Results of Radiation Therapy in Early Glottic Cancer

Sung Ja Ahn, M.D., Woong Ki Chung, M.D.
Taek Keun Nam, M.D. and Byung Sik Nah, M.D.

Department of Therapeutic Radiology, Chonnam University Medical School, Kwang-ju, Korea

A retrospective analysis was undertaken for 22 patients with early glottic cancer ($T_1N_0M_0$; 17, $T_2N_0M_0$; 5) who completed curative radiotherapy at the Department of Therapeutic Radiology, Chonnam University Hospital between November 1985 and December 1990. Median follow-up period was 39 months. The 3 year actuarial survival rate of T1, T2 was 81% and 80%, respectively. Three patients (13%) showed second malignant tumors and the site of the new primary was esophagus in two patients and lung in the other one. They were excluded from the local control analysis. The local control rate of T1, T2 group was 66% and 50%, respectively. The surgical salvage rate and the ultimate local control rate of T1 group was 80% (4/5) and 93%, and that of T2 group was 100% (2/2) and 75%, respectively. The local control rates of T1 stage were evaluated according to the various parameters. The local control rate of the superficial and exophytic lesion was better than that of the ulcerative and infiltrative one, and the involvement of anterior commissure was not seemed to be adverse prognostic factor. But the protracted treatment time showed the adverse effect on the local control of the disease.

All of the eleven patients controlled by primary radiation therapy have maintained their voice well without any significant complication.

Key Words: Early glottic cancer, Radiotherapy, Local control

INTRODUCTION

Radiation oncologists have convinced that the early glottic cancer is curable disease by radiotherapy alone. The reported local control rate of T1 and T2 stage was in the range of 85% and 93%[1~3].

The survival was strongly affected by the local control of the disease. The radiation therapy not only provide the disease control but also improve the life quality by voice preservation. So the local control of the disease by the radiation therapy is said to be very important in this aspects more than any other diseases.

We retrospectively analysed the clinical course and treatment data of the early glottic cancer patients with curative radiotherapy and tried to find out the clues that can be determinant to the final outcomes.

MATERIALS AND METHODS

Between November 1985 and December 1990 thirty eight patients with histopathologically verified invasive squamous cell carcinoma of the glottis were consulted for radiotherapy to the Department of Therapeutic Radiology, Chonnam University Hospital. Of them, T1 and T2 glottic cancer, 22 patients constituted the basis of this report.

The patients characteristics are represented in Table 1. Tumors were staged according to the recommendation of the American Joint Committee on Cancer[4]. Tumor characteristics were classified according to the findings of the laryngoscopic examination (Table 2). Routine laboratory test was

Table 1. Patient Characteristics (N=22)

Characteristics	
Sex	
Male	22 (100%)
Female	0 (0%)
Median Age	62 years
Median duration of hoarseness	3 months
Smoking history	
Yes	13 (59.1%)
No	3 (13.6%)
no information	6 (27.3%)
Stage	
T1a	16 (72.7%)
T1b	1 (4.6%)
T2	5 (22.7%)

Table 2. Tumor Characteristics by Laryngoscopic Findings (N=22)

Tumor Characteristics	No. of Pts (%)
Site	
ant. cord only	3 (13.6)
ant. cord+ant. commissure	7 (31.8)
post. cord only	8 (36.4)
whole length	4 (18.2)
Growth pattern	
superficial, exophytic	13 (59.1)
deeply ulcerative, infiltrative	8 (36.4)
no information	1 (4.5)

performed before, during and after radiotherapy.

The radiotherapy was delivered with 6 MV X-ray with curative intent. The dose was specified to the mid-plane along the central axis from parallel opposed lateral fields with or without wedge filter. The daily dose was 180 cGy or 200 cGy for conventional fractionation. The total radiation dose was prescribed from the minimum 5040 cGy to the maximum 7020 cGy (median; 6480 cGy). The treatment field was decided by simulation, encompassing the entire thyroid and cricoid cartilage. In the cases of T2 stage, we used the more generous treatment volumes. The total treatment time was ranged from 50 days to 97 days with it's median value of 60. Follow-up time was measured from the beginning of radiotherapy. The follow-up was performed by regular physical examination or mail and 3 patients were lost to follow-up. Median follow-up was 39 months.

