

Radiation Therapy of Early Glottic Cancer

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Retrospective analyses were done of 48 patients with early glottic cancer, 31 with T1NOMO and 17 with T2NOMO, who received radiation therapy from March 1979 to August 1984 at Seoul National University Hospital with the prescribed full dosage. The median follow-up period was 67 months (range: 34 months~126 months), and the percent follow-up for longer than five years was 85.4%.

The five-year actuarial overall and recurrence-free survival rates of the whole patient group were 83.2% and 69.4%, respectively. The five-year actuarial overall and recurrence-free survival rates of the T1 group were 87.1% and 76.0%, and those of the T2 group were 76.5% and 58.2%, respectively.

Possible causes of the failures to radiation therapy, the dose-response relationship, association with the second malignant tumors, and some recommendations for better treatment outcome are analyzed and discussed.

Key Words: Radiation therapy, Early glottic cancer, Five-year survival rate

INTRODUCTION

Glottic cancer is a disease which is usually diagnosed early in its course, due to the development of a striking subjective symptom, hoarseness. Also, the lymphatic network beneath the glottic mucosae are very scanty, which explains the rare occurrences of lymph node metastases. As a treatment modality, radiation therapy has played a major role with satisfiably high control rates compared to those of surgery, which employs the removal of the vocal cord(s), thus sacrificing the natural voice. Radiation therapy also has been accepted as the treatment of choice for early glottic cancer, while surgery is reserved as a last resort in case of radiation failure or recurrence in the primary site.

Lederman remarked¹⁾, "The larynx has long been the testing ground for the radiotherapist." These retrospective analyses of early glottic cancer patients who received radiation therapy are intended to confirm the effectiveness of this modality to control local tumors, identify the possible causes of the radiation failures, and provide some guidelines for a better treatment outcome, with a minimum follow-up period of five years. This study updates the three-year survival rate reported in our previous study²⁾.

MATERIALS AND METHODS

Between March 1979 and August 1984, 48 patients with early glottic cancer, T1NOMO and T2NOMO, were treated with full doses of radiation prescribed at the Department of Therapeutic Radiology of Seoul National University Hospital. All patients were examined initially by laryngologists and radiotherapists, and the stages were determined according to the staging system of the American Joint Committee on Cancer³⁾ (Table 1) after the confirmation of the cell types.

Table 1. T—stages in Glottic Cancer

T1	Tumor limited to vocal cord (s) with normal mobility
T1a	Tumor limited to one vocal cord
T1b	Tumor involves both vocal cords
T2	Tumor extends to supraglottis and/or subglottis, and/or with impaired mobility
T3	Tumor limited to the larynx with vocal cord fixation
T4	Tumor invades through thyroid cartilage and/or extends to other tissues beyond the larynx (e.g., oropharynx, soft tissue of neck)

All were irradiated using a Co⁶⁰ teletherapy unit after routine simulation with the patients lying supine. The median dose to the larynx and 6,900 cGy (range: 5,975 cGy~7,600 cGy) with fractions of 175 cGy or 200 cGy per day, and five fractions per week. The whole larynx was included in the radiation portals, where the thyroid notch superiorly and the bottom of the cricoid cartilage inferiorly were adequately included. The sizes of the radiation portals varied usually from 5 cm×5 cm to 6 cm×7 cm, but no one received elective irradiation to the neck-node bearing areas because the incidence of positive lymph nodes was lower than 5% in the T1 and T2 lesions. Some were irradiated by parallel opposing portals with or without wedge filters, while the remainder were done by angled wedge pairs; the two fields were irradiated on each treatment. The arrangement of the radiation beams was determined on an individual base to achieve the most desirable dose distribution throughout the target organ, considering the contour and thickness of the patient's neck, and the location, size, and extension of the tumor within the larynx.

The first date of the radiation therapy was used as the base of follow-up, and all but seven cases were possible to follow up for longer than five years or until their deaths. Only two cases were lost to follow-up before three years of treatment, and five cases were lost to follow-up between three to five years. The percent of follow-up for longer than five years was 85.4%. The median follow-up period for the survivors was 67 months (range: 34 months~126 months). Overall and recurrence-free survival rates were obtained by actuarial life-table method, and the comparisons of the survival rates were done by log-rank test. The relationship between the radiation dose and the local tumor control was analyzed, comparing the average nominal standard doses (NSD's) of the controlled and the failed groups by Student's t-test.

