Definitive Radiation Therapy for Early Glottic Carcinoma

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Abstract: Background: Definitive radiation therapy (RT) for early laryngeal glottic carcinoma offers an excellent probability of cure and it is associated with persistent disease or tumor recurrence in a minority of patients. The objective of treatment controlling the malignant tumor and preserving a functionally useful voice is best optimized by the use of radiotherapy in early stages. Although surgery can offer equal good results, it is best reserved in the event of radiation failure. **Aim of the work**: The aim of the present retrospective study is to identify the treatment outcomes and different prognostic variables affecting early (T1N0M0 and T2N0M0) laryngeal glottic squamous cell carcinoma (SCC) treated with definitive radiation therapy. **Methods**: The medical records of 81 patients with T1N0M0 and T2N0M0 glottic invasive SCC treated with definitive radiation therapy throughout the period from January, 2002 to September, 2010, at Clinical Oncology Department, Tanta University Hospital, were reviewed. All patients had at least 12 months of follow-up. These patients were evaluated for response to RT, local control, disease specific survival (DSS) rates and treatment toxicity. The different prognostic factors affected the local control and DSS rates were also statistically analyzed. **Results**: The median follow-up period was 45.9 months. Eleven patients (13.58%) received <65 Gy as a total irradiation dose and 86.42% received > 65 Gy. Complete disappearance of the laryngeal glottic lesion (CR) was achieved in 91.36% of patients. Five-year local control rates were 89.1% in T1 and 64.96% in T2 tumor stage. Multivariate analysis revealed that anterior commissure involvement (P=0.048) and overall treatment time (P=0.002) are adversely affected local control rates with statistical significance. Seven (9.46%) patients failed locally and 2 (2.7%) had developed distant failure. Five-year DSS rates were as follows: T1, 89.81% and T2, 70.76%. Sever early radiation reaction involving skin, larynx & pharynx were rare (1.2%, 3.7% and 6.2%, respectively), and severe late reactions was recorded in 1.2% of patients. **Conclusion**: Definitive RT cures a high proportion of patients with T1N0M0 and T2N0M0 glottic SCC and has a low rate of severe complications. The anterior commissure involvement and overall treatment time were adversely affected local control rate.
[Alaa Maria; Mohamed El-Shebiney and Omnia Abd El-Fattah. **Definitive Radiation Therapy for Early Glottic Carcinoma.** Life Science Journal 2012; 9(2):146-153]. (ISSN: 1097-8135). http://www.lifesciencesite.com. 25

Key words: Radiation therapy, larynx, early glottic carcinoma.

1. Introduction:

The treatment of choice for early glottic cancer (T1N0 and T2N0) is controversial. Radiotherapy produces an excellent cure rate and results in near-normal to normal voice restoration. Voice quality achieved with RT is generally considered superior to that obtained with cordectomy or hemilaryngectomy. Transoral laser excision (TLE) produces excellent cure rates and post-treatment voice quality comparable to RT in selected patients [(1)].

The local control rate with definitive RT treatment was reported to be in the range of 82% to 94% for T1 [(2-5)] and 65% to 80% for T2 disease [(2, 4, 6)]. However, 5% to 40% of the patients will need salvage surgery (total or partial laryngectomy) for persistent or recurrent disease [(7-9)].

The purpose of our study is to assess the treatment outcomes of definitive RT for early-stage SCC of the glottic larynx, with local control rate is considered endpoint in this study. Radiotherapy results have been analyzed according to the different clinical, pathologic, and therapeutic factors, aiming at a more precise definition of the factors predicting for better treatment results.

2. Patients and Methods

Between January, 2002 and September, 2010, a total of 81 previously untreated patients with T1N0M0 and T2N0M0 biopsy-proven invasive SCC of the laryngeal glottis were managed by definitive radiation therapy at the Clinical Oncology Department, Tanta University Hospital. Those patients were evaluated for response to RT, local control and DSS rates. Patients' data were collected from their treatment and follow up sheets.

