Clinical Outcomes of 849 Laryngeal Cancers Treated in the Past 40 Years: Are We Succeeding?

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Objective: We analyzed the clinical outcomes of 849 laryngeal cancers treated in the past 40 years, which overlapped with the era of the global treatment shift.

Methods: To compare the chronological outcomes, patients were divided into four groups according to their registration year as 1972–82, 1983–92, 1993–2002 and 2003–12; treatment trends, larynx preservation rate and overall survival rate were compared.

Results: There were 104, 173, 253 and 319 patients registered in 1972–82, 1983–92, 1993–2002 and 2003–12, respectively. Five-year overall survival rates were 74, 76.5, 75.6 and 82.2% in 1972–82, 1983–92, 1993–2002 and 2003–12, respectively. The five-year larynx preservation rates were 65.5, 75.7, 75.4 and 80.9% in 1972–82, 1983–92, 1993–2002 and 2003–12, respectively.

Conclusions: The number of patients treated at our institute increased, and the overall survival and larynx preservation rates exhibited favorable improvements over the past four decades. In the analysis of nonsurgical options, S1 combined radiotherapy showed superiority over concurrent chemoradiotherapy and radiotherapy in larynx preservation, and S1 combined radiotherapy, concurrent chemoradiotherapy and Tegafur Uracil combined radiotherapy showed superiority over radiotherapy in overall survival. In nonsurgical approaches, proper case selection is the key to success and may be much more important than pursuing radiotherapy dose escalation. In the analysis of surgical options, laser and supracricoid laryngectomy with crico-hyoidopigloptopexy contributed to larynx preservation in early- and intermediate-stage cancers, respectively. Supracricoid laryngectomy with crico-hyoidopigloptopexy demonstrated overall survival not worse than total laryngectomy, which is the prerequisite treatment basis for larynx preservation options. We must make extra efforts in pursuing an ideal balance between nonsurgical and surgical larynx preservation options.

Key words: laryngeal cancer – functional organ preservation – larynx preservation

INTRODUCTION

Total laryngectomy (TL) has long been an effective treatment option for advanced laryngeal cancers. Nonetheless, the mutilation of vocal function and alteration of the natural airway have significant negative impacts on the patient. Patients indicated for TL are often willing to make a trade-off between survival and laryngeal preservation (1). For decades, management of laryngeal cancer has focused on improving survival while preserving function.

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The advent of platinum-based chemotherapy in the 1980s brought a new era of nonsurgical approaches in larynx preservation. In 1991, the VA trial proposed an advantageous effect of induction chemotherapy followed by definitive radiotherapy (RT) over TL followed by RT (2). Subsequent to the VA trial, in 2003, the RTOG 91-11 trial advocated the superior effect of concurrent chemoradiotherapy (CCRT) over RT alone and induction chemotherapy followed by RT (3). The treatment trend for larynx preservation largely shifted from surgery to chemoradiotherapy after these two landmark trials.

In the USA, after 1991, the percentage of advanced cancers treated with chemoradiotherapy increased, while the proportion treated with TL and RT alone decreased (4).

Despite the successful results in many patients treated with chemoradiotherapy, it has become evident that a significant proportion of patients do not benefit from chemoradiotherapy because of unmanageable local failures and severe late toxicities (5,6). Meanwhile, it has emerged as a significant issue that laryngeal cancer survival has decreased based on the USA national database (7,8). In 2010, Olsen from the Mayo Clinic raised a concern about these unintended consequences and proposed a re-examination of the management of advanced laryngeal cancers (9).

Our institute, which was established in 1972 as a tertiary referral center and university teaching hospital, is dedicated to the management of head and neck cancers with a particular interest on functional organ preservation in laryngeal cancers (8). In this study, we analyzed the clinical outcomes of 849 laryngeal cancers treated in the past 40 years, which overlapped with the era of the global treatment shift.

**PATIENTS AND METHODS**

A total of 923 malignant neoplasms of the larynx were recorded at our tumor registry between 1972 and 2012. After an evaluation using the inclusion criteria (patients with definite diagnosis of squamous cell carcinoma and complete clinical data), 849 patients were eligible for the current clinical analyses.