RESULTS

1. Patients' Characteristics

As shown in Table 2, age range of the patients was 34 to 77 years, the median age was 58 years, and there was only one female patient in our study. Thirty-one patients had T1 lesions, of whom 20 were subclassified as having T1a, and 11 as having T1b; 17 had T2 lesions (Table 2). All were histologically proved to have squamous cell carcinomas. The histologic gradings were verified in 28 patients, of whom 19 were graded as well-differentiated, eight

Table 2. Patients' Characteristics

Charateristics	No. of pts.	(%)
Age		
Range :	35 - 77	Yr.
Median :	58	Yr.
Sex		
Male	47	97.9
Female	1	2.1
T-stage		
T1	31	64.6
T1a	20	
T1b	11	
T2	17	35.4
Histology		
Squamous cell	48	100.0
W/D	19	
M/D	8	
P/D	1	
Unspecified	20	

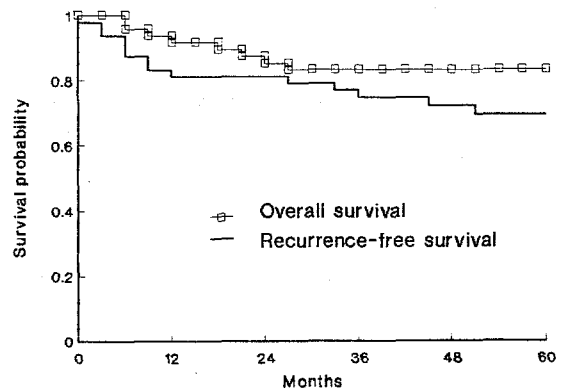


Fig. 1. Overall and recurrence-free survival of all patients.

were graded as moderately-differentiated, and only one as poorly-differentiated squamous cell carcinoma. However, no information on the histologic grading was available in 20 patients (Table 2).

2. Survival, Complication, and Second Malignant Tumors

The five-year actuarial overall and disease-free survival rates of all the patients were 83.2% and 69.4%, respectively (Fig. 1). The five-year actuarial overall survival rates for T1 and T2 lesions were 87.1% and 76.5% (Fig. 2), and the five-year actuarial

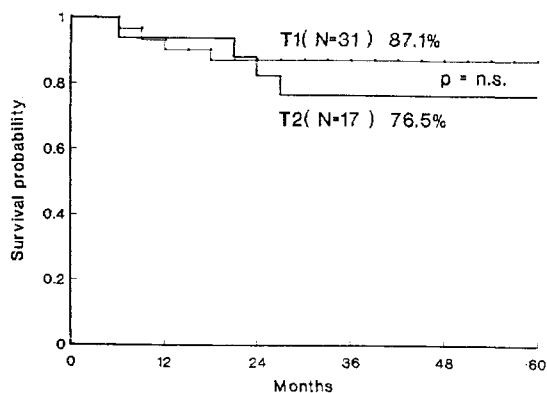


Fig. 2. Overall survival of T1 and T2 groups.

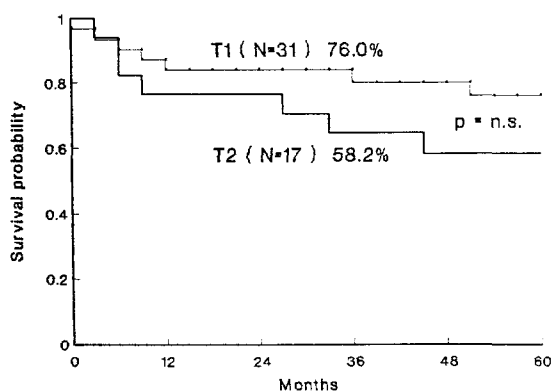


Fig. 3. Recurrence-free survival of T1 and T2 groups.

recurrence-free survival rates for T1 and T2 lesions were 76.0% and 58.2% (Fig. 3), respectively, but there were no statistically significant differences between the two groups.

Two patients with T1 disease received total laryngectomies due to severe and intractable airway obstructions (thought to be major complications of the radiation) at four months and 11 months from the base of follow-up, respectively. But there was no evidence of tumors in their operative specimens. The first of these patients is alive and well 61 months after the operation, and the second one died of an intercurrent disease (advanced stomach cancer) at 10 months after the operation.

Four patients with second malignant tumors were observed during this study, and the anatomic sites and time of diagnoses are shown in Table 3. One patient with esophageal cancer and another with stomach cancer died of their second malignancies at two and seven months, respectively, after diagnoses of the new primaries without any evidence of recurrence in the vocal cords. Thus they

Table 3. Second Malignant Tumors

Age/Sex	Site	Histology	Time to Dx
68/M	Stomach	adenoca	14 mo
69/M	Esophagus	squamous	31 mo
57/M	Tongue base	squamous	66 mo
60/M	Hypopharynx	squamous	79 mo

were regarded as intercurrent deaths.

