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# A Report of Delayed Toxicities of Intensity Modulated Radiation Therapy for Nasopharyngeal Carcinoma: A Single Center Cross-sectional Study

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## Abstract

**Background:** Based on the literature review, the available information regarding late toxicities after intensity modulated radiation therapy (IMRT) for nasopharyngeal carcinoma (NPC) is limited to a few countries.
**Objectives:** This study provides an opportunity to evaluate the delayed toxicities among Iranian patients with NPC that underwent IMRT.
**Methods:** Between February 2016 and September 2018, 32 patients were treated with IMRT for NPC at Shohada-e Tajrish Hospital. The majority of them were in the advanced clinical stage and all received platinum-based induction and/or concurrent chemotherapy. Our typical prescription dose was 70.2 Gy to the gross tumor volume (GTV) in 2 Gy per fraction. Uninvolved regional lymph nodes received 59.4 Gy. Considering the minimum follow-up time of 6 months, we aimed mainly at evaluating the rate of delayed toxicities, including xerostomia, hearing loss, and eyeball damages. Toxicities were categorized based on either RTOG/EORTC or LENT/SOMA criteria.
**Results:** The median follow-up time was 12 months (6 - 32 months). The occurrence rates of grade $\geq$ 2 xerostomia, grade $\geq$ 2 hearing loss, optic neuropathy, and retinopathy were 28%, 10%, 4%, and 7%, respectively. Based on the dose-volume histogram analysis, averages of mean doses to the parotid glands, submandibular glands, oral cavity, and cochlea were 32.3 Gy, 58.9 Gy, 41.8 Gy, and 44.9 Gy, respectively.
**Conclusions:** Our experience of using IMRT in the treatment of NPC revealed equivalent toxicities (except for hearing loss) in comparison with high-experienced centers.

*Keywords:* Nasopharyngeal Carcinoma, IMRT, Delayed Toxicity

## 1. Background

While nasopharyngeal carcinoma (NPC) is common in Southeast Asia, it is a rare condition in the rest of the world. Therefore, there is a lack of related data in the most geographical areas including Iran. In comparison with other areas, Iran has a low rate of NPC incidence. However, the rate has an increasing trend in the last years with the unknown reason (1). Radiation therapy (RT) is the mainstay of the locoregional treatment of NPC. Nevertheless, its efficient application is limited by the anatomic proximity of numerous critical organs. Recent advances in clinical imaging, treatment planning, and conformity of dose delivering have resulted in better outcomes (2). Compared with old-fashioned techniques (e.g. 2 dimensional and 3 dimensional conformal RT or 3D-CRT), intensity modulated radiation therapy (IMRT) can deliver more conformal dose to the tumor site, while better spares neighbor critical organs. Radiation-Oncology Department of Shohada-e Tajrish Hospital is the leading center employing IMRT technique in Iran. This is the pioneering article regarding the findings of Iranian patients that are treated with IMRT.

## 2. Objectives

Apart from presenting the NPC characteristics, the principal aim of this study is to evaluate the rate of delayed

IMRT toxicities.

## 3. Methods

### 3.1. Patients' Characteristics

This is a cross-sectional research regarding patients, who had NPC and received IMRT in the Department of Radiation-Oncology at Shohada-e Tajrish Hospital (affiliated to Shahid Beheshti University of Medical Sciences, Tehran, Iran). During February 2016 and September 2018, 32 patients met inclusion and exclusion criteria. The inclusion criteria were as follow:

(1) De novo histologically confirmed NPC

(2) NPC patients that were planned to receive IMRT

The exclusion criteria were as follow:

(1) Clinically or pathologically confirmed metastatic condition

(2) Patients that have received radiation to the head and neck region for any reason; to determine the toxicities attributable only to the primary treatment

The applied method of sampling was convenience sampling. This study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences with approval code of IR.SBMU.MSP.REC.1396.357. All patients filled out informed consent before participation.

