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ORIGINAL ARTICLE

Induction chemotherapy followed by radiation versus concurrent chemoradiation in supraglottic laryngeal cancer

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Abstract

Background: *Laryngeal cancer is the most prevalent malignancy affecting the upper aero-digestive tract. The management of locally advanced laryngeal cancer has transitioned from an initial strategy involving primary surgical intervention and/or radiotherapy to contemporary multi-modal approaches that encompass definitive concurrent chemoradiation (CCRT).*

Objective: *This study aimed to evaluate the effectiveness of concurrent chemo-radiotherapy and induction chemotherapy followed by radiation in supraglottic laryngeal carcinoma.*

Methods: *A Quasi-experimental study was accomplished in the Department of Radiotherapy of Rajshahi Medical College Hospital, Rajshahi, Bangladesh from July 2020 to June 2021. Sixty patients were selected purposively with biopsy-proven squamous cell carcinoma of the supraglottic laryngeal region. Total patients were divided into two equal groups non- randomly. Thirty Arm-A group were treated by concurrent chemo-radiotherapy and 30 Arm-B group patients were treated by induction chemotherapy followed by radiation. Data analysis was done by using the SPSS version 25.0 program.*

Result: *In this study, the male to female ratio was 14:1, with a mean age of 55.8±7.7 years in Arm A and 57±6.8 years in Arm B. The overall response rate was higher in Arm A (80%) compared to Arm B (63.3%), but this difference was not statistically significant (p=0.251). While functional organ preservation was achieved in more patients in Arm A (83.3%) than in Arm B (63.3%), this outcome also did not reach statistical significance (p=0.079). Although toxicities were more common in the concurrent chemoradiation (CCRT) group, these differences were not statistically significant, and all toxicities were effectively managed.*

Conclusion: *Induction chemotherapy followed by radiotherapy is equally effective as concurrent chemoradiation for patients with locally advanced supraglottic laryngeal cancer, in terms of local control and preservation of laryngeal function without any added toxicities and may be reasonable approach in low resource set-up.*

Keywords: *Chemotherapy, Radiation, Chemoradiation, Laryngeal cancer, Larynx*

Introduction

Laryngeal cancer is the most common cancer of the upper aero-digestive tract.[1] In Bangladesh, laryngeal cancer is ranked as the 9th most common cancer, with 3.4% new cases per year and 3% deaths per year.[2] Squamous cell carcinomas account for the vast majority of laryngeal tumors.[3] Supraglottis constitutes approximately one-third of all laryngeal cancers.[4] Among laryngeal cancer cases, roughly 29% are classified as locally advanced according to TNM staging, encompassing stages III-IVB.[5] The management of laryngeal cancer has long been a subject of debate. However, it is well-established that a multidisciplinary approach is essential.6 Combined regimens of chemotherapy and radiotherapy are increasingly employed as the primary treatment, as supported by meta analyses showing a survival benefit.[7] Concurrent chemoradiation (CCRT) has emerged as a promising approach for the treatment of stage III and IV laryngeal cancer in cases where patients have intact cartilage and a functional larynx. But the patients with cartilage destruction or a

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dysfunctional larynx may not be candidates for organ preservation with CCRT.[8] This reflects the evolving landscape of laryngeal cancer treatment, aiming to achieve both survival and preservation of laryngeal function.[9] Although marginal survival benefit was found with induction chemotherapy which was statistically non-significant, but still induction chemotherapy could be an acceptable treatment strategy for locally advanced supraglottic cancer as 60-90% response rate had been found in treating locally advanced head & neck squamous cell carcinoma (LAHNSCC) with induction chemotherapy with radiation.

Moreover it aids in organ preservation which is difficult in cartilage destructed laryngeal cancer with definitive CCRT and also helps in reducing distant failure which has been emerged more frequently with definitive CCRT even despite a good locoregional control.[8,10] Three-drug combination of docetaxel, cisplatin, and fluorouracil has been found to be superior when compared to fluorouracil and cisplatin in terms of larynx preservation (74% vs 58% at 5 year) and response rate (80% vs 59%).[11] 70% response rate had been demonstrated with paclitaxel and carboplatin doublet with an acceptable laryngeal preservation by Dietz et al. 2009.[12] Although overall survival was unchanged by the addition of induction chemotherapy, considering the facts of organ preservation, less distant failure and non-inferior OS this study was conducted at our low resource set-up where it had been very difficult to enroll patients for definitive CCRT due to high patients burden. The objective of this study was to evaluate the effectiveness of concurrent chemo-radiotherapy and induction chemotherapy followed by radiation in supraglottic laryngeal carcinoma.

