

HEAD AND NECK

Effect of vocal rehabilitation after chemoradiation for non-laryngeal head and neck cancers

Gli effetti della riabilitazione vocale dopo chemioradioterapia per i tumori testa e collo non laringei

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SUMMARY

Objective. This study evaluated the effect of voice intervention in patients who received chemoradiation to the neck for non-laryngeal head and neck malignancies.

Methods. Twenty individuals with non-laryngeal malignancies of the head and neck who received chemoradiation were divided by block randomisation into an intervention group that received voice rehabilitation and a control group without rehabilitation. All patients underwent acoustic analysis, perceptual and subjective analysis of voice before the commencement of chemoradiotherapy and at 1, 3 and 6 months after chemoradiotherapy.

Results. In both groups, all parameters were significantly altered at one month follow-up except for fundamental frequency (females in control group and males in intervention group). In the intervention group, all parameters returned to pretreatment levels (no statistical differences) at 6 months. In the control group, all except for a few subjective parameters (grade, breathiness and asthenia) remained significantly altered at 6 months compared to the levels before radiotherapy.

Conclusions. In non-laryngeal head and neck malignancies, voice rehabilitation offered at 1 month after treatment ameliorates chemoradiation-induced dysphonia within 6 months.

KEY WORDS: chemoradiation, non-laryngeal head and neck cancer, voice handicap index, dysphonia

RIASSUNTO

Obiettivo. Questo studio mira a valutare l'effetto della riabilitazione vocale in pazienti sottoposti a chemioradioterapia per tumori maligni della testa e del collo non laringei.

Metodi. Venti individui con neoplasie non laringee della testa e del collo che hanno effettuato trattamento chemioradioterapico sono stati divisi per randomizzazione in due gruppi: un gruppo ha ricevuto la riabilitazione vocale e un gruppo di controllo senza riabilitazione. Tutti i pazienti sono stati sottoposti ad analisi acustica, analisi percettiva e soggettiva della voce prima dell'inizio della chemio radioterapia e a tre e sei mesi dopo la chemio radioterapia.

Risultati. In entrambi i gruppi, tutti i parametri sono stati alterati in modo significativo a un mese di follow-up ad eccezione della frequenza fondamentale (femmine nel gruppo di controllo e maschi nel gruppo di intervento). Nel gruppo sottoposto a riabilitazione, tutti i parametri sono tornati ai livelli di pretrattamento (nessuna differenza statistica) a 6 mesi di follow-up. Nel gruppo di controllo, tutti tranne alcuni parametri soggettivi (grado, respiro affannoso e astenia) sono rimasti significativamente alterati a 6 mesi, rispetto ai livelli precedenti alla radioterapia.

Conclusioni. Nei tumori maligni della testa e del collo non laringei, la riabilitazione vocale offerta un mese dopo il trattamento migliora la disfonia entro sei mesi.

PAROLE CHIAVE: chemioradioterapia, cancro della testa e del collo non laringeo, indice di handicap vocale, disfonia

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Conflict of interest

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Introduction

Head and neck cancer is the most common malignancy in India among males and fifth most common among females¹. Surgery, along with radiotherapy and chemotherapy, are the three modalities employed for treatment of head and neck malignancies.

In patients with head and neck malignancies, the larynx is frequently exposed to radiation, either for treatment of the primary tumour (in the case of laryngeal malignancy) or treatment of the neck fields in case of other malignancies. Inclusion of larynx in the radiation field reduces voice quality, and patients complain of increased vocal effort, breathiness and hoarseness². These effects are due to impaired vocal fold vibration, incomplete glottic closure, insufficient lubrication/dryness of the laryngeal mucosa, muscle atrophy, fibrosis, hyperaemia and/or erythema caused by radiation². Reduced voice quality affects daily activities of the patient. This can be associated with severe functional and psychosocial problems and reduced quality of life^{3,4}.

The combination of chemotherapy and radiotherapy, either in the adjuvant setting or concurrent setting, is believed to enhance good locoregional control and survival outcomes⁵. However, these outcomes are associated with enhanced acute and long term toxicity⁶, in addition to the effects of radiation therapy.

Many studies have noted the deleterious effects of radiation or concurrent chemoradiation on both diseased^{7,8} and undiseased larynxes^{6,9,10}; however, the effects of voice rehabilitation on patients undergoing chemoradiation have only been evaluated in laryngeal malignancies^{7,8,11}. Our study attempts to evaluate the effects of vocal rehabilitation in a group of patients who underwent chemoradiation for non-laryngeal malignancies.

Materials and methods

Patients with head and neck cancer treated with chemoradiation were subjected to a time-bound randomised controlled study carried out over 2 years, between August 2016 and July 2018, in the tertiary hospitals of Kasturba Medical College, Mangalore, India.

The patients included were those diagnosed with malignancies of the head and neck (proven by biopsy and imaging) with no involvement of the larynx or hypopharynx. All patients underwent chemoradiation with or without surgery as per our institutional protocol. Patients with laryngeal malignancy, end-stage cancer in palliation, and/or history of laryngotracheal trauma, laryngeal or thyroid surgery, or neurological or neuromuscular disorders were excluded from the study. At recruitment, voice was assessed by a speech language pathologist and patients were enrolled in

the study only if the voice was deemed normal by perceptual analysis.