3. Patterns of Failure and Salvage Treatments

One patients with T1 lesion who developed multiple distant metastases in the lung and the bones died two months later of multiple remote failures. Thirteen patients failed in the primary site. The median time to local failures was 11 months (range: three months~54 months). About two-thirds (9/14: 64.3%) of these primary failures occurred within two years of radiation therapy, and five failures (35.7%) occurred after two years (Table 4).

Seven patients with primary failures were operated on as a final resort, and among them three were thought to have survived due to salvage surgery, with a resulting crude surgical salvage rate of 42.9%. But the remaining four developed regional failures following the operations, three in the neck nodes and one in the stoma, all of whom died after six, eight, 16 and 19 months from their first failures, regardless of the addition of further treatment attempts. One patient with primary failure was reirradiated at another hospital, and another patient was given chemotherapy consisting of 5-fluorouracil and cisplatinum for five cycles at another hospital, both of whom were lost to our follow-up at eight months and 31 months from the second treatments, respectively. Though the final outcomes of these two patients are not known exactly, we regarded these two as lost-to-follow-up's without evidence of disease (Table 4). Four patients with primary failures refused any further salvage treatment recommended, and all four died after one, three, eight, and 15 months from diagnoses of the relapses.

4. Radiation Dose and Local Control

The crude rates of local tumor control at various levels of total tumor doses (cGy) and NSD's (ret) are shown in Table 5 and Table 6. The comparisons of the average NSD's of the controlled and the failed groups were done by Student's t-test (Table 7). As shown in Tables 5,6 and 7 there seems to be

Table 4. Local Failures and Salvage Treatments

Case#	T-stage	Dose (cGy/ret)	Time at failure	Salvage treatment	Outcome after failure
1	T1	6,400/1,824	3 mo	---	DWD in 8 mo
2	T1	7,000/1,848	5 mo	---	DWD in 3 mo
3	T1	6,000/1,758	7 mo	HL	DWD in 6 mo
4	T1	6,600/1,859	11 mo	HL	NED at 47 mo
5	T1	6,550/1,787	12 mo	TL	DWD in 8 mo
6	T1	6,000/1,749	39 mo	Re-RT	NED at 12 mo
7	T1	7,000/1,931	54 mo	TL	NED at 11 mo
8	T2	6,825/1,796	7 mo	TL	DWD in 16 mo
9	T2	7,000/1,851	8 mo	TL	NED at 57 mo
10	T2	6,975/1,907	10 mo	---	DWD in 15 mo
11	T2	7,025/1,929	28 mo	---	DWD in 1 mo
12	T2	6,800/1,854	34 mo	Chemo	NED at 31 mo
13	T2	7,000/1,935	46 mo	HL	DWD in 19 mo

HL ; Hemilaryngectomy, TL ; Total laryngectomy, DWD ; Dead with disease, and NED ; No evidence of disease

Table 5. Dose (cGy) vs Local Control

Dose (cGy)	Number controlled/ Number treated (%)		
	T1	T2	Total
-6,499	6/ 8(75)	1/ 1(100)	7/ 9(78)
6,500-6,999	7/10(70)	4/ 7(57)	11/17(65)
7,000-	11/13(85)	6/ 9(67)	17/22(77)
Total	24/31(77)	11/17(65)	35/48(73)

One patient with distant metastasis only was considered to be controlled locally.

only a minute tendency of linear dose-response function for the T1 group, but there is no such trend for the T2 group at all, and as a whole, no significant difference exists between the local tumor control and the radiation dose in these analyses.

DISCUSSION

Glottic cancer is known as the first deep-seated malignant tumor that fractionated external beam irradiation has been able to cure⁴⁾. Traditionally, early glottic cancers, T1 and T2, have been treated primarily by radiation therapy with surgery reserved for salvage of radiation therapy failure or recurrence of the cancer after radiation therapy. But recently, patients with carcinoma in situ and/or well-localized superficial T1 lesions that do not involve the anterior commissure are thought to be

Table 6. Nominal Standard Dose (NSD) vs Local Control

Dose (ret)	Number controlled/ Number treated (%)		
	T1	T2	Total
-1,799	5/ 9(56)	1/ 2(50)	6/11(55)
1,800-1,849	7/ 8(88)	1/ 1(100)	8/ 9(89)
1,850-1,899	4/ 5(80)	6/ 8(75)	10/13(77)
1,900-1,949	6/ 7(86)	3/ 6(50)	9/13(69)
1,950-	2/ 2(100)	0/ 0 ---	2/ 2(100)
Total	24/31(77)	11/17(65)	35/48(73)

One patient with distant metastasis only was considered to be controlled locally.

