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Retrospective Analysis: Concurrent Chemoradiotherapy and Adjuvant Chemotherapy for T2N0 Glottic Squamous Cell Carcinoma

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Abstract This study aimed to evaluate the efficacy and toxicity of concurrent chemoradiotherapy and adjuvant chemotherapy for T2N0 glottic squamous cell carcinoma. Between May 1993 and March 2004, 32 patients with T2N0 glottic squamous cell carcinoma received concurrent chemoradiotherapy as the primary treatment modality for larynx preservation. Radiotherapy was delivered five days a week using a once-daily fractionation of 2.0 Gy (median total dose: 70 Gy). The chemotherapy regimen comprised carboplatin in 4 patients, carboplatin and tegafur and uracil in 7, carboplatin and futrafu in 2, and futrafu in 19 patients. Twenty-four patients received adjuvant chemotherapy with tegafur and uracil. Initial local tumor control was achieved in 30 patients (94%). The 5-year overall survival and 5-year local control rates were 97% and 70%, respectively. Univariate analysis revealed adjuvant chemotherapy as a significant prognostic factor for the local control rate (P = 0.038). The 5-year local control rate in patients treated or not treated with adjuvant chemotherapy was 82% and 42%, respectively. No significant differences in the local control rate were noted in overall treatment time, total radiation dose, age, and disease extension to the subglottis. With regard to adverse reactions, grade 3 neutropenia and grade 3 hepatotoxicity were observed in 1 and 2 patients, respectively. We observed no severe late complications (RTOG/EORTC criteria Grade 3–4) related to this combination therapy. Concurrent chemoradiotherapy and adjuvant chemotherapy was effective but with mild toxicity, and adjuvant chemotherapy significantly improved local control. We suggest the use of this combination therapy for achieving a local control of T2N0 glottic squamous cell carcinoma.

Key words: early glottic carcinoma, concurrent chemoradiotherapy, adjuvant chemotherapy

Introduction

Definitive radiotherapy is indicated as the primary treatment for early glottic carcinoma and has shown successful outcomes. Radiotherapy has the advantage of preserving the laryngeal structure and function in the majority of patients. The 5-year local control rates after radiotherapy alone are 81—94% for T1N0 glottic carcinoma and 67—80% for T2N0 glottic carcinoma14 the range in the case of T2N0 glottic carcinoma is, however, low and insufficient. Attempts that have been made to improve the local control rate include hyperfractionation or increasing fraction size in once daily fractionation57 or chemoradiotherapy. In addition, to reduce the recurrence rate, adjuvant chemotherapy was administered for head and neck carcinomas1013. In the present study, to improve the local...
control rate and reduce the recurrence rate, we administered chemoradiotherapy and adjuvant chemotherapy for T2N0 glottic carcinoma and evaluated the efficacy and toxicity of this combination treatment.

**Materials and Methods**

Between May 1993 and March 2004, a total of 32 patients with T2N0 glottic squamous cell carcinoma received concurrent chemoradiotherapy as the primary treatment for larynx preservation, according to the International Union Against Cancer (UICC, 1997) TNM classification system. The 32 patients included 31 males and 1 female with a median age of 69 years (range: 50—85 years). Patients with disease extension to the supraglottis were 26 and/or subglottis 9. No patient showed impaired vocal cord mobility. The performance status was between 0 and 1 according to Eastern Cooperative Oncology Group criteria. All patients had squamous cell carcinoma. The chemotherapy regimen consisted of carboplatin in 4 patients, carboplatin and tegafur and uracil (UFT) in 7, carboplatin and futrafusil in 2; and futrafusil in 19 patients. Carboplatin was administered intravenously once a week or daily during the period of radiotherapy. The carboplatin dose was 80 or 100 mg/week. Chemotherapy with UFT or futrafusil alone was administered daily during the period of radiotherapy. In UFT, the oral dose of tegafur was 400 mg/day. The dose of futrafusil was 250 or 400 mg/day. Radiotherapy was delivered 5 days/week using a once-daily fractionation of 2.0 Gy (median total dose: 70 Gy, range: 60—70 Gy). All the patients underwent radiotherapy with a 5–MV photon beam. Parallel-opposed lateral fields with a field size ranging from 5 × 5 to 6 × 6 cm² were used. In all, 24 patients received adjuvant chemotherapy with UFT, in which the oral dose of tegafur was 400 mg/day. Initial responses were evaluated 4 weeks after the completion of the concurrent chemoradiotherapy. The recurrence of the primary tumor and metastasis were assessed by laryngoscopy, computed tomography, and ultrasonography. The overall survival rate and local control rate were determined according to the Kaplan–Meier method, and statistical significance was determined by a log-rank test. Data analyses were performed using StatMate version III for Windows. (ATMS Co., Ltd., Tokyo, Japan). For identifying the significant prognostic factors for local control rate, we reviewed adjuvant chemotherapy regimen, overall treatment time (OTT), total radiation dose, age, and disease extension to the subglottis. Toxicity was assessed during treatment, using the Common Terminology Criteria for Adverse Events version 3.0.

