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Original Article

Comparative study between single modality radiotherapy and concurrent chemoradiation for selected patients with early-stage laryngeal cancer

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Abstract: Unfavorable T2 glottic squamous cell carcinoma with impaired vocal cord mobility and/or bulky disease has been a real treatment challenge with high local failure rates. The purpose of this study is to compare the oncological outcome of unfavorable T2 glottic carcinoma in patients treated with radical radiotherapy versus concurrent chemoradiation. This study is a prospective, open label, randomized trial, in which all patients with unfavorable T2 glottic cancer were treated with either single modality radiotherapy using hypofractionation protocol 65.25 Gy (arm A) or concurrent chemoradiation (arm B) between 2019 and 2023. The primary end points were local control and local progression free survival (PFS). Sixty-two patients were recruited in the study. Local control was significantly higher in concurrent chemoradiation (CCRT) group compared to radiotherapy (RT) group. The 3-year local progression free survival rates were significantly higher in CCRT arm (85.5%) compared to RT arm (57.8%) (P=0.015). Concurrent chemoradiation should be considered for selected patients with T2 glottic squamous cell carcinoma with impaired vocal cord mobility and/or bulky disease due to high rate of local failure with radiotherapy alone.

Keywords: Glottis cancer, T2, impaired cord mobility, bulky disease, concurrent chemoradiation

Introduction

Worldwide, there are over 180,000 new cases of laryngeal cancer with about 100,000 deaths annually [1]. Laryngeal cancer occurs mostly in men, which reflects the effects of tobacco smoking. Glottic cancers represent about two-thirds of cases, while supraglottic and subglottic cancers represent one-third and 2% of laryngeal cancers respectively [2, 3].

Early laryngeal cancer includes stage I or II tumors with no evidence of thyroid cartilage invasion or lymph node involvement [4]. Early stage glottic cancer is treated with curative intent using local single therapeutic modalities to maximize locoregional control and survival [5, 6]. Both RT and larynx-preserving surgery (open partial laryngectomy and transoral laser microsurgery) are the most optimal treatment options. The two modalities offered similar five-year local control rates with variable functional outcomes in systematic reviews [7-9]. The choice between the two approaches depends on the expected post treatment functionality [10-13].

The use of primary radiotherapy in treating unfavorable T2 glottic carcinoma has resulted in high rates of local recurrences. Poor prognostic factors, such as impaired vocal mobility, bulky disease and vertical involvement of the anterior commissure (AC) were significantly associated with high local failures rates in patients with T2 glottic cancer treated with RT [14-16].

Therefore, multiple studies have investigated the role of concurrent chemoradiation (CCRT) in maximizing the oncological cure of T2 glottic cancer with unfavorable prognostic factors [17, 18]. However, the currently available evidence to support the use of chemoradiation in unfavorable T2 laryngeal cancers is still limited.

This study is planned to evaluate the oncological outcomes of concurrent chemoradiation compared to radical RT in patients with T2 glot-

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tic squamous cell carcinoma (SCC) with unfavorable prognostic factors and to assess the impact of different variables on their oncological outcomes.

Patients and methods

This is a prospective, open label randomized study that was carried out through the period from January 2019 to October 2023. Sixty-two patients with T2N0 glottic SCC were enrolled in this trial and randomized to receive either single modality radiotherapy (30 patients) or concurrent chemoradiotherapy (32 patients). The median follow-up period was 42 weeks. The study was approved by the research ethics committee, faculty of medicine, Tanta university (Approval code number: 36264PR64/1/23). An informed consent was signed by the patients before the study.

Inclusion and exclusion criteria

This study included patients with radiologically and histopathologically confirmed stage II glottic squamous cell carcinoma (T2N0M0). All patients had T2 glottic cancer, which was defined as tumor extending to supraglottis and/or subglottis, and/or with impaired vocal cord mobility, based on American Joint Committee on Cancer (AJCC) 8th edition [4]. Eligibility criteria include patients aged ≥18 years old with performance status 0-2 and patients diagnosed with T2 glottic cancer associated with unfavorable prognostic factors, such as impaired vocal cord mobility and/or invasive bulky disease. Exclusion criteria include patients diagnosed with glottic cancer with cervical lymph node metastases or distant metastases, previously treated with RT for head and neck cancer. Patients who missed their follow-up visits were also excluded.