All patients had follow up evaluation after treatment on a monthly base in the first year, every two months in the second year and thereafter every six months with median follow-up 45.9 months (7-96 months). Patients were clinically staged according to the 2010 American Joint Committee on Cancer (AJCC) [(10)].

All patients were treated with megavoltage photon beam (Cobalt-60) in supine position using 2 lateral opposed wedge fields and the neck was

immobilized using neck pads and head thermoplastic mask.

Patients were treated to total doses ranging from 61 to 70 Gy at 1.8 to 2.25 Gy per fraction once daily, five fractions per week, over 39 to 80 days (median, 53 days). The main reason for protraction of overall treatment time was time gaps because of machine failure and/or acute toxicities necessitating treatment interruption. Twenty (24.69%) patients of the studied population had a treatment gap time > 8 days.

The treatment target was the entire larynx with limited safety margins and sparing the spinal cord from the start of radiation course. The field sizes in 68 patients was ranged from 6 x 6 cm to 7 x 7 cm and was more extended in 13 patients who received elective neck node irradiation to the internal jugular lymph nodes, depending on the discretion of the attending physician.

Typical field borders for T1 extended superiorly from the top of the thyroid notch, inferiorly to the lower border of the cricoid cartilage, with 1 to 1.5 cm falloff anteriorly. Posteriorly the field stops at the anterior edge of cervical vertebral bodies (prevertebral fascia). Frequently the collimator is rotated slightly so that the field of irradiation is parallel to slope of the neck. Both lateral fields were treated daily. No elective neck node irradiation was given.

Fields were enlarged for T2 cancers depending on the extent of the tumor. The fields were not routinely reduced in size at any point during the treatment. For patients who received elective nodal irradiation the upper border was 2 cm above the angle of the mandible.

The treatment volume was identified by the use of simulator. The dose was specified to an isodose line that covered the lesion and was 95% of the maximum dose. The dose was calculated in the mid-plane point on the central axis of the beam using 2D treatment planning system.

Treatment response was evaluated by indirect laryngoscopy. Persistent disease was considered by finding of tumor within two months after completion of radiation treatment course. Local control or complete response defined as freedom of persistent disease, while local recurrence was defined by finding malignancy in the larynx or regional lymph nodes "radiological and/or biopsy-proven" after complete response to therapy. Salvage for persistent or recurrent disease was consisted with partial or total laryngectomy.

Acute complications during RT were defined as severe if an unplanned treatment break was necessary. Late complications were defined as severe if they necessitated a surgical procedure such as placement of a gastrostomy or tracheostomy tube, or if the complication resulted in death. Acute and late toxicities are graded according to toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC).[11]

Statistical Analysis

The Kaplan-Meier method provided estimates of local control and disease specific survival [12]. Local control was calculated as the time from the pathologic diagnosis to development of failure in the larynx or regional lymph nodes or to the last date of follow-up. Disease specific survival was defined as the time from pathologic diagnosis until either death or last follow up for patients without events. Patients were censored if they died with no evidence of cancer at the time of death.

The log-rank test was used for univariate comparison between patient's, tumor and treatment parameters including age, gender, smoking, stage, anterior commissure involvement, grade, overall treatment time and radiation dose. Cox regression model was used for multivariate analysis[13]. Statistical analysis was performed using Statistical Package for Social Sciences software (SPSS v-12). Significance was prespecified as $P<0.05$.

3. Results

Patients' age ranged from 36 to 79 years (median, 58.6 years). The frequency of the laryngeal glottic SCC was greatly higher in males than females (male to female ratio was 9:1). Also it was significantly higher in smokers versus non-smokers (70.37% and 29.63%). Seventy percent of the patients had T1 disease stage and 29.63% of patients had T2 disease stage. Anterior commissure involvement of the vocal cord was encountered in 34.57% of the whole patients. Most of patients 64.20% had well and moderately differentiated SCC. The patients, tumor and treatment characteristics are listed in Table 1.