A total of 32 patients met inclusion criteria. The study subjects were divided into two groups by block randomisation using the lottery method: one group received voice therapy (intervention group) and the other did not (control group). Of the 32 patients, 7 were lost to follow-up and 5 died during the study period. Of the remainder, three month follow-up was available for 20 patients and 6 month follow-up for 15 patients. At 3 months, the intervention group (Group I) consisted of 9 patients, and the control group (Group II) consisted of 11 patients, divided by block randomisation. Six months post-radiotherapy, Group I consisted of 7 patients and Group II consisted of 8 patients.

Among the 9 patients in the intervention group, 5 patients (55.6%) received a total dose of 66 Gy and 4 patients (44.4%) received 70 Gy. Nine patients in the control group received 70 Gy, while 1 patient each received 52 Gy and 60 Gy. The "mean dose to larynx" in the control group was found 71.79 Gy and in the intervention group was 71.01 Gy.

All patients received chemotherapy during treatment with platinum based drugs (either cisplatin or carboplatin). Among the 9 patients in the intervention group, 2 patients received carboplatin, 6 patients received cisplatin and 1 patient received cisplatin + nimotuzumab. In the control group, 4 patients received carboplatin, 2 patients received cisplatin, 2 patients initially received cisplatin, but it was later changed to carboplatin (due to nephrotoxicity), 2 patients received cetuximab and 1 patient received gefitinib (250 mg daily). Cisplatin dose was calculated at 100 mg/m² for 3 weekly cycles (on day 1, 22 and 43 of radiotherapy) or 40 mg/m² for weekly cycles depending on the tolerance of the patient. Carboplatin dose was calculated using Calvert's formula to attain an AUC (area under concentration) time curve of 1.5-2.

In all cases, thorough history and detailed examination with regards to age, sex, substance abuse, site of malignancy and T and N staging were recorded in a proforma.

The diagnosis was confirmed by biopsy and imaging. All patients underwent chemoradiation with or without surgery as per our institutional protocol. Anonymity was assured and patients were given a patient information sheet. Written informed consent was received from each patient. The study was approved by the Institutional Ethics Committee Board with the reference number: IEC KMC MLR 08-16/175.

All patients underwent acoustic analysis, perceptual analysis and subjective analysis before commencement of chemoradiation and at 1 month, 3 months and 6 months after chemoradiation. For the intervention group, voice therapy

was initiated after the 1-month follow up. The speech language pathologist performing the voice analysis was blinded to the randomisation. Voice recordings of patients were maintained separately until the end of the study period and coalesced into the proforma before statistical analysis.

Acoustic measures

Acoustical measures reflect the status of vocal function, and do not relate specifically to certain voice disorders because the biomechanical changes resulting in acoustical differences can be induced by various lesions and dysfunctions¹².

The Computerized Speech Lab (CSL) (Model 4150, Kay Elemetrics Corp., Lincoln Park, NJ, USA) was used to analyse the acoustic characteristics of voice. The participants were asked to produce a sustained phonation of vowel /a/ for as long as possible at their comfortable pitch and loudness. The instructions were repeated when required. A sensitive dynamic microphone was used to record voice samples from participants into the MDVP advanced module of the CSL software. Three recordings of phonation of /a/ was recorded. The middle four-second recorded sample was analysed using the CSL software. The parameters analysed were fundamental frequency F_0 , jitter % (Jitt), shimmer % (Shim), noise to harmonic ratio (NHR) and soft phonation index (SPI). The average of the three recorded parameters were considered for analysis.

Perceptual measures

Perceptual measurement of voice was carried out using GRBAS scoring¹³, where a running speech sample on a particular topic 'About your problem' was recorded for a minimum of one-minute duration using the sound recorder. This particular scale was chosen as it is easier to use, less time consuming and has good psychometric properties¹⁴. The recorded samples were perceptually rated by two experienced speech pathologists in the field of voice disorders. The duration of all samples ranged from 62-73 seconds. Both speech pathologists rated the voice characteristics in both the group of participants. The inter-rater and intra-rater reliability for the perceptual analysis recordings were between 89% and 96% based on kappa coefficient.

Quality-of-life measures

Voice related quality of life measures was assessed using the Voice Handicap Index (VHI) - Kannada (local language) questionnaire consisting of 30 questions¹⁵. The participants responded to each question on a five point scale based on the severity of their problem. The clinician asks the individuals to rate the severity of their voice disorder as per the grades between 0-4; 0 - never, 1 - almost never, 2 - sometimes, 3 - almost always, 4 - always¹⁶.

Intervention

Voice therapy was started at the 1 month follow up. It was tailor made according to the needs of the patient as assessed by the speech language pathologist. Basic exercises like relaxation (circumlaryngeal manual voice therapy, yawn sigh phonation, and chewing), posture, breathing and physiologic approaches (resonant voice therapy) were taught. Appropriate and relevant vocal hygiene was taught which includes hydration, reflux precautions and compliance with prescribed medication regimen. First, two sessions were dedicated to vocal hygiene, breathing and relaxation exercises and later sessions focused on resonant voice therapy. The frequency of exercises (two times/day till the next follow up visit) to be practiced at home were maintained uniform for all the participants. These eclectic approaches were adopted as it was the protocol followed at the voice clinic in our institution. Patients were guided to modify the amount and type of voice use, and were encouraged to practice the same at their residence. All patients were monitored by the same clinician throughout the study period.