### 3.2. Radiation Therapy

Accurate target immobilization and localization are prerequisites for efficient radiation therapy. For patients' immobilization, we used 5-point patient-specific thermoplastic head to shoulder mask (Orfit®, Antwerp, Belgium). For treatment simulation, contrast-enhanced spiral computed tomography (CT) scan was obtained with a slice thickness of 3 mm from cranium vertex superiorly to the sternal angle inferiorly. Additionally, the magnetic resonance imaging (MRI) was performed for better delineation of the primary tumor. The CT- and MRI- images were imported into the Eclipse™ 13.5 (Varian Medical Systems, Palo Alto, CA, US) as the treatment planning system (TPS) and were fused, using the localizer-derived coordinate system. Target volumes were delineated according to the Radiation Therapy Oncology Group (RTOG) 0615 protocol (2006) (3). Furthermore, the dose constraints for all the critical organs were settled based on RTOG 0225 protocol (2008) (4). Inverse planning was performed by the Eclipse TPS, using simultaneous integrated boost IMRT (SIB-IMRT) technique. The prescribed dose was 70.2 Gy to the planning target volume (PTV) of the primary tumor and involved lymph nodes. Moreover, the dose prescribed to the PTV of all the at-risk sites (based on RTOG 0615) was 59.4 Gy. The target volumes (regarding the GTVs and CTVs) received at least 95% of the prescribed dose. Critical organs of interest outlined in 3 dimensions, including the brain stem, spinal cord, lacrimal glands, lenses, globes, optic nerves, optic chiasma, temporal lobes, cochlea, temporomandibular joints, mandible, oral cavity, submandibular glands, parotid glands, brachial plexus, and larynx. To deliver the established dose to the target, we used extended-whole field IMRT (EWF-IMRT) for all the patients. IMRT was delivered by a linear accelerator with 6 MV photons, using dynamic multi-leaf collimator (MLC). For treatment verification, we performed on-line electronic portal imaging device (EPID) once a day.

### 3.3. Chemotherapy

During the study period, our department guideline recommended RT alone for stage 1, concurrent chemoradiation (ChRT) for stage 2 and 3, and induction chemotherapy (ChTx) followed by either RT alone or concurrent ChRT for either locally advanced primary tumors (i.e. T4 lesions) or advanced nodal disease (i.e. N3). However, the treatment of a few patients did not follow the guideline because of the physician's clinical decision (e.g. due to general patient's performance status, poor response to induction treatment). All patients received ChTx. A total of 17 patients (53%) received concurrently with RT, while the remaining also received induction ChTx. The main concurrent and induction ChTx regimens were weekly 40 mg/m$^2$ cisplatin and every 3 weeks docetaxel (60 mg/m$^2$, d1), cisplatin (60 mg/m$^2$, d1), fluorouracil (600 mg/m$^2$, d1 - 5), respectively.

### 3.4. Follow-Up and Delayed Toxicity Assessment

All patients were followed-up for at least every 3 months during the first 2 years and every 6 months thereafter. Comparative head and neck gadolinium-enhanced MRI was performed at first post-treatment visit (i.e. at the end of the 3rd month) for the assessment of response to treatment. Moreover, complete history taking, physical examination, and fiber optic pharyngorhinoscopy were performed at every follow-up visit. The evaluated toxicities include xerostomia, hearing loss, and eyeball damage. These toxicities were examined by the same dentist, audiometrist, and ophthalmologist, respectively. All events were examined after a minimum period of 6 months (from the date of beginning primary RT) to include delayed events. The evaluation of the aforementioned toxicities were as follow: resting/basal salivation status with physical examination (including lipstick and tongue-blade tests) and stimulatory salivation status with stimulatory flow rate (5), hearing loss with pure tone audiometry, and eyeball damage with trimodality approach, using slit lamp plus fundoscopy, ocular coherence tomography (OCT), and retinal angiography. Delayed toxicities were graded according to either LENT/SOMA (Late Effect of Normal Tissue/Subjective, Objective, Management,

and Analytic) or RTOG/EORTC (Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer) scoring criteria (6, 7). The LENT/SOMA criteria were utilized for both xerostomia and hearing loss, while the RTOG/EORTC was employed for eyeball damage for its more applicability. We also used RTOG criteria for hearing loss to make comparison with other centers possible.