To compare the chronological outcomes, patients were divided into four groups according to their registration year as 1972–82, 1983–92, 1993–2002 and 2003–12; treatment trends, larynx preservation and overall survival rates were compared among these decades. Tumor Node Metastasis (TNM) staging was classified based on the International Union Against Cancer (UICC) classifications, fifth edition before 2001 and sixth edition after 2002 (10).

Nonsurgical treatment options incorporated at our institute could be classified into (i) RT alone, (ii) UFTRT (an oral fluoropyrimidine derivative combined with RT), (iii) S1RT (an agent that enhances antitumor activity of Tegafur Uracil (UFT) combined with RT) and (iv) CCRT (with two courses of intravenous cisplatin or nedaplatin, with or without 5-fluorouracil (5-FU), combined with RT). To best reflect the clinical efficacy and to avoid any influence from T staging modification, patients with Stage II and III glottic cancers were selected and the laryngeal preservation and overall survival rates were compared.

Surgical treatment options incorporated could be categorized into (i) laser (transoral CO\textsubscript{2} laser surgery), (ii) supracricoid laryngectomy with cricohyoidoepiglottopexy (SCL-CHEP) and (iii) TL. SCL-CHP (cricohyoidoepiglottopexy) was excluded because of our limited experience. To best reflect the clinical impact of surgical options, patients with Stage I–IV glottic and supraglottic cancers were selected and laryngeal preservation and overall survival rates were compared. Statistical analysis was limited to Stage II and III glottic cancer patients who received SCL-CHEP and TL (laser was excluded because all of the patients were in Stages I and II).

RT was administered in 2 Gy daily standard fractions using 6 MV X-rays. The total dose of radiation was fixed at 60 Gy and has not been changed over the past 40 years. The reference point for glottic cancer was set at the center of the field during 1972–2002 and after 2003, it was set at half point of the center and the posterior edge of the field. Two parallel-opposed lateral fields were used with a pair of wedge filters.

UFT (Taiho Pharmaceutical Co., Ltd, Tokyo, Japan) is an oral 5-FU derivative that combines tegafur with uracil in a molar ratio of 1:4. S-1 (Taiho Pharmaceutical Co., Ltd) is another oral 5-FU derivative. It combines tegafur, gimeracil and oteracil, in a molar ratio of 1:0.4:1. Tegafur is a prodrug of 5-FU, and uracil competitively inhibits the degradation of 5-FU by dihydropyrimidine dehydrogenase (DPD). Gimeracil, a DPD inhibitor, is about 200-fold more potent than uracil. Oteracil inhibits the conversion of 5-FU to active metabolites in the gastrointestinal tract, resulting in the reduction of gastrointestinal toxicity of 5-FU. UFT was used at 600–800 mg per day during the course of RT and S-1 was used at 80 mg/m\textsuperscript{2} per day in a split course with 1-week rest during the course of RT.

The larynx preservation rate was analyzed by the Kaplan–Meier method; the time points between the main treatment and the event dates were incorporated. The following factors were recognized as an event: (i) local recurrence or aspiration resulting in TL, (ii) patients died from local, nodal and/or distant recurrence and (iii) patients died from treatment-related complications. When the patients died from causes unrelated to primary cancer, they were not counted as an event. With respect to the Kaplan–Meier estimation of the overall survival rate, all deaths from any cause were treated as an event.

**RESULTS**

Chronological treatment details of 849 patients with laryngeal cancer are presented in Fig. 1. There were 104, 173, 253 and 319 patients registered in 1972–82, 1983–92, 1993–2002 and 2003–12, respectively. Among 849 patients, 668 (78.7%), 167 (19.7%) and 14 (1.6%) were diagnosed with glottic, supraglottic and infraglottic cancers, respectively. Glottic cancers amounted to 75 (72.1%), 119 (68.7%), 194 (76.6%) and 280 (87.7%) patients in 1972–82, 1983–92, 1993–2002 and 2003–12, respectively (Fig. 1). The average
ages in each decade were 61, 63, 64 and 67 years in 1972–82, 1983–92, 1993–2002 and 2003–12, respectively. There were one (1%), three (2%), 12 (5%) and 16 (5%) female patients in 1972–82, 1983–92, 1993–2002 and 2003–12, respectively.