Statistical analysis

All values were tabulated using a Microsoft Excel worksheet. Analysis was done using frequency, percentage, chi-square test, Fisher's exact test, Mann-Whitney's *U* test and descriptive statistics to calculate all measures with the use of a statistical package (SPSS version 17.0). The post hoc analysis (multiple comparisons) was done by adjusting *p*-value using Bonferroni's correction. A *p*-value less than 0.05 was considered significant, and a *p*-value less than 0.01 was considered highly significant.

Results

The study started with 32 patients randomised into the study and intervention groups. However, by 3 months follow-up there were only 20 patients in the study. The clinical details of the 20 patients considered for the study are outlined in Table I. When variables were compared between the 2 groups, gender (*p* value 0.028), smoking (*p* value 0.008), and alcohol (*p* value 0.25) were significantly different in the two groups. There was no difference in age, T and N staging, site of malignancy or surgery to the primary or neck between the two groups.

Acoustic analysis

The values of acoustic parameters of patients in the control and intervention groups are shown in Table II.

Comparison within the control group (Table III)

One month after chemoradiotherapy, there was significant al-

Table I. Clinical parameters of patients in control and intervention groups with T (tumour stage), N (nodal status) and type of radiotherapy (RT).

Parameter	Control		Intervention	
	N	%	N	%
Age				
Below 60	6	54.5%	5	55.6%
60 and above	5	45.5%	4	44.4%
Total	11	100.0%	9	100.0%
Sex				
F	2	18.2%	6	66.7%
M	9	81.8%	3	33.3%
Total	11	100.0%	9	100.0%
Malignancy				
Oral cavity	5	45.5%	6	66.7%
Oropharynx	6	54.5%	1	11.1%
Salivary gland	0	.0%	2	22.2%
Total	11	100.0%	9	100.0%
Smoking				
No	2	18.2%	7	77.8%
Yes	9	81.8%	2	22.2%
Total	11	100.0%	9	100.0%
Alcohol				
No	3	27.3%	7	77.8%
Yes	8	72.7%	2	22.2%
Total	11	100.0%	9	100.0%
Tobacco chewing				
No	1	9.1%	4	44.4%
Yes	10	90.9%	5	55.6%
Total	11	100.0%	9	100.0%
T				
T1	0	.0%	1	11.1%
T2	5	45.5%	4	44.4%
T3	1	9.1%	2	22.2%
T4	5	45.5%	2	22.2%
Total	11	100.0%	9	100.0%
N				
N0	5	45.5%	2	22.2%
N1	2	18.2%	4	44.4%
N2	4	36.4%	3	33.3%
Total	11	100.0%	9	100.0%
Surgery				
No	8	72.7%	4	44.4%
Yes	3	27.3%	5	55.6%
Total	11	100.0%	9	100.0%
Neck dissection				
No	8	72.7%	4	44.4%
Yes	3	27.3%	5	55.6%
Total	11	100.0%	9	100.0%
RT type				
3DCRT	1	9.1%	1	11.1%
IMRT	10	90.9%	8	88.9%
Recurrence				
No	10	90.9%	7	77.8%
Yes	1	9.1%	2	22.2%
Total	11	100.0%	9	100.0%

teration in most acoustic parameters (fundamental frequency in males, jitter percent, shimmer percent, noise-harmonic ratio, and soft phonation index) in the control group, in comparison with pre chemo radiotherapy values ($p = 0.00$). Fundamental frequency of females did not change in during follow up; however, they were only two patients.

Three months after chemoradiotherapy, jitter ($p = 0.04$), shimmer ($p = 0.02$), and noise harmonic ratio ($p = 0.04$) all showed significant decreases compared with one-month post-chemoradiotherapy values, whereas fundamental frequency in males and soft phonation index showed no significant differences.

Between 1 month and 6 months post chemo radiotherapy, there was a significant decrease noted in jitter and shimmer, but fundamental frequency in males, noise harmonic ratio and soft phonation index showed no significant differences. Six months after chemoradiotherapy, all acoustic parameters – fundamental frequency in males ($p = 0.028$), jitter ($p = 0.02$), shimmer ($p = 0.02$), noise harmonic ratio ($p = 0.01$), and soft phonation index ($p = 0.02$) – were significantly altered compared with levels before radiotherapy.

Comparison within the intervention group (Tab. III)

At one month post chemoradiotherapy, there was a highly significant change in almost all parameters compared to values before radiotherapy; fundamental frequency in females ($p = 0.028$), jitter ($p = 0.008$), shimmer ($p = 0.008$), noise harmonic ratio ($p = 0.008$) and soft phonation index ($p = 0.008$). There was no change in F0 in males; however, they were three patients.

When the 3-month values were compared to the one-month values, jitter, shimmer, noise harmonic ratio and soft phonation index showed significant decreases, while F0 in females showed an increase.

At the 6-month follow-up, no significant differences were observed when the acoustic parameters were compared with pre chemoradiotherapy values (i.e., all acoustic parameters had returned to pre-chemoradiotherapy values).

Comparison between the control and intervention groups (Tab. II, Figs. 1, 2)

Pre-chemoradiotherapy and one-month post-chemoradiotherapy values did not show significant differences between groups.

Comparisons between groups at 3-months showed a significant increase in the fundamental frequency-males ($p = 0.036$) and decrease in jitter ($p = 0.006$), and shimmer ($p = 0.00$), noise-harmonic ratio ($p = 0.015$) and soft phonation index ($p = 0.037$) in the intervention group.

