International Journal of Life Sciences. Vol. 4 No. 4. 2015. Pp. 333-338

Full Length Research Paper

Voice and Oncologic Outcomes following Radiation and Voice Therapy in Cancer Larynx

Megahed Mohamed Hassan[a], Rafaat A. Bakheet [b], Mona Elrabie Ahmed[c]

[a,c:] *Lecturer at Phoniatrics Unit, Otolaryngology Department, Faculty of Medicine, Sohag University, Egypt.*
[b:] *Lecturer at Oncology Department, Faculty of Medicine, Sohag University, Egypt.*

Abstract
Background: Radiotherapy is common conservative treatment for laryngeal tumors stages 1 and 2.However, objective voice evaluation after radiotherapy is lacking. Objective: To evaluate the outcomes of the tumor, vocal functionand survival following post-irradiated cancer larynx. Methods: In this retrospective study, 48 subjects suffered from laryngeal tumor presented to the Phoniatrics and ENT outpatient clinics. First preliminary diagnosis was achieved by endoscopy of the larynx which revealed laryngeal suspicious masses of different sizes and locations. Biopsy confirmed the diagnosis of laryngeal carcinoma. Radiotherapy was given in all cases and induction chemotherapy was done in somecases according to staging. Voice rehabilitation was performed after the end of therapy. Auditory perceptual assessment (APA) and acoustic study by Multidimensional Voice Analysis Program (MDVP) were carried out before and 3 months after end of therapy. In addition, vocal function of normal volunteers was measured to be compared with post-therapy measurements. Results: The APA revealed improved perceived voice quality after therapy with significant difference (P<0.001). Although mild dysphonia, all voice parameters showed significant improvement after end of therapy with significant differences (P<0.001). Dryness was noted in 62.5% of subjects and mild oropharyngeal dysphagia in 18.75%. The 5 year survival is 96%.Conclusion: Radiotherapy is effective treatment for laryngeal tumor stages I and II but questionable for stage III. In spite of mild dysphonia, dysphagia and dryness of vocal tract, the radiotherapy remains good conservative treatment for laryngeal tumor with improved voice outcomes and maintained quality of life.

Introduction

Although total laryngectomy is still required in cases of extensive tumors, laryngeal preservation strategies using chemotherapy and radiation therapy protocols have now become common for many advanced laryngeal cancers. The Veteran Affairs Laryngeal Cancer Study Group established the basis of laryngeal preservation therapies using chemotherapy (cisplatinum and fluorouracil) and radiation therapy protocol. These trials established that chemo-radiation provides equivalent oncologic control to surgery, while allowing a substantial number of patients to avoid the sequelae of laryngectomy. Chemotherapy is beneficial part of multimodality approach in the concurrent chemo-radiation protocols.[1]The goal of treatment of laryngeal cancer is to achieve best oncologic outcome with optimum functional preservation. The treatment options of early laryngeal cancer are trans-oral laser microsurgery, radical RT or organ preserving surgery. Some patients with laryngeal tumors developed dysphonia and phonesthenia post-irradiation.[2-5]However, the RT is preferred because of excellent and equivalent tumor control and larynx preservation. In Addition, the RT has better or equal voice quality and it is considered a time tested approach.[6]Therefore, assessment of vocal function is necessary to evaluate voice outcome following treatment of early glottic tumors. In the current research, radiotherapy with or without induction chemotherapy were used for treatment of laryngeal tumors. Voice rehabilitation was performed after radiotherapy by accent method of Smith.[7]Vocal function was evaluated by both subjective and objective voice parameters. Our subjects were followed up for at least 5 years to evaluate survival and quality of life as well.

