

## Results of radiation therapy for glottic cancer

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- Background** : *Cure and voice preservation are the primary concerns for patients seeking treatment for glottic cancer. The efficacy of radiation therapy, either alone or in combination with surgery, in glottic cancer was assessed.*
- Objective** : *To review the results of radiation treatment in patients with glottic cancer.*
- Setting** : *Division of Radiation Oncology, Department of Radiology, Faculty of Medicine, Chulalongkorn University.*
- Subjects** : *Seventy-eight patients with histologically proven squamous cell carcinoma of the glottis, from January 1983 – December 1989.*
- Design** : *Retrospective study.*
- Patients** : *The records of 78 patients with age-range of 33-84 (mean age =60.3) were reviewed. There were 74 (94.9%) males and 4 (5.1%) females. The male to female ratio was 18.5 : 1. All had histologically proven squamous cell carcinoma.*
- Method** : *The survival rate was calculated using the product limit estimate of Kaplan and Meier. Comparisons of survival were made using the log rank test. A p-value of less than or equal to 0.05 was considered significant.*
- Results** : *Seventy-eight glottic cancers had been treated by radiotherapy (RT), either alone or in combination with surgery (S + RT). The overall 5-*

*year survival rate was 91.3 % for  $T_1N_0M_0$  , 50.6 % for  $T_3N_0M_0$  and 53.5 % for any  $TN_{1-3}M_0$  . The locoregional control rates for patients treated with RT for the corresponding groups were 92.0 % , 28.6% and 40.0 % with surgical salvage rate of 100.0 % , 60.0 % and 0% respectively. For patients treated with S+RT the locoregional control rate was 71.4 % for  $T_3N_0M_0$  and 41.7 % for any  $TN_{1-3}M_0$  with radiation salvage rate of 25.0 % and 14.4 % respectively. The rates of laryngeal voice preservation in the RT group were 92.0 % for  $T_1N_0M_0$  , 75.0 % for  $T_2N_0M_0$  , 64.3 % for  $T_3N_0M_0$  and 40.0 % for any  $TN_{1-3}M_0$  . Anterior commissure involvement in  $T_1N_0M_0$  did not influence the survival. The number of patients in  $T_2N_0M_0$  ,  $T_4N_0M_0$  and any  $TanyNM_1$  were too small to obtain any meaningful analysis. Death from intercurrent disease was found to be 42.9 %.*

**Conclusion** : *Glottic cancer is radiocurable. Preservation of the larynx can be achieved with radiotherapy without jeopardizing survival.*

**Key words** : *Glottic cancer, Radiotherapy.*

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ผลการรักษามะเร็งสายเสียงด้วยรังสี. จุฬาลงกรณ์มหาวิทยาลัย 2541 ก. ค: 42(7): 495-504

