

Proposal for personalized treatment of early glottic cancer with radiation therapy

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ABSTRACT

The preservation of both the organ and its function is important for the treatment of early stage glottic cancer, and radiation therapy is an important and useful option. However, treatment with radiation therapy alone is insufficient. Therefore, to improve the local control rate even for early stage glottic cancer, attempts have been made to individualize treatment with radiation therapy (\pm chemotherapy) based on T stage and morphological characteristics. This individualized treatment greatly improved the local control rate for early glottic cancer. In the future, more suitable individualization can be achieved by investigating the radiosensitivity of biomarkers using biopsy materials before radiation therapy, in addition to T stage and morphological characteristics. Currently, many biomarkers are being investigated; however, appropriate biomarkers for predicting local control remain unknown.

Keywords: early glottic carcinoma, radiation therapy, chemoradiotherapy, biomarkers

Abbreviations:

CA: carbonic anhydrase

COX-2: cyclooxygenase-2

EpCAM: epithelial cell adhesion molecule

5-FU: fluorouracil

GC: glottic cancer

LC: local control

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INTRODUCTION

Radiation therapy for early stage glottic cancer (GC) is regarded as one of the standard treatments for the preservation of the organ and its function; it is the most popular treatment method in clinical practice. Guidelines from other countries also recommend treatments aimed at preserving the larynx as a standard treatment for early stage GC. However, in many reports,¹⁻⁴ the local control (LC) rate of GC is insufficient, and the usefulness and effectiveness of radiation therapy were not demonstrable. In particular, T2 GCs have a high recurrence rate, and the

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laryngeal preservation rate with radiation therapy alone is approximately 65%–80%, although there are variations in reports. The usefulness of radiation therapy in preserving the organ and its functions is far from convincing.

Therefore, for a long time, attempts have been made to improve the LC rate of early stage GC.⁵⁻¹⁵ These attempts specifically focused on combining radiation therapy with intravenous chemotherapy and oral anticancer drugs or by increasing the fraction size of radiation (hypofractionation) depending on T stage (T1 or T2) and morphological characteristics (bulky or non-bulky in this study) of the tumor, even in early stage GC. As a result, the LC rate has improved with this personalized treatment.

This study outlines the history of personalized treatments by T stage and morphological characteristics that have been performed so far^{12,16} and aims to personalize the treatment of early stage GC by adding the sensitivity of radiation to biomarkers.

Therefore, we propose a new treatment strategy. The usefulness of multiple biomarkers for radiosensitivity is unknown at this time, with some reports being useful and some not. We must wait for further research results in the future.

PREVIOUS RESEARCH AND EVALUATION

T2 GC is also an early stage GC, and treatment that preserves the larynx is the first choice. However, the control rate of T2 GC with radiation therapy alone is poor and unsatisfactory. Therefore, to improve the control rate with radiation therapy alone, we initiated treatment with concurrent chemoradiotherapy. The anticancer drug used in this case was a combination of low-dose cisplatin and 5-FU.⁵ Since this combination therapy has relatively few side effects and less burden on the kidneys, it can be administered to older people and patients with impaired renal function and is also indicated for patients with esophageal and lung cancers.^{16,17} The LC rate of T2 with chemoradiotherapy exceeded 90%, and the laryngeal preservation rate also improved. However, the problem was that the anti-cancer drug was administered via continuous intravenous infusion for 24 hours, and this treatment was originally intended for patients who could be treated in outpatient clinics; thus, for hospitalized patients who wish to stay out on weekends, the catheter remains indwelling. This increases the risk of infection at the catheter insertion site.⁵ Although chemoradiotherapy is a useful treatment, it cannot be reported as a treatment that can be performed at any facility as a routine medical care. However, it can be reported that this is a treatment method for early GC that is widely applicable.

