

Concurrent chemoradiotherapy provides no benefit compared to radiotherapy alone for T2 glottic carcinoma

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Abstract

Objective : To determine if chemoradiotherapy improves local control of T2 glottic squamous cell carcinoma.

Methods : From 1989 to 2003, 61 patients with T2 glottic cancer were treated with radiation alone or radiation in conjunction with various chemotherapy agents.

Results : Overall survival and local control rates for all 61 patients were 83.6% and 82.0%, respectively at five years. The addition of chemotherapy offered no survival benefit or improvement in local control rates compared to radiotherapy alone. Extending treatment duration lowered local control rates, however, no survival-related prognostic factors were identified. No treatment-related late toxicity was observed.

Conclusion : The addition of chemotherapy in patients with T2 glottic cancer treated with radiation does not improve outcomes. This validates the use of radiotherapy alone as the standard of care for patients with this disease.

Introduction

The goal of treatment for early stage glottic cancer is complete eradication of tumor with preservation of vocal cord function¹⁾. The local control rate of patients with T1 glottic cancer (UICC TNM Classification of Malignant Tumours) after radiotherapy alone is approximately 90%; unfortunately, this value drops to the ranges between 50% and 80% for patients with T2 tumors²⁾³⁾. In an effort to improve these relatively low control rates for T2 tumors, Garden et al.⁴⁾ evaluated 230 T2 patients

treated with either radiotherapy totaling 70 Gy in 35 fractions delivered once daily or with 77 Gy in 70 fractions delivered twice daily. Five year local control rates were 67% and 79%, respectively, demonstrating that twice daily fractionation was superior to conventional regimens.

In patients with locally advanced head and neck cancer, concurrent chemoradiotherapy was expected to increase local control rates and offered survival benefits when compared to radiotherapy alone⁵⁾. A meta-analysis has shown that concurrent chemoradiotherapy confers an

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absolute 4% 5-year survival benefit over radiotherapy alone. However, there are few data specifically concerning whether the addition of chemotherapy would be beneficial for patients with T2N0M0 glottic cancer. We performed a retrospective analysis of T2 glottic cancer patients treated with radiotherapy alone vs. concurrent chemoradiotherapy to determine if combination therapy improves local control rates of T2 lesions. The concurrent chemotherapy regimens were fluorouracil (5-FU), cisplatin (CDDP), carboplatin (CBDCA) or docetaxel (TXT).

Patients and Methods

A total of 61 consecutive patients with T2N0M0 glottic cancer treated between from 1989 and 2003 at our institution underwent radical radiotherapy. All 61 patients (60 men ; 1 woman) with a median age of 66 years (range : 42 to 91) had squamous cell carcinoma. A total median dose of 70 Gy (range : 60-70 Gy) in 2 Gy fractions was delivered to the glottis with an adequate margin through left and right parallel opposed ports over a median treatment period of 50 days (range : 40-77 days). Three-dimensional CT-based treatment planning was employed from July 2001 onward.

Various chemotherapy regimens including fluorouracil (5-FU), cisplatin (CDDP), carboplatin (CBDCA) or docetaxel (TXT) were combined with radiotherapy concurrently. Patients who refused chemotherapy or in whom it was contraindicated because of their general medical condition underwent radiotherapy alone. We treated 13 patients with 5-FU at 250 mg/m²/day for 20 days, 11 with CDDP at 7 mg/m²/day for 20 days, 12 with CBDCA at 200 mg/m²/day for 4 days, and 8 were treated with TXT at 10 mg/m²/day for 6 days. The remaining 17 patients underwent radiotherapy alone (Table 1).

Overall survival, cause-specific survival and local control rates were calculated from the beginning of radiotherapy using the Kaplan-Meier method. The treatment time was considered extended if the total treatment period was longer than planned by 7 days or more. Age, total dose, treatment period, radiation field size, the addition of chemotherapy, and the utilization of three-dimensional

CT-based treatment planning were evaluated as factors that may be predictive of overall survival, cause-specific survival, and local control. Differences in these rates were tested with a univariate analysis using a log-rank test and multivariate analysis based on the Cox proportional hazard model. A statistical software (SPSS Inc., Chicago, IL, USA) was used for the analysis. The National Cancer Institute Common Toxicity Criteria version 2.0 was used for evaluating treatment related toxicities.

Results

During a median observation period of 64 months (range : 3 to 214), 12 patients died. Of these patients, 3 died from glottic cancer, 5 from cancer at other sites (cancer of the oropharynx, lung, bronchus, esophagus and pancreas), and the remaining 4 from other causes (myocardial infarction, cardiac failure, rupture of dissecting aneurysm of the aorta, and drowning).

