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Original Article

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 futraful in 2, and futraful 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 carcinoma[1)~4)] 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 fractionation[5)~7)] or chemoradiotherapy[8)9)]. In addition, to reduce the recurrence rate, adjuvant chemotherapy was administered for head and neck carcinomas[10)~13)].

In the present study, to improve the local

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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 was 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 futraful in 2; and futraful 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 futraful alone was administered daily during the period of radiotherapy. In UFT, the oral dose of tegafur was 400 mg/day. The dose of futraful 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 cm^2 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.

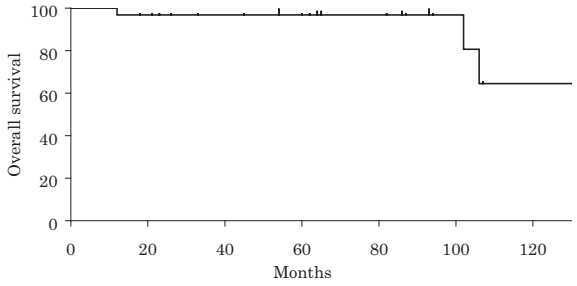

Fig. 1 Overall survival rate of 32 patients

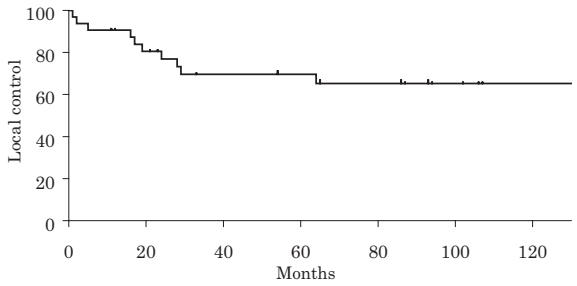

Fig. 2 Local control rate of 32 patients

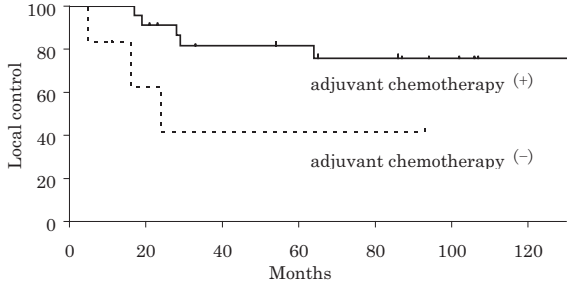

Fig. 3 Local control rates according to with or without adjuvant chemotherapy (solid; adjuvant chemotherapy (+), dotted line; adjuvant chemotherapy (−), P = 0.038)

Table 1 Acute toxicity

Parameter	Grade* 1	2	3	4
Hematological				
Leukocytes	11	2	0	0
Neutrophils	4	4	1	0
Hemoglobin	15	0	0	0
Platelets	12	1	0	0
Laryngitis	20	0	0	0
Hepatic toxicity	8	2	2	0

*Common Terminology Criteria for Adverse Events (version 3.0, 2003)

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[4)~7)] or chemoradiotherapy[8)9)]. 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[8)]. 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%[9)]. 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

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[3)14)~16)]. 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[10)11)]. 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 Iet 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

1) Howell-Burke D, Peters LJ, Goepfert H and Oswald MJ : T2 glottic cancer. Recurrence, salvage, and survival after definitive radiotherapy. Arch Otolaryngol Head Neck Surg. 116 : 830-835, 1990.
2) Inoue T, Ikeda H, Teshima T and Murayama S : Prognostic factor of telecobalt therapy for early glottic carcinoma. Cancer. 70 : 2797-2801, 1992.
3) Le QT, Fu KK, Kroll S, Ryu JK, Quivery JM, Meyler TS Krieg RM and Phillips TL : Influence of fraction size, total dose, and overall time on local control of T1-T2 glottic carcinoma. Int J Radiat Oncol Biol Phys. 39 : 115-126, 1997.