The survival rate and local control rate was calculated by Kaplan-Meier method.

RESULTS

The 3 year actuarial survival rate was 81% in T1 stage (N=17) and 80% in T2 stage (N=5), respectively. Second malignant tumors were observed in 3 patients. Two patients had the esophageal cancer and the other one had the lung cancer (Table 3).

The local control rate by radiotherapy was 66% in T1 stage and 50% in T2 stage, respectively. Of the eight failure patients (T1 : 5, T2 : 3) operation was performed in seven patients (Table 4). The salvage rate of T1 and T2 group was 80% (4/5) and 100% (2/2), respectively. The ultimate local control rate was 93% in T1 stage and 75% in T2 stage. The voice quality was good in all of eleven cured patients by radiotherapy alone and there was no significant complication also.

Table 3. Details of Second Malignant Tumors

Stage	Site	Diagnosis Time	Survival
T1a	lung	17 M	21M (D)
T1b	esophagus	synchronous	3M (D)
T2	esophagus	6 M	8M (D)

D: dead due to uncontrolled new primary disease.

Table 4. Salvage Management in the Radiation Failure Group

Stage	Failure Time	Treatment	Survival
T1	4M	Total Laryngectomy	46M (A)
T1	4M	Total Laryngectomy	48M (A)
T1	7M	Total Laryngectomy	25M (D)*
T1	16M	Total Laryngectomy	21M (A)
T1	5M	Hemilaryngectomy	35M (A)
T2	2M	Total Laryngectomy	21M (A)
T2	37M	Hemilaryngectomy	61M (A)

*dead due to the uncontrolled disease.
M: month, A: alive

Table 5. Comparison of Treatment Parameters in T1 Glottic Cancer

Local Control	Yes		No		t-test
Parameter	Mean	Median	Mean	Median	
Fraction size (cGy)	180	180	184	180	–
Total dose (cGy)	6572	6480	6264	6480	–
NSD	1701	1725	1750	1782	NS
TDF	93.9	95	97.6	100	NS
Field Size (cm^2)	40.5	42	42.4	42	NS
Tx. Time (day)	60.8	58	70.2	66	NS

NS: Statistically not significant.

The local control rates of T1 stage were analyzed according to the various parameters. The hemoglobin level at the time of diagnosis was compared. The local control rate of high hemoglobin concentration group (above 14 g%) was 70% (7/10) and that of low concentration (below 14 g%) was 60% (3/5). Posteriorly located tumor and ulcerative type tumor was the worst result group (Fig. 1). The local control rate according to the dose and treatment time was showen in Figure 2 and Figure 3, respectively.

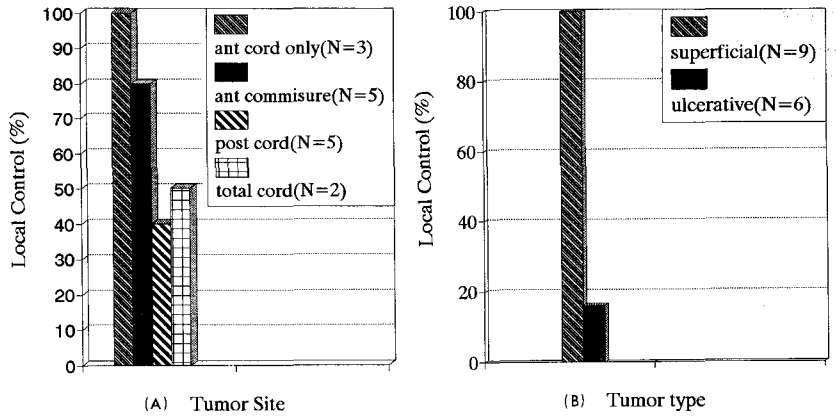

Fig. 1. Local control rate according to the tumor site (A) and involvement pattern (B) in $T_1N_0M_0$ glottic cancer patients.