## 4. Results

### 4.1. Patients' Characteristics

Of the 32 patients, 22 (68%) were men and 10 (32%) were women. The mean age was 43 years (range 14 - 67 years). According to the 7th edition of the American Joint Committee on Cancer (AJCC) staging criteria, 9 patients were stage 2, 10 patients were stage 3, and 13 patients were stage 4. A brief description regarding 7th edition of AJCC is as follows: T0 (no evidence of primary tumor), T1 (tumor is limited to nasopharynx, oropharynx, or nasal cavity), T2 (involvement of parapharyngeal space), T3 (involvement of bony structures and/or paranasal sinuses), T4 (intracranial, hypopharynx, orbit, infratemporal fossa, masticatory space, and/or cranial nerve involvement), N0 (no lymphadenopathy), N1 (unilateral cervical and/or unilateral or bilateral retropharyngeal node (s) involvement, $\leq$ 6cm in greatest dimension), N2 (bilateral cervical node(s), $\leq$ 6cm in greatest dimension), N3 (> 6cm in greatest dimension and/or supraclavicular lymphadenopathy), M0 (no distant metastasis), M1 (distant metastasis). In line with this, the stage grouping based on 7th edition of AJCC is as follows: SI (T1N0M0), SII (T1N1M0 or T2N0-1M0), SIII (T1-2N2M0, T3N0-2M0), SIVa (T4N0-2M0), SIVb (any TN3M0), SIVc (any T any N M1). One of the patients had suspicious small pulmonary nodules that disappeared after receiving the treatment, thus classified as stage 4c. Histological diagnosis was graded based on World Health Organization (WHO) classification for NPC. Almost all (97%) of the specimens were the non-keratinizing type. Epstein-Barr virus (EBV) presence was examined in 15 patients that two-thirds of them had positive results. For detailed characteristics of patients and diseases, see Table 1. Moreover, the actual exposure doses of targets and organ at risks are presented in Table 2.

**Table 1.** Patient Demographics and Disease Characteristics

| Characteristics | No. (%)[a] |
|---|---|
| **Age, y** | |
| Mean $\pm$ SD | 43 $\pm$ 16.1 |
| Range | 14 - 67 |
| **Gender** | |
| Male | 22 (68) |
| Female | 10 (32) |
| **T stage** | |
| T1 | 8 (25) |
| T2 | 12 (37) |
| T3 | 3 (10) |
| T4 | 9 (28) |
| **N stage** | |
| N0 | 3 (10) |
| N1 | 9 (28) |
| N2 | 16 (50) |
| N3 | 4 (12) |
| **M stage** | |
| M0 | 31 (97) |
| M1 | 1 (3) |
| **Clinical stage** | |
| Stage 0 | 0 (0) |
| Stage 1 | 0 (0) |
| Stage 2 | 9 (28) |
| Stage 3 | 10 (32) |
| Stage 4a | 8 (25) |
| Stage 4b | 4 (12) |
| Stage 4c | 1 (3) |
| **Histological type** | |
| Non-keratinizing (UD) | 25 (78) |
| Non-keratinizing (D) | 6 (19) |
| Keratinizing | 1 (3) |
| Basaloid | 0 (0) |
| **EBV status** | |
| Positive (IHC) | 4 (26) |
| Positive (RT-PCR) | 6 (40) |
| Positive (Total) | 10 (66) |
| Negative | 5 (34) |

Abbreviations: D, differentiated; SD, standard deviation; UD, Undifferentiated.
[a] All of the percent scores rounded for feasibility to express.

### 4.2. Delayed Toxicities

The median follow-up time for assessment of delayed treatment toxicities was 12 months (range 6 - 32 months, SD: 4.9 months). Totally 2, 5, and 5 of the patients were unavailable for the assessment of xerostomia, hearing loss, and eyeball damage, respectively until the deadline time for study. According to the LENT/SOMA criteria, $\geq$ grade 2 xerostomia and hearing loss had an occurrence rate of 10% and 44%, respectively. According to RTOG/EORTC criteria, 7% of the patients had $\geq$ grade 2 eyeball damage and 15% suffered from grade > 2 hearing loss. In the following, the detailed reports of delayed toxicities are presented.