Bulky glottic tumors defined as Large exophytic infiltrative lesions involving the entire vocal cord or at least more than two thirds of the vocal cord and horseshoe-shaped lesions involving more than the anterior one-third of both true vocal cords identical to that published by Reddy et al. [16].

Pre-treatment evaluation

A pretreatment evaluation was performed to all patients, including careful history taking, a complete head and neck examination, flexible laryngoscopy, and direct laryngoscopy under general anesthesia for tumor mapping. All patients had thin cuts CT scan of the neck with contrast and chest CT scan, when required. Baseline complete blood count and biochemical profile were obtained for all patients. The details of all patients were discussed in our head and neck cancer multidisciplinary tumor board for review of our treatment recommendations.

Treatment details

Radiotherapy: Radiotherapy (RT) for glottic cancer was delivered using 3-dimensional conformal radiotherapy (3DCRT) techniques or intensity modulated radio therapy (IMRT) with a 6 MV linear accelerator.

In hypofractionated radiotherapy arm, the clinical target volume (CTV) covered the entire larynx, including glottis, part of supraglottic region cranially to thyroid notch, and subglottic region caudally to cricoid cartilage (may extend to first tracheal ring with subglottic extension). Planning target volume included a 5 mm from CTV. In this group, patients received 65.25 Gy/2.25-Gy daily/29 fractions (hypofractionation protocol based on NCCN guidelines).

In concurrent chemoradiotherapy arm (CCRT), CTV 60 Included the entire larynx, from the caudal edge of the hyoid or the top of the thyroid notch to the bottom of the cricoid cartilage and extend caudally with subglottic extent. We included level II-IV cervical lymph nodes in CTV 54, gross lesion boosted to 70 Gy.

Concurrent chemotherapy: The patients in arm B received cisplatin (40 mg/m^2 weekly). Carboplatin (AUC=2 weekly) was used as an alternative for some patients with significant hearing or renal impairment.

Follow-up

A complete history taking and head and neck examination with flexible laryngoscopy was performed for almost all patients every 2 months for the first 2 years and every 6 months thereafter. All patients should be asked for any suspicious features of recurrence, including hoarse voice, stridor, sore throat, dysphagia, and neck lumps. Once local recurrence was suspected

Table 1. Patient characteristics

Characters	Arm A (RT)		Arm B (CCRT)		Total		*p*
	n (30)	%	n (32)	%	n	%	
Age							0.450
>61	14	46.7	18	56.3	32	51.6	
<61	16	53.3	14	43.8	30	48.4	
Gender							0.562
Male	26	86.7	26	81.2	52	83.9	
Female	4	13.3	6	18.8	10	16.1	
Smoking status							0.311
Yes	18	60	22	68.8	40	64.5	
No	10	33.3	10	31.2	20	32.3	
Ex	2	6.7	0	0	2	3.2	
Differentiation							0.924
Well	4	13.3	4	12.5	8	12.9	
Moderate	18	60	18	55.3	36	58.1	
Poor	8	26.7	10	31.2	18	29	
VC impairment							0.056
Yes	23	76.7	30	93.8	53	85.5	
No	7	23.3	2	6.3	9	14.5	
AC involvement							0.469
Yes	17	56.7	21	65.6	38	61.3	
No	13	43.3	11	34.3	24	38.7	
Extensive/bulky disease							0.158
Yes	22	73.3	28	87.5	50	80.6	
No	8	26.7	4	12.5	12	19.4	
RT technique							0.097
3DCRT	19	63.4	13	40.7	32	51.6	
IMRT	11	36.6	19	59.3	30	48.4	

Abbreviations: RT, radiotherapy; CCRT, concurrent chemoradiation; VC, vocal cord; AC, anterior commissure; 3DCRT, 3Dimentional conformal radiotherapy; IMRT, intensity modulated radiotherapy.

on flexible laryngoscopy, follow-up neck CT scan with contrast was obtained with direct laryngoscopy and biopsy for histopathological confirmation. Timing of local, regional, and/or distant recurrence was reported with the required salvage treatment.