Methods

During the period from July 2020 to June 2021, a quasi experimental study was conducted at the Department of Radiotherapy at Rajshahi Medical College Hospital. The study focused on sixty patients who had biopsy confirmed squamous cell carcinoma of the supraglottic laryngeal region. These patients were divided into two groups: Arm A. consisting of 30 individuals, received intravenous Cisplatin at a dose of 40 mg/m² weekly for six weeks, concurrent with radiotherapy of 66 Gray administered in 33 fractions of 2 Gray each via Cobalt 60 External Beam Irradiation. Arm B, also comprised of 30 patients, underwent induction chemotherapy involving intravenous Paclitaxel (175 mg/m² given over 3 hours on day 1) and intravenous Carboplatin (administered with an AUC of 6 on day 1) every three weeks for a total of three cycles. This was followed by radiotherapy with 66 Gray delivered in 33 fractions of 2 Gray each using Cobalt 60 External Beam Irradiation.

Inclusion Criteria

- Patients with histology confirmed locally advanced laryngeal cancer (stage III to IVB).
- Patients' performance status (ECOG score < 2).
- Patients of age 18 to 75 years of both sexes.

Exclusion Criteria

- Patients with a history of prior radiotherapy to the head and neck region within the last three years.
- Initial surgery (excluding diagnostic biopsy) of the primary site.
- Patients with double primaries.
- Serious concomitant medical illnesses include severe cardiac disease, uncontrolled diabetes mellitus, hypertension or renal diseases, and the COVID-19 pandemic.

Patients were assessed weekly during treatment and after treatment 4 weekly up to 12 weeks. Tumor response was evaluated according to the RECIST 1.1 (Response Evaluation Criteria in Solid Tumors, version 1.1, 2008. ECOG performance status was assessed to evaluate the quality of life of the patients. To assess acute toxicity, the national cancer institute Common Terminology Criteria for Adverse Events, v.5.0 was used.[11] The final response and toxicity evaluation was carried out through clinical examination, functional organ preservation assessment, and relevant imaging.

Data analysis was performed using the SPSS (Statistical Package for Social Science) software program for Windows, version 25.0. The results were presented through tables, figures, and diagrams. Microsoft excel had been used for graph/chart. All reported p-values are two-sided, and statistical significance was considered at $p < 0.05$ at 95% confidence interval, determined through the Chi-square test.

The research protocol received approval from the Institutional Review Board and the Ethical Committee of Rajshahi Medical College.

Result

In this study, the mean age of the patients in the Arm A group was 55.8+7.7 years. and in the Arm-B group, it was 57.0+6.9 years, with majority of patients

(48.33%) fell within the age group of 50-59 years. Most of the patients (93.3% in both groups) were male in both groups. Regarding the TNM stage, stage III, stage IVA and stage-IVB were found in 56.7% vs 60%, 60% vs 36.7% and 6.7% vs 3.3% patients in Arm A, Arm B. The majority of patients in both Arms had a tumor category of T3, with 26 patients in this category. The next largest group had a T4a category, with 24 patients. A total of 42 patients across both arms were node-positive, while 18 were node negative. The most common histological finding in both arms was poorly differentiated squamous cell carcinoma, with 29 patients presenting with this type. ECOG performance status was almost equally distributed in both the groups between PS 0-2 (Table I).

