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Research Article

The Effect of Androgen Deprivation Therapy on Voice Quality in Patients Having Localized Prostate Cancer

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Abstract

Objective

To evaluate the voice quality in patients having localized prostate cancer, who were treated with radiotherapy and androgen deprivation therapy, by subjective and objective methods.

Material and Methods

Sixteen patients having localized prostate cancer, were included in the study. Before androgen deprivation therapy, baseline acoustic analyses were performed by the Multi-Dimensional Voice Program (MDVP; Kay Elemetrics Corporation, Lincoln Park, NJ) and the movements of the vocal cords were examined by videolaryngostroboscopy (VLS). Maximum phonation time was examined and Voice Handicap Index (VHI) is used for subjective evaluations.

Baseline total testosterone levels are also recorded. Follow-up visits were planned on the first, the third and the sixth month of the treatment. Androgen deprivation therapy, which is used as a supplementary method to radiotherapy, includes a LHRH analogue and anti-androgen. One sample t test was used for the difference between the fundamental frequency values. Paired-sample T test was used to compare the maximum frequency times with 3 audio analyzes. $p<0.05$ value was considered for statistical significance.

Results

Serum testosterone levels decreased with the effect of ADT. At the same time, the recorded fundamental frequencies were also changed. The baseline frequency values showed a significant increase at the first month, but it was observed that this increase did not continue and remained constant in the subsequent follow-ups (p=0,04). As a result of the one month of treatment, 12.5% of patients had mild voice disorder during treatment. No significant difference was found between the Jitter, Shimmer, NHR and maximum frequency times of the patients in the three voice analyzes. (p=0,2556, p=0,3894, p=0,1738).

Conclusion

Androgen deprivation therapy affects the fundamental frequency of the voice temporarily. Long term results will show the course, duration and severity of this effect and will also be useful to inform our patients in the "quality of life".

Introduction

Prostate cancer is the second most common diagnosis and the fourth most common cause of death is malignancy, which is a major health problem worldwide [1]. In recent years, great progress has been made in the diagnosis and treatment of prostate cancer. Surgery or radiotherapy with similar results at the localized stage in the treatment of patients with primary prostate cancer [2]. Radiotherapy and hormonotherapy are usually used in the treatment of locally advanced prostate cancer. It was determined that the hormonotherapy added to the treatment was the survival contribution [3-6].

It is intended to block the production of testosterone and / or block the binding of androgens to its receptors in the hormone therapy of prostate cancer. Luteinizing hormone-releasing hormone (LHRH) analogues are used as orchiectomy to block testosterone production or as a medical approach. LHRH anologists work by blocking bioactive LH secretion at the level of the anterior pituitary. In this way, the production of androgens in the testicles is blocked. After treatment with LHRH analogues has begun, the decrease in androgen level should last for about 5-15 days, until it is fully functional. During this time a transient increase in the serum testosterone level is observed. Blocking of binding to androgen receptors may be achieved using antiandrogen monotherapy or combined androgen blockade methods. Antiandrogens may be steroidal or nonsteroidal and show a high affinity for the androgen receptor.

Side effects include cardiovascular complications, decreased libido, gynecomastia, weight loss, digestion (nausea, abdominal pain), and liver disorders. LHRH agonists and antiandrogen drugs are used together in the treatment of prostate cancer. This provides combined androgen blockade [7].

The effects on the quality of life of the treatments applied due to the prolongation of the life span of the patients gained importance [8,9]. Radiotherapy and androgen deprivation therapy (ADT), which are currently available treatment options for local invasive prostate cancer, have been used since 1990. Recently, publications that question the side effects of ADT and its impact on quality of life are frequently found in the literature [10].

In this study, the effect of ADT on the sound changes, which is a parameter that can affect the quality of life, is investigated.