Overall and cause-specific survival rates at 5 years were 82.0 and 95.1%, respectively (Fig 1). Of the potential predictive factors mentioned above, none were significantly correlated with survival. Tumor progression during radiotherapy was noted in two patients. Eight patients developed a local recurrence after a median of 17.5 months (range : 4 to 43 months). One patient suffered from cervical lymph node metastasis. The five-year local control rate was 83.6% (Fig. 2). These patients with recurrent tumors successfully underwent surgery for salvage. None of the above factors were correlated with improved local control, however, extension of treatment period and employment of three-dimensional CT-based treatment planning contributed to a significant decrease in local control rates (Table 2). Notably, concomitant chemotherapy was not shown to significantly affect survival or local control rates (Fig. 3, Fig. 4).

Thirty-seven patients suffered grade 1 acute treatment-related toxicity and 17 patients experienced grade 2 toxicity. All recovered without medical intervention. There was no acute toxicity of grade 3 or higher, nor was there any evidence of late treatment-related toxicity.

Table 1 Treatment's parameters

Parameters	Distribution
Age	42-91 years old (median 66)
Male/Female	60/1
Dose	60-70Gy (median 70Gy)
Treatment time	40-77days (median 50day)
Field size	25-52.5cm ² (median 36 cm ²)
RTP (+)/(-)	11/50
Chemotherapy (+)/(-)	44/17

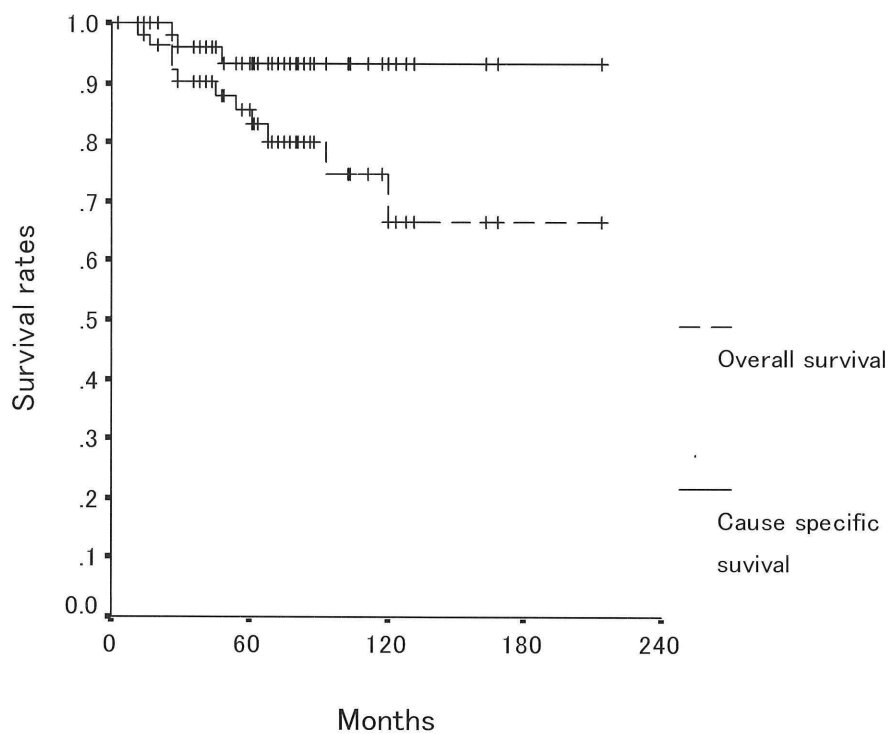


Fig. 1 Survival rates

Five-year overall and cause-specific survival rates of 82.0% and 95.1% were achieved, respectively.