Table I

Disease characteristics of the patients

Characteristics		Arm-A	Arm-B	p-value
Mean age		55.8±7.7	57.0±6.9	>0.05
	Male	28	28	
Sex	Female	2	2	>0.05
	T1	2	2	
	T2	2	3	
T stage	T3	13	13	>0.05
	T4a	13	9	
	T4b	0	1	
	NO	8	10	
	N1	12	8	
N stage	N2	8	12	>0.05
	N3	2	0	
	Stage-III	17	18	
Stage group	Stage-IVA	11	11	>0.05
	Stage-IVB	2	1	
	Well differentiated	9	6	
Differentiation	Moderately differentiated	7	9	>0.05
	Poorly differentiated	14	15	
	0	10	11	
ECOG PS	1	9	6	>0.05
	2	11	13	

Hoarseness of voice (86.7% in Arm-A and 80% in Arm-B) was the commonest symptoms experienced by the patients in both groups. Dysphagia was present in 26.7% of Arm-A and 16.7% of Arm-B patients. Neck node enlargement occurred in 73.3% of Arm-A and 66.7% of Arm-B patients. Otalgia was reported by 3.3% in Arm-A and 6.7% in Arm-B. Cough or haemoptysis was observed in 3.3% of Arm-A and 6.7% of Arm-B. No statistically significant differences in presenting symptoms were found between the two groups (p>0.05) (Table II)

Table II

Distribution of presenting symptoms

Symptoms	Arm A N	%	Arm B n	%	p-value
Hoarseness of voice	26	86.7	24	80	0.488
Dysphagia	8	26.7	5	16.7	0.347
Neck node	22	73.3	20	66.7	0.573
Referred otalgia	1	3.3	2	6.7	0.553
Others	1	3.3	2	6.7	0.553

After 12 weeks, complete clinical response was observed in 80% of patients in Arm-A and 63.3% of patients in Arm-B. Partial clinical response occurred in 20% of Arm-A patients and 36.6% of Arm-B patients (Figure 1).

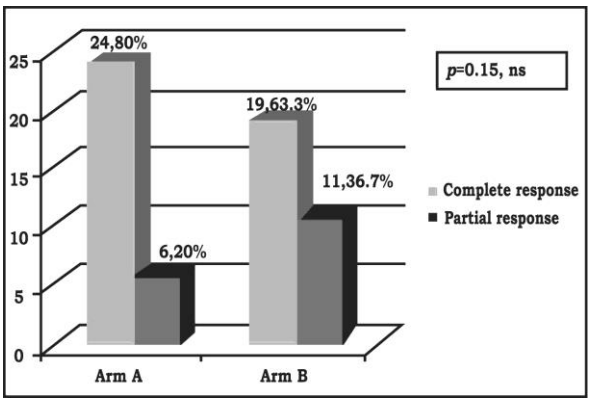

Figure 1: Overall response after 12 weeks

When considering the TNM stage analysis, it is noteworthy that the majority of patients in stage III demonstrated a complete response, with 94.1% in Arm-A and 66.7% in Arm-B (Table III).

Table III

Response of primary tumor as per TNM stage

Respondents	TNM stage	Complete response n	%	Partial response n	%	p-value
Arm A (n=17)	III	16	94.1	01	5.9	
Arm B (n=18)		12	66.7	06	33.3	0.042*
Arm A (n=11)	IVA	08	72.7	03	27.3	
Arm B (n=11)		07	63.3	04	36.7	>0.05
Arm A (n=2)	IVB	0	0.0	02	6.7	
Arm B (n=1)		0	0.0	01	3.3	>0.05

[* Significant]

n the final follow-up, functional larynx was present in 83.3% of patients in Arm-A and 63.3% in Arm-B. Hoarseness of voice was a common issue, affecting 60% of patients in both arms. Normal voice quality or speech was observed in 30% of patients in Arm-A and 23.3% in Arm-B. A small proportion of patients, 10% in Arm-A and 30% in Arm-B, had a whispering voice.

Swallowing ability was generally retained, with 86.7% in Arm-A and 80% in Arm-B able to swallow, while 13.3% in Arm-A and 20% in Arm-B experienced difficulties with swallowing. Before initiating treatment, tracheostomy tubes were present in 36.7% of patients in Arm-A and 40% in Arm-B. During treatment, only 1 patient in Arm-A required emergency tracheostomy. Following treatment, 10% of patients in Arm-A and 20% in Arm-B remained tracheostomy-dependent (Table IV).