Among all patients, 276, 288, 132 and 153 patients were classified as Stages I (T1N0), II (T2N0), III and IV, respectively. Of 132 Stage III patients, 104 (79%) were T3N0 and among 153 Stage IV patients, 67 (44%) were T4N0; consequently, 735 of 849 patients (86.5%) were diagnosed as N0 status. Of supraglottic cancers, 17, 53, 27 and 70 patients were classified as Stages I, II, III and IV, respectively. Of glottic cancers, 256, 228, 102 and 82 patients were classified as Stages I, II, III and IV, respectively.

Regarding treatment options incorporated, in 1972–82, we initiated treatment with RT and TL. In 1983–92, laser, UFTRT and CCRT were added to the treatment options. From 1993 to 2002, supracricoid laryngectomy (SCL) was introduced. From 2003 to 2012, UFTRT was replaced by S1RT, a new version of UFT. The numbers of the patients treated by each treatment option in each decade are listed in Fig. 1.

Chronological changes in overall survival and larynx preservation rates from the four decades are presented in Figs 2 and 3.

Figure 1. Chronological details of 849 laryngeal cancer patients treated in the past 40 years (1972–2012). INFRA, infraglottic cancers; SUPRA, supraglottic cancers; GLOTT, glottis cancers; RT, radiotherapy alone; TL, total laryngectomy; CCRT, concurrent chemoradiotherapy; UFTRT, UFT combined radiotherapy; SCL, supracricoid laryngectomy; S1RT, S1 combined radiotherapy.

The 5- and 10-year overall survival rates are listed in Fig. 2. There was no statistical difference between decades. The median follow-up durations were 94 (ranging from 6 to 456 months), 108 (1–353), 79 (1–237) and 37 (1–119) months in 1972–82, 1983–92, 1993–2002 and 2003–12, respectively.

Among 220 deceased patients, 105, 104 and 11 patients died from primary cancers, intercurrent diseases and unknown causes, respectively. Of 105 patients who died from primary cancers, 48, 34 and 23 patients developed locoregional failure, distant failure and both failures, respectively. Of 104 patients who died from intercurrent diseases, 53 (51%) died from second primaries (gastrointestinal, lung, urinary tract and other malignancies in 24, 18, 5 and 6 patients, respectively) and 51 (49%) died from other causes (cardiac, pulmonary, cerebral failures, senile status and accidents in 16, 11, 7, 14 and 3 patients, respectively). Among the 11 patients who succumbed to pulmonary failure, eight and three patients received RT and UFTRT, respectively.

The 5- and 10-year survival rates are listed in Fig. 3. There was a statistically significant (P = 0.03) elevation from 1972–82 to 2003–12.

Of 849 patients, 222 (Stage II–III, glottic cancers) were selected for clinical analyses of nonsurgical options; RT, CCRT, UFTRT and S1RT were applied to 54 (3), 26 (3), 90 (2) and 52 (0) patients, respectively (node-positive cases). The 5- and 9-year larynx preservation rates are listed in Fig. 4. There were statistically significant differences between RT and S1RT (P < 0.001) and CCRT and S1RT (P = 0.01). The median follow-up durations were 40, 79, 86 and 43 months in RT, CCRT, UFTRT and S1RT, respectively.

The 5- and 9-year overall survival rates are listed in Fig. 5. There was a statistically significant difference between RT and UFTRT (P = 0.04). The median follow-up durations were 75, 107, 102 and 43 months in RT, CCRT, UFTRT and S1RT, respectively.

Among 849 patients, 262 (stage I-IV, glottic and supraglottic cancers) were selected for clinical analyses of surgical options;
laser, SCL-CHEP and TL were applied to 85, 93 and 84 patients, respectively. The 5-year larynx preservation rates were 92.4 and 98.5% in SCL-CHEP and laser, respectively; 10-year larynx preservation rates were 88.9 and 98.5% in SCL-CHEP and laser, respectively. The 5-year overall survival rates were 62.6, 84.7 and 98.5% in TL, SCL-CHEP and laser, respectively; the 10-year overall survival rates were 50.6, 70.3 and 98.5% in TL, SCL-CHEP and laser, respectively.