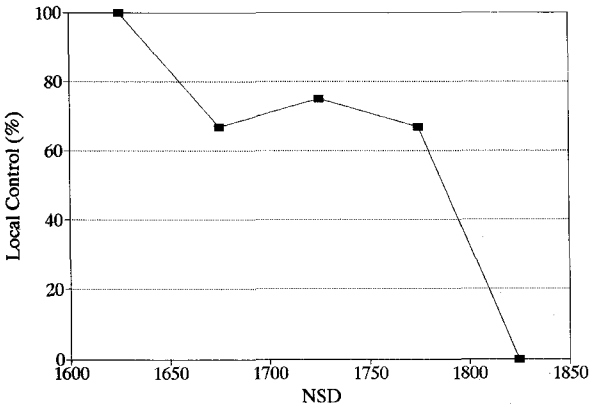

Fig. 2. Local control rate by radiation dose in $T_1N_0M_0$ glottic cancer patients.

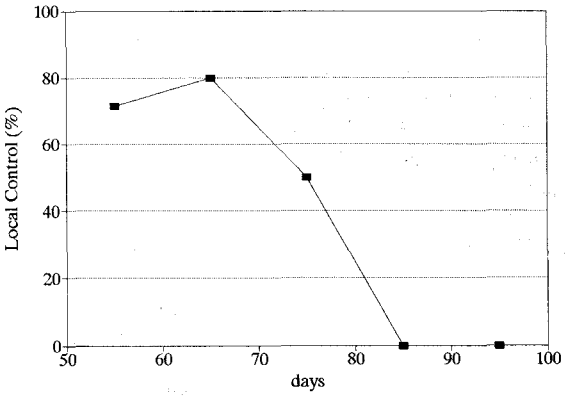

Fig. 3. Local control rate by treatment time in $T_2N_0M_0$ glottic cancer patients.

Table 5 showed the mean and median values of fraction size, radiation dose, field size, and treatment time between the controlled and the failure group.

DISCUSSION

The glottic cancer has the favorable clinical aspects because the regional node or distant metastases is rare. The local control of the primary disease is the ultimate goal of therapy. One of the local treatment modalities, the radiation therapy confers another advantage of voice preservation in addition to the disease control. Voice preservation rate after radical radiotherapy was reported to be 83~91%[2,5].

Teshima et al[2] retrospectively analyzed the various factors to investigate the prognostic factors of local control in the early glottic cancer (T1N0M0). Among the host factors, no straight prognostic factor was observed. Patients in this study who were controlled had mean hemoglobin level of 14.8 g% and those that failed 13.8 g% (range; 12.5 g%~17.3 g%). As for tumor factors such as lesion site, width of tumor, length of tumor and involvement pattern all were significant prognostic factors for the local control. The ulcerative type had the worse prognosis, exophytic had a moderate prognosis, and superficial had the best prognosis[2]. Our study showed the similar result. The local control rate of superficial, exophytic type was 100% (9/9) in the while that of ulcerative, infiltrative type was 17% (1/6). The influence of hypoxia seems less important in laryngeal than in

pharyngeal tumors[6]. Opinions differ concerning the significance of the involvement of the anterior commissure by tumors on local control[3,7,10]. In our study anterior commissure involvement did not seem to impact on local control. However, patients with posterior or whole cord involvement had higher local failure rates when compared to patients with anterior cord involvement. It appeared that reduced local control rate is not a results of increased biologic aggressiveness but rather a faulty radiotherapeutic technique that underdoses the posterior cords[3]. Fletcher et al[6] indicated that the major cause of radioresistance of laryngeal cancer were the inappropriate evaluation of tumor extension of deep invasion and the problem of radiation technique such as insufficient dose or field. Poor prognosis of whole length lesion of one vocal cord might need some technical improvement in dose distribution, immobilization or wider field size[2]. Harwood et al[8] reported that field size was an important prognostic factor for early glottic cancer and that local recurrence could be reduced from 18% (5×5 cm^2) to 9% (6×6 cm^2) with ^{60}Co therapy. In this study, the field size was more generous than the conventional field with its median value of 6×7 cm^2. But it seems that the more important thing is daily accurate patients set-up and immobilization technique.