- วัตถุประสงค์ : เพื่อศึกษาถึงประสิทธิภาพของรังสีรักษาอย่างเดียวหรือรังสีรักษา ร่วมกับการผ่าตัดในการรักษามะเร็งสายเสียง
- สถานที่ทำการศึกษา : หน่วยรังสีรักษา ภาควิชารังสีวิทยา คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
- รูปแบบการวิจัย : ศึกษาย้อนหลัง
- ผู้ป่วยที่ทำการศึกษา : ผู้ป่วยมะเร็งสายเสียงจำนวน 78 ราย ตั้งแต่ มกราคม พ.ศ.2526 ถึง ธันวาคม 2532 ซึ่งมีพยาธิสภาพเป็นมะเร็งชนิด squamous ผู้ป่วยชาย 74 ราย (94.9%) หญิง 4 ราย (5.1%) อัตราส่วนชาย : หญิง = 18.5:1 อายุตั้งแต่ 33-84 ปี เฉลี่ยอายุ 60.3 ปี
- วิเคราะห์ทางสถิติ : อัตราการอยู่รอดคำนวณโดยวิธี Kaplan และ Meier ใช้ log rank test ในการเปรียบเทียบอัตราการอยู่รอด ค่าของ p-value เท่ากับหรือน้อยกว่า 0.05 ถือว่ามีนัยยะสำคัญทางสถิติ
- ผลการศึกษา : ผู้ป่วยในระยะ  $T_1N_0M_0$  ได้รับการรักษาด้วยรังสีอย่างเดียว อัตราการอยู่รอด 5 ปี โดยเฉลี่ย = 91.3% อัตราการควบคุมโรคเฉพาะที่ = 92.0% ผู้ป่วยที่มะเร็งกลับเป็นใหม่หลังรังสีรักษาสามารถทำ salvage surgery ได้ 100% การลุกลามของมะเร็งถึง anterior commissure ไม่ได้ทำให้อัตราการอยู่รอดลดลงผู้ป่วยที่ไม่ได้มีการกลับเป็นใหม่หลังรังสีรักษาสามารถคงกล่องเสียง และพูดได้ปกติ อัตราการอยู่รอดโดยเฉลี่ยของผู้ป่วยในระยะ  $T_2N_0M_0$  = 75.0% 3 ใน 4 ราย ที่ได้รับการรักษาด้วยรังสีและไม่มีอาการกลับเป็นใหม่ของมะเร็งสามารถคงกล่องเสียงและพูดได้ปกติ อัตราการควบคุมโรคเฉพาะที่ ในผู้ป่วยระยะ  $T_3N_0M_0$  ที่ได้รับการรักษา ด้วยการฉายรังสีอย่างเดียวและการรักษาด้วยรังสีร่วมกับการผ่าตัด = 28.6% และ 35.7% ตามลำดับ การ salvage ด้วยการผ่าตัดและรังสี = 60.0% และ 25.0% ตามลำดับ อัตราการอยู่รอด 5 ปี โดยเฉลี่ย = 50.6% ซึ่งไม่แตกต่างกันระหว่างการรักษาด้วยรังสีหรือรังสีร่วมกับการผ่าตัด 64.0% ของผู้ป่วยที่ได้รับการรักษาด้วยรังสี สามารถคงกล่องเสียง และพูดได้ปกติ อัตราการอยู่รอดโดยเฉลี่ยของผู้ป่วยที่มะเร็งลุกลามไปต่อมน้ำเหลือง = 53.5% ในผู้ป่วยที่ได้รับการรักษาด้วยการผ่าตัดร่วมกับฉายรังสีมีอัตราการกลับเป็นใหม่ของโรคและอัตราการอยู่รอด = 58.3% และ 58.9% ตามลำดับ ส่วนผู้ป่วยที่ได้รับการรักษาด้วยรังสีอย่างเดียว = 60.0% และ 44.4% ตามลำดับ พบอัตราตายจากสาเหตุอื่นนอกเหนือจากมะเร็งสายเสียง 42.9%

สรุป : มะเร็งสายเสียงสามารถรักษาให้หายด้วยรังสีรักษา ข้อดีของรังสีรักษาคือ สามารถคงกล่องเสียงไว้และพูดได้ปกติ

ดัชนีเรื่อง : มะเร็งสายเสียง รังสีรักษา

Cancer of the larynx is the second most common head and neck cancer encountered at Chulalongkorn Hospital. From the 1996 Tumor Registry Statistical Report of Chulalongkorn Hospital <sup>(1)</sup> laryngeal cancer constitutes approximately 18.2 % of all head and neck cancers or 2.5 % of all new cancers. Early glottic cancer may be treated either by radical radiotherapy reserving surgical salvage (RRSS) for recurrence or by conservation surgery. Unquestionably radiation therapy results in better voice quality. <sup>(2)</sup> Locally advanced cancer is usually treated with laryngectomy with or without radiation therapy.

The purpose of this retrospective study is to present results of 5 - years of radiation treatment, either radiation alone (RT) or in combination with surgery (S + RT), of patients with glottic cancer who were seen at the Department of Radiology, Faculty of Medicine, Chulalongkorn University.

### Materials and Methods

From January 1983 to December 1989, 78 patients with glottic carcinoma were treated with radiation (either radiation alone or combined with surgery) at the Division of Radiation Oncology, Department of Radiology, King Chulalongkorn Memorial Hospital. The staging was performed according to the International Union Against Cancer (UICC) 1987 staging system, <sup>(3)</sup> retrospectively based on the information recorded in the radiation therapy charts. There were 74 (94.9 %) males and 4 (5.1 %) females. The male to female ratio was 18.5 : 1. The patients were aged 33 to 84 years (mean age = 60.3). All patients had histologically confirmed diagnosis. The patient characteristics are shown in Table 1.