At the 6-month follow-up, there was a significant increase in fundamental frequency in males ($p = 0.017$) and a decrease in

Table II. Acoustic parameters-fundamental frequency (F_0 females and F_0 males), jitter (Jitt), shimmer (Shim), noise harmonic ratio (NHR), and soft phonation index (SPI) before chemoradiotherapy and at 1-, 3- and 6-months follow-up in the control and intervention groups; comparison done using Mann Whitney test, significant p values in bold.

Parameter	Timing of analysis	Group	N	Mean	Std. Deviation	Median	Inter-quartile range	p value
F_0 Female	Pre RT	Control	2	199	0	199	198.95(148.95-149.475)	0.071
		Intervention	6	176	23	183	(162.4-190.925)	
	1 month post RT	Control	2	145	7	145	(105.3-112.725)	0.143
		Intervention	6	123	21	127	(100-141.325)	
	3 months post RT	Control	2	150	5	150	(109.425-115.1025)	0.286
		Intervention	6	169	13	171	(161.4275-179.95)	
6 months post RT	Control	1	133	0	.	(-)	0.400	
		Intervention	4	169	21	164	(152.325-191.1125)	
	Pre RT	Control	9	138	18	135	(125-155.75)	0.145
Intervention		3	155	13	151	(143.7-169.8)		
F_0 Male	1 month post RT	Control	9	113	16	114	(97.05-121.55)	0.600
		Intervention	3	118	9	114	(112.78-128.4)	
3 months post RT	Control	9	117	15	121	(100.305-126.235)	0.036	
	Intervention	3	136	5	133	(132.21-141.94)		
6 months post RT	Control	7	124	13	130	(110.67-131.48)	0.017	
	Study	3	151	2	152	(149.65-152.9)		
Jitt	Pre RT	Control	11	0.95	0.38	1.00	(0.8-1.05)	0.171
		Intervention	9	0.68	0.34	0.81	(0.3985-1.015)	
	1 month post RT	Control	11	2.49	1.03	2.10	(1.64-3.59)	0.820
		Intervention	9	2.67	1.00	2.55	(1.7925-3.34)	
	3 months post RT	Control	11	2.35	0.97	1.96	(1.53-3.01)	0.006
		Intervention	9	1.25	0.46	1.29	(1.115-1.55)	
6 months post RT	Control	8	2.17	0.81	2.11	(1.4375-2.8125)	0.002	
	Intervention	7	0.84	0.30	0.91	(0.82-1.03)		
NHR	Pre RT	Control	11	0.11	0.03	0.12	(0.08-0.13)	0.320
		Intervention	9	0.10	0.02	0.09	(0.08-0.115)	
	1 month post RT	Control	11	0.41	0.29	0.25	(0.21-0.6)	0.676
		Intervention	9	0.40	0.23	0.34	(0.24-0.5)	
	3 months post RT	Control	11	0.35	0.22	0.26	(0.2-0.44)	0.015
		Intervention	9	0.17	0.06	0.13	(0.115-0.2205)	
6 months post RT	Control	8	0.28	0.07	0.30	(0.212-0.335)	0.002	
Intervention	7	0.12	0.03	0.12	(0.1-0.139)			
Shim	Pre RT	Control	11	3.36	0.54	3.20	(2.98-3.96)	0.074
		Intervention	9	2.65	0.77	2.88	(2.04-3.305)	
	1 month post RT	Control	11	5.54	1.11	5.34	(4.6-6.71)	0.270
		Intervention	9	5.00	0.74	5.00	(4.26-5.755)	
	3 months post RT	Control	11	5.22	1.18	5.10	(4.28-6.08)	0.000
		Intervention	9	2.97	0.85	3.02	(2.05-3.79)	
6 months post RT	Control	8	4.29	0.71	4.07	(3.865-4.345)	0.002	
	Intervention	7	2.93	0.75	3.10	(2.08-3.67)		
SPI	Pre RT	Control	11	20.80	5.00	21.03	(18.45-22.9)	0.939
		Intervention	9	21.75	4.21	22.03	(17.4-24.35)	
	1 month post RT	Control	11	30.01	4.15	31.21	(24.82-32.59)	0.425
		Intervention	9	31.92	5.34	31.50	(26.48-36.565)	
	3 months post RT	Control	11	28.79	2.51	29.65	(26.54-30.65)	0.037
		Intervention	9	25.19	3.96	24.53	(21.75-29.88)	
6 months post RT	Control	8	27.14	2.32	27.44	(25.24-29.345)	0.015	
Intervention	7	22.42	3.21	20.92	(20.1-23.8)			

Table III. Comparison of acoustic parameters [fundamental frequency (F_0 female and F_0 male), jitter (Jitt), shimmer (Shim), noise harmonic ratio (NHR), and soft phonation index (SPI)], GRBAS scores [grade (G), roughness (R), breathiness (B), asthenia (A), Strain(S)] and Voice Handicap Index (VHI) between different time intervals in the same group - pre and 1 month after chemo radiotherapy, 1 month and 3 months after chemo radiotherapy, 1 month and 6 months after chemo radiotherapy, and pre and 6 months after radiotherapy in control and intervention groups; p value calculated using Wilcoxon signed rank, significant values in bold.