Materials and Methods

Sixteen patients over 50 years of age who were diagnosed with localized prostate cancer and signed informed consent were included in the prospective single-arm study. The mean age of the patients was 71 years (61-81). The clinical stage was median T2 (T1c-T4a). Median radiotherapy was applied on 72Gy (66-74Gy) conformal radiotherapy. LHRH analogue (goserelin acetate 10.8 mg / 12 weekly or leuprolide acetate 11.25 mg / 12 weekly) and antiandrogen (bicalutamide 50 mg / day / 1 ay) were applied.

Patients previously diagnosed with voice impairment, patients who had previously undergone hormonal therapy for prostate cancer, patients who received hormone therapy for any reason, laryngeal microsurgery, patients who underwent endotracheal intubation within the last 6 months, primary laryngeal patients with tumors and patients with laryngeal, lung, and mediastinal tumor metastasis were not included in the study.

ENT examinations of the patients thought to be appropriate for the study were performed by the same expert. The functions of the fund were evaluated by objective and subjective methods. To assess the maximum phonation time (MFZ), events were measured in seconds as long as they were able to extract the "a" sound at the frequency and intensity of sound they were most comfortable following a deep inspirium. For computerized sound analysis, the sound recordings of the events were taken in a room with a noise level below 40 dB. For this purpose, voice recording was performed using a Sure SM58 (Niles, IL, USA) unidirectional (cardioid) dynamic microphone and a Dell Latitude D505 laptop computer with a sampling frequency of 44100 Hz.

Voice analyzes were conducted with Kay Elemetrics' MDVP (Multi-Dimensional Voice Program) program. In this program, fundamental frequency (Fo), frequency and amplitude perturbation characteristics (jitter percent, shimmer percent) and harmonic / noise ratio (NHR) were determined. The vibratory functions of the larynx were examined according to the standard VLS evaluation parameters with videoolngostroboscopy (VLS) (Karl Storz Laryngostrobe 8020, Tuttlingen, Germany) [11]. GRBAS scale (Grade: sound impairment grade, Roughness: thickness, Breathiness: 4 points) (0: no, 1: light, 2: medium, 3: advanced) by a total of four judges consisting of two otorhinolaryngologists and two sound therapists , Asthenicity: weakness, Strain: sharpness) [12].

They were also asked how they found their own voices and were asked to mark one of the normal, slightly corrupted, corrupted or very corrupted ones. The same evaluations were repeated at the 1st and 6th months of androgen deprivation therapy and the results were compared before treatment. These evaluations were performed concurrently with the serum total testosterone levels of the patients and the total testosterone level was lowered to the castration level and examined according to the treatment period.

One sample t test was used for the difference between the fundamental frequency values. Paired-sample T test was used to compare the maximum frequency times with 3 audio analyzes. $p<0.05$ value was considered for statistical significance.

Results

At first month visit, in all patients, total testosterone levels were lower than the normal limits ($p<0.001$) and fundamental frequencies were higher than the baseline values (p: 0.009).

Serum testosterone levels were decreased due to the effect of ADT on patients' follow-up. It was observed that the fundamental sound frequencies recorded at the same time changed as well (Table 1). The baseline frequency values showed a significant increase at 1 month, but it was observed that this increase did not continue and remained constant in the subsequent follow-ups (p= 0,04).

Table 1: *Changes in total testosterone and sound frequency*

Follow up time	Average total testosterone	Average Basic frequency
Before treatment	4,203 ± 1,501ng/ml	159,01 ± 31,505
1st month of treatment	0,4949 ± 0,5544ng/ml	169,80 ± 30,237
6th month of treatment	0,2271 ± 0,4076 ng/ml	169,57 ± 30,729

No significant difference was found between the Jitter, Shimmer, NHR and maximum frequency times of the patients in the three voice analyzes (p= 0,2556, p= 0,3894, p= 0,1738).

As a result of one-month treatment, 2 of 16 patients (12.5 %) observed mild impairment of voice during treatment, It was reported that this deterioration had improved at the 6th month control, Other patients did not report any deterioration in their voice during treatment. It was seen that 2 patients who recognized voice distortion were also professional voice users.