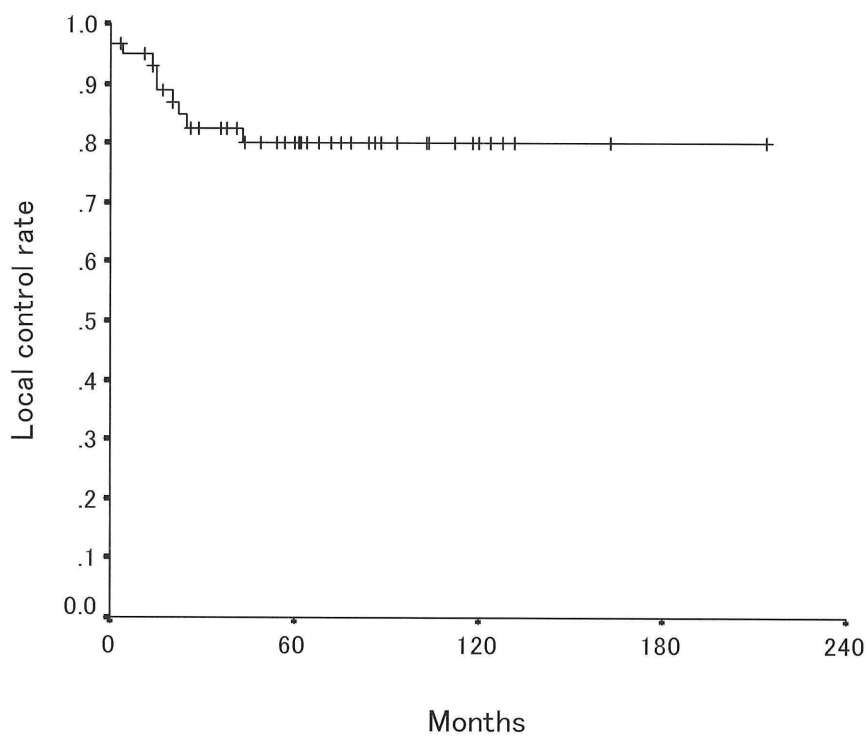


Fig. 2 Local control rate

Five-year local control rates of 83.6% was achieved. Concurrent chemoradiotherapy provided no benefit compared to radiotherapy alone for T2 glottic carcinoma.

Discussion

Our results show that modest success has been achieved

in the treatment of T2 tumors. We achieved relatively high overall survival, cause-specific survival, and local control rates at 5 years of 82.0, 95.1 and 83.6%,

Table 2 Factors which affect local control rates

	Univariate analysis	Multivariate analysis
	<i>p</i> value	<i>p</i> value
Age	0.44	0.96
Total dose	0.37	0.81
Treatment time	0.55	0.95
Field size	0.25	0.79
Chemotherapy	0.19	0.95
RTP	0.14	0.18

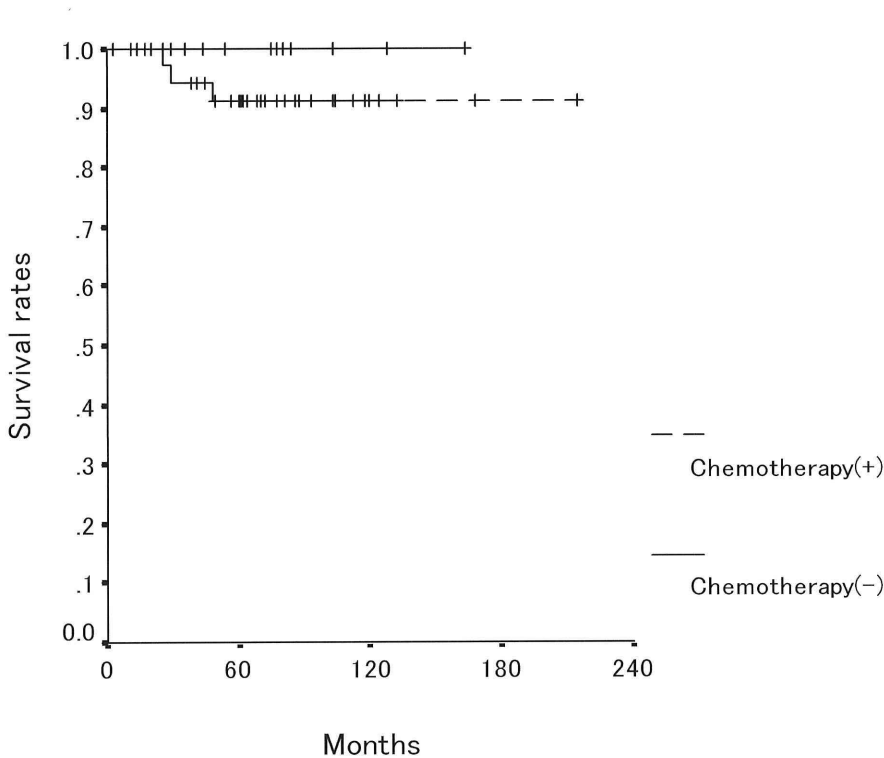


Fig. 3 Cause specific survival rates of radiotherapy with or without chemotherapy.
The addition of chemotherapy offered no improvement in survival rates compared to radiotherapy alone.

respectively. Of the 12 patients who died during the study, deaths from cancers at other sites outnumbered deaths from glottic carcinoma. This suggests that a high incidence of secondary cancer affects overall survival rates, and that the development of a secondary tumor, especially if arising in the head and neck after successful radiotherapy for glottic cancer, remains a challenging problem⁶.

Combination chemotherapy and radiotherapy was expected to further increase local control rates. Taguchi et al. achieved a local control rate of 100% during a median follow-up period of 32 months using a total dose of 66-72 Gy concurrently administered with weekly carboplatin and UFT⁷.