Local control rate

With definitive RT, complete disappearance of the laryngeal glottic lesion was achieved in 91.36% (74 patients). The remaining 7 patients had residual tumor and were referred to be salvaged surgically. Three patients underwent successful total laryngectomy, while the other 4 patients were not operated. Out of 74 patients who had achieved complete response, 7 patients developed local recurrence with a median time of the local recurrence was 14.1 months (10-21 months). They underwent salvage surgery (two partial laryngectomy and five total laryngectomy), later on three of them had developed regional neck failure.

Table (1): Patients, tumor & treatment characteristics

	Patients (n=81)	%
Age		
< 60	39	48.15%
≥60	42	51.85%
Gender		
Male	73	90%
Female	8	10%
Smoking		
Yes	57	70.37%
No	24	29.63%
Stage		
T1	57	70.37%
T2	24	29.63%
AC involvement		
Yes	28	34.57%
No	53	65.43%
Tumor Grade		
G I	19	23.46%
G II	33	40.74%
G III	29	35.80%
Total dose		
<65 Gy	11	13.58%
>65 Gy	70	86.42%
Dose/fraction		
1.8 Gy	11	13.58%
2 Gy	61	75.31%
2.25 Gy	9	11.11%
Overall treatment time		
≤53 days	55	67.9%
>53 days	26	32.1%
AC: Anterior Commissars		

Local tumor control by different prognostic variables

Univariate analysis of factors affecting local control revealed that patients age (P=0.026), disease stage (P=0.012), anterior commissure invasion (P=0.0001), pathologic differentiation (P=0.003) and overall treatment time (P<0.0001) significantly impacted this end point. Multivariate analysis demonstrated that anterior commissure involvement (P=0.048) and overall treatment time (P=0.002) are significantly influenced this end point (Table 2). The 5-year local control rate for the whole patients after RT was 82% (Figure 1).

Distant failure occurred in 2 patients (2.47%), the first one developed brain metastasis 55 months after therapy and received palliative cranial irradiation and the second patient developed pulmonary metastasis 58 months after therapy and treated with chemotherapy.

Disease specific survival by different prognostic variables

Univariate analysis of factors affecting the DSS rate revealed that; patients age (P=0.005), disease stage (P=0.036), anterior commissure invasion (P=0.0009), pathologic differentiation (P=0.001) and overall treatment time (P<0.0001) significantly impacted this end point. Multivariate analysis demonstrated that age (P=0.009), anterior commissure invasion (P=0.011) and overall treatment time (P=0.0002) significantly influenced this end point (Table 3). The 5-year DSS rate for the whole patients was 84.63% (Figure 2).

Radiation toxicity

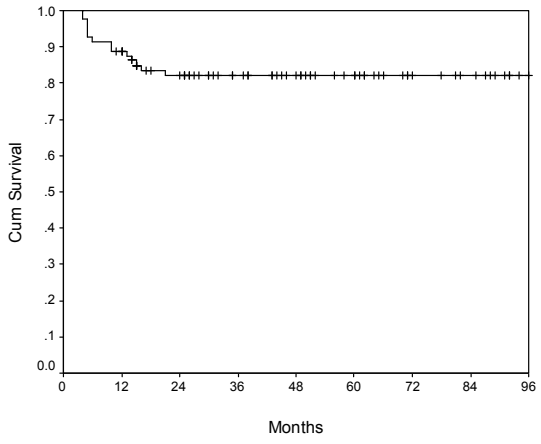
Grades 3 & 4 acute radiation toxicities in this study including skin, larynx and pharynx were rare (1.2%, 3.7% and 6.2% respectively), Table 4. However, 9 (11%) patients suffered acute toxicities necessitating unintended treatment breaks. The common late radiation reactions recorded were mild. One patients (1.2%) required tracheostomy after RT because of persistent laryngeal edema.

Table (2): 5-year local control after radiation therapy for 81 patients.