Table IV

Treatment response according to functional outcome

Functional outcome	Arm		ArmB		p-value
	n	%	n	%	
	Status of larynx				
Functional larynx	25	83.3	19	63.3	0.566
	Voice quality speech				
Normal voice	9	30	7	23.3	0.153
Hoarseness of voice	18	60	14	46.7	
Whisper	3	10	9	30	
	Swallowing				
Able to swallow	26	86.7	24	80	0.488
Difficulty in swallowing	4	13.3	6	20	
	Persistent tracheostomy				
Pretreatment tracheostomy	11	36.7	12	40	0.078
Treatment tracheostomy	1	3.3	0	0	
Post-tracheostomy	3	10	6	20	
No Tracheostomy	15	50	12	40	

In terms of acute toxicities, the majority of patients in both arms experienced Grade I and II toxicities. While there was no statistical significance, it's worth noting that toxicities were more common in Arm A compared to Arm B. Importantly, no Grade IV toxicities were observed in any patient in either group (Table V)

Table V

Overall toxicity assessment in two groups

Toxicity	Grade	Arm A		Arm B		p-value
		n	%	n	%	
Anaemia	GI	8	26.7	9	30	0.765
	G2	3	10	6	20	
	G3	2	6.7	2	6.7	
Oral mucositis	GI	13	43.3	10	33.3	0.923
	62	12	40	10	33.3	
	G3	2	6.7	1	3.3	
Skin reaction	GI	10	33.3	10	33.3	0.944
	G2	7	23.3	8	26.7	
	G3	3	10	4	13.3	
Vomiting	GI	7	23.3	4	13.3	0.882
	G2	6	20	5	16.7	
	G3	1	3.3	1	3.3	
Diarrhoea	GI	4	3.3	3	10	0.62
	G2	3	10	2	6.7	
	G3	0	0	0	0	
Weight loss	G1	4	13.3	4	13.3	0.808
	G2	3	10	4	13.3	
	G3	0	0	0	0	
Nephrotoxicity	G1	3	10	6	20	0.851
	G2	2	6.7	5	16.7	
	G3	1	3.3	1	3.3	
Dysphagia	G1	6	20	9	30	0.936
	G2	5	16.7	7	23.3	
	G3	2	6.7	2	6.7	
Aspiration pneumonia	GI	2	6.7	2	6.7	0.716
	G2	1	3.3	2	6.7	
	G3	2	6.7	1	3.3	
Laryngeal oedema	GI	2	6.7	2	6.7	0.667
	G2	1	3.3	2	6.7	
	G3	1	3.3	0	0	

Discussion

In this study, the mean age of diagnosis was 56.4 years, with a majority of patients falling in the 50 to 59 age group. This age distribution may be attributed to weakened immune systems and genetic repair mechanisms in older individuals. Similar age distributions were reported in previous studies.[13,14] The male-female ratio in this study was 14:1, consistent with findings from another study in Bangladesh.[15-17] In contrast, Western countries often have a ratio of 5-6:1, possibly due to factors like smoking and alcohol consumption among females.[4] Numerous studies have established a correlation between smoking, alcohol, and larynx cancer development.[16,17] While alcohol is common in the Western world, tobacco leaf/jorda is prevalent in our

