administered according to the recommendations of the local institutional multidisciplinary tumor board. Patients with adverse pathologic features after surgery received adjuvant treatment with radiation alone or combined chemoradiation to the laryngopharynx. Adverse pathologic features included positive or close margins, lymphovascular invasion, perineural invasion, or advanced T category. Radiotherapy and chemotherapy protocols varied between institution.

Data collection included preoperative patient characteristics, history of head and neck cancer (HNC) treatment, primary site, TNM staging, method of TOS, presence of tracheostomy, surgical margin evaluation, postoperative adjuvant therapy, and oncologic outcomes of late laryngo-pharyngeal cancer occurrence after initial TOS and survival. For positive surgical margins, we further classified whether the margin was horizontal or vertical margin, and whether the exposed lesion was invasive carcinoma or carcinoma in situ. In addition, late laryngo-pharyngeal cancers after initial TOS were classified into two categories: local recurrence and metachronous multiple cancers. Local recurrence was defined as cancers occurring less than 5 mm proximal to the surgically resected site, and metachronous multiple cancers were defined as cancers occurring more than 5 mm apart. Oncological outcomes were evaluated based on overall survival (OS; event: all-cause death), disease-specific survival (DSS; event: death from LPSCC), local recurrence-free survival (LRFS; event: local recurrence), and metachronous multiple cancer-free survival (MMCFS; event: detection of metachronous multiple cancer). In addition, we evaluated the patient and lesion characteristics that significantly influence LRFS and MMCFS. We also examined the impact of additional treatment on local recurrence and survival, as well as salvage treatment for recurrence in cases with positive

surgical margins. Institutional review board approval was obtained for a waiver of consent for this retrospective review at each institution. Each data set was de-identified and then collected from each institution using a standardized data collection form. Individual institutions collected data sets, and the analysis was pooled across institutions.

Statistical analysis was performed using R software, version 4.2.2 (The R foundation for Statistical Computing, Vienna, Austria). Kaplan-Meier methods were used for oncologic outcomes, with the log-rank test used to compare between groups. Multivariate analysis was performed to identify independent risk factors for late LPSCC using Cox proportional hazards regression models. Factors with a p-value  $<0.05$  by univariate analysis were included in those models, as were factors that could be clinically relevant. The estimated hazard ratio (HR) and 95% confidence interval (CI) were calculated. All p-values  $<0.05$  were considered to be statistically significant.

## Results

### Patient and lesion characteristics

Four hundred and fifty-seven patients met the criteria for analysis in the study. Patient and lesion characteristics are shown in Table 1. The median age at TOS was 70.0 years, ranging from 36 to 92 years. Patients who had previously undergone surgery or radiotherapy for HNC accounted for 14.7% and 14.9%, respectively. Regarding the department that detected the lesion, 34.6% of the patients were diagnosed by otolaryngologists and 64.8% by gastroenterologists, respectively. The primary site of LPSCC was oropharyngeal (OPC), hypopharyngeal (HPC), and supraglottic carcinoma (SGC) in 136 (29.8%), 277 (60.6%), and 44 (9.6%) patients, respectively.

### T category and surgical methods for each primary site

Various surgical procedures were included in this study, and the T category and surgical methods for each primary site are shown in Table 2. Overall, the T categories of Tis, T1, T2, and T3 were 32.5%, 40.7%, 23.1%, and 3.7%, respectively, with no significant differences among the primary sites. The curved rigid laryngoscope was used in most cases for HPC in terms of surgical field instruments, and either the flexible-tip rigid endoscope or the flexible gastrointestinal endoscope was used in most cases for visual instruments. Most patients underwent en bloc resection for any primary site, and multiple lesions were resected simultaneously in 11.8% to 14.8% of cases, with no significant difference by the primary site. Tracheostomy was performed in 22.7% of TOS for SGC, which was significantly higher than TOS for other primary sites, most of which were planned preoperatively.

#### Surgical margin and adjuvant therapy

The results of surgical margin assessment and adjuvant treatment are shown in Table 3. Overall, positive surgical margins were observed in 121 patients (26.5%), including 32 patients (23.5%) with OPC, 76 patients (27.4%) with HPC, and 13 patients (29.5%) with SGC, with no significant difference between primary sites. There was also no difference between primary sites when positive surgical margins were classified into three categories: positive horizontal margin of carcinoma in situ only, positive horizontal margin of invasive carcinoma, and positive vertical margin. In terms of postoperative treatment, only 22 patients (4.8%) received additional treatment, and most of them received either adjuvant RT or CRT, although surgery was performed in a minority of patients. The number of patients who received additional treatment was very small compared to the number of patients with positive surgical margins.