	Event/ patients	5- year local control	Univariate analysis *P*-value	Multivariate analysis *P*-value
Age				
< 60	3/39	91.27%	0.026	NS
≥60	11/42	73.12%		
Gender				
Male	13/73	81.62%	0.742	---
Female	1/8	87.50%		
Smoking				
Yes	12/57	78.09%	0.184	---
No	2/24	91.67%		
Stage				
T1	6/57	89.10%	0.012	NS
T2	8/24	64.96%		
AC involvement				
Yes	11/28	58.33%	0.0001	0.048
No	3/53	94.04%		
Tumor Grade				
G I & II	4/52	91.93%	0.003	NS
G III	10/29	64.51%		
Total dose				
<65 Gy	3/11	71.59%	0.351	---
>65 Gy	11/70	83.77%		
Dose/fraction				
1.8 Gy	3/11	71.59%	0.618	---
2 Gy	10/61	83.00%		
>2 Gy	1/9	88.89%		
Treatment time				
≤53 days	1/55	98.18%	<0.0001	0.002
>53 days	13/26	46.13%		

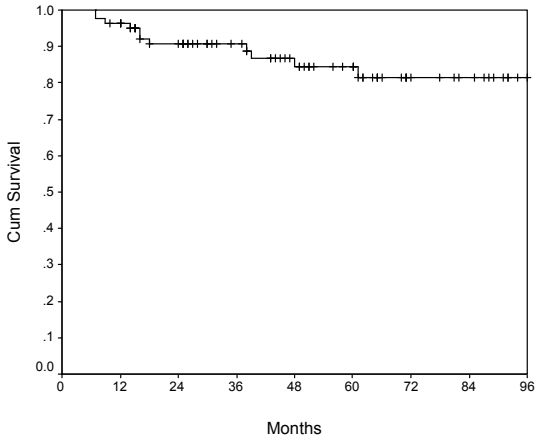
AC: Anterior commissure; NS: non-significant

Fig (1): Local control for the whole patients after definitive RT (81 patients)



5-year local control rate 82%

Fig (2): Disease specific survival for the whole patients (81 patients)



5-year DSS rate 84.63%

Table (3): 5-year DSS for the whole group (81 patients)

	Event/ patients	5-year DSS	Univariate analysis *P*-value	Multivariate analysis *P*-value
Age				
< 60	1/39	96.88%	0.005	0.009
≥60	10/42	72.83%		
Gender				
Male	10/73	83.28%	0.982	---
Female	1/8	100%		
Smoking				
Yes	9/57	78.87%	0.286	---
No	2/24	95.83%		
Stage				
T1	5/57	89.81%	0.036	NS
T2	6/24	70.76%		
AC involvement				
Yes	9/28	65.68%	0.0009	0.011
No	2/53	96.23%		
Tumor Grade				
G I & II	3/52	93.86%	0.001	NS
G III	8/29	56.70%		
Total dose				
<65 Gy	2/11	80.81%	0.632	---
>65 Gy	9/70	85.10%		
Dose/fraction				
1.8 Gy	2/11	80.81%	0.813	---
2 Gy	8/61	85.65%		
>2 Gy	1/9	88.89%		
Treatment time				
≤53 days	1/55	96.43%	<0.0001	0.0002
>53 days	10/26	62.20%		

AC: Anterior commissure; NS: non-significant

Table (4): Radiation toxicity in 81 patients with glottic carcinoma

	G1-2	G3-4
Acute toxicity		
Skin	80 (98.8%)	1 (1.2%)
Larynx	78 (96.3%)	3 (3.7%)
Pharynx	76 (93.8%)	5 (6.2%)
Late toxicity		
Skin	11 (13.6%)	0
Larynx	10 (12.3%)	1 (1.2%)
Pharynx	9 (11.1%)	0

4. Discussion

The goals of treating T1–T2N0 glottic cancer with RT are to cure the disease, preserve the larynx, maintain good voice quality, and minimize RT-related complications. Local control is arguably the most important end point and, if successful, predicts favorable disease-free survival.[14]

In the present study, univariate analysis of the studied patients, tumor and treatment characteristics showed that, patients age ≥60, T2 stage, involvement of the anterior commissure, histologic grade III and increased overall treatment time had poor predictive influence on the local control rate at 5 years, while with the multivariate analysis, anterior commissure involvement and overall treatment time had poor influence on the local control rate at 5 years. Also, by the multivariate analysis the patients age, anterior commissure involvement and overall treatment time were the prognostic variable that significantly influenced the 5-years DSS rate.

