RESEARCH ARTICLE

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Study Protocol: Prospective Study of Concurrent Chemoradiotherapy with S-1 and Hypofractionated Radiotherapy for Outpatients with Early Glottic Squamous Cell Carcinomas

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Abstract

Background: The recommended treatment strategies for early glottic carcinoma with intent of larynx preservation are primarily radiotherapy. However, the outcomes of radiotherapy for bulky T1 or T2 glottic carcinoma are unsatisfactory. We designed a protocol consisting of concurrent chemoradiotherapy using S-1 as the radiosensitizer. We have performed this protocol in patients with favorable T2 lesions and demonstrated its efficacy and safety. In contrast, we have treated non-bulky T1 glottic carcinomas with 2.25 Gy per fraction, for a total of 25-28 fractions, starting in 2011 to improve efficacy and shorten the treatment period. Since this treatment strategy was implemented for T1 disease, no local failure has occurred to date, and it appears to be almost as safe as radiotherapy using 2.0 Gy per fraction. With the aim of improving the local control rate and shortening the treatment period primarily for favorable T2 disease, we changed the dose of radiation in our protocol from 2.0 Gy to 2.25 Gy per fraction, for a total of 25 fractions (from 30 fractions). The present study aims to evaluate the efficacy and safety of this new protocol. **Methods:** This study will be conducted as a clinical, prospective, single-armed, non-randomized trial. Patients are to receive S-1 (55.3 mg /m^2 /day, once daily) and radiotherapy (2.25 Gy per fraction, for a total of 25 fractions). S-1 and radiotherapy are started on the same day that radiotherapy is performed, 3-6 hours after oral administration of S-1. The primary study aim is the 3-year local control rate. The secondary study aims are overall survival, voice-preservation survival, disease-free survival, complete response rate, completion rate, and toxicity. **Result and conclusion:** This is the first single-center, non-randomized, prospective study of concurrent chemoradiotherapy with S-1 and hypofractionated radiotherapy to be conducted. The trial will evaluate the efficacy and safety of our protocol.

Keywords: S-1- early glottic cancer- concurrent chemoradiotherapy- prospective study- hypofractionated radiotherapy

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Introduction

The treatment goals for patients with early glottic carcinoma (GC) include cure, laryngeal preservation (LP) with acceptable voice quality, and minimal treatment-related morbidity. The recommended treatment strategies for early GC with intent of LP are primarily radiotherapy (RT), transoral laser therapy, and partial laryngectomy (National Cancer Institute at the National Institutes of Health, 2017; Pfister et al., 2006). RT is preferred because it can preserve the larynx and maintain the quality of voice after the treatment.

For T1 GC, the local control (LC) rate for RT alone has been reported to range from 82%-93%; however, the LC rate for T2 GC has been reported to range from 65%-80% (Mendenhall et al., 2004; Mendenhall et al., 2013; Frata et al.,2005). In contrast, the rate of LP among patients with locally advanced laryngeal cancer receiving RT with concurrent cisplatin has been reported to be >80 % (Forastiere et al., 2003; Forastiere et al., 2013). Thus, the outcomes of RT alone for T2 GC are unsatisfactory.

In our institution, for patients with favorable T2 or bulky T1 disease, who are usually recommended to receive RT alone, we have performed concurrent