#### Survival analysis

The OS and DSS for oncologic outcomes of TOS for LPSCC without lymph node metastasis were compared among several characteristics at 3 and 5 years (Figure 1). When compared among the primary sites, the 3-year OS was 93.4% for OPC, 99.0% for HPC, and 100% for SGC, and the 5-year OS was 93.4% for OPC, 96.5% for HPC, and 100% for SGC, with no significant difference among the primary sites at either time point. The 3-year DSS was 93.4% for OPC, 99.0% for HPC, and 100% for SGC, and the 5-year DSS was 93.4% for OPC, 97.7% for HPC, and 100% for SGC, also with no significant difference. When compared among T categories, the 3-year OS was 100% for Tis, 96.2% for T1, 96.3% for T2, and 93.8% for T3, and the 5-year OS was 97.7% for Tis, 94.2% for T1, 96.3% for T2, and 93.8% for T3, with no significant difference among T categories at either time point, and the 3-year DSS was 100% for Tis, 96.2% for T1, 96.3% for T2, and 93.8% for T3, and the 5-year DSS was 97.7% for Tis, 96.2% for T1, 96.3% for T2, and 93.8% for T3, also with no significant difference. Furthermore, when compared by the presence or absence of local recurrence, OS was 91.2% vs. 98.3% at 3 years and 85.8% vs. 97.5% at 5 years, and DSS was 91.2% vs. 98.3% at 3 years and 85.8% vs. 98.3% at 5 years, with significantly worse prognosis in patients with local recurrence. However, when compared by the presence or absence of metachronous multiple cancers, OS was 94.7% vs. 97.8% at 3 years and 89.7% vs. 96.9% at 5 years, and DSS was 94.7% vs. 97.8% at 3 years and 94.7% vs. 96.9% at 5 years, none of which were significantly different.

To explore risk factors affecting DSS, univariate analyses were performed on various variables (Table 4). Among them, 3-year DSS was significantly worse in patients with a history of surgery or (C)RT for HNC, and in those with muscle invasion of the lesion.

Local recurrence and metachronous multiple cancers

Univariate and multivariate analyses of 3-year LRFS and 3-year MMCFS were performed to explore risk factors for local recurrence and metachronous multiple cancers (Table 5). For 3-year LRFS, multivariate analysis revealed that independent risk factors were positive horizontal margin of invasive carcinoma (HR = 2.71 [95% CI: 1.31-5.60] vs negative horizontal margin,  $p = 0.003$ ) and positive horizontal margin of carcinoma in situ only (HR = 2.31 [95% CI: 1.08-4.95] vs negative horizontal margin,  $p = 0.032$ ). Similarly, for 3-year MMCFS, univariate analysis showed a decrease in the presence of history of surgery for HNC, history of (C)RT for HNC, and synchronous multiple lesions, but multivariate analysis showed that the only independent risk factor was history of (C)RT for HNC (HR = 3.33 [95% CI: 1.79 - 6.19],  $p < 0.001$ ).

We examined the effect of additional postoperative treatment in patients with positive surgical margins, which showed an independent effect on local recurrence in a multivariate analysis (Table 6). There were 46 cases in which only the horizontal margin was positive for carcinoma in situ and the vertical section was negative, and only one of these cases underwent additional surgery. The 3-year LRFS of 45 patients who were followed up without additional treatment was 80.7% (95% CI: 65.0 – 89.9%), but all patients with local recurrence received salvage treatment, and the 3-year DSS was 100%, which was excellent. Seventy-two patients were positive for invasive carcinoma at the horizontal and/or vertical margin, and 16 of these patients received additional treatment. The 3-year LRFS was 100% in the group that received additional treatment and 75.5% (95% CI: 60.8% - 85.4%) in the group that did not receive additional treatment, which was significantly worse in the group that did not receive additional treatment. However, the 3-year DSS was 100% after salvage treatment in most cases of local recurrence, and there was no significant difference between patients with and without additional treatment.

## Discussion

TOS for LPSCC has been widely used as a minimally invasive and function-preserving treatment. Especially in Japan, transoral non-robotic surgery using various instruments has been performed for LPSCC, since robot-assisted surgery using the da Vinci Surgical System was approved by the Pharmaceutical Affairs Agency in August 2018 and has just been covered by the Japanese public insurance in April 2022. This multicenter retrospective study evaluated the oncologic outcomes of transoral non-robotic surgery.