Therefore, we conducted a phase I/II clinical trial using the oral anticancer drug S-1, an anticancer drug that can be administered to outpatients, as the chemotherapeutic agent. We planned an administration schedule that would use S-1 as a single agent and that would have the most sensitizing effect on radiation. To determine the recommended dose of S-1, a phase I clinical trial was conducted with postoperative irradiation cases for head and neck cancer,⁹ and then a phase II clinical trial was conducted for early GC. To date, no recurrence has been observed in all GC cases treated with this protocol.^{10,14} In addition, in T2 patients with unfavorable or poor vocal cord mobility, chemoradiation was performed with high-dose cisplatin. No recurrence was observed in patients treated with this treatment either.¹² Aggressive treatment of T2 with simultaneous chemoradiotherapy resulted in an improvement in the outcome of T1 and T2 GCs and the LC rate at Nagoya University Hospital. T1 GCs were previously treated with 70 Gy/35 fractions once,⁸ and a control rate exceeding 90% was not obtained. Therefore, we changed to hypofractionation of 2.25 Gy/fraction. The LC rate of T1 GC with hypofractionation exceeded 90% in Japan and other countries.^{18,19} The Tokai Study Group for Therapeutic Radiol-

ogy and Oncology treated T1 GC with 2.25 Gy at 10 institutions, with 202 patients enrolled. The median follow-up period was 34.2 months. The 2- and 4-year LC rates were 93.8% and 93.1%, respectively.¹⁵ Similarly, good results were obtained in the treatment results for T1 GC in multiple centers and with large numbers.

PERSONALIZED TREATMENT BY T STAGE AND MORPHOLOGICAL CHARACTERISTICS

So far, we have set a policy of individualized treatment of GC¹² based on T stage and morphological characteristics, and we treated 80 patients from 2007 to 2019 according to this treatment policy.¹² The 5-year LC rate of patients who received this treatment was 97.3% (unpublished data). However, patients who could not follow the treatment policy owing to medical problems such as poor renal function or simultaneous multiple cancers or old age and patients who did not agree to the treatment policy did not have a good 5-year LC rate (75.7%, with a significant difference [P=0.02]). Meanwhile, the 5-year LC rate of patients who received chemotherapy was 100% (unpublished data). Therefore, we believe that our personalized treatment strategy based on T stage and morphological characteristics of tumors for early stage GC is appropriate. However, in the future, by making complete use of new biomarkers, more appropriate individualization will be developed, with advance knowledge of radiosensitivity status. A high laryngeal preservation rate and low recurrence rate are expected. For example, the overexpression of cyclooxygenase-2 (COX-2), p53, epithelial cell adhesion molecule (EpCAM), hypoxia inducible factor 1 α subunit, and carbonic anhydrase IX has been reported as a risk factor for a high local recurrence rate, and a high total microvessel perimeter per tumor area was a predictor of 337 optimized radiation therapy strategies for early GC.²⁰⁻²³ However, in a recent systematic review, EGFR and P53 could not predict LC after radiation therapy,²⁴ and other clusters of markers (markers involved in angiogenesis and hypoxia, apoptosis markers, cell cycle markers, COX-2, and DNA properties) also did not provide evidence for the prediction of LC after radiation therapy. In addition, according to an ancillary study of a multi-institutional randomized phase III trial of accelerated fractionation versus standard fractionation radiation therapy for T1-2N0M0 GC (JCOG0701), it could not be concluded whether EpCAM, p16, and p53 were prognostic factors for early stage GC after primary radiation therapy.^{25,26}

The usefulness of biomarkers for radiosensitivity has not yet been concluded; thus, we must wait for the results of future research on how to proceed. However, treatment results have improved owing to the personalized treatment strategy based on T stage and morphological characteristics being performed at the Nagoya University Hospital.¹²

Here, we propose a new treatment strategy that considers biomarkers in addition to individualized treatment for T1-T2 early stage GC at Nagoya University Hospital. Fig. 1 shows the proposed personalized treatment strategy for early stage GC.

In addition to confirming the histological diagnosis with biopsy and histology in advance, the presence or absence of radiosensitivity is confirmed, and treatment methods were sorted based on sensitivity. In a T1 tumor, if radiosensitivity is confirmed, irradiation with 63 Gy in 28 fractions (2.25 Gy/fraction) is recommended for radiation alone. If the tumor is not radiosensitive, laryngeal preservation by surgery or laser therapy is recommended rather than radiation therapy. If surgery or laser therapy is not desirable, radiation therapy in combination with anticancer drugs should be considered. So far, no recurrence has been reported after the simultaneous treatment with S-1 and radiation has been observed for 11 years, and it is unlikely that there were no radiation-resistant tumors among the registered cases. It is judged that the radiation therapy

