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Radiation Therapy for T2N0 Glottic Cancer

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Purpose: This study evaluated the results of definitive radiation therapy and the prognostic factors that affect survival rates for T2N0 glottic cancer patients.

Materials and Methods: Thirty patients with T2N0 glottic cancer who were treated with definitive radiation therapy at our institution between September 1986 and June 2004 were retrospectively reviewed. All patients were pathologically confirmed as having squamous cell carcinoma and were staged as AJCC T2N0. The age of the patients ranged from 39 to 79 (median 62) years and all were male. A total dose of 66~70 Gy (median 66 Gy) was delivered with a 6-MV linear accelerator in 6.5~7 weeks. The median follow-up period was 63 months.

Results: The actuarial disease-free survival rate for the entire group of the patients was 79% at 5 years. The five-year disease-free survival rates for patients without and with subglottic extension were 90% and 56%, respectively (p=0.03). However, anterior commissure involvement, supraglottic extension, and impaired cord mobility were not statistically significant prognostic factors. The five-year disease-free survival rates for patients with and without concurrent chemotherapy were 86% and 69%, respectively (p=0.47).

Conclusion: Subglottic extension can be considered a poor prognostic factor for T2N0 glottic cancer.

Key Words: Glottic cancer, Radiation therapy

Introduction

The appropriate treatment for patients with T2N0 glottic cancer remains controversial. T2N0 glottic cancers can be initially treated with either radiation therapy or surgery.[1] Local control and survival rates are comparable with both modalities of treatment.[2] Therefore, the treatment of choice is often made with regard to the patient's preference based on functional outcome and potential side effects.

The control rate after radiation therapy alone has been reported to be in the range of 80% to 95% in patients with T1 glottic cancer and 50% to 85% in patients with T2 lesions.[1,3-5] These results suggest that the local control in patients with T2 laryngeal cancer leaves much room for improvement. Several approaches have been employed in an attempt to improve the control rate of T2 laryngeal cancer, including hyperfractionated radiation therapy,[6] concurrent chemoradiotherapy (CCRT),[7] and induction chemotherapy followed by partial laryngectomy.[8]

In this analysis, we retrospectively evaluated the clinical records of patients with T2N0 glottic cancer who were treated by radiation therapy at our institution, where the use of CCRT for T2N0 glottic cancer was started in 1997 to improve the control rate. The purpose of this study was to evaluate the result of definitive radiation therapy and the prognostic factors to affect survival rates in T2N0 glottic cancer patients.

Materials and Methods

The characteristics of the 30 patients in this study are shown in Table 1. Age of the patients ranged from 39 to 79 (median 62) and all were male. All patients were pathologically confirmed as squamous cell carcinoma and were staged as T2N0 according to the 2002 AJCC criteria. Clinical

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Table 1. Characteristics of the Patients

Characteristics	No. of patients
Tumor location	
Anterior 2/3	21
Entire vocal cord	9
Anterior commissure involvement	
No	17
Yes	13
Subglottic extension	
No	21
Yes	9
Supraglottic extension	
No	12
Yes	18
Cord mobility	
Normal	24
Impaired	6
Concurrent chemotherapy	
No	23
Yes	7
Total	30

diagnostic staging work-up included medical history, physical examination, indirect and direct laryngoscopy, CBC, chest X-rays, and laryngeal CT. The locations of the lesion varied. Unilateral involvement was noted in 25 patients. The most common location was the anterior two-thirds (21/30) and diffuse infiltrations were also noted (9/30).

All of the patients were treated with external beam radiation treatment. Radiation therapy was delivered with a 6-MV linear accelerator. Treatment was given once a day, five times a week. Patients received a dose of 66~70 Gy (median 66 Gy) in 6.5~7 weeks. Daily fractionation was 2 Gy. Patients were treated with the use of opposed lateral portals. The upper margin of the field extended superiorly to the hyoid bone. In patients with supraglottic extension, the margin was enlarged upward. The inferior border included the entire cricoid cartilage and was lowered when subglottic extension was noted. Anteriorly, the field extended to 1 cm beyond the thyroid notch and posteriorly to the leading edge of the vertebral bodies. The field size ranged from 5×5 cm^2 to 6×6 cm^2. The mean irradiated field area was 30 cm^2 (range 25 to 36 cm^2).