Regarding the evaluation of oncologic outcomes in this study, the 3-year DSS was very good, approximately 93% for OPC and more than 97% for HPC and SGC. This is partly due to the characteristics of the patients and lesions included in the study: more than 60% of the patients had lesions identified by gastroenterologists, and a relatively high percentage (more than 30%) of the patients had Tis in the T category. In Japan, the importance of endoscopic detection of superficial carcinoma is shared by gastroenterologists<sup>8)</sup>, and this may be because laryngo-pharyngeal cancers are often detected during routine endoscopic examination for other diseases, leading to treatment. In addition, although not significantly different, the DSS was slightly lower in OPC cases, but the T category was not different from that of HPC or SGC cases. This difference may be due to the relatively small number of p16-positive OPC cases in this study, although this is uncertain because p16 staining results were not available in many cases. We also examined the difference in survival with and without local recurrence and with and without metachronous multiple cancers, and found significantly worse survival with local recurrence, but no significant difference between patients with and without metachronous multiple cancers. It is difficult to clearly distinguish between local recurrence and

metachronous multiple cancers, and we tentatively defined local recurrence as lesions occurring less than 5 mm proximal to the previously resected site and metachronous multiple cancers as lesions occurring more than 5 mm apart, which we considered to be an acceptable definition in terms of whether it affects survival.

Positive surgical margins were found in 26.3% of all cases, which was comparable to a previous multicenter retrospective study in Japan<sup>9)</sup>. In the United States, a study using the National Cancer Database included only OPC<sup>10)</sup> which is not similar to the background of this study, but the positive surgical margin rate in transoral non-robotic surgery was about 28%, which is similar to that of this study. However, only 4.8% of the patients in our study received additional treatment, including adjuvant (C)RT, and most of the patients with positive margins were followed up without additional treatment. Nevertheless, in univariate analysis, the 3-year DSS did not worsen in the positive cases for either horizontal or vertical margin, and the survival was worse in the group that received additional treatment. The latter may be due to the fact that the multidisciplinary tumor board at each institution decides whether or not to recommend additional treatment or not from different perspectives, and thus there is no uniformity in the decision-making process.

Positive margins did not affect 3-year DSS, but positive horizontal margins significantly decreased 3-year LRFS in this study. However, a history of (C)RT for head and neck cancer significantly reduced 3-year MMCFS. Indeed, in a previous systematic review by Gorphe et al, close margins did not reduce local control compared to clear margins in patients undergoing transoral surgery, whereas positive margins significantly reduced local control<sup>11)</sup>. However, the results of the phase II clinical trial ORATOR<sup>12)</sup> showed that outcomes of swallowing-related quality of life outcomes at 1 year were better in the

definitive (C)RT arm than in the TORS and neck dissection  $\pm$  (C)RT arm, so the addition of adjuvant (C)RT can never be considered a minimally invasive treatment. Furthermore, (C)RT to the head and neck is also a risk factor for metachronous multiple cancers, and the criteria for adjuvant (C)RT should be more carefully considered.

In the present study, we analyzed the impact of additional treatment on local control and survival in patients with positive surgical margins. Most of the patients with only carcinoma in situ at horizontal margins received no additional treatment, and the 3-year LRFS was 80%, indicating some degree of local recurrence, but the 3-year DSS was very good due to effective salvage treatment. In addition, 22% of the patients with invasive carcinoma in the surgical margins, either horizontal or vertical, received additional treatment, and although local control was significantly reduced in the group that did not receive additional treatment, there was no significant difference in 3-year DSS with salvage treatment. In transoral surgery for LPSCC without lymph node metastasis, positive margins alone may not necessarily require additional treatment if there is a follow-up system that allows prompt salvage surgery in the event of local recurrence. In endoscopic resection of esophageal cancer, careful surveillance is recommended for positive horizontal margins due to the risk of local recurrence, and additional treatment such as surgery or (C)RT is recommended for positive vertical margins. Cases involving muscularis mucosae or with vascular invasion are also considered to be non-curative by endoscopic resection, and additional treatment is recommended<sup>13</sup>). Obviously, the criteria for esophageal cancer cannot be directly applied to LPSCC due to anatomical and oncological differences, such as the absence of mucosal muscularis in the pharynx as opposed to the esophagus. However, in this study, the pathologic features of the lesions that significantly decreased the 3-year DSS were neither horizontal nor vertical positive

margins, but rather muscle layer invasion of the tumor, which may be similar to esophageal cancer. Another factor that may have contributed to the low need for additional treatment in cases with positive surgical margins is the characteristics of the lesions that are candidates for TOS. Transoral resection beyond the pharyngeal constrictor muscle is somewhat risky, especially for HPC and SGC, and a larger resection including the laryngeal cartilage would increase the risk of postoperative dysphagia and would not be considered minimally invasive treatment. Therefore, lesions with a marked tendency to deep invasion are unlikely to be selected for TOS and thus may not be included in this study. Criteria for the indication of additional treatment based on the assessment of surgical margins, including the pathologic characteristics of the lesions amenable to TOS, should be considered in the future.