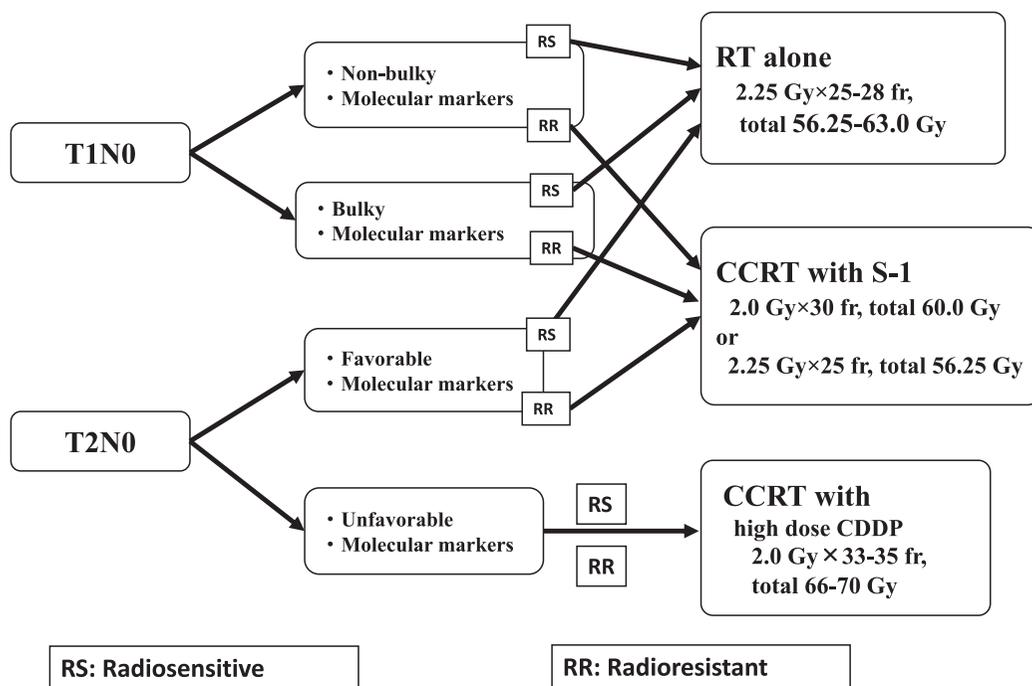


Fig. 1 The personalized treatment strategy proposal of radiation therapy for T1-2 glottic cancer based on both radiosensitivity and morphological characteristics

RT: radiotherapy

Gy: gray

fr: fraction

CCRT: concurrent chemoradiotherapy

CDDP: cisplatin

regimen might have overcome the radiation resistance. Chemoradiotherapy with S-1 (60 Gy in 30 fractions at 2 Gy/fraction)^{10,12,14} or 2.25 Gy/fraction with a total dose of 52.25 Gy/25 fractions with short-term fractionated irradiation,¹³ which is currently being administered in clinical trials, may be used. Combination therapy with short-term irradiation has a shorter treatment period and lower medical costs than the conventional irradiation alone with 70 Gy/35 fractions. For T2 GC, 2.25 or 2.4 Gy/fraction²⁶ radiation alone is recommended, except in a bulky tumor in which radiosensitivity is unlikely. For bulky tumors, simultaneous doses of S-1 and 2.25 Gy/fraction, and for unfavorable or poor vocal cord mobility, high doses of cisplatin and radiation (70 Gy/35 fractions) are recommended. If the tumor is radiation resistant, laryngeal preservation by surgery may be performed, and depending on the size and spread of the tumor lesion, partial resection may be difficult even for T2 GCs, and laryngectomy may be performed. High doses of cisplatin and radiation (70 Gy/35 fractions) are also indicated if laryngeal preservation is strongly desired.

CONCLUSION

Individualized treatment is required to improve LC centered on radiation therapy for early stage GC. Depending on biomarkers, tumor stage, and morphological characteristics, it is speculated that

a more appropriate individualized treatment can be achieved by determining the radiosensitivity status. Meanwhile, further research is required.

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CONFLICTS OF INTEREST

The authors declare that we have no competing interests.

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