### 4.3. Xerostomia

Overall, the most common complaint among delayed toxicities was xerostomia. The subjective LENT/SOMA grading of pre-treatment status was performed to ensure that xerostomia was caused by the treatment. All of the patients confirmed normal salivation before treatment. The severity of xerostomia was grade 1 in 63% and grade 2 in 10%

**Table 2.** The Actual Exposure Doses to Targets and Organ at Risks

| Structure | Mean Doses, Gy[a] | Max Doses, Gy[a] | Specific Criteria | |
|---|---|---|---|---|
| | | | Mean ± SD | Range |
| **GTV** | | | | |
| Primary | 69.1 ± 5.8 | - | Primary volumes, $cm^3$: 37.1 ± 27.7 | 4.8 - 103.9 |
| Nodal | 68.3 ± 6.1 | - | Nodal volumes, $cm^3$: 28.5 ± 73.2 | 0.5 - 281.6 |
| **CTV** | | | | |
| CTV1 | | | | |
| Primary | 68.8 ± 3.8 | - | - | |
| Nodal | 69.1 ± 3.1 | - | - | |
| CTV2 | | | | |
| Primary | 66.0 ± 2.0 | - | - | |
| Nodal | 62.2 ± 2.5 | - | - | |
| **Brain stem** | - | 48.0 ± 8.0 | D1%, Gy: 43.8 ± 7.2 | |
| **Spinal cord** | - | 41.6 ± 5.1 | D1cc, Gy: 36.8 ± 5.7 | |
| **Chiasma** | - | 35.0 ± 16.3 | D1%, Gy: 33.8 ± 15.4 | |
| **Eye** | | | | |
| Lens | | | | |
| Right | - | 12.5 ± 10.2 | - | |
| Left | - | 9.6 ± 7.2 | - | |
| Globe | | | | |
| Right | 14.4 ± 9.8 | 37.8 ± 15.5 | - | |
| Left | 12.5 ± 7.9 | 36.8 ± 15.5 | - | |
| ON | | | | |
| Right | - | 37.3 ± 17 | D1%, Gy: 33.7 ± 16.2 | |
| Left | - | 34.6 ± 16.4 | D1%, Gy: 32.3 ± 14.5 | |
| **Cochlea** | | | | |
| Right | 45.1 ± 10.7 | 50.4 ± 11.9 | V55, %: 21.3 ± 37.2 | |
| Left | 44.7 ± 10.9 | 51.1 ± 11.9 | V55, %: 19.6 ± 33.4 | |
| **Salivary** | | | | |
| Parotid gland | | | | |
| Total | 32.3 ± 5.3 | - | - | |
| Right | 30.7 ± 5.4 | - | - | |
| Left | 32.7 ± 7.2 | - | - | |
| SMG | | | | |
| Right | 58.9 ± 6.9 | - | - | |
| Left | 58.9 ± 7.0 | - | - | |
| Oral cavity[b] | 41.8 ± 6.9 | - | - | |

Abbreviations: GTV, gross tumor volume; ON, optic nerve; SD, standard deviation; SMG, submandibular gland.
[a] Values are expressed as mean ± SD.
[b] Includes sublingual glands

of patients (no grade 3 toxicity was recorded). The mean doses to parotid glands, submandibular glands, and oral cavity (as an indicator of sublingual and minor salivary glands) were 32.3, 58.9, and 41.8 Gy, respectively (Table 2). Considering normal stimulatory saliva rate as 0.5 mL/min, the rate of stimulatory hyposalivation was 27% (8). For detailed post-treatment salivation results, see Table 3.