**Results**

The follow-up period for all the patients was 12—164 months (median: 65 months). No patient exhibited metachronous malignancy of another primary organ. Initial local control of the primary tumor was achieved in 30 of the 32 patients (94%). Two patients showing partial response underwent total laryngectomy. Local recurrence occurred in 8 of these 30 patients; of these 8 patients, 5 received adjuvant chemotherapy and 3 did not receive, and 6 underwent total laryngectomy while 2 were diagnosed with inoperable carcinoma. One patient with local recurrence showed lymph node and lung metastasis. The overall survival rate and local control rate are shown in Figures 1 and 2. The 5-year overall survival rate and the 5-year local control rate of the 32 patients were 97% and 70%, respectively.

Adjuvant chemotherapy was administered to 24 of 30 patients who achieved complete response after concurrent chemoradiotherapy. Adjuvant chemotherapy was continued for 2—41 months (median: 14 months). The 5-year local control rate in patients treated or not treated with adjuvant chemotherapy was 82% and 42%, respectively. Univariate analysis showed that adjuvant chemotherapy had statistically significant impacts on the local control rate (Fig. 3).
For all the patients, the range of OTT was 53–80 days (median: 65 days). The local control rate was analyzed by comparing the shorter OTT group (<65 days) with the longer OTT group (≥65 days); the 5-year local control rates were 74% and 70%, respectively. In the case of the 24 patients who received adjuvant chemotherapy, the range of OTT was 53–80 days (median: 65 days). The local control rate in this group was also analyzed by comparing the shorter OTT group (<65 days) with the longer OTT group (>65 days); the 5-year local control rates were 88% and 78%, respectively. No significant differences in the local control rate were observed with respect to OTT, total radiation dose, age, and disease extension to the subglottis.

Data regarding the occurrence of acute toxicity are listed in Table 1. With regard to acute adverse reactions, grade 3 neutropenia and grade 3 hepatotoxicity were observed in 1 and 2 patients, respectively. Thus, the use of chemoradiotherapy and adjuvant chemotherapy did not result in severe treatment–related acute toxicity. We observed no severe late complications (RTOG/EORTC criteria Grade 3-4) related to this combination therapy.

### Discussion

In most institutions, T2N0 glottic carcinomas are treated using conventional radiotherapy as the primary treatment for laryngeal preservation; however, treatment with conventional radiotherapy alone for the local control of T2N0 glottic carcinoma is insufficient. Attempts that have been made to improve the local control rate include hyperfractionation or increasing fraction size in once daily fractionation or chemoradiotherapy. Itoh et al. documented that low-dose cisplatin and 5-fluorouracil chemotherapy along with radiotherapy resulted in an initial local control rate of 91%, and ultimate laryngeal preservation by cordectomy was achieved in all cases. Taguchi et al. reported that chemotherapy with carboplatin and UFT along with radiotherapy led to an initial local control rate of 95% and a 3-year local control rate of 95%. In the present study, the initial local control rate was 94% and the 5-year local control rate was 70%. Although the initial local control

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<td>Hepatic toxicity</td>
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*Common Terminology Criteria for Adverse Events (version 3.0, 2003)
rate was adequate, the 5-year local control rate was low. Several investigators have reported that OTT is the most significant local control factor in early glottic cancer[1011]. In this study, for all the subjects, the median OTT was 65 days, and the analysis of local control rate by comparing the shorter OTT group (<65 days) with the longer OTT group (≥65 days) revealed that the 5-year local control rates were 74% and 70%, respectively. Prolongation of the OTT may result in a poor 5-year local control rate.