Parameter	Time interval	Control group P values	Intervention group P values
G	Pre-RT – 1 month post RT	0.048	0.026
	1 month post RT – 3 months post RT	0.317	0.206
	1 month post RT – 6 months post RT	0.257	0.016
R	Pre-RT – 6 months post RT	0.132	0.083
	Pre-RT – 1 month post RT	0.010	0.012
	1 month post RT – 3 months post RT	1.00	0.180
B	1 month post RT – 6 months post RT	0.157	0.024
	Pre-RT – 6 months post RT	0.014	1.00
	Pre-RT – 1 month post RT	0.026	0.015
A	1 month post RT – 3 months post RT	0.334	0.034
	1 month post RT – 6 months post RT	0.066	0.059
	Pre-RT – 6 months post RT	1.00	1.00
S	Pre-RT – 1 month post RT	0.046	0.014
	1 month post RT – 3 months post RT	0.212	0.038
	1 month post RT – 6 months post RT	0.330	0.020
F ₀ Female	Pre-RT – 6 months post RT	0.589	0.317
	Pre-RT – 1 month post RT	0.033	0.038
	1 month post RT – 3 months post RT	0.206	0.317
F ₀ Male	1 month post RT – 6 months post RT	0.739	0.059
	Pre-RT – 6 months post RT	0.034	0.317
	Pre-RT – 1 month post RT	0.180	0.028
Jitt	1 month post RT – 3 months post RT	0.180	0.028
	Pre-RT – 3 months post RT	0.180	0.249
	Pre RT – 1 month post RT	0.008	0.109
Shim	Pre RT – 3 months post RT	0.008	0.109
	Pre RT – 6 months post RT	0.028	1.000
	1 month post RT – 6 months post RT	0.043	0.109
NHR	Pre-RT – 1 month post RT	0.00	0.008
	1 month post RT – 3 months post RT	0.04	0.01
	1 month post RT – 6 months post RT	0.04	0.02
SPI	Pre-RT – 6 months post RT	0.02	0.09
	Pre-RT – 1 month post RT	0.00	0.008
	1 month post RT – 3 months post RT	0.02	0.01
VHI	1 month post RT – 6 months post RT	0.09	0.02
	Pre-RT – 6 months post RT	0.01	0.25
	Pre-RT – 1 month post RT	0.00	0.01
VHI	1 month post RT – 3 months post RT	0.16	0.01
	1 month post RT – 6 months post RT	0.03	0.03
	Pre-RT – 6 months post RT	0.01	0.46

jitter ($p = 0.002$), shimmer ($p = 0.002$), noise-harmonic ratio ($p = 0.002$) and soft phonation index ($p = 0.015$) in the intervention group (Figs. 1, 2). The fundamental frequency in females did not show a significant change between 3 and 6 months, but there was only one patient left in the control group.

GRBAS scores

Comparison of GRBAS scores at different time intervals in the control and intervention groups are shown in Table III.

Comparison within the control group (Tab.III)

Using the GRBAS scale, there was a significant increase in all scores in the control group at 1 month after chemoradiotherapy compared with scores before chemoradiotherapy; significant changes were seen for grade ($p = 0.048$), roughness ($p = 0.01$), breathiness ($p = 0.026$), asthenia ($p = 0.046$) and strain ($p = 0.033$).

At 3 months, there was no significant change in the parameters compared to the scores at 1 month. There were no significant differences between post-chemoradiotherapy scores at 1 and 6 months.

At 6 months post-chemoradiotherapy, roughness ($p = 0.014$) and strain ($p = 0.034$) were still significantly different from pre-chemoradiotherapy values, while grade, breathiness, and asthenia showed no significant differences.

Comparison within the intervention group (Tab. III)

Statistically significant differences were noted in all parameters when pre-chemoradiotherapy and 1-month post-chemoradiotherapy values were compared; grade ($p = 0.026$), roughness ($p = 0.012$), breathiness ($p = 0.015$), asthenia ($p = 0.014$) and strain ($p = 0.038$).

Three months after radiotherapy, breathiness had improved significantly ($p = 0.034$) whereas none of the other parameters showed significant change compared to one-month post RT values.

At 6 months after chemoradiotherapy, a significant difference was noted in grade ($p = 0.016$), roughness ($p = 0.024$) and asthenia ($p = 0.020$) compared with the values at 1 month after chemoradiotherapy.

There were no significant differences between the pre-radiotherapy perceptual scores and those at 6 months.

Comparison between the control and intervention groups (Tab. IV, Fig. 3)

The perceptual voice was normal before chemo radiotherapy in most patients. At 1 month after radiotherapy, mild-moderate differences were observed in both groups, with no significant differences between the two.

Three months after chemoradiotherapy, the perceptual voice parameters in the intervention group had improved

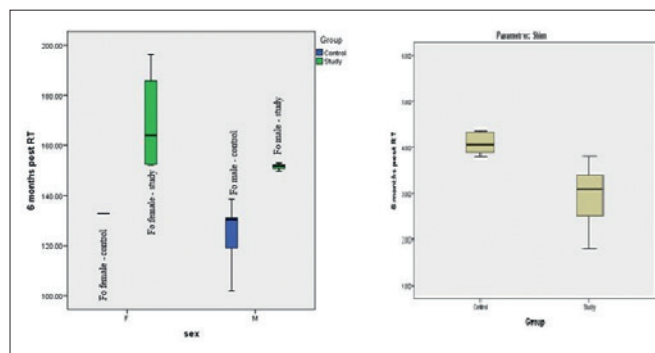


Figure 1. Box plots representing F0 Fundamental frequency (for males and females) and shimmer (Shim) in the control and study group at 6 month post-chemoradiotherapy.