4) Mendenhall WM, Amdur RJ, Morris CG and Hinerman RW : T1-2N0 squamous cell carcinoma of the glottic larynx treated with radiation therapy. J Clin Oncol. 19 : 4029-4036, 2001.
5) Haugen H, Johansson K and Mercke C : Hyperfractionated accelated or conventionally fractionated radiotherapy for early glottic cancer. Int J Radiat Oncol Biol Phys. 52 : 109-119, 2002.
6) Garden AS, Forster K, Wong P, Morrison WH, Schechter NR and Ang KK : Results of radiotherapy for T2N0 glottic carcinoma : dose the "2" stand for twice-daily treatment? Int J Radiat Oncol Biol Phys. 55 : 322-328, 2003.
7) Nomiya T, Nemoto K, Wada H, Takai Y and Yamada S : Advantage of Accelerated Fractionation Regimens in Definitive Radiotherapy for Stage II Glottic Carcinoma. Ann Otol Phinol Laryngol. 115 : 727-732, 2006.
8) Itoh Y and Fuwa : N Concurrent chemoradiotherapy using protracted continuous infusion of low-dose cisplatin and 5-fluorouracil for T2N0 glottic cancer. Radiat Med. 24 : 277-281, 2006.
9) Taguchi T, Tsukuda M, Mikami Y, Horiuchi C, Ishitoya J and Katori H : Concurrent chemoradiotherapy with Carboplatin and uracil-ftegaur in patients with stage two (T2N0M0) squamous cell carcinoma of the glottic larynx. J Laryngol Otol. 120 : 478-481, 2006.
10) Ervin TJ, Clark JR, Weichselbaum RR, Fallon BG, Miller D, Fabian RL, Posner MR, Norris CM Jr, Tuttle SA and Schoenfeld DA : An analysis of induction and adjuvant chemotherapy in the multidisciplinary treatment of squamous cell carcinoma of the head and neck. J Clin Oncol. 5 : 10-20, 1987.
11) Tsukuda M, Ogasawara H, Kanako S, Komiyama S, Horiuchi M, Inuyama Y, Uemura T, Uchida M, Kamata S and Okuda M : A prospective randomized trial of adjuvant chemotherapy with UFT for head and neck carcinoma. Jpn J Cancer Chemother. 21 : 1169-1177, 1994.
12) Kurita H, Koike T, Miyazawa T, Uehara S, Kobayashi H and Kurashina K : Retrospective Analysis on prognostic impact of adjuvant chemotherapy in the patients with advanced and resectable oral squamaous cell carcinoma. Jpn J Cancer Chemother. 33 : 915-921, 2006.
13) Fujii M, Ohno Y, Tokumaru Y, Imanishi Y, Kanke M, Kanzaki J and Inuyama Y : Adjuvant chemotherapy with oral tegaful and uracil for maxillary sinus carcinoma. Oncology. 55 : 109-115, 1998.
14) Sakata K, Aoki Y, Karasawa K, Hasegawa K, Muta N, Nakagawa K, Terahara A, Onogi Y, Sasaki Y and Akanuma A : Radiaion therapy in early glottic carcinoma : uni- and multivariate analysis of prognostic factors affecting local control. Int J Radiat Oncol Biol Phys 30 : 1059-1064, 1994.
15) Fein DA, Lee WR, Hanlon AL, Ridge JA, Curran WJ and Coia LR : Do overall treatment time, field size, and treatment energy influence local control of T1- T2 squamous cell carcinomas of the glottic larynx? Int J Radiat Oncol Biol Phys 34 : 823-831, 1996.
16) Nishimura Y, Nagata Y, Okajima K, Mitsumori M, Hiraoka M, Masunaga S Ono K, Shoji K and Kojima H : Radiation therapy for T1, 2 glottic carcinoma. : impact of overall treatment time on local control. Radiother Oncol 40 : 225-232, 1996.
17) Steiner W, Vogt P, Ambrosch P and Kron M : Transoral carbon dioxide laser microsurgery for recurrent glottic carcinoma after radiotherapy. Head Neck 26 : 477-484, 2004.
18) De Gier HHW, Knegt PPM, de Boer MF, Meeuwis CA, van der Velden L, Kerrebijn JDF. CO2-laser treatment of recurrent glottic carcinoma. Head Neck 8 : 520-523, 2000.
19) Ganly I, Patel SG, Matsuo J, Singh B, Kraus DH, Boyle JO, Wong RJ, Shaha AR, Lee N and Shah JP : Results of surgical salvage after failure of definitive radiation therapy for early-stage squamous cell carcinoma of the glottic larynx. Arch Otolaryngol Head Neck Surg. 132 : 59-66, 2006.
20) Watters GWR, Patel SG, Rhy-Evans PH : Partial laryngectomy for recurrent laryngeal carcinoma. Clin Otolaryngol 25 : 146-152, 2000.

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（和文抄録）

T2N0 声門癌に対する化学放射線療法，補助化学療法の遡及的検討

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小野　稔[2)]，本田　浩[1)]

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 日 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，カルボプラチンとフトラフールの併用が 2 例，フトラフール単独が 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．重篤な晩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．