Clinical end points

The primary endpoints were local control and local progression free survival (PFS). Local or regional control was defined as freedom from local or regional failure. The Local PFS is a time interval to documented locoregional recurrence or death from any cause, whichever occurred first.

The secondary endpoints were overall survival (OS) and Treatment related toxicities. Overall survival is defined as death from any cause from the time of randomization until the end of follow-up. Toxicities were reported and scored according to morbidity criteria of common terminology criteria of adverse events (CTCAE), version 5 one month after RT completion and during follow-up visits for acute and late toxicity effects.

Statistical analysis

The patients baseline features, treatment modalities and treatment related toxicities were compared using the chi-square test for categorical variables.

The survival outcomes were calculated by The Kaplan-Meier technique and differences were compared using the log-rank test. Cox proportional hazards modeling was used for Univariate and multivariate analysis. *P* value <0.05 was significant.

We estimated that the trial would have 80% power to detect a hazard ratio for local PFS using a log-rank test with a two-sided significance level of 0.05. We further assumed that 5% of the patients would discontinue treatment through the trial.

Results

Sixty-two participants were randomly assigned in this study and completed the entire course of treatment and follow-up duration. The median age was 61 (46-83) years old, most of cases are male patients (83.9%). Fifty-three (85.5%) patients had vocal cord (VC) impairment, fifty (80.6%) patients had bulky disease, and thirty-eight (61.3%) patients had vertical involvement of the anterior commissure. Forty-one (66.1%) patients had bulky lesion and VC impairment. No significant difference was found between the treatment arms in terms of age, gender, history of smoking, tumor grade, VC impairment,

Table 2. Local control and prognostic factors

Local control	Yes		No		*p*
	n	%	n	%	
Age					0.456
>61	26	54.2	6	42.9	
<61	22	45.8	8	57.1	
Gender					0.299
Male	39	81.3	13	92.9	
Female	9	18.8	1	7.1	
Smoking status					0.408
Yes	29	60.4	11	78.6	
No	17	35.4	3	21.4	
Ex-smoker	2	4.2	0	0	
Grade					0.776
G1	6	12.5	2	14.3	
G2	27	56.3	9	64.3	
G3	15	31.2	3	21.4	
VC impairment					0.404
Yes	42	87.5	11	78.6	
No	6	12.5	3	21.4	
AC involvement					0.717
Yes	30	62.5	8	57.1	
No	18	37.5	6	42.9	
Extensive/bulky disease					0.037*
Yes	36	75	14	100	
No	12	25	0	0	
Treatment modality					0.010*
CCRT	29	60.4	3	21.4	
RT	19	39.6	11	78.6	

Abbreviations: VC, vocal cord; AC, anterior commissure; RT, radiotherapy; CCRT, concurrent chemoradiation. *p<0.05 (significant).

bulky lesion or anterior commissure (AC) involvement. Patient features are presented in (**Table 1**).

Local control

The median duration of follow-up was 42 months (range, 12-72 months). Forty-eight patients achieved local control in both arms [twenty-nine patients (90.6%) in the CCRT arm compared to 19 patients (63.3%) in the RT arm (**Table 2**)]. Local control was significantly higher in CCRT group compared to RT group (*P*=0.010). Also, the absence of bulky glottic disease was significantly associated with better local control (*P*=0.037). Recurrences were reported in a total of 14 patients (3 patients in the CCRT arm and 11 in the RT arm).

Local progression free survival

The 3-year Local PFS for all patients was 71.4% (**Figure 1A**). The 3-year Local PFS was significantly higher in the CCRT arm compared to the RT arm (85.5% vs. 57.8%, P=0.015) (**Figure 1B**).

The 3-year local PFS rates were 62.3% for patients with bulky glottic lesion. The difference was statistically significant (*P*=0.031) (**Table 3**).

Head and neck examination with flexible laryngoscopy was performed for almost all patients every 2 months for the first 2 years to reveal any progression or to confirm the local control (**Figure 3**).