**Table 1. Patient Characteristics.**

Total	78 (100 %)
Sex	
Female	4 (5.1 %)
Male	74 (94.9 %)
Male : Female	18.5 : 1
Age	
Mean	60.3 yr.
Minimum	33.0 yr.
Maximum	84.0 yr.
Follow - up	
Mean	40.4 mo.
Minimum	2.0 mo.
Maximum	138.0 mo.
50 % of patients	>24.0 mo.
Histologic type	
Squamous cell carcinoma	78 (100.0 %)

The irradiation was given using Cobalt-60. Lateral parallel opposed fields were used in most of the cases. Anterior oblique wedged fields were used in some patients with short necks. Patients with radical radiation treatment were treated with a range of doses from 6000 cGy in 6 weeks to 7000 cGy in 7 weeks. The doses for pre- and post-operative radiation were 4000 cGy in 4 weeks and 5000 cGy in 5 weeks, respectively.

Total laryngectomy (TL) with or without neck dissection was used in surgical treatment for (S + RT) or salvage. The distribution of patients by stage and treatment is shown in Table 2.

The minimum follow-up was two months, and maximum 138 months. Mean follow-up was 40.4 months with 50 % of the patients followed for more than two years or until death. The cause of death could

**Table 2.** Patient Distribution by Stage and Treatment.

Stage	Treatment	
	Radiation	Combined therapy
T <sub>1</sub> N <sub>0</sub> M <sub>0</sub>	25	-
AC +	15	-
AC -	10	-
T <sub>2</sub> N <sub>0</sub> M <sub>0</sub>	4	2
T <sub>3</sub> N <sub>0</sub> M <sub>0</sub>	14	14
T <sub>4</sub> N <sub>0</sub> M <sub>0</sub>	-	1
Any T N <sub>1-3</sub> M <sub>0</sub>	5	12
Any T, Any N, M <sub>1</sub>	1	-
Total	49	29 (78)

AC = anterior commissure

not be established in every deceased patient, thus the survival rate was based on numbers of patients dying from both glottic cancer and intercurrent diseases.

The survival was calculated using the product limit estimate of Kaplan and Meier.<sup>(4)</sup> Comparisons of survival were made using the log rank test.<sup>(5)</sup> A p-value of less than or equal to 0.05 was considered significant.

**Results**

T<sub>1</sub>N<sub>0</sub>M<sub>0</sub>. This group of patients was treated by RT. The overall 5-year survival rate was 91.3 %. The survival rates of those with and without anterior commissure involvement were 85.1 % and 100.0 % respectively (p = 0.06). Two patients (8.0 %), one in each group, developed local recurrence and were successfully treated by TL. The surgical salvage rate was 100.0 %. The larynx was retained free of cancer in 92.0 % of these cases.

T<sub>2</sub>N<sub>0</sub>M<sub>0</sub>. The overall 5-year survival rate was

75.0 %. The number of patients was too small to obtain meaningful conclusions when comparing modes of treatment. One patient from the RT group was lost to follow up and counted as dead from cancer. The remaining, three patients from the RT group survived and retained their larynxes. In the S+RT group, one patient was lost to follow - up one year after treatment and the other died one year and four months after treatment, the cause of death being unknown.

T<sub>3</sub>N<sub>0</sub>M<sub>0</sub>. The overall 5-year survival rate was 50.6 %. Patient treated by S+RT had a 56.3 % survival rate, versus 46.4 % survival rate among those treated with RT. This difference in survival was not statistically significant (p = 0.45). Of the 14 patients who were treated by S + RT, 4 (28.6 %) had loco-regional recurrences; 3 regional and 1 local. Radiation salvage was successful in one (25.0%) patient who had regional failure. Of the 14 patients who were treated by RT, 5 (35.7 %) had local recurrence. Surgical salvage (total laryngectomy) was performed successfully in 3 (60.0 %) patients. The 9 (64.3 %) patients in the RT group who did not develop recurrence retained their larynxes with useful voice until the last follow up or death.

T<sub>4</sub>N<sub>0</sub>M<sub>0</sub>. There was one patient in this category. He was treated by S+RT. He survived more than 5 years.