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chemoradiotherapy (CCRT) to improve the LP rate (Itoh et al., 2006). T2 tumor may be either favorable or unfavorable. Favorable T2 glottic lesions are defined as superficial tumors on radiographic imaging, with normal cord mobility, while unfavorable T2 glottic lesions are defined as deeply invasive tumors on radiographic imaging, with or without subglottic extension, with impaired cord mobility (indicating deeper invasion). Some studies have reported the poor local control of unfavorable T2 lesions (Itoh et al., 2006; Hirasawa et al., 2010). Therefore, in 2007, we designed a CCRT protocol using S-1 as the radiosensitizer (Fujimoto et al., 2014), that we have performed for patients with favorable T2 lesions. In contrast, we perform CCRT using high-dose CDDP in patients with unfavorable T2 lesions. To date, the outcomes of patients receiving these regimens have been satisfactory, with a 100% LP rate. In our S-1-containing CCRT protocol, S-1 is taken orally once daily after breakfast, and RT consisting of 2.0 Gy per day, 5 days per week, to a total of 30 fractions (total dose, 60 Gy), is delivered. Oral S-1 and RT are started on the same day, and RT is performed 3-6 hours after oral S-1 administration. S-1 is not administered on Saturdays or Sundays, when RT is also not performed. The dose of S-1 is 55.3 mg/m^2/ day, which was determined to be the recommended dose in our phase I study (Fujimoto et al., 2014). For early T2 GC, we have performed CCRT using S-1 in a prospective study, demonstrating the efficacy and safety of this protocol (Kimura et al., 2015). Initially, we administered this protocol in the hospital due to safety concerns. However, after confirming the safety of this protocol, we performed it in the outpatient clinic. By combining S-1 and RT, the treatment period was shortened from 7 weeks to 6 weeks, as 7 weeks required for RT alone, to a total of 35 fractions (total dose, 70 Gy). This shorter duration should lighten the burdens of both the medical facilities and patients.

While we performed this prospective study primarily in patients with favorable T2 lesions, a new strategy for T1 GC has been presented. In our hospital, the 5-year LC rates for patients with T1a and T1b lesions were 85.9% and 83%, respectively (Hirasawa et al., 2010). We considered these results unsatisfactory, so investigated other treatment methods to improvement efficacy. Several institutes overseas have reported highly successful LC rates associated with hypofractionated RT. For example, researchers at the University of Florida reported that hypofractionated RT using 2.25 Gy per fraction, with the following 5-year LC rates: T1a, 94%; T1b, 93% (Mendenhall et al., 2001). In Japan, Yamazaki et al. (2006) reported the long-term outcome of a randomized phase III trial using 2.0 Gy or 2.25 Gy per fraction. A significant difference in LC rates were observed between the 2.0 Gy arm (77% at 5 years; 95% confidence interval, 67–87%) and the 2.25 arm (92%; 95% confidence interval, 86-98%; p= 0.004). Based on these results, the RT dose per fraction in our hospital was changed from 2.0 Gy to 2.25 Gy, and the number of fractions was reduced from 35 fractions to 28 fractions. This new strategy was implemented in 2011, and no local treatment failure has been observed to date. Furthermore, in clinical practice, early GC has been treated with RT with 2.25 Gy per fraction at several institutions in the Tokai District of Japan. To analyze the outcomes of these patients, the Tokai Study Group for Therapeutic Radiology and Oncology (TOSTRO) administered a questionnaire survey about RT for early GC beginning in 2011, and the data of 104 patients from 10 institutions were recorded. To date, only 2 patients experienced local failure, and no apparent differences in toxicity were observed between patients receiving 2.25 Gy versus 2.0 Gy.

Thus, with the aim of improving the LC rate of primary RT and shortening the treatment period primarily for patients with favorable T2 GC, we improved our S-1-containing CCRT protocol by reducing the S-1 administration period to 5 weeks while maintaining the daily dose, and reducing the RT dose to 2.25 Gy per fraction for a total of 25 fractions. The present study evaluates the efficacy and safety of this new protocol.

Materials and Methods

Methods/Design

Primary and secondary study aims

The Primary study aim is the 3-year LC rate. The secondary study aims are: (1) overall survival (OS), (2) voice-preservation survival (VPS), (3) disease-free survival (DFS), (4) complete response (CR) rate, (5) completion rate, and (6) toxicity.

Study design

This study is a prospective, single-armed, non-randomized clinical trial.

Randomization

None.