Table 7. Average NSD vs Local Control

	Average NSD (1 SD*)		
	T1 (N=31)	T2 (N=17)	Total (N=48)
Controlled (N=35)	1,860 (78.7)	1,865 (54.6)	1,861 (71.9)
Failed (N=13)	1,804 (46.2)	1,875 (50.3)	1,843 (59.3)
Total (N=48)	1,849 (76.3)	1,867 (51.5)	1,856 (68.6)

* ; Standard deviation.

Student's t-test showed no statistical significance.

the best candidates for laser surgery.

The fact that glottic cancer, like other malignant tumors in the upper aerodigestive tracts, is related to smoking and alcohol drinking is widely accepted⁵. In addition, heredity, voice abuse, asbestos, and poor hygiene are recognized as important causal factors of laryngeal cancer⁶. This is known to be the disease of heavy smokers in their fifth to seventh decades of life.

Histologically, carcinomas of the true vocal cord(s) are usually well- to moderately-differentiated squamous cell carcinomas. In our study, all were confirmed to have squamous cell carcinomas, and though the histologic gradings were not known in 20 patients, all except one of those whose histologic gradings were known, were well- to moderately-differentiated squamous cell carcinomas.

Approximately 4% to 20% of the patients with laryngeal cancer have been reported to have second malignant tumors, with the lung being the most frequently involved organ⁷. The occurrence of second malignant tumors is hypothesized by the "condemned mucosa syndrome" proposed by Slaughter et al⁸ in 1957. De Vries et al⁹ conclude that the epithelial tissues, exposed simultaneously to smoking and alcohol, are bound to undergo focal malignant changes surrounded by multiple additional cancerous foci or areas of premalignancy. The prognoses of the second malignant tumors are, in general, poorer than the original primary malignancies in spite of more aggressive therapeutic approaches⁷. These associations with the appearance of the second malignant tumors, combined with their poorer prognoses, signify the importance of continued follow-up for patients with glottic cancer, even after a long period of absence of disease recurrence. In our study, four cases of second malignant tumors were identified, and the crude incidence rate was 8.3%, but no case of the lung primary was seen. Instead, one case of gastric cancer was seen, which might reflect the high prevalence of this cancer in our country, and two cases of head and neck malignancies were identified after five years of the initial treatment.

Fletcher et al¹⁰ suggest that the so-called "late recurrences" are actually new cancers and not the reactivations of the initial lesions. This assumption was supported in his article by the fact that half of the failures were associated with leukoplakias. Our cases with "late failures" after three years were three in number (6.3%) and might be new primaries rather than true failures.

Local control rates by radiation therapy are

reported to be about 80% to 90%, in T1 lesions, and 70% to 80% in T2 lesions by many authors at various institutions. Yoo et al¹¹ report that five-year survival rates of T1 and T2 glottic cancers are 75.0% and 73.1%, respectively. Kondo et al¹² report that five-year actuarial survival rates for T1a, T1b and T2 are 84.8%, 48.7%, and 68.5%, respectively. They also report that five-year actuarial relapse-free survival rates for T1a, T1b, and T2 are 76.3%, 38.1%, and 65.7%, respectively. The relatively low survival rates for the T1b group might be due to the small sample size and the inclusion of one patient who was lost to follow-up, according to the authors' explanations. The results presented in this study do not seem much better or worse than those from other hospitals, considering the small sample size.

In general, the majority of the failures occurred in the primary sites rather than in the regional nodal or distant organs, which may be explained by the association of this cancer with higher degrees of histologic differentiation and the scantiness of the lymphatic interconnections. Thirteen out of 14 total failures were observed in the primary site, while only one distant failure occurred in our study. Four regional failures were observed after the salvage operations, but not presenting as initial failures.

Surgical salvage rates have been reported, in general, to be in the range of 50% to 90%. Hemilaryngectomy or total laryngectomy are the preferred procedures. For the well-localized T1 lesions, cordectomy may be attempted. The surgical salvage rate of our report (42.9%) may be regarded as the lower limit of the usually reported results, which might be due to the late references of the patients with residual or regrowing tumors to the surgeons. Thus the policy of quick reference of the patients in doubt of residual or recurrent tumors during follow-up laryngoscopic examinations for biopsies that employ laryngomicroscopy should be pursued. This is also true for those with prolonged arytenoid edema and/or for those with unhealing or new vocal cord erosions. The earlier the diagnoses of and surgical salvages of the radiation failures and recurrences can be achieved, the more quickly and safely the patients can be saved and recover.