Methods

This research was conducted in Sohag University Hospital - Egypt during the period from January 2009 to February 2015. Ethics committee approved the study. Written informed consents were obtained from every subject in the study. This study included 48 subjects(43 males and 5 females) with their ages ranged from 45 – 80 years. Laryngeal examination and vocal function measurements were conducted before and 3 months after the end of therapy. All subjects underwent full ENT examination and laryngeal endoscopy using fiberopticnasolaryngoscope model (FNL-10RP3, Hoya Pentax Co., Japan) and rigid laryngoscope (Karl-Storz Endoscope, model 20045020 Germany). Laryngeal endoscopy was made for visualization of the tumor and rest of the larynx. Also, assessment of dynamic movement of the laryngeal structures during spontaneous respiration and phonation was performed for proper staging. Computerized Tomography was carried out in selected cases. Evaluation of the vocal function included subjective and objective voice parameters. Subjective assessment was done by auditory perceptual assessment (APA) of the voice quality while objective assessment was carried out by acoustic voice analysis.The video-recordings of all subjects were assessed individually by 2 doctors (Phoniatricians). All recorded videos were present blindly to the examiners. The APA was carried out through Grade-Roughness-Breathiness-Asthenia-Straining (GRBAS) voice scale.[8]The mean rating of the 2 examiners was considered. The aim of blind and individual assessment was to reduce any possible bias. The acoustic voice analysis was performed by Multi-Dimensional Voice analysis Program (MDVP) model 5105 version 3.3.0 using Kay PENTAX-CSL Model 4500. Using Microphone Shure model SM 48 connected to the CPU, each subject was instructed to phonate the vowel /a/ with comfortable pitch and intensity at a distance of 20 cm from the microphone. The acoustic voice parameters measured were jitter, shimmer, noise-to-harmonic ratio, pitch perturbation quotient (PPQ), amplitude perturbation quotient (APQ),Voice Turbulence Index (VTI) and Soft Phonation Index (SPI). The noise-to-harmonic ratio (NHR) was converted into harmonic-to-noise ratio (HNR) using a specific formula (HNR = 10 X log 1/NHR).[9]Apparently healthy volunteers were recruited from the hospital staff and relatives of the patients. They have matched age and sex distribution to the included subjects. These controls have their ages ranged from 42-76 years with mean 63 years. Evaluation of the vocal functionwas conducted for controls by the same measurements to be compared.

All subjects with diagnosis of laryngeal cancer were presented in a weekly Seminar at Otolaryngology Department, Sohag University Hospital where diagnosis is confirmed and treatment is determined. All patients subjected to receive curatively intended radiation therapy with or without chemotherapy were asked to participate in the current research. Radiation therapy was carried out using Linear accelerator machine; model Philips SL-6(15) England. The inclusion criteria were good airway, good cognitive ability of the patient and sufficient knowledge of the written Arabic language to be able to fill out the questionnaires by themselves. Oncologic treatment was given in accordance to regional treatment guidelines with conventional radiation therapy. The conventionally fractionated radiation therapy was given once a day in 1.8 to 2 Gy fractions to a total of 62.4 to 68 Gy.Most of the patients (81.25%) with T2-T3 tumors received irradiation to the lymph nodes in a total of 46 Gy (2.0 Gy once a day, 5 days a week). In addition, patients with T3tumors(n=12) were treated with concomitant chemotherapy as well (cisplatin 100 mg/m2 every 3 weeks during radiotherapy course). The time intervals passed between the following time points (complaint, clinical diagnosis, histopathological diagnosis and beginning of therapy) were shown in Table (1).

Statistics
Comparison of vocal function measurements before and after therapy was performed using paired *t*-test (two-tailed *P* value; confidence interval 95%). Also, comparison of the vocal function between post-therapy and normal controls was conducted using unpaired *t*-test (two-tailed *P* value; confidence interval 95%). The statistical analysis and graphs were made by Graph Pad Prism software version 5.