Table 2: *Three different sound analysis results*

Follow up time	Jitter	Shimmer	NHR	Maximum phonation time
Before treatment	0,833 ± 0,592	1,820 ± 0,652	0,1292 ± 0,012	15,813 ± 5,036
1st month of treatment	0,677 ± 0,402	1,584 ± 0,828	0,1208 ± 0,011	14,938 ± 4,090
6th month treatment	0,629 ± 0,352	1,661 ± 0,403	0, 1251 ± 0,007	15,750 ± 4,313

Discussion

There is a deterioration in the quality of life due to the effects of physical and sexual activities on follow-up of prostate cancer patients under androgen deprivation therapy [10]. During the treatment of the patient; Side effects such as loss of libido, development of erectile dysfunction, increase in body fat, decrease in muscle mass, hot flashes, breast pain and gynecomastia affect the "masculine feelings" and "quality of life" of patients [7].

Androgens are important at every phase of a man's life [13,14].The effect of testosterone on the reproductive organs is known [15]. Androgen is particularly effective on the prostate and cardiovascular system as well as muscle, bone, haemopoietic system, behavioural, skin and skin effects [16-20]. Side effects such as coarsening of the voice, hirsutism, baldness were observed when testosterone was given from the outside [21]. Women undergoing androgen therapy, reduction in fundamental voice frequency (F0) or vocal pitch has been shown to be a function of androgen and testosterone levels [22]. Indeed, research has found that only 1 injection of testosterone may cause irreversible vocal changes in women [23], with 1 study of 38 women with congenital adrenal hyperplasia (CAH) aged 18 to 63 years showing that these women had a significantly lower F0 than normal controls [24].

In males, increased levels of testosterone and DHT during puberty are responsible for the increase in size of the laryngeal cartilages. This increase is accompanied by increased bulk of the laryngeal muscles and ligaments, leading to a drop of about one octave in the pitch of the voice [25]. Although the greatest F0 reduction in men occurs during puberty, male F0 may still continue to decrease until the fourth decade, and may subsequently increase during the sixth decade [26-27]. Modifications in laryngeal size in adult men may also be caused by congenital growth hormone deficiency (GHD), which leads to development of an F0 of between 174 and 266 Hz, a range typical of normal adult women. The timing of GHD is a determining factor in pitch alteration, with research showing that patients who experience adult-onset GHD between 31 and 40 years of age have a normal male pitch and an F0 varying from 117 to 154 Hz [28].

Tobias *et al* were showed that the effect of Dihidrotestosteron (DHT) treatment on the fiber size and number of the androgenic susceptible laryngeal muscle was examined. It has been found that the number of fibers with hormone is particularly effective in female frogs [29].

Although there are literature on hormone preparations used in adults, particularly women, and publications on voice changes [30,31], There are two studies which were about the effect of antiandrogen therapy on voice of prostate cancer patients in the literature. Salturk *et al.* Reported that 35 male patients are included their study [32]. Acoustic and aerodynamic voice analyses and voice handicap index-10 were applied to control and patient's groups. Maximum phonation time, fundamental frequency, jitter, shimmer, and noise-to-harmonic ratio were determined during acoustic and aerodynamic voice analyses. Hamdan et al reported that 32 recruited for their study [33]. Patients underwent acoustic analysis, and the following acoustic variables were measured: fundamental frequency, relative average perturbation, shimmer, noise-to-harmonic ratio, and voice turbulence index. Compared with the control group, there was no statistical difference in any of the phonatory symptoms. Our results were represented short term results of acoustic analysis. The baseline frequency values showed a significant increase at 1 month, but it was observed that this increase did not continue and remained constant in the subsequent follow-ups. No significant difference was found between the Jitter, Shimmer, NHR and maximum frequency times of the patients in the three voice analyzes as other two studies.

Conclusion

In our study, 12.5% of patients had short-term sound quality deterioration. However, more patients and longer follow-ups are needed to say that it affects the sound quality

Conflict of Interest

None

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