Many authors had reported a numbers of factors that adversely affect local control rates of early laryngeal carcinoma treated with radical RT such as, longer overall treatment time, poorly differentiated histology, smaller fraction size, subglottic extension, treatment delays/interruptions, age, smaller field sizes, lower total dose, gender, stage, higher beam energy, anterior commissure involvement, pretreatment hemoglobin levels, and impaired vocal cord mobility [3, 4, 6, 15-22].

In our study, 5-years local control rate was 82% and 5-years disease specific overall survival rate was 84.63%. **El-Assal *et al.*** [23] reported, 10-years local control rates were 84% and 70% while the 10-years survival were 76% and 69% for T1 and T2 lesions respectively. **Le *et al.*** [20] reported 10-years local control of 81% for T1 and 61% for T2 glottic carcinoma. **Dinshaw *et al*.** [24] achieved 82% and 70% 10-years local control rates for T1 and T2 tumors. **Sakata *et al*.** [25] reported 10-years recurrence free survival of 74% for T1 and 62% for T2 tumors. Warde et al [4] reported survival of 91% for T1 and 69% for T2 lesions.

In our study, the 5-years local control rates were 89.1% and 64.96% while 5-years DSS were 89.81% and 70.76% for T1 and T2 lesions respectively. **Cellia *et al*.** [3] reported that, 831 T1 glottic with histologically confirmed SCC were classified as T1N0, 3-, 5-, and 10-year OS was equal to 86%, 77%, and 57%, respectively. Corresponding values for local control were 86%, 84%, and 83% and for DSS 96%, 95%, and 93%, taking into account surgical salvage of relapsed cases. **Frata *et al*.** [6] reported that, among 256 T2N0 glottic cancer patients, 3-, 5-, and 10-year OS rates were, respectively, 73%, 59%, and 37%. Corresponding values for cumulative local control probability were 73%, 73%, and 70% and for DSS, 89%, 86%, and 85%, taking into account surgical salvage of relapsed cases.

The significant effect of anterior commissure involvement on the local control rates of early laryngeal carcinoma treated with definitive RT, have been controversial, some investigators failed to show a correlation between commisure involvement and increased local control rate and survival and others found a significant decrease in local control.[26, 27] The concern is that, because the anterior commissure is only approximately 1 cm from the skin of the anterior neck, tumors in this location could be under-dosed by low energy photon beam.[28] Besides, modification of the RT treatment technique like adding anterior field/anterior oblique field can be considered to combat under-dosage at anterior commissure.[29] Moreover, the anterior commissure may represent a weak point with regards to tumor spread because it is here that Broyles' ligament penetrates the thyroid cartilage, and this disruption of its continuity might induce susceptibility to tumor invasion.[23]

Although there is a general recommendation that delay in starting or completing of RT -especially when definitive- should be avoided, review of the published literatures reveals controversial data of the prognostic impact of the time gap and overall treatment time on definitive RT treatment outcomes of early glottic carcinoma. **Voet *et al*.** [30] emphasized the negative impact of prolonged overall treatment time on the local control rate, but **Fein *et al*.** [31] reported that overall treatment time had only borderline significance in a multivariate analysis model and no significance in univariate analysis. In the study of Van den **Bogaert *et al*.** [32] a negative impact of overall treatment time was found in patients treated by a split course protocol, irrespective of side effects, even so in the subgroups of T1N0M0 patients, overall treatment time did not influence local control rate.