### 4.4. Hearing Loss

According to WHO definition, a hearing threshold of ≥ 25-decibel hearing loss at 2000 - 8000 Hz frequencies was considered significant for hearing impairment (9). Moreover, we defined asymmetric hearing loss based on Margolis and Saly's definition (10). A total of 12 patients (44%) developed hearing loss. Seven of them (58%) are classified as grade 4 based on LENT/SOMA score. Among this group, pretreatment assessment with subjective LENT/SOMA criteria revealed grade 3, grade 2, grade 1, and grade 0 hearing loss in 1, 2, 1, and 3 patients, respectively. The pattern of hearing impairment of our study mainly affects the high-frequency range (8000 Hz). For detailed post-treatment pure tone audiometry results, see Table 4.

**Table 3.** Post-Treatment Salivation Results

| Salivary Assessment Items | No. (%)[a] |
|---|---|
| **Subjective** | |
| Hyposalivation | 22 (73) |
| Normal moisture | 8 (27) |
| **Objective** | |
| Basal salivation | |
| Impaired | 16 (53) |
| Normal | 14 (47) |
| Stimulatory salivation | |
| Impaired | 8 (27) |
| Normal | 22 (73) |
| **LENT/SOMA score** | |
| Grade 0 (normal moisture) | 8 (27) |
| Grade 1 (scant saliva) | 19 (63) |
| Grade 2 (absence of moisture, viscous saliva) | 3 (10) |
| Grade 3 (absence of moisture, coated mucosa) | 0 (0) |

[a] All of the percent scores rounded for feasibility to express.

**Table 4.** Post-Treatment Pure Tone Audiometry Results

| Pure Tone Audiometry Items | No. (% from Hearing Loss Group)[a] |
|---|---|
| **Normal hearing** | 15 (56 from total) |
| **Hearing loss**[b] | 12 (44 from total) |
| Frequency | |
| Low (2000 Hz) | 0 (0) |
| Low - High (2000 - 4000 Hz) | 0 (0) |
| High (4000 Hz) | 1 (8) |
| High - very high (4000 - 8000 Hz) | 10 (84) |
| Very high (8000 Hz) | 1 (8) |
| Symmetricity[c] | |
| Symmetric | 10 (84) |
| Asymmetric | 2 (16) |
| Type | |
| Sensorineural | 11 (92) |
| Conductive | 0 (0) |
| Mixed | 1 (8) |
| **LENT SOMA score** | |
| Grade 0 (no problem) | 15 (56 from total) |
| Grade 1 (< 10 db hearing loss) | 0 (0) |
| Grade 2 (10 - 15 db hearing loss) | 0 (0) |
| Grade 3 (15 - 20 db hearing loss) | 5 (42) |
| Grade 4 (> 20 db hearing loss) | 7 (58) |
| **RTOG criteria** | |
| Grade 0 | 15 (56 from total) |
| Grade 1 | 5 (42) |
| Grade 2 | 3 (25) |
| Grade 3 | 4 (33) |
| Grade 4 | 0 (0) |

Abbreviations: db, decibel; Hz, hertz.
[a] All of the percent scores rounded for feasibility to express.
[b] World Health Organization criteria 2008.
[c] If the points for each ear occur within 10 db of each other.

### *4.5. Eye Ball Damage*

Totally, eye damage encountered less in comparison with salivary glands and ears. Based on RTOG/EORTC criteria, 8 patients suffered from eyeball damage, which was mainly related to relatively benign events (e.g. cataract). The severity of eyeball damage (based on RTOG/EORTC) was grade 1 in 23% and grade 2 in 7% of the patients (no grade 3 or 4 damage was recorded). The number of patients suffered from corneal damage, cataract, dry eye, optic neuropathy, and retinopathy were 4, 8, 5, 1, and 2, respectively. Regarding the only patient that was diagnosed with optic neuropathy, there was no past medical history of neither diabetes mellitus nor hypertension. For more detailed information, see Table 5.