region.[16,17] Although poorly differentiated squamous cell carcinoma is far less than well differentiated and moderately differentiated variety,[18] in this study the major histologic grade was poorly differentiated (48.3%). Some studies had demonstrated about the high prevalence of poorly differentiated squamous cell cancer.[19] In terms of response to treatment in both groups, concurrent chemotherapy yielded an 80% complete response and a 20% partial response, while induction chemotherapy followed by radiotherapy resulted in a 63.3% complete response and a 36.7% partial response. These findings were consistent with those reported by Rana et al. in 2020.[20] and Das et al. in 2021 but Dietz et al. 2009 demonstrated a bit lower rate of overall response (70%) with induction chemotherapy using paclitaxel cisplatin doublet followed by radiotherapy.[21] The dominance of stage- could be the reason for lower response rate.[12] Another possible reason for higher response rate in the current study would be the fewer sample size as highest amount of response rate was observed with docetaxel, cisplatin, 5-FU regimen in phase-3 RCT.[11] When analyzing this response, the study also examined the relationship between the performance status of patients and the TNM staging of the tumor. Stage III patients demonstrated a better complete response, with rates of 94.1% in Arm-A and 60% in Arm-B, respectively. Responses in stages IVA and IVB in both groups were less convincing. Partial responses displayed a similar distribution in stage III and stage IV in both groups. These results align with previous research.[22,23] At the final follow-up, functional larynx preservation was achieved in 83.3% of patients in Arm-A and 63.3% in Arm-B, which aligned with the results of previous studies.[11,24,25] Voice quality did not significantly improve after treatment, with 30% of patients in Arm-A and 23.3% in Arm-B having normal speech. Hoarseness persisted in 60% and 46.7% of patients in Arm-A and Arm-B, respectively. Some patients in both groups experienced minor swallowing difficulties, with rates of 13.3% in Arm A and 20% in Arm B. These results were consistent with findings from other studies.27 One of the major drawback is concerned about induction chemotherapy is treatment related mortality. 5% incidence of treatment induced mortality in the sequential arm compared to 0% in the CCRT arm had been seen in the phase 3 clinical trial named 'DeCIDE.[26] But in this study none of patient had experienced treatment related death. Toxicities were similar between two groups. The most notable toxicities in both groups included oral mucositis and skin reactions, while anemia and dysphagia were not uncommon. This study employed a non randomized sampling technique and faced limitations such as the inability to perform MRI of the head-neck region due to financial constraints and the use of conventional radiation planning. Additionally, the study was conducted at a single hospital with a relatively small sample size, which may limit the generalizability of the results to the broader community.

Conclusion

The study findings indicate that concurrent chemoradiation and induction chemotherapy followed by radiation are comparably effective in the treatment of supraglottic laryngeal carcinoma. Additionally, the functional outcomes and immediate toxicity levels associated with both treatment approaches appear to be quite similar. These results suggest that both strategies can be considered as viable options for managing this particular form of laryngeal carcinoma, offering flexibility in treatment selection without significantly compromising treatment effectiveness or immediate patient outcomes.

References

1. Deng Y, Wang M, Zhou L, Zheng Y, Li N, Tian T, et al. Global burden of larynx cancer, 1990-2017: estimates from the global burden of disease 2017 study. Aging (Albany NY) 2020; 12: 2545
2. Globocan 2020: Incidence, Mortality and Prevalence by cancer site Global Cancer Observatory, March, 2021
3. Chu EA, Kim YJ. Laryngeal cancer: diagnosis and preoperative work-up. Otolaryngologic Clinics of North America. 2008; 41: 673-95
4. American Cancer Society. Cancer Facts & Figures 2019. Atlanta: American Cancer Society; 2019
5. Pazdur R, Wagman LD, Camhausen KA, Hoskins WJ. Cancer Management: A Multidisciplinary Approach, 13th edn. New York: UBM Medica LLC: 2010
6. Chen AY, Schrag N, Hao Y, Flanders W D, Kepner J, Stewart A, Ward E. Changes in treatment of advanced laryngeal cancer 1985-2001. Otolaryngology-Head and Neck Surgery. 2006; 135: 831-7
7. Pignon JP, Le Maitre A, Maillard E, Bourhis J, Mach-Nc Collaborative Group. Meta- analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiotherapy and oncology. 2009; 92: 4-14
8. Bhattacharyya T, Kainickal CT. Current status of organ preservation in carcinoma larynx. World journal of oncology. 2018; 9: 39