To date, there have been only a few multicenter studies of transoral non-robotic surgery for cancers not only in the oropharynx but also in the hypopharynx and supraglottic region, and the present study included a larger number of patients. A multicenter retrospective study of TORS for LPSCC with 88% oropharyngeal cancer also found that positive margins significantly worsened local control but were not significantly associated with overall survival<sup>14</sup>). However, in this study, positive margins are one of the criteria for considering adjuvant (C)RT as an adverse pathologic feature, and about half of the patients received adjuvant (C)RT, so the effect of adjuvant treatment should be considered. In addition, most of the reports on TORS have focused only on OPC, and although there have been a few reports on TORS for HPC<sup>15)16</sup>), adjuvant (C)RT was performed in 84% and 51% of patients, respectively, due to the presence of lymph node metastasis in 76% and 46% of patients, respectively, and therefore, it is considered insufficient to evaluate local control by TORS itself. We believe that this study shows the possibility of a less

invasive treatment for LPSCC without lymph node metastasis by omitting adjuvant (C)RT, although it is necessary to follow up patients with positive margins after TOS with caution for local recurrence. On the other hand, this observational study has several limitations. First, it is a retrospective study and thus has several biases. The heterogeneity in the determination of indications for surgery and adjuvant treatment between centers, as well as the variability and missing data in the reported pathological data, limit a definitive comparative analysis. Prospective studies with standardized endpoints and protocols are needed to overcome this problem. In addition, the mean follow-up time is approximately 34 months, which may limit definitive conclusions regarding oncologic outcomes. Nevertheless, this study may still be useful in achieving good oncologic outcomes with a less invasive combination of TOS and other treatments for LPSCC.

## Conclusion

A multicenter retrospective study of transoral non-robotic surgery in patients with oropharyngeal, hypopharyngeal, and supraglottic carcinoma without cervical lymph node metastasis was performed to compare late laryngo-pharyngeal cancers after initial surgery. Patients with positive margins have an increased incidence of local recurrence, but do not necessarily require additional postoperative treatment due to the effectiveness of salvage therapy. Patients with a history of (C)RT for head and neck cancer have a higher frequency of metachronous multiple cancers and should be followed carefully.

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#### Data availability statement

Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available.

## Figure legends

### Table 1: Patient and lesion characteristics

Abbreviations: HNC, head and neck cancer. OPC, oropharyngeal cancer. HPC, hypopharyngeal cancer. SGC, supraglottic cancer. (C)RT, (chemo)radiotherapy.

### Table2: T category and surgical methods for each primary site

Abbreviations: OPC, oropharyngeal cancer. HPC, hypopharyngeal cancer. SGC, supraglottic cancer.

\*  $p < 0.05$ .

### Table3: Surgical margin and adjuvant therapy

Abbreviations: OPC, oropharyngeal cancer. HPC, hypopharyngeal cancer. SGC, supraglottic cancer. TOS, transoral surgery. RT, radiotherapy. CRT, chemoradiotherapy.

### Table 4: Risk factors for DSS

Abbreviations: DSS, disease-specific survival. HNC, head and neck cancer. OPC, oropharyngeal cancer. HPC, hypopharyngeal cancer. SGC, supraglottic cancer. (C)RT, (chemo)radiotherapy.

\*  $p < 0.05$ .

### Table 5: Risk factors for local recurrence and metachronous multiple cancer

Abbreviations: LRFS, local recurrence-free survival. MMCFS, metachronous multiple cancer-free survival. HR, hazard ratio. CI, confidence interval. HNC, head and neck cancer. OPC, oropharyngeal cancer. HPC, hypopharyngeal cancer. SGC, supraglottic

cancer. (C)RT, (chemo)radiotherapy.

\*  $p < 0.05$ .

† Comparison with negative

Table 6: Relationship between surgical margin assessment and local recurrence with and without adjuvant treatment

Abbreviations: LRFS, local recurrence-free survival. DSS, disease specific survival. CI, confidence interval. TOS, transoral surgery. RT, radiotherapy. CRT, chemoradiotherapy.

\*  $p < 0.05$ .

Figure 1: Disease-specific survival (DSS) by primary site, T category, and late laryngo-pharyngeal cancers.