Statistical analysis was limited to 100 patients (Stage II–III, glottic cancers) who received SCL-CHEP (node-positive cases/total cases = 2/68) and TL (4/32). Laser was excluded from the analysis because all 85 patients were of Stage I (n = 77) and II (n = 8). Among 100 patients, the 5- and 10-year overall survival rates were 60.4 and 53.7% for TL and were 91.2 and 73.8% for SCL-CHEP, respectively. There was a statistical difference between the two options (P = 0.04) (Fig. 6).

Local recurrence was identified in six of 93 (6.5%) SCL-CHEP patients; among six recurrent patients, five are currently alive without disease after salvage TL, but one died after refusing further surgery.
Currently, nine patients have received percutaneous endoscopic gastrostomy (PEG); five, two and one patient had been treated by SCL, RT and S1RT, and all patients received PEG within 2 years after the original treatments.

**DISCUSSION**

**Swing of the Pendulum**

In 2007, Holsinger and Weber used the term ‘Swing of the pendulum’ to describe the current treatment shift of laryngeal cancers from surgery to chemoradiotherapy, and stressed that when the pendulum swings back, we must establish risk-based criteria for treatment selection and functional outcome, rather than celebrating a single modality over various treatment options (11,12). Ten years after the landmark publication in 2012, Forastiere et al. reported the long-term outcomes of the RTOG 91-11 trial (13). Although 10-year local control and larynx preservation rates in the concomitant cisplatin/RT arm continued to exhibit superiority over cisplatin/FU followed by RT and RT-alone arms, in 7- to 10-year overall survival rates the concomitant arm showed inferiority (no statistical difference: NS) to the other two arms. Most of the events that

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**Figure 4.** Five- and 9-year larynx preservation rates in different nonsurgical treatment options (222 glottic cancers, Stage II and III, 1972–2012).

**Figure 5.** Five- and 9-year overall survival rates in different nonsurgical treatment options (222 glottic cancers, Stage II and III, 1972–2012).
occurred after 5 years were noncancer deaths, which were unrecognized in the initial 2003 report. Forastiere et al. stated that the superior effects on local control and larynx preservation in the concomitant arm may have been accompanied by an increased risk of serious late effects, perhaps as a consequence of more acute mucosal toxicity; the reason for the increase in late noncancer deaths in the concomitant group remains speculative.

As the pendulum gradually swung back from CCRT and more surgical options such as laser and SCL gained recognition, ultimate multidisciplinary care is needed to balance chemo-based RT and surgical options. To attain optimal results in functional organ preservation while not jeopardizing survival, it is crucial to constantly recognize where the pendulum is located.

**Clinical Features and Treatment Outcomes of 849 Patients**

The number of patients treated at our institute increased over the past four decades reflecting the increased trend of laryngeal cancer patients and the favorable development of our head and neck services in a local area. The average age and female population also showed a slight elevation over the four decades, suggesting a correlation with an aging society and the increased smoking rate in the female population.

Among 849 patients, 668 (78.7%) were classified as glottic cancer patients and the proportion reached 87.7% in the latest decade; comparably, 86.5% of the patients were categorized as N0. These trends reflected the social and provincial backgrounds of our institute. In such a patient group with predominantly glottic cancers and N0 status, definite control of the T-position is the key to success (14).

Although no statistically significant difference was observed, both 5- and 10-year overall survival rates showed improvements. The 5-year overall survival rate long remained at around 75%, but reached 82.2% in the latest decade. The 10-year overall survival rate likewise manifested a similar improvement over the four decades, but the data continue declining after 5 years, presumably due to deaths related to second primary malignancies. Second primary malignancies are well known as a risk factor influencing the long-term survival of laryngeal cancers (14). In our series, among 104 patients who succumbed to intercurrent diseases, 53 (51%) died from second primary malignancies; gastrointestinal and respiratory cancers were the two most common malignancies encountered. While, cardiac, pulmonary, cerebral failures and senile status were the main causes of other deaths; whether the 11 patients who succumbed to pulmonary failure (eight and three patients received RT and UFTRT) related to late toxicities remained speculative.

The 5- and 10-year larynx preservation rates were 65.5 and 63.1% in the first decade (1972–82) and showed a statistically significant increase to 80.9 and 79.9% in the latest decade (2003–12). In our series, both overall survival and larynx preservation rates exhibited favorable improvements over the past four decades.