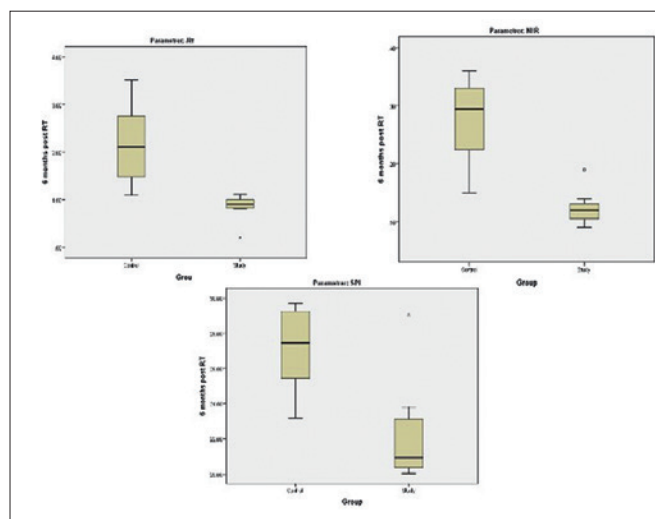


Figure 2. Box plots showing the acoustic parameters Jitter (Jitt), noise harmonic ratio (NHR) and Soft Phonation Index (SPI) in the control and intervention groups at 6 months post-chemoradiotherapy.

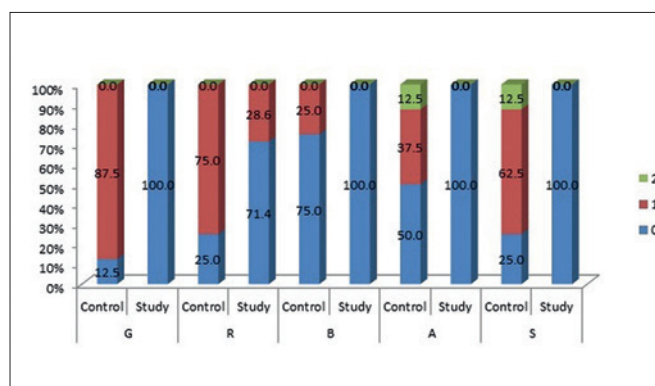


Figure 3. Bar diagram showing the proportion of patients with 0 (normal), 1 (mild) and 2 (moderate) severity of changes in perceptual evaluation of patients using GRBAS scores (grade, roughness, asthenia, breathiness and strain) at 6 months post-chemo radiotherapy in control and intervention groups.

Table IV. Comparison of GRBAS scores [grade (G), roughness (R), breathiness (B), asthenia (A), Strain(S)] and Voice Handicap Index (VHI) before chemo radiotherapy and at 1-, 3- and 6-month follow-up between control and intervention groups using Mann Whitney test, significant p values in bold.

Parameter	Pre chemo RT P value	1 month post chemo RT P value	3 months post chemo RT P value	6 months post chemo RT P value
G	0.073	1.000	0.015	0.001
R	0.189	0.277	0.841	0.100
B	0.145	0.374	0.070	0.267
A	1.000	0.245	0.479	0.130
S	0.711	0.213	0.814	0.012
VHI	0.759	0.939	0.011	0.003

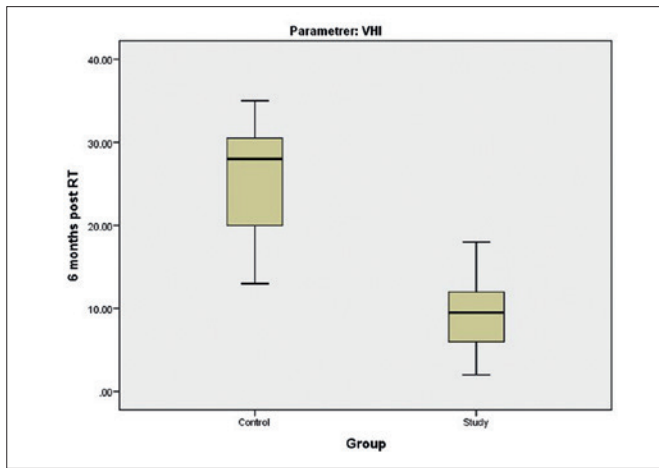


Figure 4. Box plot showing Voice Handicap Index (VHI) in the control and intervention groups at 6 months post-chemoradiotherapy.

compared to the control group; significant improvement was seen for grade ($p = 0.015$).

Six months after chemoradiotherapy, a significant improvement in grade ($p = 0.001$) and strain ($p = 0.012$) were noted in the intervention group in comparison with the control group.

Voice handicap index

Comparison of VHI scores at different time intervals in control and intervention groups are shown in Table III.

Comparison within the control group

Subjective analysis of quality of voice using VHI showed a significant increase in the scores 1 month after chemo radiotherapy ($p = 0.00$). Between 1- and 3-months, no significant differences were noted in VHI. Significant differences ($p = 0.01$) were seen when the values before chemoradiotherapy and 6 months after radiotherapy were compared.

Comparison within the intervention group

At 1 month after radiotherapy, VHI scores significantly in-

creased, whereas at 3 months there was a significant decrease compared scores at 1 month ($p = 0.01$). At 6 months, the VHI values had almost returned to baseline values. No significant differences were noted between values before radiotherapy and those at 6 months.