A: DSS by primary site

B: DSS by T category

C: DSS with and without local recurrence

D: DSS with and without metachronous multiple cancers

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Table 1: Patient and lesion characteristics

| Characteristics                  | No. of patients (%) or median (range) |
|----------------------------------|---------------------------------------|
| Age (year, median, range)        | 70.0 (36 - 92)                        |
| Gender                           |                                       |
| Male                             | 408 (89.3%)                           |
| Female                           | 49 (10.7%)                            |
| Tobacco smoking                  |                                       |
| Current smoker                   | 129 (28.9%)                           |
| Quit < 10 years                  | 95 (21.3%)                            |
| Quit $\geq$ 10 years             | 163 (36.5%)                           |
| Never                            | 60 (13.4%)                            |
| Habits of alcohol consumption    | 302 (67.4%)                           |
| History of surgery for HNC       | 64 (14.7%)                            |
| History of (C)RT for HNC         | 68 (14.9%)                            |
| Department that noted the lesion |                                       |
| Otorhinolaryngology              | 157 (34.6%)                           |
| Gastroenterology                 | 294 (64.8%)                           |
| Follow-up period (days)          | 1046.0 (5 ~ 2946)                     |
| Primary subsite                  |                                       |
| OPC (N=136)                      |                                       |
| Anterior wall                    | 46 (10.1%)                            |
| Posterior wall                   | 22 (4.8%)                             |
| Superior wall                    | 26 (5.7%)                             |
| Lateral wall                     | 42 (9.2%)                             |
| Positive p16 status              | 30 (22.1%)                            |
| Negative p16 status              | 59 (43.4%)                            |
| Unknown p16 status               | 47 (34.6%)                            |
| HPC (N=277)                      |                                       |
| Pyriform sinus                   | 180 (39.4%)                           |
| Posterior wall                   | 30 (6.6%)                             |
| Posterior wall                   | 66 (14.7%)                            |
| SGC (N=44)                       |                                       |
| Epiglottis                       | 21 (4.6%)                             |
| Arytenoid                        | 12 (2.6%)                             |
| Aryepiglottic fold               | 4 (0.9%)                              |
| False vocal fold                 | 7 (1.5%)                              |

Table2: T category and surgical methods for each primary site

|                                     | OPC (N=136) | HPC (N=277) | SGC (N=44) | p value |
|-------------------------------------|-------------|-------------|------------|---------|
| T category                          |             |             |            | 0.335   |
| Tis                                 | 35 (25.7%)  | 98 (35.4%)  | 15 (35.7%) |         |
| T1                                  | 58 (42.6%)  | 106 (38.3%) | 21 (50.0%) |         |
| T2                                  | 37 (27.2%)  | 62 (22.4%)  | 6 (14.3%)  |         |
| T3                                  | 6 (4.4%)    | 10 (3.6%)   | 0          |         |
| Surgical field instruments          |             |             |            |         |
| Curved rigid laryngoscope           | 59 (43.7%)  | 270 (97.9%) | 28 (63.6%) |         |
| FK-WO retractor                     | 13 (9.6%)   | 3 (1.1%)    | 2 (4.5%)   |         |
| Straight rigid laryngoscope         | 8 (5.9%)    | 3 (1.1%)    | 14 (31.8%) |         |
| Others                              | 55 (40.6%)  | 0           | 0          |         |
| Visual instruments                  |             |             |            |         |
| Flexible-tip rigid endoscope        | 95 (69.9%)  | 164 (59.2%) | 26 (59.1%) |         |
| Flexible gastrointestinal endoscope | 34 (25.0%)  | 104 (37.5%) | 8 (18.2%)  |         |
| Rigid endoscope                     | 5 (3.7%)    | 6 (2.2%)    | 1 (2.3%)   |         |
| Microscope                          | 2 (1.5%)    | 3 (1.1%)    | 9 (20.5%)  |         |
| En bloc resection                   | 131 (96.3%) | 270 (97.5%) | 42 (95.5%) | 0.682   |
| Resection of multiple lesions       | 16 (11.8%)  | 41 (14.8%)  | 6 (13.6%)  | 0.702   |
| Tracheostomy                        |             |             |            |         |
| Total                               | 14 (10.3%)  | 22 (7.9%)   | 10 (22.7%) | 0.016*  |
| Planned                             | 13 (9.6%)   | 18 (6.5%)   | 9 (20.5%)  |         |
| Intraoperative decision             | 1 (0.7%)    | 2 (0.7%)    | 1 (2.3%)   |         |
| Postoperative emergency             | 0           | 2 (0.7%)    | 0          |         |