Results
Diagnosis of cancer larynx was confirmed in all subjects by laryngeal endoscopy, biopsy and histopathological examination. Clinical, histopathological and observational data were shown in Table (2). Subjects with T1 and T2 (75%) were subjected to radiation therapy guided by doctor direction; while, T3 subjects (25%) refused surgical treatment and chose chemo-radiotherapy after all treatment options were discussed with them.After chemo-radiotherapy, only one subject with T3 tumor showed recurrence after 3 months which was discovered in the first post-therapy follow up endoscopy. Biopsy confirmed the diagnosisand total laryngectomy was performed with permanent tracheostomy. Two subjects with T3N1M0 died after 5 years 6 months and 6 years after the end of combined chemo-radiotherapy. The cause of death was unclear in both subjects. Five subjects with T3 tumors have unilateral vocal fold immobility on the diseased side and hence have breathy dysphonia.

Laryngeal endoscopy was conducted for volunteers and confirmed that all have normal larynx with no tumor or any other pathology. Vocal function of volunteers was measured and compared with the post-therapy measurements of our subjects. The vocal function in all subjects revealed significant improvement following therapy. The subjective voice quality of dysphonia as scored by GRBAS scale was decreased (Fig. 1; a) and the harmonics-to-noise ratio was increased (Fig. 1; b) with significant differences (P<0.001). Although both parameters were improved, they did not reach normal range with still significant differences compared to controls. Similarly, jitter and shimmer showed significant decrease after therapy which did not reach the normal range (Fig. 2). In addition, the pitch perturbation quotient (PPQ) and amplitude perturbation quotient (APQ) revealed significant decrease following therapy (Fig. 3; a & b respectively). Both PPQ and APQ means were still higher than control with significant differences. Moreover, the voice turbulence index (VTI) decreased following therapy with significant difference (P<0.001). However, the mean VTI did not reach the normal range of our control (Fig. 4; a). The soft phonation index (SPI) increased after therapy with significant difference (P<0.001). The mean SPT became even significantly higher than that of our control following the end of therapy.

Discussion
Thirty subjects (62.5%) reported feeling dryness of mouth and throat following radiotherapy. However, this dryness was so minimal in the majority of subjects (81.25%) that did not affect the quality of life. In 9 subjects (18.75%) the dryness adversely affect the swallowing in mild degree. These subjects adapted for taking liquid and semisolid diets or drinking a plenty of water just following solid bolus.Our subjects underwent voice therapy by accent method of Smiththrough receiving 3-5 voice therapy sessions after the radiation therapy. This method aimed at decreasing muscle tension or hyper-functional dysphonia through improving abdomino-diaphragmatic breathing during speech. The vocal function was improved as evidenced by significant improvement ofthe acoustic parameters and perceptual voice quality. The HNR reflects the amount of harmonic component relative to the amount of noise in a voice signal. Its value increasesin good voice quality as here in our subjects. Jitter refers to vocal fold vibration abnormalities and is associated with sensation and perception of voice roughness. It is frequency variation among successive periods of mucosal vibration of the vocal folds.[10] It always increase with vocal fold pathology or irregularity and decreased in healthy and smooth mucosal surface of the vocal folds. All our subjects revealed decreased jitter with good voice quality after therapy. Also, shimmer is a cycle to cycle

variation of voice amplitude and considered a measure of micro-instability of the vocal folds.[10]So, more shimmer is associated with more amplitude variation and micro-instability. Good voice is associated with low shimmer.