Since 1997 CCRT has been added for T2 glottic cancer patients. Of the 30 patients, 7 patients received CCRT. Six patients were treated with cisplatin plus fluorouracil (5-FU). Cisplatin was given as a single i.v. bolus (60 mg/m^2) on Days 1 with hydration, and 5-FU (1,000 mg/m^2/day) was administered as a continuous infusion for 4 days on Days 2 to 5. Another cycle of chemotherapy was repeated after 3 weeks. One patient was treated with capecitabine 825 mg/m^2 b.i.d. plus pyridoxine 100 mg t.i.d. on days 1~14 followed by a 7-day rest period and another cycle of chemotherapy. Patients of CCRT group were treated with the same radiation dose and schedule.

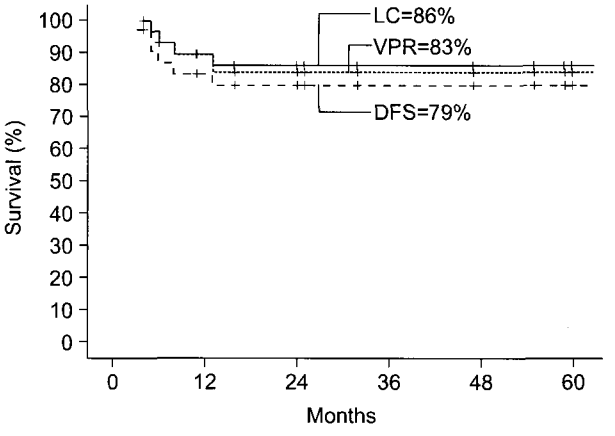

Fig. 1. Disease-free survival (DFS) rate, voice preservation rate (VPR), and local control (LC) rate for entire group of patients.

One month after radiotherapy, clinical evaluation of the response was done. Response was judged as complete (CR) when all clinical evidence of the tumor had disappeared and as persistent (PER) when there was any evidence of tumor masses. Patients were followed regularly, and median follow-up period was 63 months (range 4 to 171 months).

Treatment-related acute and late toxicities were graded according to the RTOG/EORTC toxicity criteria. Various prognostic factors such as tumor location, anterior commissure involvement, subglottic extension, supraglottic extension, cord mobility, and CCRT were evaluated. Survival time was counted from the end of radiation treatment. Kaplan-Meier method was used to calculate survival, and evaluation of the prognostic factors was performed with log rank test. Multivariate analysis was performed using a Cox regression analysis in a forward stepwise manner.

Results

Complete response (CR) was noted in 28 out of 30 patients (93%) and persistent disease (PER) in 2 patients (7%). All 30 patients were seen alive at last follow-up except one patient who died of gastric cancer at 24 months after radiation therapy.

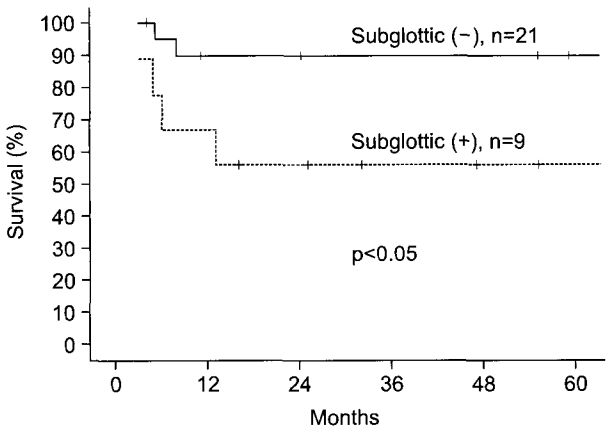

Fig. 2. Disease-free survival rates according to subglottic extension.

Actuarial disease-free survival rate for entire group of the patients was 79% at 5 years (Fig. 1). Five-year disease-free survival rates for patients without and with subglottic extension were 90% and 56%, respectively (Fig. 2, p=0.03). However, anterior commissure involvement, impaired cord mobility, and supraglottic extension were not statistically significant prognostic factors. Five-year disease-free survival rates for patients with and without concurrent chemotherapy were 86% and 69%, respectively (p=0.47). Multivariate analysis, however, showed no significant prognostic factors (Table 2).