A clear relationship has been noted between fraction size and rate of local control[1,3,11,12,14]. A trend toward improved local control treated with higher daily fraction size was noted. But in the aspect of the complication the unusual regimen of relative hypofractionation may produce more long-term effects and complications than conventional fractionation[11]. The fractionation regimen is also considered relating to the treatment time factor. The prospective investigation has indeed underlined the importance of treatment time, and strongly indicates that a radiation treatment once commenced should be completed as soon as possible without any unnecessary delay. Fowler et al[13] reviewed the twelve published clinical results of radical radiotherapy to determine the magnitude of time factor relating local control to overall time. The median rate of loss of local control rate was 14% in only 1 week of treatment delay (range: 3 ~25%) and approximately to a median loss of 26% in 2 weeks (5~42%). They concluded that moderate prolongation is associated with a lower chance of local control. In this analysis median treatment time was 60 days and ranged from 50 to 97 days. This prolonged treatment time may be explained as the one of the causative factors for the lowered local control results than the others.

Overgaard et al[6] provided a clinical radiobiological analysis of parameters related to regeneration in tumors and focused on the importance of overall treatment time. The results indicate a significant repopulation corresponding to more than 0.5 Gy/day, equivalent to an up to 100-fold increase of the number of clonogenic tumor cells during the pause. This increase in clonogenic cells occurs despite a clinical decrease in tumor volume and the clinical prediction therefore does not necessarily reflect the number of clonogenic tumor cells. The radiation induced morbidity during and immediately after treatment may be lower on a split course regimen than in a continuous daily schedule. However, in a rapidly proliferating tumor, like a squamous cell carcinoma of the larynx, a very high price in terms of total doses must be paid to obtain a similar tumor control probability as the one achieved with a continuous regimen[6]. During a continuous course of treatment, the pain associated with mucositis usually appears at 2 weeks and is maximal during the third week of treatment. However, if one continues the treatment without a break, there is usually a decline in the pain, even though the mucositis may appear worse.

It has been suggested that inherent differences in radiosensitivity are responsible for recurrence in the small proportion of patients with early glottic cancer in whom primary radiotherapy fails[15]. It is evident that biologic aspects of tumor cell heterogenicity cannot be discussed from routine pathologic examination. Walter et al[16] employed flow cytometry to predict radioresistance in early glottic squamous cell carcinoma by DNA content and concluded that aneuploidy was associated with radioresistance. On the basis of their results, they suggested that patients with aneuploid T1 glottic lesions should be referred for primary surgical therapy.

The criteria of local control varied somewhat by institution, but generally included no evidence of local disease at least for 2 years after local therapy because almost all recurrence occurred within 2 years after radiation therapy[2]. In this study, 7 out of 8 local recurrence were observed within 2 years. The early detection of recurrence can be salvaged mainly by operation. The surgical salvage rate is 83 ~99% and the ultimate local control rate is 97%[2,9,11]. In this analysis six patients out of seven who had undergone hemi or total laryngectomy were salvaged.

Voice quality was good in all 11 patients controlled with primary radiotherapy without any significant complications in our study. The most miserable complication may be the treatment failure and loss of larynx by salvage operation. We must caution the daily patient set-up and immobilization and remember to complete the treatment schedule as soon as possible with moderate fraction size to improve local control rate.