On univariate analysis, concurrent chemoradiation and absence of bulky disease were significantly associated with improvement of the 3-year local PFS rate. Multivariate analysis confirmed that chemoradiation is an independent variable for local relapse [*P*=0.011, HR=5.273, 95% CI (1.459-9.055)] (**Table 3**).

Salvage therapy

In the hypofractionated arm, eight patients out of 11 developed local recurrences and 3 patients had isolated regional recurrences in cervical lymph nodes. Salvage surgical therapy was offered to seven patients with a local and/or regional recurrence in hypofractionated radiotherapy arm; six patients underwent salvage laryngectomy, and one patient had a neck dissection alone. The remainder either refused surgery or were medically unfit for salvage surgery.

In the concurrent chemoradiation arm, 2 patients developed local recurrences, and one patient developed locoregional recurrence. Two patients underwent salvage laryngectomy, and the third refused salvage surgery.

Overall survival

The median overall survival rates (OS) were 86% (**Figure 2A**). The 3-year OS for the CCRT and RT arms were 93.2% and 77.1%, respec-

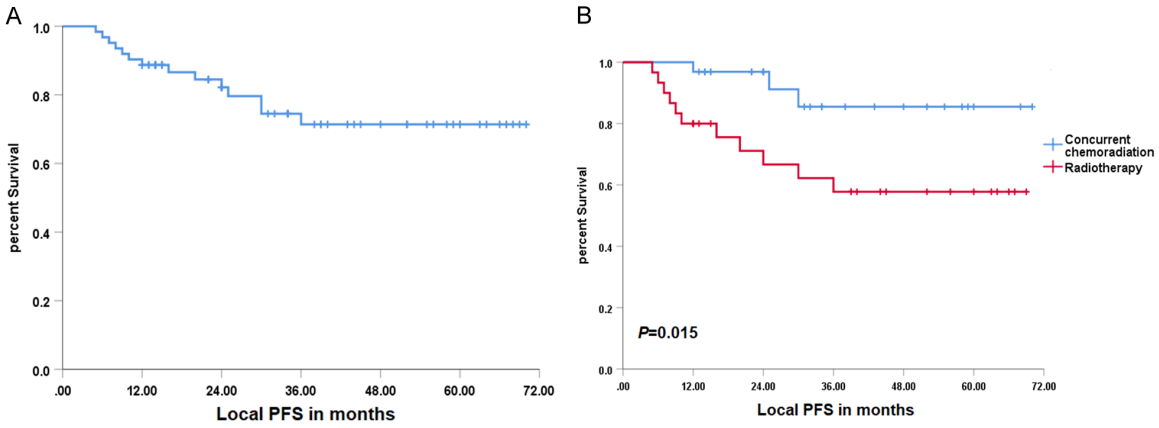

Figure 1. A. Kaplan Myer curve of local progression free survival for 62 patients in both treatment groups. B. Kaplan Myer curve of local progression free survival for 30 patients received radiotherapy and 32 patients received concurrent chemoradiation.

Table 3. Univariate and multivariate prognostic factors analysis for local progression free survival

Variables	Univariate		Multivariate	
	P	HR (95% C.I.)	P	HR (95% C.I.)
Age	0.778	1.165 (0.402-3.371)		-
Smoking	0.477	0.493 (0.152-1.603)		-
Grade	0.960	0.985 (0.422-2.302)		-
VC impairment	0.506	0.511 (0.427-5.511)		-
AC involvement	0.810	1.139 (0.394-3.292)		-
Bulky disease	0.031*	3.044 (1.002-5.691)	0.071	0.153 (0.020-1.177)
Treatment modality	0.015*	4.271 (1.189-7.344)	0.011*	5.273 (1.459-9.055)

Abbreviations: VC, vocal cord; AC, anterior commissure. *p<0.05 (significant).