## 5. Discussion

Overlooking Southeast Asia, NPC is an uncommon malignancy around the world. Its age-adjusted incidence rate (per 100 000 people per year) among men ranges from 0.6 in the United States to 26.8 in Zhongshan, China. Iran is located at Middle East area with the intermediate risk of incidence; however, the epidemiological studies of Iran has shown a low-risk pattern with the incidence rate of 0.38 among men. As is shown in our study, the male to female incidence ratio in Iran is approximately 2:1 (1, 11). Interestingly, the histologic subtypes of NPC followed the pattern of intermediate incidence populations in order that undifferentiated non-keratinizing subtype constitutes most of the pathological specimens (Table 1) (12). Considering high cancer-specific survivorship of NPC with recent advances in the radiotherapeutic management, QOL and late toxicities become more crucial. There are several studies in the literature that have reported the delayed toxicities of NPC IMRT (13-16). However, these data are limited to count finger countries. This study has provided an opportunity to fill this gap for Iran. In line with this, a study has been recently completed in Iran that evaluated the acute post-radiation toxicities of hearing loss (17). The results of this study indicate that approximately 38% of the patients

**Table 5.** Post-Treatment Eye Examination Results

| Eye Examination Items | No. (%)[a] |
|---|---|
| **Cornea** | |
| Clear | 23 (85) |
| Opaque | 4 (15) |
| **Lens** | |
| Clear | 19 (70) |
| Cataract | 8 (30) |
| **Dry eye** | |
| Not exist | 22 (81) |
| Exist | 5 (19) |
| **RON** | |
| Not exist | 26 (96) |
| Exist | 1 (4) |
| **RR[b]** | |
| Not exist | 25 (93) |
| Exist | 2 (7) |
| **RTOG/EORTC score** | |
| Grade 0 (normal) | 19 (70) |
| Grade 1 (asymptomatic cataract and/or keratitis) | 6 (23) |
| Grade 2 (symptomatic cataract, keratitis, or glaucoma) | 2 (7) |
| Grade 3 (severe keratitis, RD, or glaucoma) | 0 (0) |
| Grade 4 (panophthalmitis and/or blindness) | 0 (0) |

Abbreviations: RON, radiation-induced optic neuropathy; RR, radiation-induced retinitis.
[a] All of the percent scores rounded for feasibility to express.
[b] Based on slit lamp examination, OCT and retina angiography results.

suffered from hearing loss after 3 months follow-up. The higher rate of hearing loss in comparison with this study was unexpected and may be as a result of a higher rate of platinum application in our study.

In comparison with the previous ones, this study has focused on a comprehensive evaluation of delayed toxicities. For instance, regarding the evaluation of retinopathy, we utilized the trimodality approach (i.e. fundoscopy, OCT, and retinal angiography) to increase the accuracy of diagnosis. Moreover, to differentiate parotid glands toxicities from other parts of the salivary system, we utilized various methods for the evaluation of basal and stimulatory salivation status. Table 6 summarizes the treatment method and the results of Shohada-e Tajrish Hospital in comparison with the main centers around the world. With an initial glance to the Table 6, xerostomia rate of this study seems high. However, follow-up time should be considered. Lee et al. (shown as UCSF study in Table 6) reported that xerostomia significantly decreases over time. They showed that the rate of grade 2 xerostomia was approximately 62%, 30%, and 2% in the 3rd, 12th, and 24th month after treatment, respectively (18). Considering this report, the xerostomia rate of our study is approximately in equivalent with UCSF at a median 12 months follow-up.

The obtained results from our study contain crucial points that should be mentioned. The marked difference between the rates of basal and stimulatory hyposalivation may be due to our approach of treatment that was parotid-sparing IMRT. What is surprising is a higher rate of hearing loss in this study (15%). A possible explanation for this might be due to a higher rate of cisplatin application in comparison with similar studies. Moreover, the presence of more locally advanced stages among the patients evaluated in our study (in comparison with UCSF report) may play role in this result (13-15). Nonetheless, the deafness rate as high as 42% has been reported in cisplatin-based concurrent ChRT (19). Regarding 8 patients suffered from cataract, 7 patients were more than 60 years old; therefore, this finding could be secondary to natural occurring senile process. Regarding the only patient with optic neuropathy, the local extension staging was T4 with intracranial extension. This notion caused the extra unilateral retinal dose.