9. Yang ES, Murphy BM, Chung CH, Netterville JL, Burkey BB, Gilbert J, et al. Evolution of clinical trials in head and neck cancer. Critical Reviews in Oncology/ Hematology. 2009; 71: 29-42
10. Brockstein B, Vokes EE. Concurrent chemoradiotherapy for head and neck cancer. InSeminars in oncology. WB Saunders 2004; 31: 786-793
11. Janoray G, Pointreau Y, Garaud P, Chapet S, Alfonsi M, Sire C, et al. Long-term results of a multicenter randomized phase III trial of induction chemotherapy with cisplatin, 5-fluorouracil, ±docetaxel for larynx preservation. Journal Of The National Cancer Institute. 2016; 108: 368
12. Dietz A, Rudat V, Dreyhaupt J, Pritsch M, Hoppe F, Hagen R, ey al. Induction chemotherapy with paclitaxel and cisplatin followed by radiotherapy for larynx organ preservation in advanced laryngeal and hypopharyngeal cancer offers moderate late toxicity outcome (DeLOS-I-trial). European archives of oto-rhino-laryngology. 2009; 266: 1291-300
13. Selim MS, Islam MM, Rahim MM, Zafar MH, Asad MK, Rahman MM. Topographical Distribution of Carcinoma Larynx. Bangladesh Journal of Otorhinolaryngology. 2018; 24: 56-61
14. Sheahan P. Management of advanced laryngeal cancer. Rambam Maimonides Medical Journal. 2014; 5:p
15. Khan JA, Siddque MA, Haque MN, Kundu SC, Ahmed MU, Bhuiyan AS. Etiology of Laryngeal Squamous Cell Carcinoma: Study of 50 Cases in Mymensingh Medical College Hospital. Mymensingh Medical Journal: MMJ. 2015; 24: 492-6
16. Menach P, Oburra HO, Patel A. Cigarette smoking and alcohol ingestion as risk factors for laryngeal squamous cell carcinoma at Kenyatta National Hospital, Kenya. Clinical Medicine Insights: Ear, Nose and Throat. 2012; 5: CMENT-S8610
17. Goldenberg D, Lee J, Koch WM, Kim MM, Trink B, Sidransky D, Moon CS. Habitual risk factors for head and neck cancer. Otolaryngology-Head and Neck Surgery. 2004; 131: 986-93
18. Nocini R, Molteni G, Mattiuzzi C, Lippi G. Updates on larynx cancer epidemiology Chinese Journal of Cancer Research. 2020; 32: 18
19. Ciobîrcă DM, Vlăescu AN, Ciolofan MS, Ioniță E, Anghelina F, Ioniță I, Capitanescu AN, Mitroi MR, Oprişcan IC, Mogoantă CA. Etiopathogenesis of the hypopharyngeal cancer. ORL. 2017; 37
20. Rana A, Rana P, Gupta M, Seam R, Gupta M. Conventional chemoradiation vs. induction chemotherapy followed by conventional chemoradiation for locally advanced head and neck cancer: A prospective, randomized study. World Academy of Sciences Journal. 2020; 2: 1
21. Das S, Lahiri D, Dam A, Maji T, Roy S, Ray DK, Mandal S. Definitive concurrent chemoradiation versus laryngectomy and postoperative radiation using IMRT in locally advanced laryngeal cancer: experience from a regional cancer centre of Eastern India. Journal of Radiotherapy in Practice. 2021; 20: 71-7
22. Cmelak AJ, Li S, Goldwasser MA, Murphy B, Cannon M, Pinto H, et al. Phase II trial of chemoradiation for organ preservation in resectable stage III or IV squamous cell carcinomas of the larynx or oropharynx: results of Eastern Cooperative Oncology Group Study E2399. Journal of clinical oncology. 2007; 25: 3971-7
23. Sessions DG, Lenox J, Spector GJ. Supraglottic laryngeal cancer: analysis of treatment results. The Laryngoscope. 2005; 115:1402-10.
24. Chitapanarux I, Tharavichitkul E, Chakrabandhu S, Klunklin P, Onchan W, Pukanhapan N, et al. The treatment outcome of radical radiotherapy in laryngeal cancer. J Med Assoc Thai. 2014; 97: 101-6
25. Knab BR, Salama JK, Solanki A, Stenson KM, Cohen EE, Witt ME, et al. Functional organ preservation with definitive chemoradiotherapy for T4 laryngeal squamous cell carcinoma. Annals of oncology. 2008; 19: 1650-4
26. Cohen EE, Karrison TG, Kocherginsky M, Mueller J, Egan R, Huang CH, et al. Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck cancer. Journal of clinical oncology. 2014; 32: 2735