Any TN<sub>1,2,3</sub>M<sub>0</sub>. The overall 5-year survival rate was 53.5 %. In the S+RT group 7 (58.3 %) patients recurred regionally. Only one patient was successfully salvaged by radiation. In the RT group 2 (40.0%) achieved loco-regional control and survived more than 5 years with intact larynxes. The remaining 3 patient in the RT group died of uncontrolled disease. The overall 5-year survival rates in the S + RT and RT groups

were 58.9 % and 44.4 % respectively ( $p = 0.65$ ).

Any T, any N,  $M_1$ . There was only one patient who presented with distant metastasis (lung and paratracheal lymphadenopathy). He was treated with palliative radiotherapy but expired 2 months later.

Death from intercurrent diseases. Most of the patients who had been successfully treated for glottic

carcinoma died from known causes, 6 out of 14 (42.9 %) patients died from other causes. Since the actual causes of death could not be established in all patients under this study, death rates from intercurrent diseases could have been higher.

The treatment results are shown in Table 3.

**Table 3. Treatment Results.**

Stage (Number of patients)	5-yr survival (%)	Recurrence No (%)	Salvage treatment No (%)	Larynx retained (%)
$T_1N_0M_0$ (25)	91.3	2/25 (8.0)		
with AC involvement (15)	85.1	} $p = 0.06$ 1/15 (6.7)	1/1 (100.0)	93.3
without AC involvement (10)	100.0		1/1 (100.0)	90.3
$T_2N_0M_0$ (6)	75.0			
RT (4)	75.0	1*	-	75.0
S+RT (2)	+			
$T_3N_0M_0$ (28)	50.6			
RT (14)	46.4	} $p = 0.45$ 5 (35.7)	3/5 (60.0)	64.3
S+RT (14)	56.3		4 (28.6)	1/4 (25.0)
$T_4N_0M_0$ (1)				
S+RT	Survived passing 5 years			
Any $TN_{1-3}M_0$ (17)	53.5			
RT (5)	44.4	} $p = 0.65$ 3 (60.0)++	0	40.0
S+RT (12)	58.9		7 (58.3)	1/7 (14.4)
Any T any $NM_1$ (1)				
RT (1)	Survived 2 months			

\* lost, counted as death from cancer

+ one patient lost to follow-up 1 year after treatment the other died one year and four months after treatment

++ the two patients who survived had  $T_1N_1M_0$  and  $T_3N_1M_0$  diseases

## Discussion

Data in the present report confirm that stage I and II glottic carcinomas can be controlled with RT. For  $T_1N_0M_0$  (Stage I) lesions, the overall 5-year survival rate was 91.3 %. The loco-regional control rate was 92.0 %. The two patients who had local recurrences were successfully saved by surgery, making the surgical salvage rate of 100.0 %. The remaining patients (92.0 %) who did not have recurrence retained their cancer-free larynxes with useful voice. The results of our study are comparable to those of the literature in terms of survival and local control rates of 80.0 - 93.0 % and 97.0-99.0 % respectively. <sup>(6,7)</sup> Patients with anterior commissure involvement showed poorer survival compared to those without AC involvement, 85.1% and 100.0 % respectively. However, the difference was not significant ( $p = 0.06$ ). This study also supports previous reports suggesting that  $T_1$  glottic carcinoma involving the AC is not associated with a higher rate of treatment failure. <sup>(8)</sup> For  $T_2N_0M_0$  lesion the overall 5-year survival rate was 75.0 %. There have been reports addressing the prognostic significance of vocal cord mobility in  $T_2$  lesions treated by irradiation. The local control rate was reduced by 10.0-30.0 % for patient with impaired cord mobility. <sup>(9-11)</sup> In this report, impaired cord mobility could not be analysed separately due to the small number of such patients. Our two patients with cord impairment were both treated with S+RT: one patient was lost to follow - up 1 year after treatment, the other died 16 months after treatment. The four patients without impaired cord mobility were treated by RT, and 3 of these survived with intact larynxes without recurrence. The local control rate was 75.0 %.