Fletcher et al¹⁰ explain that irradiation failure can be due to (1) geographic miss, (2) specific extensions of the tumor with an unfavorable tumor bed, (3) low dose for the tumor volume, (4) techniques not assuring daily coverage of the tumor, and (5) the sigmoid-shaped dose-response curve. Involve-

ment of the anterior commissure, which was traditionally thought to be a cause of treatment failures, proved to have no adverse effect according to his paper¹⁰). The involvement of the anterior commissure is reported to be an adverse prognostic factor by some, while it is reported to not be by others. This point has been much debated. In our study, there seems to be no adverse relationship between tumor control and involvement of the anterior commissure within the T1 group.

Harwood et al¹³) observe within the T2 group that the five-year corrected actuarial survival rate is about 12% less in patients with impaired cord mobility (75.2%) when compared to those with normal cord mobility (86.8%), while there is no such difference with increasing degrees of surface extension of disease when correction for the effects of impairment of mobility is performed. These authors suggest that stage T2 be subdivided into T2a for those tumors with normal cord mobility and T2b for those with impaired cord mobility.

Van den Bogaert et al¹⁴) report that local control rates with radiotherapy alone are the same in T2a and T2b, but final survival is lower for T2b patients because of less successful salvage surgery, and that impaired mobility by itself is not a bad prognostic factor, but it is when combined with tumor extension. The authors state that the adverse prognostic influence of impaired cord mobility seems to be eliminated by the treatment policy of surgery for those patients with poor regressions after radiotherapy.

Karim et al¹⁵) suppose that the heterogeneity of stage II glottic cancer can be overcome by delivering higher doses with quality controlled radiotherapy using a 4-MV linear accelerator. In their study, they chose a dose range of 68 Gy to 74 Gy, which is slightly higher than the usual schemes employed at other institutes, with a shrinkage of the radiation fields during the treatment course to deliver an additional dose to the tumor and reduce normal tissue complications. They also report that the results are the same in the groups with or without impaired cord mobility (79% vs 81% of local control, respectively).

In our study, the local control probability of the T2 group showed a slightly lower rate than that of the T1 group. This might be explained partly by the association of known adverse prognostic factors, impaired cord mobility plus tumor extensions within the larynx, and partly by the small sample size.

We have shown, in these retrospective analyses, that (1) radiation therapy is highly useful in the

control of early glottic cancer and that it has the ability to preserve the natural voice intact, using a dose range of about 6,000 cGy to 7,600 cGy; (2) the majority of the failures occurred in the primary site, which could be salvaged by prompt and proper operative procedures; (3) there were four cases of second malignant tumors in other sites and three late recurrences in the primary site; and (4) there was no definable dose-response relationship within this dose range.

For better treatment outcome in the future, we suggest that (1) those with carcinoma in situ and/or superficial T1 glottic cancer be treated initially by laser surgery; (2) those with more advanced early glottic cancers be treated initially by radiation therapy with surgery in reserve for salvage of failure or recurrence; (3) the radiotherapists exercise care in the set-up of daily treatments, delivering adequate doses; (4) the clinicians try to find the residual or recurrent tumors as soon as possible for early application of salvage treatments; and (5) the policy of continued follow-up as long as possible, preferably longer than 10 years, be adhered to in order to identify and manage any second malignant tumors.

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= 국문초록 =

초기성문암의 방사선치료

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1979년 3월부터 1984년 8월 사이에 서울대학교병원에서 방사선치료를 받은 31명의 TINOMO와 17명의 T2NOMO를 포함하는 48명의 초기성문암 환자에 대한 후향적 조사분석을 시행하였다. 대상 환자들에 대한 추적조사기간의 중간값은 67개월이었으며(범위 : 34개월~126개월), 85.4%의 환자에서 5년이상 추적이 가능하였다.

전체 환자군의 5년 생존율 및 무병 생존율은 각각 83.2% 및 69.4%였다. T1 병기환자군의 5년 생존율 및 무병생존율은 각각 87.1% 및 76.0%였으며, T2 병기 환자군에서는 각각 76.5% 및 58.2%였다.

초기 성문암의 방사선치료에 있어서의 치료실패의 원인, 선량-반응 관계, 이차성 악성종양의 발현 및 보다 좋은 치료성적을 얻기 위한 제언 등에 대한 분석 및 토론을 하였다.