**Options Supported Favorable Outcomes**

**Nonsurgical Options**

In the 222 patients with Stage II and III glottic cancers, S1RT showed statistically significant superiority over CCRT ($P = 0.01$) and RT ($P < 0.001$) in larynx preservation, and
S1RT (NS), CCRT (NS) and UFTRT ($P = 0.04$) manifested superiority over RT in overall survival. The unfavorable result for CCRT in larynx preservation may be related to inappropriate case selection, but the reason remains speculative. S1RT did not show any statistically significant difference over RT in overall survival, possibly due to the limited follow-up period.

In our institute, the total dose of RT-based options was fixed at 60 Gy and has not been increased over the past 40 years. According to the National Comprehensive Cancer Network (NCCN) guidelines for glottic cancers, 60–70 and 66–72 Gy are recommended for RT alone and CCRT, respectively (15). Low-dose RT (<60 Gy) and prolonged overall treatment time have been known to adversely affect treatment effect (16,17). Also, in the European Organization for Research and Treatment of Cancer Phase III, randomized trial, 60 Gy-based CCRT (experimental arm) revealed comparative effects on larynx preservation and survival over a 70 Gy-based CCRT (control arm) (18). Even though 70 Gy is the standard adopted RT dose today, we have reported a favorable oncologic outcome with 60 Gy-based S1RT in T2 glottic cancers (19); the present study, including extended phase II S1RT analysis, reconfirmed the effectiveness of our S1RT regimen. Reports from other institutes have also advocated CCRT over RT in early laryngeal cancers (20,21). We preferred to use 5-FU derivatives because (i) an orally available agent combined with 60 Gy RT enables most of the patients to be treated at an outpatient setting, (ii) the regimen has demonstrated satisfactory treatment effect with limited toxicities (19) and (iii) most of the patients maintained good quality of life. However, considering the intermediate follow-up duration of S1RT regimen, continuing efforts must be paid to detect the occurrence of late adverse events.

Considering the limited complications associated with salvage surgeries after RT doses <65 Gy (22), it may be worth planning a randomized trial comparing standard 70 Gy RT versus down dose RT, as achieved in the RTOG 96-05 trial for esophageal cancers (23). Above all, in the larynx preservation nonsurgical approaches, proper case selection is the key to success and may be much more important than pursuing RT dose escalation. In the analysis of surgical options, laser and SCL-CHEP contributed to larynx preservation in early- and intermediate-stage cancers, respectively. SCL-CHEP demonstrated overall survival not worse than TL, which is the prerequisite treatment basis for larynx preservation options.

In functional organ preservation of laryngeal cancers, the patient’s benefit should be considered before clinical interests. Treatment selection should not merely be decided by guidelines, and each patient’s individual status must be taken into consideration. We must make extra efforts in pursuing an ideal balance between nonsurgical and surgical larynx preservation options. The weight of larynx preservation options must be carefully balanced as potential complications and pitfalls do exist and may be beyond expectations; the role and benefits of TL should always be taken into consideration and discussed with each patient.

How can we recover from the survival deterioration? We can always learn from Confucius’s proverb: ‘Find wisdom by taking lessons from the past’. The lesson can be found in the description of the VA trial by Wolf et al. (2) as organ sparing approaches require (i) a high level of skill and cooperation among various disciplines, (ii) adequate compliance from patients and (iii) careful documentation and appropriate surveillance.

**CONCLUSIONS**

We conducted a thorough clinical review of 849 laryngeal cancers treated over the past 40 years. The number of patients treated increased, and overall survival and larynx preservation rates exhibited favorable improvements over the past four decades. In the analysis of nonsurgical options, S1RT showed superiority over CCRT and RT in larynx preservation, and S1RT, CCRT and UFTRT showed superiority over RT in overall survival. In nonsurgical approaches, proper case selection is the key to success and may be much more important than pursuing RT dose escalation. In the analysis of surgical options, laser and SCL-CHEP contributed to larynx preservation in early- and intermediate-stage cancers, respectively. SCL-CHEP demonstrated overall survival not worse than TL, which is the prerequisite treatment basis for larynx preservation options.

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