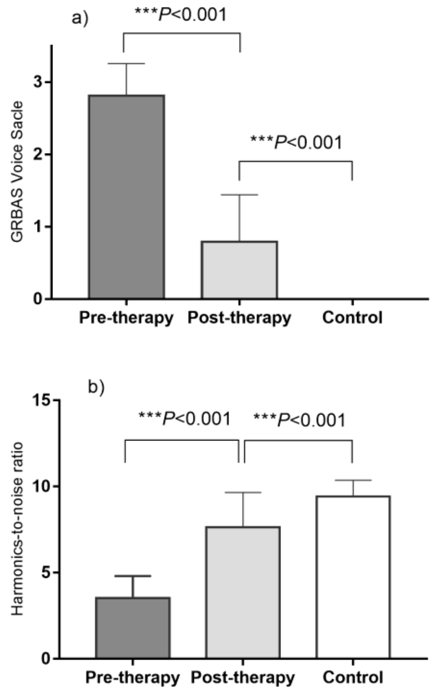

Fig (1) revealed the outcome of auditory perceptual assessment of voice quality by (GRBAS)and harmonics-to-noise ratio (HNR) compared to controls. Note the marked improvement post-therapy; however, still mild dysphonia present. GRBAS means G grade overall, R roughness, B breathiness, Aathenic or leaky voice and S strained voice.

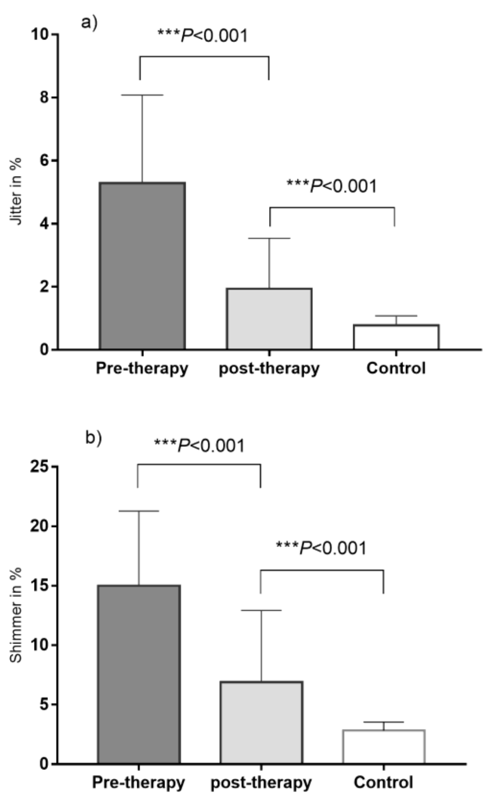

Fig (2) showed the outcomes of acoustic voice parameters (jitter and shimmer). Note both jitter and shimmer improved to nearly normal voice following radiation and voice therapy.

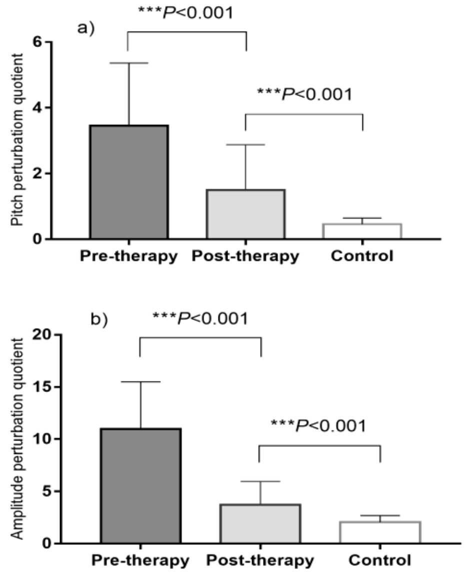

Fig (3) showed the outcomes of acoustic voice parameters (PPQ and APQ). Note both parameters improved to nearly normal voice following radiation and voice therapy. PPQ means pitch perturbation quotient; APQ means amplitude perturbation quotient.