In the present study the prognostic effect of technical factors such as total RT dose and dose per fraction was not significant. All our patients were treated with Cobalt-60 photons beam as the low energy linear accelerator was not available at the time of study. However, there is extensive published data regarding management of early glottic carcinoma treated by RT with Cobalt-60 or 2-4 megavoltage photons beam, with local control rates ranging from 85% to 94%.[4,19,28] The reported treatment outcome of early glottic carcinoma by primary irradiation with 6 MV photons is limited and conflicting. Some authors reported comparable results with lower energies whereas others raised concern about a poorer outcome.[33-36]

In the present study field sizes ranging from 6 x 6 cm to 7 x 7 cm and RT doses ranging from 1.8 to 2.25 Gy per fraction were applied without significant impact on the local control or survival rates. Small field sizes are favored by the results of the randomized study authored by **Teshima** and coworkers.[37] **Cellai *et al*.** had reported that, the use of doses in excess of 65 Gy (2 Gy/fraction) and of field sizes of 36–49 cm^2, along with modern treatment planning procedures and immobilization devices, is probably the best technical choice available, aiming at the best local control probability with the least incidence of damage.[3] **Kim *et al*.** had reported that, local control rate was higher with doses of 2.0 to 2.25 Gy per fraction than with 1.8 Gy per fraction given to a similar total dose.[38] Le et al reported that total dose, fraction size, and overall time contribute to lower control rates for T2 but not for T1 glottic carcinomas.[20]

In our study, seven out of seventy-four (9.46%) patients had a local recurrence at 5-years follow up. In a retrospective study reported with **Chera *et al*** [22], the medical records of 585 patients with T1N0 to T2N0 invasive SCCs of the glottic larynx treated between 1964 and 2006 were reviewed revealing that, thirteen local recurrences (2%) which were likely second glottic primary cancers occurred over 3 years after RT. A total of 67 (80%) of the local

failures were isolated, and 17 (20%) were associated with simultaneous neck failures.

In the present study, while 8 patients had underwent total laryngectomy, only two patients were surgically salvaged with partial laryngectomy making unavailability to statistically comparing the outcome of the type of salvage surgery. In general, surgical salvage is often performed by total laryngectomy because the belief of increased complications that associated with partial laryngectomy of irradiated cartilage and the negative tumor margins are difficult to achieve in a fibrotic edematous larynx. Five-year local control rates with salvage total laryngectomy have been reported at 65% to 85% for T1 and T2 glottic tumors.[39] Salvage partial laryngectomy is possible in select patients who do not progress with therapy or who experience recurrence with early-stage disease. Five-year local control rates following salvage partial laryngectomy have been reported at 66% to 96%.[40-42]

In conclusion, with definitive radiation therapy, a 5-year local control probability of 82% can be expected, with an incidence of 1.2% of severe late effects; therefore, this type of treatment could be considered as a standard treatment for T1-T2N0 glottic cancer. Anterior commissure involvement and overall treatment time are prognostic factors that adversely affecting the disease local control rate.