The information provided here was limited to the post-treatment period. Therefore, there is abundant room for further progress in determining delayed toxicities of IMRT for NPC through comparing with pre-treatment status. Another subject for further research is the comparison between IMRT- and 3D-CRT-associated delayed toxicities. Moreover, following the trend of delayed toxicities is another option for developing a full picture of this subject among Iranian patients with NPC. Further studies on the current topic are, therefore, recommended.

The strong point of this study is mainly regarding the approach for the assessment of adverse effects. All of the toxicity categories were evaluated by the same specialists. Regarding the salivation and eye examination, using various evaluations make the results more reliable.

This research, however, is subject to a few limitations. This study is limited by the lack of information on pre-treatment clinical assessment. Pre-treatment evaluation was limited to history taking. Another limitation regards the time of evaluation for delayed toxicities. Some problems like xerostomia recover over time. Another limitation of the study is the impossibility of differentiation between ChTx and RT for developing the toxicities. This is because all of the evaluated patients had received both arms of treatment. In spite of its limitations, this study certainly adds to our understanding of the delayed toxicities status among Iranian NPC patients undergone IMRT in Shohada-e Tajrish Hospital in the hope that it paves a new way for our center for either escalating the quality of treatments or accomplishing further studies.

In conclusion, this study set out to report the results of the initial experience of IMRT for NPC in Iran. In general,

**Table 6.** Results of Nasopharyngeal Carcinoma IMRT by Different Centers

| | Shohada-e Tajrish | UCSF | MSKCC | PWH | QMH |
|---|---|---|---|---|---|
| **Treatment period** | 2016 - 2018 | 1995 - 2003 | 1998 - 2004 | 2000 - 2002 | 2000 - 2002 |
| **No. of patients** | 32 | 118 | 74 | 63 | 50 |
| **T category** | All | All | All | All | T1 - T2 |
| **Total dose, Gy** | 70.2 | 70 | 70.2 | 66 | 68-70 |
| **Dose per fraction** | 2 | 2.12 | 2.34 | 2 | 2 - 2.06 |
| **Chemotherapy, %** | 100 | 90 | 93 | 30 | NA |
| **Median follow-up, mo** | 12 | 30 | 35 | 29 | 14 |
| **Mean parotid dose, Gy** | 32.3 | 26.9 | 26 | 31 | 38.3 |
| **Late toxicities, %** | | | | | |
| Xerostomia (grade $\geq$ 2) | 27[a] | 2[a] (30% at 12th mo) | 32[b] | 23[a] | NR |
| Hearing loss (grade $\geq$ 2) | 15[a] | 7[a] | 15[b] | 15[a] | NR |
| RON | 4 | NR | NR | NR | NR |
| RR | 7 | NR | NR | NR | NR |

Abbreviations: MSKCC, Memorial Sloan Kettering Cancer Center (US); NA, not available; NR, not reported; PWH, Prince of Wales Hospital (Hong Kong); QMH, Queen Mary Hospital (Hong Kong); RON, radiation-induced optic neuropathy; RR, radiation-induced retinitis; UCSF, University of California San Francisco (US).
[a] Based on RTOG/EORTC criteria.
[b] Based on CTCAE criteria.

therefore, it seems that our experience in IMRT for NPC is in good accordance with other well-known centers regarding delayed toxicities. However, this statement was not correct for hearing loss. This issue may be due to a higher rate of chemotherapy application in our study. Further trials are warranted to evaluate it.

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## Footnotes

**Authors' Contribution:** Farzad Taghizadeh-Hesary performed main parts of data acquisition, literature review, and manuscript draft. Afshin Rakhsha, Samira Azghandi, and Ahmad Ameri performed the patient treatment and participated in data acquisition. Amir Shahram Yousefi Kashi revised the manuscript. Saeed Karimi and Saranaz Azari-Marhabi performed eye and salivary examination, respectively. All authors read and approved the final manuscript.

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