Overall 7 failures (23%) were observed after initial radiation therapy. There were 3 local failures (including 2 PER lesions), 2 isolated regional failures, and 2 locoregional failures (Table 3). There was no distant metastasis. Local failures included 2 PER lesions and one failure at 72 months after radiation therapy. There were 2 regional failures at 6 and 60 months, respectively. Two locoregional failures occurred at 8 and 13 months, respectively. The location of the initial nodal failures (2 regional+2 locoregional) was level II and out-field. Three of 4 patients with nodal failures had lesions in supraglottic area. Local failures were treated with total laryngectomy, and regional failures were treated with radical neck dissection. Of the 7 failures, 3 local failures and 2 regional failures were successfully salvaged with surgery. However, 2 locoregional failures were not salvaged with surgery due to remnant disease after radical surgery. The ultimate local control rate at 5 years was 86%, and 25 out of 30 patients (83%) were able to preserve their larynges (Fig. 1).

Three patients who were treated with CCRT suffered grade 3 mucositis during treatment, while remaining 27 patients who were treated with radiation alone suffered grade 1 or 2 mucositis. Three patients suffered grade 2 laryngeal edema after treatment which was controlled by appropriate medication.

Table 2. Five-year Disease-free Survival Rates according to Prognostic Factors

Prognostic variable	5YDFS* (n)	p-value
Tumor location		
Anterior 2/3	85% (21)	
Entire vocal cord	57% (9)	0.498
Anterior commissure involvement		
No	85% (17)	
Yes	63% (13)	0.313
Subglottic extension		
No	90% (21)	
Yes	56% (9)	0.03
Supraglottic extension		
No	83% (12)	
Yes	67% (18)	0.551
Cord mobility		
Normal	83% (24)	
Impaired	70% (6)	0.65
Concurrent chemotherapy		
No	67% (23)	
Yes	86% (7)	0.469

*5-year disease-free survival

Table 3. Types of Relapse and Salvage Surgery

	No. of relapse	TL	RND	TL+RND
Local only	3*	3	-	-
Regional only	2	-	2	-
Locoregional	2	-	-	2†

TL: total laryngectomy, RND: radical neck dissection. *Two persistent lesions were included. †Remnant lesions were noted in surgical specimens.

Discussion

Cumulative 5-year voice preservation, disease-free survival, and ultimate local control rates were 83%, 79%, 86% in our study, respectively, which were comparable with other retrospective results.[4,9,10]

In the present study, anterior commissure involvement was

not related with decreased disease-free survival. Anatomically, the anterior commissure is attached directly to the thyroid cartilage, which lacks a protective perichondrial lining as a potential tumor barrier.[11] This barrier is a relatively weak area concerning tumor dissemination[12] where the Broyles' ligament penetrates into the thyroid cartilage. Anterior commissure could be a theoretical site for cancer breakthrough and lymphatic spread. Some investigators reported anterior commissure involvement to be associated with decreased local control following radiation therapy,[13~15] while others did not.[10,16,17] Poor local control rates in some series for lesions with anterior commissure extension might be secondary to inadequate radiation dose at the anterior commissure due to improper treatment technique. A prominent feature of 6-MV X rays is the longer distance of secondary electrons to attain an electronic equilibrium in comparison with photons of lower energies. Inadequate build-up of electrons may be found beneath the skin of the neck and at the surface of the vocal cord. Akine et al.,[18] however, reported that 6-MV X-rays could be used as an alternative to lower energy photons in the treatment of early glottic cancer. At our institution all lesions were treated with adequate dose distribution and dose build-up at the anterior commissure. Patients were contoured and computer-assisted planning was used with or without wedges to insure adequate dose distribution within the tumor volume.