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References

1. Kadish SP**.** (2005): Can I Treat This Small Larynx Lesion with Radiation Alone? Update on the Radiation Management of Early (T1 and T2) Glottic Cancer**.** Otolaryngol Clin N Am., 38: 1–9**.**
2. Wang CC. (1997): Carcinoma of the larynx. In: Wang CC (ed). Radiation therapy for head and neck neoplasms, p. 237. New York: Wiley-Liss;.
3. Cellai E., Frata P., Magrini SM., *et al*. (2006): Radical radiotherapy for early glottic cancer: results in a series of 1087 patients from two Italian radiation oncology centers. I. The case of T1N0 disease. Int J Radiat Oncol Biol Phys., 63: 1378–86.
4. Warde P., O'Sullivan B., Bristow R., *et al*. (1998): T1/T2 glottic cancer managed by external beam radiotherapy: the influence of pre-treatment hemoglobin on local control. Int J Radiat Oncol Biol Phys., 41: 347–53.
5. Mendenhall WM., Amdur RJ., Morris CG., *et al*. (2001): T1-T2N0 squamous cell carcinoma of the glottic larynx treated with radiation therapy. J Clin Oncol., 19: 4029–36.
6. Frata P., Cellai E., Magrini SM., *et al*. (2006): Radical radiotherapy for early glottic cancer: results in a series of 1087 patients from two Italian radiation oncology centers. II. The case of T2N0 disease. Int J Radiat Oncol Biol Phys., 63: 1387–94.
7. Lydiatt WM., Shah JP. & Lydiatt KM. (1996): Conservation surgery for recurrent carcinoma of the glottic larynx. Am J Surg., 172: 662-664.
8. McLaughlin MP., Parsons JT., Fein DA., *et al*. (1996): Salvage surgery after radiotherapy failure in T1-T2 squamous cell carcinoma of the glottic larynx. Head Neck, 18: 229-235.
9. Yiotakis J., Stavroulaki P., Nikolopoulos T., *et al*. (2003): Partial laryngectomy after irradiation failure. Otolaryngol Head Neck Surg., 128:200-209.
10. American Joint Committee on Cancer. AJCC Cancer Staging Manual, 7th ed., p 57-67. New York: Springer Verlag; 2010.
11. Cox JD., Stetz J. & Pajak TF. (1995): Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys., 31(5): 1341-6.
12. Kaplan EL. & Meier P. (1958): Nonparametric estimation from incomplete observations. J Am Stat Assoc., 53: 457– 481.
13. Cox DR. (1972): Regression models and life tables—Series B (Methodological). J R Stat Soc., 34: 187–220.
14. Jones DA., Mendenhall CM. & Kirwan J. (2010): Radiation therapy for management of T1–T2 glottic cancer at a private practice. Am J Clin Oncol., 33: 587–590.
15. Nomiya T., Nemoto K., Wada H., *et al*. (2008): Long-term results of radiotherapy for T1a and T1bN0M0 glottic carcinoma. Laryngoscope, 118: 1417–1421.
16. Groome PA., O'Sullivan B., Mackillop WJ., *et al*. (2006): Compromised local control due to treatment interruptions and late treatment breaks in early glottic cancer: Population-based outcomes study supporting need for intensified treatment schedules. Int J Radiat Oncol Biol Phys., 64: 1002–1012.
17. Cho EI., Sasaki CT. & Haffty BG. (2004): Prognostic significance of pretreatment hemoglobin for local control and overall survival in T1–T2N0 larynx cancer treated with external beam radiotherapy. Int J Radiat Oncol Biol Phys 58: 1135–1140.
18. Gowda RV., Henk JM., Mais KL., *et al*. (2003): Three weeks radiotherapy for T1 glottic cancer: The Christie and Royal Marsden Hospital Experience. Radiother Oncol., 68: 105–111.
19. Garden AS., Forster K., Wong PF., *et al*. (2003): Results of radiotherapy for T2N0 glottic carcinoma: Does the ''2'' stand for twice-daily treatment? Int J Radiat Oncol Biol Phys., 55: 322–328.