Inclusion criteria

The inclusion criteria are : (1) glottis confirmed as the primary tumor site by laryngoscopy within 28 days before enrollment; (2) diagnosis of bulky T1 or T2 disease without impaired cord mobility by fiberscopy; (3) histologically confirmed glottic squamous carcinoma; (4) N0M0 stage disease confirmed by chest X-ray or contrast-enhanced computed tomography (CT); (5) no history of tumor chemotherapy in the past 5 years; (6) aged 20-80 years; (7) Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; (8) no prior history of radiotherapy or surgery to the planned irradiation area; (9) willingness to participate and sign informed consent; and (10) adequate bone marrow, liver, and kidney functions.

Exclusion criteria

The exclusion criteria are: (1) inability to take oral S-1; (2) with a history of severe allergy; (3) severe clinical infection; (4) active double cancer, including simultaneous cancer or metachronous cancer within 5 years, except for in situ or intramucosal carcinoma; (5) currently pregnant or breast feeding; (6) mental disease that would interfere with participation; (7) history of severe lung disease, such as interstitial pneumonia of pulmonary fibrosis; (8) history of collagen disease; (9) uncontrolled diabetes mellitus or insulin-dependent diabetes mellitus; (10) uncontrolled

hypertension; (11) clinically significant cardiovascular diseases, such as heart failure or history of myocardial infarction or angina in the past 6 months; (12) currently taking drugs as following agents: other anticancer pyrimidines or flucytosine; and (13) judged as inadequate case by head physician.

Therapeutic advantages

Advantages for patients participating in the present trial include:

1) Expected improved antitumor efficacy due to the shortened treatment duration, which might inhibit tumor cell repopulation during the latter half of RT, and due to increased radiation sensitivity resulting from S-1 given prior to RT.

2) Shortening the treatment period could lighten the burdens of both the medical facilities and patients.

Toxicity

The incidence of toxicities might be higher than that of other regimens; no data exist regarding the safety of CCRT using S-1 and RT with 2.25 Gy per fraction. In this study, radiation dermatitis and mucositis are expected to be the most frequently experienced adverse events. In addition to this, gastrointestinal toxicity (primarily diarrhea) and hematological toxicity might also occur. Although the incidence of S-1-specific adverse events is expected to decrease due to the smaller total S-1 dose resulting from the shortened treatment period, RT-associated adverse events might be enhanced by CCRT.

Study plan

Chemotherapy

S-1 is taken orally once daily after breakfast. Oral S-1 and RT are started on the same day (generally Monday), and RT is performed 3-6 hours after oral administration of S-1. S-1 is not administered on Saturdays or Sundays, when RT is not performed. The dose of S-1 is 55.3 mg/m2/day, which was determined to be the recommended dose in our phase I study (Fujimoto et al.,2014).

Radiotherapy

Conventional RT is performed with 4-MV photons at 2.25 Gy/fraction/day. The total dose delivered is 56.25 Gy/25 fractions over a 5-week period. RT is planned for all patients after appropriate immobilization, with a thermoplastic mask and 3D CT-based techniques. Two parallel-opposed lateral fields are used with a pair of wedge filters. The field size is reduced after administration of 45 Gy based on the reduction of the tumor.

Results

Study plan and duration of regular study participation

Figure 1 shows the protocol schedule of. At study enrollment, potential participants will be asked standardized questions about their medical histories. In addition, physical examination; routine blood examination and biochemistry; electrocardiography; routine urine testing; imaging examination including fiberscopy, upper gastrointestinal endoscopy, chest X-ray, and neck enhanced CT; pathological diagnosis; and determination of ECOG performance status (PS) will also be performed and used to check for inclusion/exclusion criteria.

After registration, eligible participants will be monitored for toxicity throughout the treatment. Complete blood counts and blood chemistry measurements will be conducted every 2 weeks. When 15 fractions of RT have been delivered, fiberscopy will be performed to confirm efficacy and that no apparent progressive disease or severe adverse events are present.