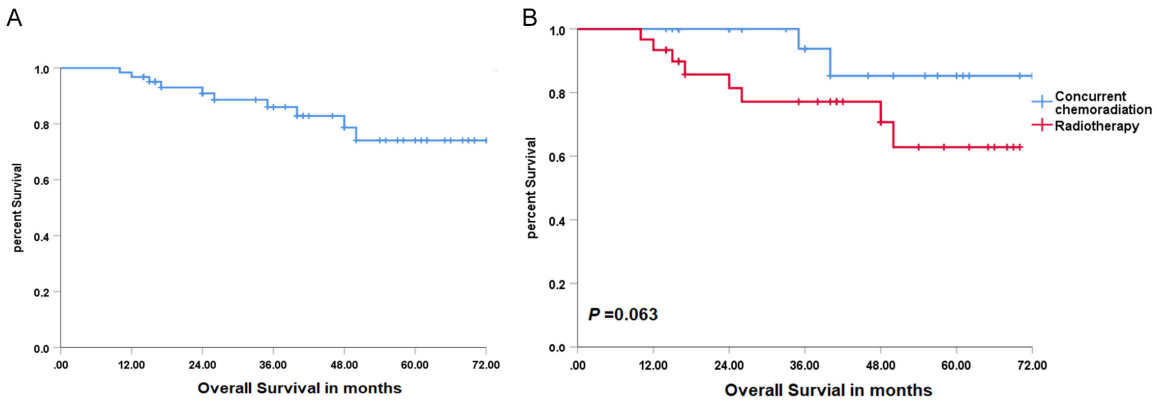

Figure 2. A. Kaplan Myer curve of overall survival for 62 patients with unfavorable T2 glottic caner. B. Kaplan Myer curve of overall survival for 30 patients received RT and 32 patients received chemoradiation.

tively (*P*=0.063; **Figure 2B**). In the univariate analysis, there was no significant correlation between other prognostic factors and OS (**Table 4**).

Treatment related toxicity

Radiation mucositis (grade 2-3) was significantly higher in CCRT arm (P=0.001). Grade 3 dys-

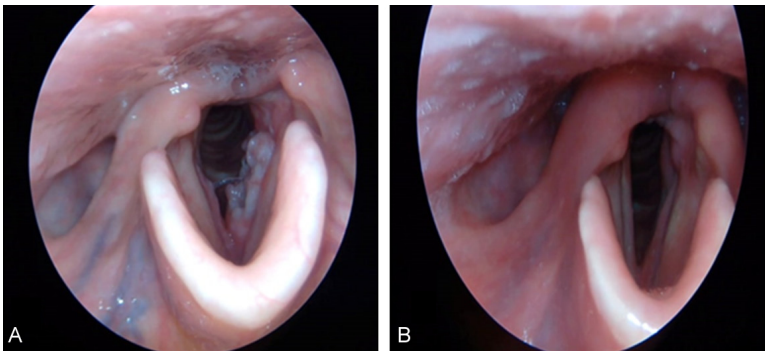

Figure 3. Laryngoscopic view of T2 bulky glottic cancer with impaired mobility. A. Before chemoradiation. B. After 2 years follow up.

Table 4. Univariate and multivariate prognostic factors analysis for overall survival

Variables	Univariate		Multivariate
	P	HR (95% C.I.)	
Age	0.659	0.773 (0.247-2.424)	-
Smoking	0.325	0.493 (0.121-2.016)	-
Grade	0.545	1.065 (0.471-2.409)	-
VC impairment	0.554	0.636 (0.137-2.942)	-
AC involvement	0.369	1.757 (0.541-6.013)	-
Extensive/bulky disease	0.226	0.384 (0.082-1.806)	-
Treatment modality	0.063	6.87 (0.495-1.654)	-

phagia was significantly higher in CCRT arm (P=0.033). Seven patients in the CCRT arm required hospitalization due to decreased oral intake. No patients required placement of a percutaneous gastrectomy tube during treatment in both arms. Grade 1-2 of skin toxicity, pain and fatigue were observed in both groups with no significant difference. Treatment related toxicities in both arms are listed in **Table 5**.