Some investigators have described that adjuvant chemotherapy administered after radical treatment for head and neck cancer was effective in reducing the rate of distant metastasis[1011]. Kurita H et al. suggested that adjuvant chemotherapy for resectable oral squamous cell carcinoma had a significant benefit in improving disease-free survival[12]. Fujii M et al. suggested that adjuvant chemotherapy with UFT for maxillary carcinoma was effective with regard to not only the survival rate but also time to disease progression[13]. However, few studies have investigated the efficacy of adjuvant chemotherapy in T2N0 glottic carcinoma. In the present study, 24 patients received adjuvant chemotherapy with UFT. The 5-year local control rate in these 24 patients who had achieved complete response after concurrent chemoradiotherapy was 82%. Six patients who had achieved complete response after concurrent chemoradiotherapy did not receive adjuvant chemotherapy; the 5-year local control rate in these 6 patients was 42%. There was a statistically significant difference in the local control rate between the 2 groups; therefore, adjuvant chemotherapy with UFT can be considered to be efficient in reducing the rate of local recurrence.

Recurrent or residual glottic carcinoma after radiotherapy is commonly treated with total laryngectomy. We experienced a residual tumor in 2 patients and local recurrence in 8 patients. Of these 10 patients, 8 underwent total laryngectomy. Some investigators have reported that the application of transoral laser microsurgery or partial laryngectomy as a salvage treatment after radiotherapy. Steiner W et al. documented that 24 of 34 patients (71%) were cured with one or more transoral laser microsurgeries for recurrent glottic carcinoma[17]. De Gier et al. reported that 50% of patients were cured with a maximum of 2 transoral laser microsurgeries for recurrent glottic carcinoma[18]. Ganly I et al. documented that patients who underwent salvage partial laryngectomy for recurrent early glottic carcinoma exhibited an excellent survival outcome: their 5-year overall survival and disease specific survival 88% and 93%, respectively[19]. Watters GWR et al. reported that the 5-year disease-related survival after partial laryngectomy for recurrent laryngeal carcinoma was 97%[20]. We need to consider transoral laser microsurgery and partial laryngectomy as treatment modalities for residual or recurrent glottic carcinoma after definitive radiotherapy.

In conclusion, in this study, additional adjuvant chemotherapy improved the local control rate of T2N0 glottic squamous cell carcinoma. However, the local control rate of the patients treated without adjuvant chemotherapy was lower than those in the literature, and the number of the patients in this study is too small to conclude the superiority of the combination of concurrent chemoradiotherapy and adjuvant chemotherapy. Further investigation is necessary.

References


(Received for publication November 14, 2008)
目的：T2N0 声門癌に対する化学放射線療法、補助化学療法の効果、有害事象の遡及的検討

対象・方法：1993 年 5 月から 2004 年 3 月に喉頭温存を目的に初回治療として化学放射線療法を施
行された T2N0 声門癌の 32 例, 放射線治療は 1 回 1 回, 1 回 2Gy, 週 5 回施行され, 総線量の中央
値は 70Gy. 化学療法はカルボプラチン単独が 4 例, カルボプラチンと UFT の併用が 7 例, カルボ
プラチンとトラフルールの併用が 2 例, トラフルール単独が 19 例, 化学放射線療法終了後 24 例に
UFT による補助化学療法を施行.

結果：一次治療効果で CR であったのは 30 例 (94%), 5 年粗生存率, 5 年局所制御率はそれぞれ
97%, 70%. 局所制御に関する単変量解析では, 補助化学療法の施行により有意な改善を認め
た (P=0.038). 5 年局所制御率は補助化学療法の有無でそれぞれ, 82%, 42%. 総治療期間, 総線量,
年齢, 病変の声門下への進展の有無では有意差は認めなかった. 有害事象に関しては grade3 の好
中球減少を 1 例, grade3 の肝機能障害を 2 例に認めた, 重篤な晚期有害事象は認めなかった.

結論：T2N0 声門癌に対する補助化学療法は局所制御に関して統計学的に有意な改善が認められ,
また有害事象は軽度であり, 有用性が示唆された.