Our policy of initial management of  $T_3N_0M_0$

has gradually changed over the years. In the past, these patients were treated by total laryngectomy, either alone or in combination with irradiation. In our study population a number of patients were offered RRSS and these constituted half of the patients of this group in this report. The overall 5-year survival rate was 50.6%. The survival rates for the S+RT and RT groups were 56.3 % and 46.4 % respectively. This difference was not significant. The loco-regional recurrence rates for these two modalities were 28.6 % and 35.7 % respectively with no statistical significant difference. Surgical salvage for radiation failure was successful in 60.0 % of the cases whereas radiation salvage resulted in only a 25.0 % success rate. The 9 patients (64.3 %) in the radiation alone group who did not have recurrence retained their larynxes with useful voice. Our results are comparable to others reported in the literature. Vermund, et al <sup>(12)</sup> reported the primary loco-regional recurrence rates in the groups of S+RT and RT alone of 14.0 %-29.0 % and 5.0 %-57.0 % respectively. Cancerfree larynxes were retained in 43.0 %-71.0 % of cases. In this era of advancements in clinical radiotherapeutic techniques, better understanding of radiobiology and improvements in radiation deliver with the goal of organ preservation, are available for patients with early glottic cancer, and should be made use of for this group of patients. However difficulties are sometimes encountered during follow - up of these irradiated patients. Differentiating recurrence from edema and necrosis is not always easy and delays in salvage surgery could result in more advanced tumors or distant metastasis. Close observation with regular examinations by experienced specialists should be emphasized. For patients with positive nodes without distant metastasis (any  $TN_{1-3}M_0$ ), the overall survival



rates in the S + RT and RT alone were 58.9 % and 44.4 % respectively. The difference was not significant. The loco-regional control rate in the S+RT group was 41.7% and in the RT group 40.0 %. Although the loco-regional control rates in both groups were similar, patients in the combined group had more advanced primary tumor and neck disease. The two patients in the RT group who survived without recurrence and with intact larynxes all had  $N_1$  disease. This substantiates reports that lymph nodes up to 3.0 cm. in ( $N_1$ ) diameter can be controlled by RT alone.<sup>(13)</sup> We acknowledge the limited value of comparing results based on retrospective reviews and small numbers of patients but we continue to advocate treatment by RRSS for this group of locally advanced (up to  $T_3, N_1$ ) tumors because our results, in terms of local control and retaining the larynx, are too good to sacrifice the larynx at the outset of the treatment. Laryngeal cancer presenting with distant metastasis is rare, only 1.3 % in this report.

Among patients who had been successfully treated for glottic carcinoma, 42.9% (6/14) died from other causes. Since the causes of death in this report could not be established in every case, death from other diseases could have been higher.

### Conclusion

The primary goal in the treatment of any malignant tumor is cure of the cancer. However, preservation of cosmesis and function are equally important, especially for cancer in the head and neck region. For glottic cancer, the prospects of cure and voice preservation are the primary concerns of patients seeking treatment. In the present analysis, we draw some conclusions regarding the roles of radiation

therapy in the management of glottic cancer.

Early glottic cancers, stage I and II, respond excellently to irradiation and recurrences respond well to salvage surgery. Lesions involving the anterior commissure in stage I glottic cancer did not influence the survival rates. Preservation of the larynx was achieved in 91.3% and 75.0% of the stage I and II cases, respectively. For locally advanced tumors, ( $T_3 N_0 M_0$ ) the loco-regional control rate for irradiation was slightly inferior to combined surgery and radiation. However, a high success rate of surgical salvage and laryngeal preservation could be achieved, being 60.0% and 64.3% respectively. For loco-regionally advanced lesions (any primary tumor with positive lymph node and without distant metastasis), the loco-regional control rate in the two groups of treatment was similar. But the surviving patients in the RT group who had  $N_1$  disease survived with retained larynxes. This confirms the efficacy of radiation therapy in controlling neck nodes up to 3 cm. in size. Almost half of the larynx in loco-regionally advanced tumors could be preserved by RT. Only 1.3% of glottic cancer presented with distant metastasis. Death from intercurrent disease was substantial, being 42.9 % in this report. In summary we would like to emphasize that glottic cancer is curable. Organ preservation, as evident from this analysis, is probable with radiation treatment for early glottic carcinoma. A realistic expectation for patients with advanced tumor could probably be achieved with combined modality approaches. These include the use of concurrent chemotherapy and radiation or, induction chemotherapy prior to radiation alone. Hopefully as our experience in this area increases, preservation of laryngeal functions in advanced glottic tumor cases will be finally

achieved.

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