At about 6 weeks after the end of treatment, the clinical responses will be assessed for each patient using fiberscopy. We define neoplastic lesions as follows: (1) erosive change with the irregularity and (2) apparent upheaval and ulcer. When the fiberscopy findings do not suggest neoplastic lesions or active mucositis, the case will be defined as a CR. When fiberscopy findings suggest neoplastic lesions and tumor cells are identified by biopsy, the case will be defined as having progressive disease (PD). A case that does not match with either CR or PR criteria will be defined as incomplete response/stable disease (IR/SD). In such cases, fiberscopy will be repeated every 2 weeks until it is judged to be either CR or PD.

After the assessment of clinical response, follow-up evaluations will be conducted every month for 6 months and every 3 months thereafter. Assessment of efficacy will be conducted by fiberscopic evaluation at each follow-up. Radiation-associated adverse events will be classified by the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) 4.0 standard.

	At enrollment	During treatment period	6 weeks after completion of treatment	First 6 months after completion of treatment	Until the end of the study
General condition					
Height and the weight	○				
Performance status	○	●	○	▼	■
Clinical examination					
Routine blood examination and biochemistry	○	□		▼	■
Routine urine test	○				
Electrocardiography	○				
Imaging					
Fiberscopy	○	▲	○	▼	■
Upper gastrointestinal endoscopy	○				
Chest X-ray	○	▲		▲	▲
Neck enhanced CT	○	▲		▲	▲
Adverse events					
Examination of the presence of subjective and objective symptoms		●	○	▼	■

○: Indicates mandatory items.
●: Perform more than once weekly
○: Perform during the weekends of the 1st, 3rd, and 5th weeks of treatment
▲: Perform if needed
▼: Perform once every month
■: Perform more than once every 3 months (until 3 years after the end of the study)

Figure 1. Observation, Assessment, and Follow-up Schedule

Chronic radiation damage will be classified using the criteria of the Radiation Therapy Oncology Group/ European Organization for Research and Treatment of Cancer (RTOG/EORTC), with common signs and severity recorded.

Study duration

The recruiting phase of the study will end after inclusion of the planned patient number of n = 27. This trial will be conducted until December 31, 2024.

Statistical design and analysis

The threshold value of 3-year LC rate and the expected value of 3-year LC rate are expected to be 70 % and 95 %, respectively. As both the intended registration and observation durations are 5-years, 24 patients are required to provide 80 % power, with the use of a two-sided significance level of 0.05. In consideration of patients with who leave the trial, the planned patient number has been set at 27.

LC rate is defined as the time until an event of local disease progression or a residual tumor. OS is defined as the time from date of registration to date of death, VPS is defined as the time until the Grade 3 or 4 voice change or death from any cause, and DFS as the time from registration to documented progression or death from any cause, whichever occurred first. The completion rate is determined as the proportion of patients who completed the treatment. The time-to-event data of primary and secondary endpoints are estimated by using the Kaplan-Meier method. The proportions of response and toxicity are calculated and their 95% confidence intervals are estimated based on the Clopper-Pearson method.

Status of the study

The study is currently recruiting patients.

Discussion

Clinicians have reported several S-1-based CCRT regimens (Nonoshita et al., 2010; Nakayama et al., 2010; Ikeda et al., 2008; Tsuji et al., 2006) and hypofractionated RT protocols (Mendenhall et al., 2001; Yamazaki et al., 2006) for early GC. However, there is no regimens that combine these methods and once-daily administration of S-1 before RT exist. The present study is the first one-armed non-randomized trial of CCRT with S-1 and hypofractionated RT. Recently, several institutions have attempted to reduce radiation dose to the carotid arteries with intensity-modulated radiotherapy (IMRT) (Gomez et al., 2010; Rosenthal et al., 2010; Chera et al., 2010). However, the role of IMRT in early-stage larynx cancer is controversial. Increased conformity also increases the risk of marginal misses though contouring errors and organ motion. In addition to anecdotal reports of increased failure with IMRT, the major concerns are the potential for underdosing the tumor through target delineation errors, complications resulting from the hot spots, increased cost, and increased treatment complexity leading to prolonged contouring, planning, and treatment time (Zumsteg et al., 2015; Damast et al., 2012; Chen et al., 2011; Chen et al., 2010). Because of these reports, we chose a conventional RT using two parallel-opposed lateral fields. Yet, Chera et al. (2010) reported RT using three-dimensional conformal radiotherapy could make the dose to carotid arteries lower than that using traditional two parallel-opposed lateral fields statistically. Therefore, we are going to plan the prospective study for patients with early GC treating with three-dimensional conformal radiotherapy to reduce the dose of carotid arteries.