Table3: Surgical margin and adjuvant therapy

|                                                  | OPC (N=136) | HPC (N=277) | SGC (N=44) | p value |
|--------------------------------------------------|-------------|-------------|------------|---------|
| Positive surgical margin                         |             |             |            |         |
| Total                                            | 32 (23.5%)  | 76 (27.4%)  | 13 (29.5%) | 0.600   |
| Positive horizontal margin of carcinoma in situ  | 15 (11.5%)  | 37 (14.0%)  | 3 (7.1%)   | 0.417   |
| Positive horizontal margin of invasive carcinoma | 17 (13.1%)  | 33 (12.5%)  | 10 (23.8%) | 0.137   |
| Positive vertical margin                         | 5 (4.0%)    | 17 (6.4%)   | 3 (7.7%)   | 0.543   |
| Adjuvant therapy                                 |             |             |            |         |
| Additional TOS                                   | 1 (0.7%)    | 1 (0.4%)    | 0          |         |
| Open surgery                                     | 0           | 1 (0.4%)    | 1 (2.3%)   |         |
| RT                                               | 3 (2.2%)    | 7 (2.5%)    | 1 (2.3%)   |         |
| CRT                                              | 2 (1.5%)    | 5 (1.8%)    | 0          |         |

Table 4: Risk factors for DSS

| Variable (number)                   | 3y DSS | p value |
|-------------------------------------|--------|---------|
| Age                                 |        |         |
| ≥75 year (112)                      | 94.9%  | 0.115   |
| < 75 year (345)                     | 98.2%  |         |
| Gender                              |        |         |
| Male (408)                          | 97.1%  | 0.249   |
| Female (49)                         | 100%   |         |
| Tobacco smoking                     |        |         |
| Current (129)                       | 98.6%  | 0.180   |
| Quit and never (328)                | 97.0%  |         |
| Habits of alcohol consumption       |        |         |
| Yes (302)                           | 98.2%  | 0.925   |
| No (146)                            | 96.8%  |         |
| History of surgery for HNC          |        |         |
| Yes (67)                            | 90.5%  | 0.007*  |
| No (390)                            | 98.5%  |         |
| History of (C)RT for HNC            |        |         |
| Yes (68)                            | 89.0%  | 0.002*  |
| No (389)                            | 99.0%  |         |
| Primary site                        |        |         |
| OPC (136)                           | 93.4%  | 0.068   |
| HPC (277)                           | 99.0%  |         |
| SGC (44)                            | 100%   |         |
| Number of resected subsite          |        |         |
| Over 2 (80)                         | 94.5%  | 0.066   |
| One (377)                           | 98.1%  |         |
| T category                          |        |         |
| Tis, T1 (333)                       | 98.0%  | 0.097   |
| T2, T3 (122)                        | 96.0%  |         |
| Muscle invasion                     |        |         |
| Yes (47)                            | 89.1%  | 0.005*  |
| No (339)                            | 98.7%  |         |
| Resection of multiple lesions       |        |         |
| Yes (63)                            | 97.7%  | 0.725   |
| No (394)                            | 97.4%  |         |
| Horizontal margin                   |        |         |
| Positive of invasive carcinoma (60) | 97.9%  | 0.652   |
| Positive of carcinoma in situ (55)  | 97.8%  |         |
| Negative (321)                      | 97.3%  |         |
| Vertical margin                     |        |         |

|                  |       |        |
|------------------|-------|--------|
| Positive (25)    | 95.0% | 0469   |
| Negative (404)   | 97.5% |        |
| Adjuvant therapy |       |        |
| Yes (22)         | 88.4% | 0.017* |
| No (435)         | 97.9% |        |