Vocal cord mobility was not found to influence disease-free survival in this present study. Other authors have demonstrated vocal cord mobility to be significantly related to local control with radiation therapy.[3] Some authors recommended high dose radiation therapy or hyperfractionated radiation therapy to improve local control for glottic cancers with impaired cord mobility.[19,20]

In the present analysis, patients with subglottic extension had a lower disease-free survival compared with those without subglottic extension. Other investigators have also demonstrated subglottic extension to be related to local control with radiation therapy.[3,21] Therefore, more effective treatment modalities such as hyperfractionated radiation therapy or CCRT need to be developed for T2N0 glottic cancer with subglottic extension. Garden et al.[6] reported that hyperfractionated radiation therapy for T2N0 glottic cancer had an improvement in local control compared with conventional radiation therapy by increasing total dose to 77 Gy.

Akimoto et al.[5] reported that CCRT yielded a significantly improved disease-free survival rate as compared with radiation therapy alone in cases of T2N0 glottic cancer. Kumamoto et al.[7] reported that 5-year voice preservation rate was 91% when CCRT was done for T2N0 glottic cancer. We could not find any survival advantage with CCRT in this analysis. The number of patients who were treated with CCRT seemed to be too small (n=7) for a statistical significance. Further clinical studies need to be developed to define a subset of patients who will be benefited by CCRT.

In this study, there were approximately 13% nodal failures (2 regional+2 locoregional), which might be attributed to misdiagnosis of supraglittic cancers with glottic extension as glottic cancers. Three of 4 patients with nodal failures had initial supraglottic lesions, and the location of failures was level II. Though two regional failures were successfully salvaged with surgery, 2 locoregional failures were not salvaged. If a surgery cannot salvage the neck failure for a reason of medical contraindications, nodal irradiation can be considered as an initial treatment. Spector et al.[1] recommended elective neck treatment especially for advanced T2N0 lesions to achieve higher cure rates. Mendenhall et al.,[22] however, reported that elective neck treatment was not indicated for T2N0 glottic cancer. Frata et al.[23] also reported that the complete formal inclusion in the treated volume of the first echelon of the lymphatic drainage was not worthwhile.

Mendenhall et al.[24] reviewed that the rates of disease-free survival, voice preservation, and ultimate local control for T2 glottic cancer were comparable for patients treated with transoral laser excision, open partial laryngectomy, and radiation therapy. A subset of unfavorable T2 lesions may have a better local control rate after open partial laryngectomy, though it results in poorer voice quality compared with either laser excision or radiation therapy.[24]

In conclusion, considering the high percentage of voice preservation with initial radiotherapy, radiotherapy should be the first choice treatment of T2N0 glottic cancer. However, more effective treatment modalities need to be developed for T2N0 glottic cancer with subglottic extension.

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국문초록

T2N0 병기 성문암의 방사선치료

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김 재 철

목 적: T2N0 병기 성문암 환자에서 방사선치료의 결과 및 무병생존율에 영향을 미치는 예후인자를 알아보고자 하였다.

대상 및 방법: 1986년 9월부터 2004년 6월까지 본원에서 방사선치료를 받은 30예의 T2N0 병기 성문암 환자를 후향적으로 분석하였다. 대상 환자 모두 남자였으며 연령 범위는 39세에서 79세였다(중간값 62세). 조직학적 유형은 30예 모두 편평상피세포암이었다. 방사선치료는 6 MV 선형가속기를 이용하였고, 후두에 조사된 총방사선량은 66~70 Gy의 범위였다(중간값 66 Gy). 추적기간의 중간값은 63개월이었다.

결 과: 대상 환자 전체의 5년 무병생존율은 79%였다. 성문하 침범이 있는 환자에서는 5년 무병생존율이 감소하는 양상을 보였다($p<0.05$). 전연합 침범, 성문상 침범, 성문 운동성 감소 등은 5년 무병생존율의 감소와 무관하였다. 동시 화학요법 추가 또한 통계적 의의가 없었다. 원발병소 재발 3예 및 경부림프절 재발 2예는 근치적 수술로 구제되었으나, 원발병소 및 림프절 동시재발 2예는 근치적 수술로 구제되지 못하였다. 최종 국소제어율은 86%였고, 성대 보존율은 83%였다.

결 론: T2N0 성문암에서 근치적 방사선치료 시 성문하 침범이 무병생존율에 영향을 줄 수 있는 인자로 분석되었다.

핵심용어: 성문암, 방사선치료