In our study, a total dose of 60-70 Gy in 30-35 frac-

tions was given concurrently with chemotherapeutic agents. For patients who were 75 years or older or for those who refused chemotherapy, radiotherapy was given alone to a total dose of 70 Gy in 35 fractions. Although the patients to whom chemotherapy was contraindicated were in the radiotherapy alone group, we did not identify any benefit associated with the addition of chemotherapy. Therefore, radiotherapy alone remains the standard of care for patients with T2 glottic cancer treated at our institution.

Extension of the treatment period was significantly associated with lower local control rates in this study. Chatani et al. reported the effects of extending the treatment period in 273 T1 glottic cancer patients treated with a dose of 60 Gy in 30 fractions⁸. Five-year local con-

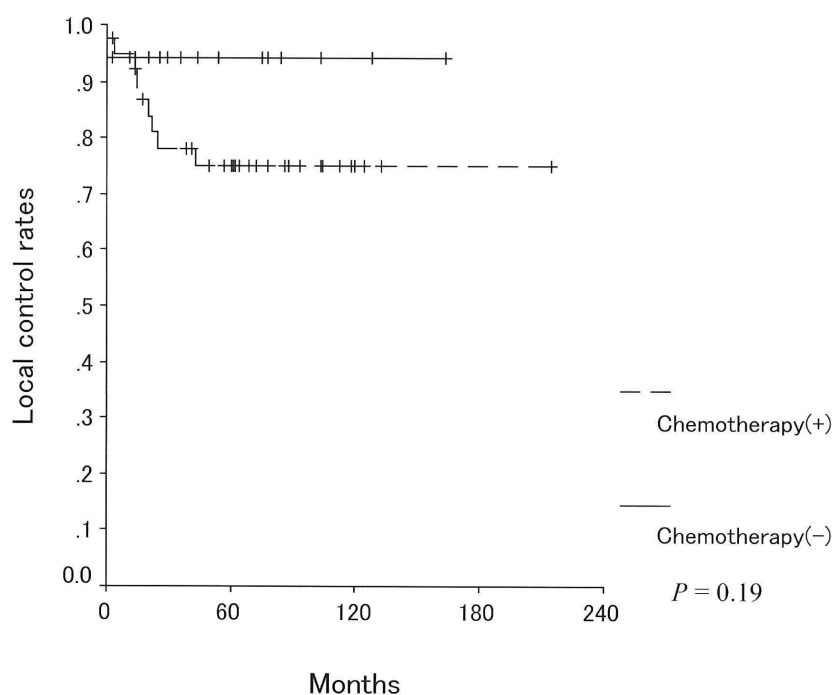


Fig. 4 Local control rates of radiotherapy with or without chemotherapy.

The addition of chemotherapy offered no improvement in local control rates compared to radiotherapy alone.

trol rates were 95% for 77 patients treated over 6 weeks, 89% for 141 patients over 7 weeks, and 80% for 35 patients treated for more than 7 weeks. Fowler et al.⁹⁾ reviewed 12 published clinical results of radical radiotherapy for head and neck cancer, and noted a median reduction in 5-year local control rates of 14% if treatment was extended by one week, and of 26% if treatment duration was 2 weeks greater than initially prescribed.

The use of three-dimensional CT-based treatment planning also significantly correlated with a lower local control rate. Although the technique is theoretically superior based on its ability to reduce dose delivered to normal tissue, 4 of our patients suffered local recurrence in the anterior commissure. Cellai et al. reported that involvement of the anterior commissure worsens local control for T1 glottic cancers, especially if the anterior commissure forms a large horseshoe shape¹⁰⁾. Therefore, it is important to ensure that sufficient dose is delivered to the anterior commissure for T2 glottic cancer, especially when sophisticated radiotherapy techniques, such as intensity modulated radiation therapy, are used.

This study was undertaken to determine if the addition of chemotherapy to radiotherapy improves outcomes for patients with T2 glottic cancers. Surprisingly, we found no benefit associated with concurrent chemoradiotherapy over radiation alone, reinforcing that radiotherapy alone should be the standard of care for patients with T2 glottic cancer.

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T2 声門部癌に対する放射線単独療法と化学放射線量療法との比較検討

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【目的】 T2 声門扁平上皮癌に対する化学放射線療法の有効性を検討する。

【対象】 1989 年から 2003 年までに放射線単独療法あるいは化学放射線療法にて治療された、61 例の T2 声門扁平上皮癌を対象とした。

【結果】 5 年全生存率 83.6%、5 年局所制御率は 82.0% であった。放射線単独療法と比較して、化学療法の併用は生存率と局所制御率の改善に寄与しなかった。治療期間の延長が局所制御率を低下させたが、生存率に関する因子は同定されなかった。治療関連晩期有害事象は認めなかった。

【結語】 T2 声門扁平上皮癌に対する治療においては化学療法の併用は治療成績の改善に寄与せず、放射線単独療法が標準的治療法である。

〈キーワード〉 T2 声門部癌、放射線療法、化学放射線療法