Table 5: Risk factors for local recurrence and metachronous multiple cancer

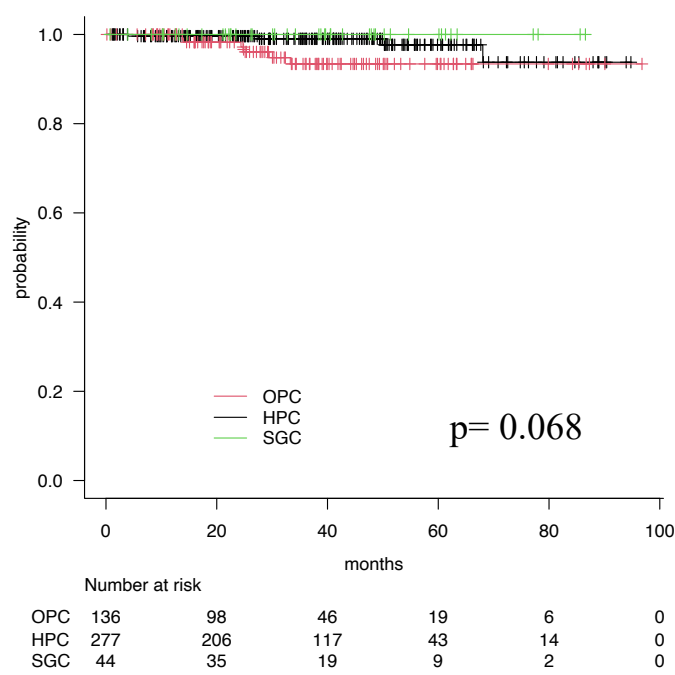
| Variables (number)                  | 3y LRFS |                     |                    | 3y MMFS |       |             |                             |
|-------------------------------------|---------|---------------------|--------------------|---------|-------|-------------|-----------------------------|
|                                     |         | p value             | HR (95% CI)        | p value |       | HR (95% CI) | p value                     |
| Age                                 |         |                     |                    |         |       |             |                             |
| ≥75 year (112)                      | 86.0%   | 0.246               |                    |         | 84.4% | 0.853       |                             |
| < 75 year (345)                     | 90.4%   |                     |                    |         | 89.2% |             |                             |
| Gender                              |         |                     |                    |         |       |             |                             |
| Male (408)                          | 90.1%   | 0.313               |                    |         | 88.4% | 0.544       |                             |
| Female (49)                         | 82.8%   |                     |                    |         | 87.4% |             |                             |
| Tobacco smoking                     |         |                     |                    |         |       |             |                             |
| Current (129)                       | 89.8%   | 0.775               |                    |         | 91.0% | 0.247       |                             |
| Quit and never (328)                | 89.1%   |                     |                    |         | 87.3% |             |                             |
| Habits of alcohol consumption       |         |                     |                    |         |       |             |                             |
| Yes (302)                           | 88.0%   | 0.335               |                    |         | 87.3% | 0.980       |                             |
| No (146)                            | 92.3%   |                     |                    |         | 89.8% |             |                             |
| History of surgery for HNC          |         |                     |                    |         |       |             |                             |
| Yes (67)                            | 85.5%   | 0.308               |                    |         | 76.9% | 0.002*      | 1.52 (0.77 – 3.00) 0.226    |
| No (390)                            | 89.9%   |                     |                    |         | 90.1% |             |                             |
| History of (C)RT for HNC            |         |                     |                    |         |       |             |                             |
| Yes (68)                            | 84.4%   | 0.018*              | 1.93 (0.98 – 3.79) | 0.057   | 69.2% | < 0.001*    | 3.33 (1.79 – 6.19) < 0.001* |
| No (389)                            | 90.2%   |                     |                    |         | 91.7% |             |                             |
| Primary site                        |         |                     |                    |         |       |             |                             |
| OPC (136)                           | 87.7%   | 0.474               |                    |         | 84.4% | 0.153       |                             |
| HPC (277)                           | 90.7%   |                     |                    |         | 90.7% |             |                             |
| SGC (44)                            | 85.6%   |                     |                    |         | 85.3% |             |                             |
| Number of resected subsite          |         |                     |                    |         |       |             |                             |
| Over 2 (80)                         | 84.5%   | 0.170               |                    |         | 94.4% | 0.125       |                             |
| One (377)                           | 90.3%   |                     |                    |         | 87.1% |             |                             |
| T category                          |         |                     |                    |         |       |             |                             |
| Tis, T1 (333)                       | 88.9%   | 0.722               |                    |         | 86.7% | 0.220       |                             |
| T2, T3 (122)                        | 90.6%   |                     |                    |         | 92.8% |             |                             |
| Muscle invasion                     |         |                     |                    |         |       |             |                             |
| Yes (47)                            | 85.8%   | 0.386               |                    |         | 87.4% | 0.614       |                             |
| No (339)                            | 88.9%   |                     |                    |         | 87.1% |             |                             |
| Resection of multiple lesions       |         |                     |                    |         |       |             |                             |
| Yes (63)                            | 86.1%   | 0.794               |                    |         | 82.7% | 0.025*      | 1.85 (0.97 – 3.54) 0.063    |
| No (394)                            | 89.9%   |                     |                    |         | 89.2% |             |                             |
| Horizontal margin                   |         |                     |                    |         |       |             |                             |
| Positive of invasive carcinoma (60) | 78.9%   | 0.003* <sup>†</sup> | 2.71 (1.31 – 5.60) | 0.007*  | 89.8% | 0.988       |                             |
| Positive of carcinoma in situ (55)  | 84.3%   | 0.069 <sup>†</sup>  | 2.31 (1.08 – 4.95) | 0.032*  | 86.3% |             |                             |
| Negative (321)                      | 91.5%   |                     |                    |         | 88.0% |             |                             |
| Vertical margin                     |         |                     |                    |         |       |             |                             |

|                  |       |       |       |       |
|------------------|-------|-------|-------|-------|
| Positive (25)    | 82.9% | 0.225 | 85.7% | 0.683 |
| Negative (404)   | 89.3% |       | 88.8% |       |
| Adjuvant therapy |       |       |       |       |
| Yes (22)         | 100%  | 0.131 | 94.4% | 0.373 |
| No (435)         | 88.8% |       | 88.0% |       |