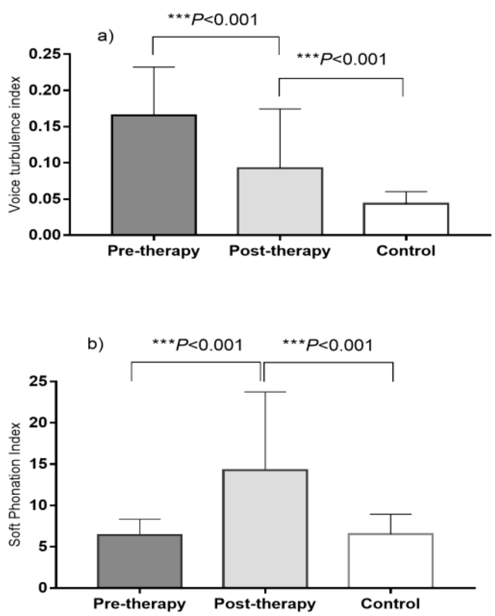

Fig (4) showed the outcomes of acoustic voice parameters (VTI and SPI). Note the mean VTI showed moderate improvement due to breathy dysphonia in subjects with vocal fold immobility. Also, the SPT worsen after radiation in subjects with vocal fold immobility due to the increased glottal phonatory gap after eradication of the tumor.

Table (1): Subjects' information and clinical data.

Total subjects	**48**
Age	Range (45 – 80 years); average (62.4); SD (9.6)
Sex distribution (n)	Females (5); males (43)
Site of tumor (n)	Glottic (30); transglottic (18)
TNM Staging (n)	T1N0M0 (19), T2N0M0 (13), T2N2M0 (4) T3N0M0 (9), T3N1M0 (3)
Histopathology (n)	Squamous cell carcinoma (48)
Survival	46/48
5 year survival rate	96%

Table (2). Time schedule for diagnosis, intervention and observation in subjects:

Time interval	Average	SD	Min	Max
Complaint to clinical diagnosis (in months)	4.46	3.4	0.5	12
Clinical to histopathological diagnosis (in days)	18.5	4.2	14	30
Histopathological diagnosis to radiotherapy (in days)	8.6	2.8	4	14
Observation period after radiotherapy (in years)	6.3	0.9	5	6.5

This was found in post-therapy acoustic analysis of our subjects' voices. In addition, both PPQ and APQ reflect roughness of voice quality and PPQ reflectssome breathiness as well.[11]Both were improved after therapy with less improvement of PPQ. This is because some subjects with T3 have vocal fold paralysiswhich results in air escape during phonation with remained breathy dysphonia.In addition, lostor decreased tone of the thyroarytenoid muscle in vocal fold paralysis adversely affected pitch control with more pitch variations and higher PPQ. The VTI decreased showing significant improvement in our subjects. The VTI refers to regular variation in the fundamental frequency (F0) of voice. The VTI is not related to the vocal fold pathology but it reflected the turbulence resulted from vocalization of air escape into a voice signal.[12]This turbulence may also result from improper mucosal wave vibration of the vocal folds due toinadequate vocal folds approximation related to immobility as in the current study. Lastly and unexpectedly, the SPI showed increase in post-therapy follow up with significant difference.

The SPI is an indicator of the extent of vocal folds closure during phonation.[11] Its valueusually increases with glottal gap and breathy voice which is an indication of poor voice quality. The glottal masses were closing the potentially exist glottal phonatory gap before treatment. In the current study, the SPI increased following therapy because the glottal masses wereeradicated leaving glottal gap in subjects with vocal fold immobility (n=5). The irradiation effect on the larynx resulted in poor voice quality compared to normal speakers.[13]This can be explained by dryness of vocal folds due to radiation-induced damage of the mucous gland of the laryngeal saccules. The function of the saccule's secretions is to lubricate the vocal folds which ease mucosal vibration during phonation. This comes in line with the mucoviscoelastic-aerodynamic theory of phonation which included that the undulating movement of the vocal fold mucosa diminished if it was dry.[14]Generally speaking, our subjects showed improved vocal function with satisfaction by organ preservation and maintained quality of life in spite of mild dysphonia remained and other minor complaints. Two cases with T3 tumors died after passing 5 years of therapy and the cause of death was unclear in both subjects. However, most probably the cause of death was related to recurrence and local extension of the tumor. All subjects were satisfied because they can communicate by their voices although the mild dysphonia in some. Unlike trans-oral laser microsurgery and organ preservation surgeries, in radiation therapy the mucosa and lamina propria (vocal ligament) of the vocal folds remains intact. This guarantees no serious affection of the vocal function.