Discussion

Although T1 and T2 are heterogenous regarding the extent of the disease and mobility of VC, the NCCN guidelines recommend single modality RT for early stage, node-negative (T1-2N0) glottic cancer [19]. The current study is the first to evaluate the oncological outcome of radiotherapy versus concurrent chemoradiation for highly selected T2 glottic cancer specifically with impaired cord mobility and/or bulky invasive. Impaired vocal cord mobility is a poor prognostic indicator of local control in the patients with early-stage laryngeal cancer [14].

In our study, the addition of chemotherapy concurrent with RT improved local control in this subset of patients with unfavorable features compared to single modality RT. Two studies by Khan MK and Trotti A, documented lower local control for T2 glottic cancer with impaired vocal cord mobility treated with radiotherapy alone when compared with T2 cancers without impaired cord mobility, the 5-year local control rates for T2b were 65% and 63% respectively [15, 17].

In the current study, the 3-year Local PFS was significantly higher in the CCRT arm compared to the RT arm (85.5% vs. 57.8%, P=0.015). In 2022, Alexandra et al. evaluated the oncological outcome of early stage glottic cancer treated with hypofractionated radiotherapy with or without concurrent chemotherapy [20], where the 2-year local control among patients with impaired cord mobility was (88% vs. 61%, *P*=0.12) in agreement with our results. A multi-institutional Japanese study reported comparable results with the addition of chemotherapy to RT arm (5-year local control for T2 glottic cancer with RT alone 64.4% versus 80.7% in CCRT arm) [21].

Although VC impairment, AC involvement and bulky disease are considered as poor prognostic factors, they did not affect the local control, in agreement with other studies [20, 22, 23]. Although our univariate analysis clarified that chemoradiation and absence of bulky disease were significant prognostic factors associated with improvement of local PFS, the multivariate analysis confirmed that chemoradiation is an independent variable for local control [*P*=0.011, HR=5.273, 95% CI (1.459-9.055)].

No difference in 3-year OS was reported among patients who received CCRT compared with those who received RT alone. The 3-year OS for the CCRT and RT arms were 93.2% and 77.1%,

Table 5. Treatment related toxicity

Toxicity	CCRT arm		RT arm		*P*
	n	%	n	%	
Radiation dermatitis					0.081
G1	20	62.5	25	83.3	
G2	12	37.5	5	16.7	
Radiation mucositis					0.001*
G1	0	0	11	36.6	
G2	26	81.2	19	63.4	
G3	6	18.8	0	0	
Dysphagia					0.033
G1	6	18.8	15	50	
G2	19	59.2	12	40	
G3	7	22	3	10	
Pain					0.322
G1	12	37.5	14	46.6	
G2	20	62.5	16	53.3	
Fatigue					0.342
G1	10	31.2	12	40	
G2	22	68.8	18	60	

Abbreviations: RT, radiotherapy; CCRT, concurrent chemoradiation. *p<0.05 (significant).

respectively (*P*=0.063), including the subgroups with VC impairment, bulky disease or AC involvement, similar to other considerable studies [20, 22].

Altered fractionation (eg, accelerated fractionation or hyper fractionation) may improve local control in patient with T2 glottic cancer [24, 25]. Radiation Therapy Oncology Group 9512 compared hyper fractionation versus conventional fractionation in T2 glottic cancer, the trial showed modest improvement of 5-year local control with hyper fractionation versus standard fractionation (78% vs. 70%) and the outcomes in the T2b subset remained inferior (63%) [17]. In our trial we used the hypofractionation protocol in agreement with NCCN guidelines.

Detailed comprehensive studies are required to settle a more accurate definition of T2 glottic disease and analyze the impact of treatment intensification for patients with unfavorable T2 glottic cancer, either with altered RT fractionation or use of concurrent systemic therapy with alternative agents.

Conclusion

The current study suggests modification of T2 glottic cancer staging and treatment. The T2 glottic cancer should be sub-classified as favorable and unfavorable T2 stage based on presence or absence of negative prognostic factors specifically impaired vocal cord mobility and bulky disease. Single modality radiotherapy may be more considerable for favorable T2 glottic lesion. Concurrent chemoradiation should be considered for unfavorable T2 glottic cancer with impaired vocal cord mobility and/or bulky disease due to high rate of local failure with radiotherapy alone.

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Disclosure of conflict of interest

None.

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