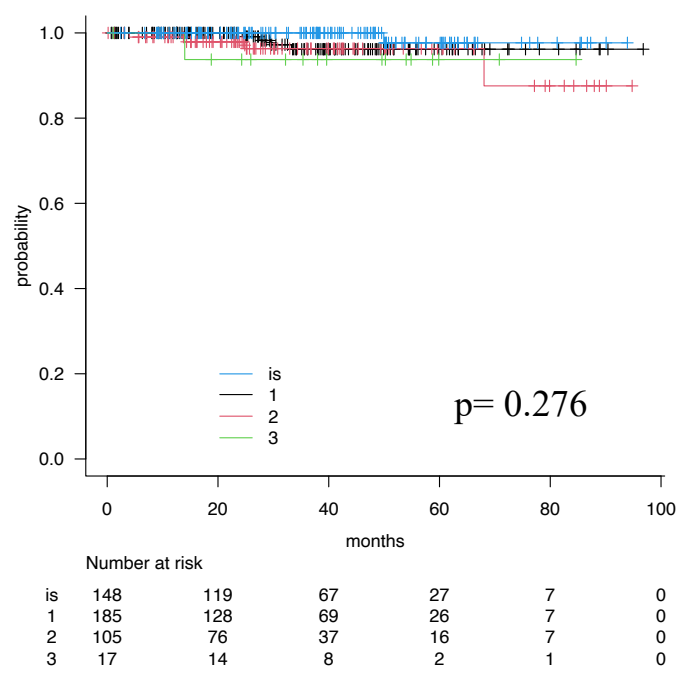
Table 6: Relationship between surgical margin assessment and local recurrence with and without adjuvant treatment

| Characteristics (number)                                                          | 3y LRFS | p value | Salvage therapy (number)                                   | 3y DSS | p value |
|-----------------------------------------------------------------------------------|---------|---------|------------------------------------------------------------|--------|---------|
| Positive horizontal margin of carcinoma in situ and negative vertical margin (46) |         |         |                                                            |        |         |
| With adjuvant therapy (1):<br>Open surgery (1)                                    | NA      | 0.583   | None                                                       | NA     | 1       |
| Without adjuvant therapy (45)                                                     | 80.7%   |         | TOS (8), RT (1)                                            | 100%   |         |
| Positive margin of invasive carcinoma (72)                                        |         |         |                                                            |        |         |
| With adjuvant therapy (16):<br>TOS (2), Open surgery (1), RT (8), CRT (5)         | 100%    | 0.049*  | None                                                       | 92.3%  | 0.387   |
| Without adjuvant therapy (56)                                                     | 75.5%   |         | TOS (8), Open surgery (1), CRT (2), Palliative therapy (1) | 100%   |         |

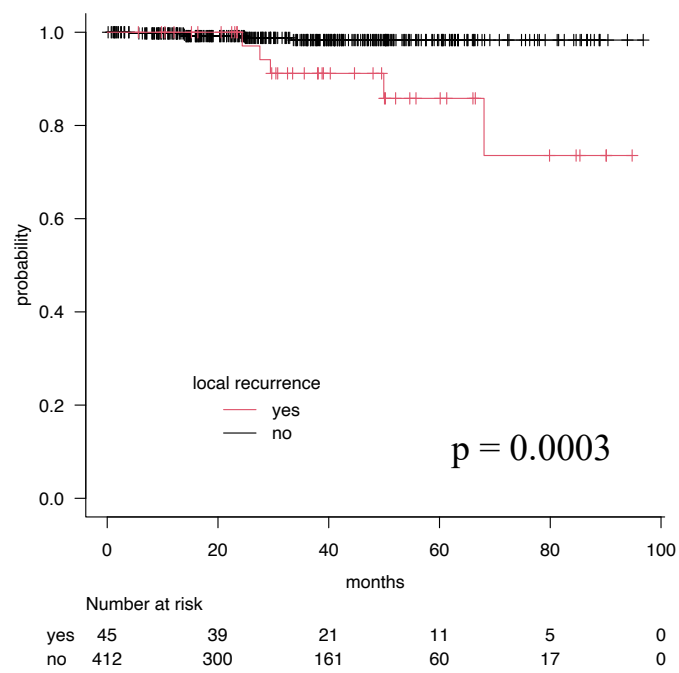
Figure 1: Disease-specific survival (DSS) by primary site, T category, and late laryngo-pharyngeal cancers.  
A



B



C



D