Conclusion

In conclusion, radiation therapy with or without chemotherapy is successful treatment for T1 and T2 laryngeal tumors with good vocal function and maintained quality of life. However, chemo-radiotherapy remains controversy for T3 and needs further longitudinal studies to prove its efficacy. Radiotherapy with or without induction chemotherapy followed by voice therapy provided good oncologic and vocal outcomes with maintained quality of life particularly for early glottic tumors (T1 and T2).

References

1- Department of Veterans Affairs Laryngeal Cancer Study Group., Wolf GT, Fisher SG, Hong WK, Hillman R, Spaulding M, Laramore GE, Endicott JW, McClatchey K, Henderson WG. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer.NEngl J Med. 1991;324(24):1685-1690.
2- Peeters AJGE, van Gogh CDL, Goor K, Verdonck-de Leeuw IM, Langendijk JA, Mahieu HF. Health status and voice outcome after treatment for T1a glottic carcinoma. European Archives of Oto-Rhino-Laryngology and Head & Neck. 2004;261(10):534–540. doi: 10.1007/s00405-003-0697-5
3- Szuecs M, Kuhnt T, Punke C, Witt G, Klautke G, Kramp B, Hildebrandt G. Subjective voice quality, communicative ability and swallowing after definitive radio (chemo)therapy, laryngectomy plus radio (chemo)therapy, or organ conservation surgery plus radio (chemo) therapy for laryngeal and hypopharyngeal cancer. J Radiat Res. 2015
4- Hocevar-Boltezar I, Zargi M, Strojan P. Risk factors for voice quality after radiotherapy for early glottic cancer. RadiotherOncol. 2009;93(3):524–529. doi: 10.1016/j.radonc.2009.09.014.
5- Bergström L, Ward EC, Finizia C. Voice rehabilitation for laryngeal cancer patients: functional outcomes and patient perceptions. The Laryngoscope:n/a-n/a. 2016
6- Bhattacharyya T, Kainickal CT. Current status of organ preservation in carcinoma larynx. World J Oncol. 2018;9(2): 39-45.
7- Dalhoff K, Kitzing P. Voice therapy according to Smith. Comments on the accent method of treating voice and speech disorders. Rev LaryngolOtolRhinol (Bord). 1989;110(4):407-413.
8- Hirano M. Clinical examination of the voice. In: Arnold GE, Winckle F, Wyke BD, eds. Disorders of Human Communication. New York: Springer-Verlag. 1981;81– 84.
9- Godino-Llorente J.I., Osma-Ruiz V., Saenz-Lechon N., Cobeta-Marco I, González-Herranz R, Ramírez-Calvo C.Acoustic analysis of voice using WPCVox: a comparative study with Multi Dimensional Voice Program. Eur Arch Otorhinolaryngol. 2008; 265:465-476.

10- Deliyski, S. A. X. D. Effects of aging on selected acoustic voice parameters: Preliminary normative data and educational implications. Educational Gerontology.2001; 27(2), 159168.

11- Baken, R. J., &Orlikoff, R. F. Clinical measurement of speech and voice. Cengage Learning. 2000.

12- Deliyski, D. D. Acoustic model and evaluation of pathological voice production. In Eurospeech. 1993; 93: 1969-1972.

13- Honocodeevar-Boltežar I, Žargi M. Voice quality after radiation therapy for early glottic cancer. 2000;126(9):1097-1100. doi:10.1001/archotol.126.9.1097

14- Hiroto I.The Mechanism of Phonation: Its Pathophysiological Aspect (In Japan). PractOtolaryngol (Kyoto), 1966; 39: 229 – 291.