REFERENCES

1. **Mendenhall WM, Parsons JT, Million RR:** T1~T2 squamous cell carcinoma of the glottic larynx treated with radiation therapy: Relationship of dose-fractionation factors to local control and complications. Int J Radiat Oncol Biol Phys 15: 1267-1273, 1988
2. **Teshima T, Chatani M, Inoue T:** Radiation therapy for early glottic cancer (T1N0M0): I. Results of conventional open field technique. Int J Radiat Oncol Biol Phys 17:1199-1202, 1989
3. **Schwaibold F, Scariato A, Nunno M, et al:** The effect of fraction size on control of early glottic cancer. Int J Radiat Oncol Biol Phys 14:451-454, 1988
4. **American Joint Committee on Cancer:** Manual for staging of cancer 3rd edition, Philadelphia: JB Lippincott, 1988, pp 39-44
5. **Marks JE:** Session, DG Cancer of the larynx. In: Perez CA, Brady LW. eds. Principles and practice of radiation oncology. Philadelphia: Lippincott; 1987:598-618
6. **Overgaard M, Hjelm-Hansn L. Vendelbo JL, Andersen AP:** Comparison of conventional and split-course radiotherapy as primary treatment in carcinoma of the larynx. Acta Oncologica 27:147-161, 1988
7. **Fletcher GH, Lindberg RD, Hamberger A, et al:** Reasons for failure in squamous cell carcinoma of the larynx. Laryngoscope 85:987-1003, 1975
8. **Harwood AR, Hawkins NV, Rider WD, et al:** Radiotherapy of early glottic cancer. Int J Radiat Oncol Biol Phys 5:473-476, 1979
9. **Hendrickson FR:** Radiation therapy of larynx. Cancer 55:2058-2061, 1985
10. **Akine Y, Tokita N, Ogino T, et al:** Radiotherapy of T1 glottic cancer with 6 MeV x-rays. Int J Radiat Oncol Biol Phys 20:1215-1218, 1991
11. **Randall ME, Springer DJ, Raben M:** T1~T2 carcinoma of the glottis: Relative hypofractionation. Radiology 179:569-571, 1991
12. **Million RR, Cassisi NJ:** Time-dose-volume relationships in radiation therapy. In MillionRR, Cassisi NJ, eds. Management of head and neck cancer: a multidisciplinary approach. Philadelphia: Lippincott; 1984:145-147, 1983
13. **Fowler JF, Lindstrom MJ:** Loss of local control with prolongation in radiotherapy. Int J Radiat Oncol Biol Phys 23:457-467, 1992
14. **Maciejewski B, Preuss-Bayer G, Trott KR:** The influence of the number of fractions and overall treatment time on local control and late complication rate in squamous cell carcinoma of the larynx. Int J Radiat Oncol Biol Phys 9:321-328, 1983
15. **Fernberg J-O, Ringborg U, Silfversward C, et al:** Radiation therapy in early glottic cancer. Acta Otolaryngol (Stockh) 108:478-481, 1989
16. **Walter MA, Peters GE, Peiper SC:** Predicting radioresistance in early glottic squamous cell carcinoma by DNA content. Ann Otol Rhinol Laryngol 100:523-526, 1991

= 국문초록 =

초기성문암의 방사선 치료 성적

전남대학교 의과대학 치료방사선과학교실

안성자 · 정웅기 · 남택근 · 나병식

1985년 11월부터 1990년 12월까지 전남대학교병원 치료방사선과에서 근치목적의 방사선치료를 시행한 22명의 초기성문암환자($T_1N_0M_0$; 17명, $T_2N_0M_0$; 5명)를 대상으로 후향적분석을 시행하였으며 추적조사기간의 중간값은 39개월이었다.

T1, T2 병기환자의 3년 생존율은 각각 81%, 80%였다. 이차성 악성종양의 동반율은 13% (3/22)로 2명은 식도에서, 나머지 한명은 폐에서 발병하였으며 이들은 국소종양치유율의 분석에서 제외되었다. 방사선치료후 T1과 T2 병기의 국소종양치유율은 각각 66%와 50%였다. 방사선치료에 실패한 환자의 수술적구제율은 T1에서 80% (4/5), T2에서 100% (2/2)였으며 이에 따른 총 종양치유율은 각각 93%, 75%였다.

T1 병기군을 대상으로 방사선치료성적에 영향을 줄 수 있는 여러 요인을 분석하여 보았다. 표재성 및 외장성 병변은 괴양성 및 침윤성 병변보다 방사선에 의한 종양치유율이 높았으나 성대의 앞교차 연결부위의 침범으로 인한 치료성적의 저하는 보이지 않았다. 그러나 치료기간의 연장은 종양치유율을 저하시킬 수 있는 요인으로 보였다.

방사선치료로 종양이 치유된 11명 환자 모두 심각한 후유증을 호소하지 않았으며 정상적인 목소리를 유지하였다.