Comparison between control and intervention groups (Tab. IV, Fig. 5)

In the intervention group, voice therapy significantly improved voice quality as assessed by VHI at 3 months ($p = 0.011$). During the 6-month follow-up, VHI showed a highly significant improvement in the intervention group ($p = 0.003$). This trend is depicted in Figure 4.

Discussion

Head and neck malignancies are common malignancies in India, and surgery, chemotherapy and radiotherapy are the three modalities employed in the management of these tumours. Radiation damage to the larynx is expected when laryngeal disease is treated with radiation; the larynx can also suffer radiation damage when the neck is included in

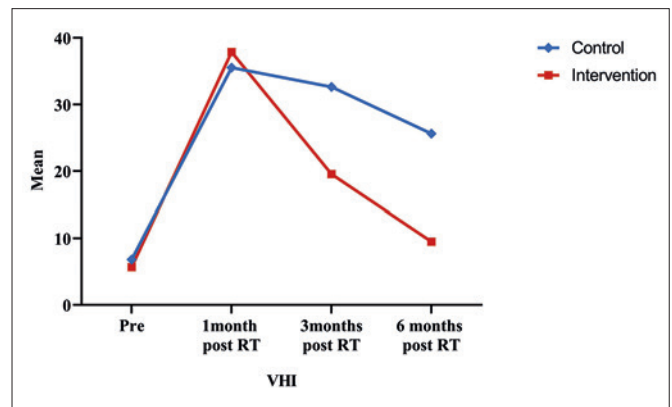


Figure 5. Graph depicting the trend in Voice Handicap Index (VHI) between the intervention and control group before radiotherapy, and at 1, 3 and 6 months after radiotherapy.

the radiation fields in non-laryngeal disease. The radiation damage to the larynx can be acute or chronic. Acute voice changes are attributed to oxidative damage resulting in injury to both diseased and normal tissue; this can lead to mucosal oedema, necrosis and epithelial sloughing. As the acute phase subsides, a fibroblastic response develops which causes long-term deposition of collagen and fibrosis. Fibrosis leads to reduced tissue viscosity, which reduces the normal vibratory patterns that are required for normal voice. These tissue changes make long-term rehabilitation difficult¹⁷.

The addition of chemotherapy to radiotherapy provides a synergistic effect between the two therapies. The chemotherapeutic agent may act as an enhancer or potentiator of radiation. Some of these drugs interfere with cellular DNA repair after sub-lethal or potentially lethal damage, while others reduce tumour cell repopulation by enhancing the cytotoxic effects of radiotherapy¹⁸. The addition of chemotherapy to radiotherapy is done in various settings in the management of head and neck cancer: as part of the organ preservation protocol, as an adjuvant to surgery in locoregionally advanced head and neck cancer, and as palliation in inoperable head and neck cancer. While chemoradiation has a beneficial effect on tumour tissue, it unfortunately has a highly toxic effect on normal tissues in the irradiated field, such as the larynx.

Non-pharmacologic treatment is the main line of rehabilitation for a radiated larynx, and consists of indirect voice therapy in the form of vocal hygiene and direct voice therapy in the form of vocal exercises.

Vocal hygiene primarily focuses on hydration. Radiation to the larynx causes damage to laryngeal salivary tissue, which results in laryngeal desiccation. As a result, vocal performance is affected^{19,20}. This can occur either as an early- or late- phase response to radiation. Patients are taught to maintain adequate systemic hydration to maximise vocal function during and after radiation treatment. Local hydration using environmental humidification or steam inhalation is also beneficial¹⁷. Voice therapy focuses on helping the patient produce voice without using inefficient compensatory behaviours such as increased laryngeal strain and supraglottic constriction². Tuomi et al. recommended that voice rehabilitation should be focused on relaxation and on decreased phonatory effort with more support from respiration. This is expected to improve the harmonic noise ratio and perturbation results, improving patient-rated voice quality outcomes⁸.

Many studies have evaluated vocal function in patients with laryngeal tumours treated with radiotherapy, but only a few have concentrated on the un-diseased larynx receiving radiation to the neck as a part of the treatment protocol^{21,22}. Our

aim was to evaluate the effect of voice therapy on various objective or subjective voice parameters in a randomised controlled study. However, in the third month there were only 11 patients in the control group (females = 2, males = 9) and 9 patients in the study group (males = 3, females = 4). By 6 months, control group had only 1 female (n = 7) and the study group had 3 males and 4 females. Since all the investigators were blinded, this gender variation between the groups was noticed only in the end of the study. The increased number of males in the control group also resulted in an increase in smoking and alcohol use in the study group.

Acoustic parameters

In the control group, all acoustic parameters showed mild improvement at 6 months, but were still significantly different (except F0 females) from levels before radiotherapy. In the intervention group, all acoustic parameters returned to pre-treatment levels by 6 months.

In the intervention group, improvement in jitter, and shimmer was found to be highly different from the control group at 6 months. Fundamental frequency in males, soft phonation index and noise-harmonic ratio had significantly improved in the intervention group at 6 months compared to the control group.

In a study by Fung et al., fundamental frequency and harmonic noise ratio significantly worsened (compared with age- and gender-matched controls) while jitter and shimmer showed no statistical significance at 1 year after irradiation of the non-diseased larynx²³.