Our protocol shortens the treatment period by about 1 week, which lightens the burdens of both the medical facilities and patients and makes outpatient treatment possible. Therefore, this study will evaluate not only the efficacy and safety but also the clinical utility of our protocol.

List of abbreviations

GC: Glottic carcinoma; LP: laryngeal preservation; CCRT: concurrent chemoradiotherapy; TOSTRO: Tokai Study Group for Therapeutic Radiology and Oncology; ECOG: Eastern Cooperative Oncology Group; OS: overall survival; VPS: voice-preservation survival; DFS: disease-free survival; CR: complete response; UMIN: University Hospital Medical Information Network.

Declarations

Ethics approval and consent to participate

The protocol and informed consent form have been reviewed and approved by the Institutional Review Boards of the Nagoya University Hospital (no. 8736), and written informed consent was obtained from all patients included in this study. This clinical trial is registered in the UMIN Clinical Trials Registry (UMIN000023416).

Authors' contributions

KK, YI, HT, NN, MH, YF, TM, and AH contributed to the development of the study protocol.

YI is the principal investigator and is managing the protocol.

KK and YI are involved in writing the initial draft of the manuscript.

KK, YI, TO, SK, MK, RI, YO, YK, YT, HT, NN, MH, and YF are responsible for participant enrollment, follow-up, and data entry.

All authors read and approved and the final manuscript.

The present study was approved by the investigational review board of our hospital (number 8736), and written informed consent was obtained from all patients included in this study. This clinical trial is registered in the UMIN Clinical Trials Registry (UMIN000023416).

Statement conflict of Interest

The authors declare that they have no competing interests.

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References

American Society of Clinical Oncology, Pfister DG, Laurie SA, Weinstein GS, Mendenhall WM, Adelstein DJ, et al (2006). American Society of Clinical Oncology clinical practice guideline for the use of larynx- preservation strategies in the treatment of laryngeal cancer. *J Clin Oncol*, **24**, 3693-704.

Chen AM, Farwell DG, Luu Q, et al (2010). Misses and near-misses after postoperative radiation therapy for head and neck cancer: Comparison of IMRT and non-IMRT techniques in the CT-simulation era. *Head Neck*, **32**, 1452-59.

Chen AM, Farwell DG, Luu Q, et al (2011). Marginal misses after postoperative intensity-modulated radiotherapy for head and neck cancer. *Int J Radiat Oncol Biol Phys*, **80**, 1423-9.

Chera BS, Amdur RJ, Morris CG, Mendenhall WM (2010). Carotid-sparing intensity-modulated radiotherapy for early-stage squamous cell carcinoma of the true vocal cord. *Int J Radiat Oncol Biol Phys*, **77**, 1380-5.

Damast S, Wolden S, Lee N (2012). Marginal recurrences after selective targeting with intensity-modulated radiotherapy for oral tongue cancer. *Head Neck*, **34**, 900-6.

Forastiere AA, Goepfert H, Maor M, et al (2003). Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med*, **349**, 2091-8.

Forastiere AA, Zhang Q, Weber RS, et al (2013). Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *J Clin Oncol*, **31**, 845-52.

Frata P, Cellai E, Magrini SM, et al (2005). Radical radiotherapy for early glottic cancer: Results in a series of 1087 patients from two Italian radiation oncology centers. II. The case of T2N0 disease. *Int J Radiat Oncol Biol Phys*, **63**, 1387-94.