20. Le QT., Fu KK., Kroll S., *et al*. (1997): Influence of fraction size, total dose, and overall time on local control of T1-T2 glottic carcinoma. Int J Radiat Oncol Biol Phys., 39: 115–126.
21. Burke LS., Greven KM., McGuirt WT., *et al*. (1997): Definitive radiotherapy for early glottic carcinoma: Prognostic factors and implications for treatment. Int J Radiat Oncol Biol Phys., 38: 37–42.
22. Chera BS., Amdur RJ., Morris CG., *et al*. (2010): T1N0 to T2N0 squamous cell carcinoma of the glottic larynx treated with definitive radiotherapy. Int. J. Radiation Oncology Biol. Phys., 78:461–466.
23. El-Assal S., El-Medany A. & Sadek A. (2006): Laryngeal Glottic Carcinoma Outcome: Retrospective Study on 150 Patients. Journal of the Medical Research Institute, 27: 15-20.
24. Dinshaw KA., Sharma V., Agarwal JP. & Havaldar R. (2000): Radiation therapy in T1-T2 glottic carcinoma: Influence of various treatment parameters on local control/complications. Int J Radiat Oncol Biol Phys., 48: 723-35.
25. Sakata K., Oouchi A. & Nagakura H. (2000): Accelerated radiotherapy for T1,2 glottic carcinoma: Analysis of results with Ki-67 index. Int J Radiat Oncol Biol Phys., 47: 81-8.
26. Nozaki M., Furata M., Murakami Y., *et al*. (2000): Radiation therapy for T1 glottic cancer: Involvement of the anterior commissure. Anticancer Res., 20: 1121–4.
27. Tong CC., Au KH., Ngan RK., *et al*. (2011): Impact and relationship of anterior commissure and time-dose factor on the local control of T1N0 glottic cancer treated by 6 MV photons. Radiation Oncology, 6: 53
28. Sombeck MD., Kalbaugh KJ., Mendenhall WM., *et al*. (1996): Radiotherapy for early vocal cord cancer: A dosimetric analysis of 60Co versus 6 MV photons. Head Neck, 18: 167-173.
29. Franchin G., Minatel E., Gobitti C., *et al*. (2003): Radiotherapy for patients with early-stage glottic carcinoma. Cancer, 98: 765-772.
30. Voet JM., Keus RB., Hart AA., Hilgers FJ. & Bartelink H. (1998): The impact of treatment time and smoking on local control and complications in T1 glottic cancer. Int J Radiat Oncol Biol Phys., 42: 247-55.
31. Fein DA , Lee WR., Hanlon AL., Ridge JA. & Coia LR. (1996): Do overall treatment time, field size and treatment energy influence local control of T1-T2 squamous cell carcinoma of the glottic larynx. Int J Radiat Oncol Biol Phys., 34: 823-31.
32. Van den Bogaert M., Van der Leest A. & Rijinders A. (1995): Does tumor control decrease by prolonging overall treatment time or interrupting treatment in laryngeal cancer? Radiother Oncol., 36: 177-82.
33. Foote RL., Grado GL., Buskirk SJ., *et al*. (1996): Radiation therapy for glottic cancer using 6-MV photons. Cancer, 77: 381-386.
34. Akine Y., Tokita N., Ogino T., *et al*. (1991): Radiotherapy of T1 glottic cancer with 6 MeV x-rays. Int J Radiat Oncol Biol Phys., 20: 1215-1218.
35. Izuno I., Sone S., Oguchi M., *et al*. (1990): Treatment of early vocal cord carcinoma with 60 Co gamma rays, 8/10 MV X-rays, or 4 MV X-rays – are the results different? Acta Oncol., 29: 637-639.
36. Devineni VR., King K. & Perez C. (1992): Early glottic carcinoma treated with radiotherapy: impact of treatment energy on sucess rate. Int J Radiat Oncol Biol Phys., 24: 106.
37. Teshima T., Chatani M. & Inoue T. (1990): Radiation therapy for early glottic cancer (T1N0M0). II. Prospective randomized study concerning radiation field. Int J Radiat Oncol Biol Phys., 118: 119–123.
38. Kim RY., Mark ME. & Salter MM. (1992): Early stage glottic cancer: importance of time-dose fractionation in radiation therapy. Radiology, 182: 273–5.
39. Schwaab G., Mamelle G., Lartigau E., *et al*. (1994): Surgical salvage treatment of T1/T2 glottic carcinoma after failure of radiotherapy. Am J Surg., 168: 474-475.
40. Lydiatt WM., Shah JP. & Lydiatt KM. (1996): Conservation surgery for recurrent carcinoma of the glottic larynx. Am J Surg., 172: 662-664.
41. McLaughlin MP., Parsons JT., Fein DA., *et al*. (1996): Salvage surgery after radiotherapy failure in T1-T2 squamous cell carcinoma of the glottic larynx. Head Neck 18: 229-235.
42. Watters GW., Patel SG. & Rhys-Evans PH. (2000): Partial laryngectomy for recurrent laryngeal carcinoma. Clin Otolaryngol., 25:146-152.

3/13/2012