These results show that in the absence of voice intervention, some of the acoustic parameters will show significant worsening compared to controls at one year post-radiation. Our results show that most acoustic parameters can improve with voice therapy as early as 6 months.

However, the benefits of intervention seem to be limited in patients with laryngeal cancer. In their study of 69 males with laryngeal cancer undergoing chemoradiation, Tuomi et al. found no significant change in acoustic variables in the intervention group when compared with a control group at 6 months⁸. Assessment of vocal range profile (VRP) also showed no significant differences between the two groups²⁴.

Perceptual voice analysis

At 1 month post-chemoradiation, all perceptual voice parameters in both the control and intervention groups showed significant differences when compared with pre-treatment levels. At 6 months after treatment, roughness and strain in the control group remained significantly altered compared to pre-treatment levels. Grade, breathiness and asthenia had

improved, although they did not reach normal levels. Six months after radiotherapy, perceptual voice parameters in the intervention group had improved to pretreatment levels. A few studies have evaluated the effects of chemoradiation on the perceptual quality of voice in the non-diseased larynx. In one such study, perceptual voice parameters showed significant deterioration from pre-treatment values to early post-treatment values (mean 16.5 weeks), but by the late post-treatment evaluation (12 months), had returned to baseline values⁶. Van der Molen et al. noted that in patients treated with chemoradiation, perceptual voice parameters (GRBAS) at 1 year showed significant improvements in overall voice quality, roughness and breathiness compared with the voice at 10 weeks after radiation¹⁰. Analysing these results along with ours, help us conclude that in non-laryngeal head and neck cancer, the changes in the perceptual parameters of voice brought about by chemoradiation revert to almost normal levels by one year. However, our study has shown that intervention with voice therapy leads to early normalisation of voice.

The effects of intervention on the after-effects of radiation in laryngeal cancer patients seem to be less beneficial. Van Gogh et al. reported that roughness and breathiness in laryngeal cancer patients did not change significantly when vocal intervention was offered after treatment with either radiotherapy or laser. After 16 sessions of voice therapy, a significant decrease was seen only in vocal fry⁷.

Voice handicap index

In both the control and intervention groups, VHI deteriorated significantly at one month post-treatment when to pre-treatment levels. At 6 months, VHI was not significantly different from pre-treatment levels in the intervention group, while the opposite was true of the control group.

In the study by Paleri et al. on advanced non-laryngeal malignancies undergoing chemoradiation, patient-reported voice quality (VoiSS) deteriorated during the initial assessment (12-20 weeks) and even further during the 12-month assessment⁶.

Our study suggests that early voice intervention can effectively counter these effects and return VHI back to pre-treatment levels.

When radiation or chemoradiation is used for the treatment of laryngeal cancers, significant changes in voice quality and communication occur; these can last up to a year²⁴. Though voice handicap parameters improve by themselves to a certain extent, vocal intervention greatly improves quality and communication. Fung et al. found that 27% of patients had moderate to severe voice handicap at 1 year after radiation of laryngeal cancer; it was surmised that deterioration of vocal function over time is likely potentiated by ongoing use of an

abnormal voice²³. Quality of life assessment using the Swedish Self-Evaluation of Communication Experiences after Laryngeal Cancer (S-SECEL) found a significant improvement in the Environmental, Attitudinal, and Total domains between baseline and 6 months, after which it remained more or less constant for up to 12 months after chemoradiation²⁴. Another study in Sweden on patients with primary laryngeal cancer found that the intervention group showed significant improvement in all domains, except in the general domain of S-SECEL²⁵.

Our study shows that the changes in perceptual, acoustic and patient-reported voice quality measures brought about by chemoradiation can be reversed by voice therapy in 6 months. Unfortunately, although we started with 32 patients, we lost 7 patients to follow-up, and 5 to death, which is a characteristic of cancer studies in India. This resulted in a small sample size. The preponderance of males in the control group with increased usage of alcohol and inhaled tobacco in the past may have impacted the results; further studies are needed to clarify this point. The number of sessions of voice therapy was also limited, since some of the patients were not local residents. Moreover, since our maximum follow-up was only 6 months, we do not know whether the benefits seen at 6 months will be retained at a later date. Further studies are recommended with a larger sample size and longer follow up. A longer follow-up is important since radiation induced fibrosis can cause late changes in voice. If a longer follow up reveals recurrent or late changes in voice, patients may require prolonged vocal rehabilitation.

Radiotherapy comes with many complications; dysphonia, with its negative impact on communication and quality of life, is certainly one of them. Our study indicates that voice therapy has a positive impact on patients undergoing chemoradiation for non-laryngeal head and neck malignancies. We recommend that voice therapy be included as a part of the routine rehabilitation protocol in patients undergoing chemo-radiation. This would render patients more compliant and receptive to treatment, and would also reduce the social and psychological impact associated with dysphonia. Because a speech language pathologist is present at most hospitals/centres, a multidisciplinary approach that includes them will make radiation treatment as comfortable as possible for the patient, with a minimal impact on quality of life.

Conclusions

Acoustic, perceptual and subjective evaluation of voice showed that all patients with non-laryngeal cancers undergoing chemoradiation to the neck had severe damage to voice at 1 month post-treatment except for F0 females

(control group) and F0 males (study group). Six months after chemoradiotherapy, the control group showed significant alterations in these parameters compared to baseline. In the vocal intervention group, all parameters returned to normal at 6 months.

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