Fujimoto Y, Kato S, Itoh Y, Naganawa S, Nakashima T (2014). A phase I study of concurrent chemoradiotherapy using oral S-1 for head and neck cancer. *Anticancer Res*, **34**, 209-13.

Gomez D, Cahlon O, Mechalakos J, Lee N (2010). An investigation of intensity-modulated radiation therapy versus conventional two-dimensional and 3D-conformal radiation therapy for early stage larynx cancer. *Radiat Oncol*, **5**, 74.

Hirasawa N, Itoh Y, Ishihara S, et al (2010). Radiotherapy with or without chemotherapy for patients with T1-T2 glottic carcinoma: retrospective analysis. *Head Neck Oncol*, **2**, 20.

Ikeda Y, Tsukuda M, Tanigaki Y, et al (2008). Concurrent chemoradiotherapy with S-1 for T2N0 glottic carcinoma. *Jpn J Chemother*, **35**, 789-92.

Itoh Y, Fuwa N (2006). Retrospective analysis: concurrent chemoradiotherapy using protracted continuous infusion of low-dose cisplatin and 5-fluorouracil for T2N0 glottic cancer. *Radiat Med*, **24**, 277-81.

Kimura K, Itoh Y, Okada T, et al (2015). Critical evaluation of a prospective study of concurrent chemoradiotherapy with S-1 for early glottic carcinoma. *Anticancer Res*, **35**, 2385-90.

Mendenhall WM, Amdur RJ, Morris CG, Hinerman RW (2001). T1-T2N0 squamous cell carcinoma of the glottic larynx treated with radiation therapy. *J Clin Oncol*, **19**, 4029-36.

Mendenhall WM, Werning JW, Hinerman RW, Amdur RJ, Villaret DB (2004). Management of T1-T2 glottic carcinomas. *Cancer*, **100**, 1786-92.

Mendenhall WM, Mancuso AA, Amdur RJ, Werning JW (2013). Laryngeal cancer. In: Perez and Brady's principles and practice of radiation oncology. 6th edition. Halperin EC, Perez CA and Brady LW (Eds.). Philadelphia: Lippincott William and Wilkins, pp 850-68.

Nakayama M, Hayakawa K, Okamoto M, et al (2010). Phase I/II trial of concurrent use of S-1 and radiation therapy for T2 glottic cancer. *Jpn J Clin Oncol*, **40**, 921-6.

National Cancer Institute at the National Institutes of Health (2014) Laryngeal Cancer Treatment (PDQ®). www.cancer.gov/ cancertopics/pdq/treatment/laryngeal/HealthProfessional (Accessed, March 20th, 2017).

Nonoshita T, Shioyama Y, Nakamura K, et al (2010). Concurrent chemoradiotherapy with S-1 for T2N0 glottic squamous cell carcinoma. *J Radiat Res*, **51**, 481-4.

Rosenthal DI, Fuller CD, Barker JL. Jr, et al (2010). Simple carotid-sparing intensity-modulated radiotherapy technique and preliminary experience for T1-2 glottic cancer. *Int J Radiat Oncol Biol Phys*, **77**, 455-61.

Tsuji H, Kiba T, Nagata M, et al (2006). A phase I study of concurrent chemoradiotherapy with S-1 for T2N0 glottic carcinoma. *Oncology*, **71**, 369-73.

Yamazaki H, Nishiyama K, Tanaka E, Koizumi M, Chatani M (2006). Radiotherapy for early glottic carcinoma (T1N0M0): results of prospective randomized study of radiation fraction size and overall treatment time. *Int J Radiat Oncol Biol Phys*, **64**, 77-82.

Zumsteg ZS, Riaz N, Jaffery S, et al (2015). Carotid sparing intensity-modulated radiation therapy achieves comparable locoregional control to conventional radiotherapy in T1-2N0 laryngeal carcinoma. *Oral Oncol*, **51**, 716-23.