European Archives of Oto-Rhino-Laryngology (2019) 276:977–984
https://doi.org/10.1007/s00405-019-05299-7

OTOLOGY

Is intensity-modulated radiotherapy superior to conventional techniques to prevent late ear complications of nasopharyngeal cancer?

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Received: 23 November 2018 / Accepted: 16 January 2019 / Published online: 22 January 2019

Abstract

Purpose This study analyzed the late ear complications of radiotherapy for nasopharyngeal cancer (NPC) and compared the conventional and intensity-modulated radiotherapy (2D-RT and IMRT, respectively).

Methods At 2–21 years after the end of NPC treatment, 104 ears of 52 patients were evaluated with the otoscopic examination, pure tone audiometry test, tympanometry, and subjective complaints by being blinded to the radiotherapy technique.

Results There were no differences in terms of the pathology of the external, middle or inner ear, air and bone-conduction hearing thresholds, and the air–bone (A–B) gap at 500, 1000, 2000, and 4000 Hz, and tympanometry types between 2D-RT and IMRT groups ($p > 0.05$). There were positive correlations between the values of A500 and A1000 thresholds; gap 500, 4000, and mean cochlear RT dose ($p < 0.05$). There were positive correlations between the values of A500, A1000, and A4000 thresholds; gap 500, 1000, 2000, 4000, and maximum cochlear RT dose ($p < 0.05$).

Conclusion IMRT was not found to be superior to 2D-RT to prevent RT-induced ear complications. The solution of the middle ear problems must be the goal of the strategies for complications treatment.

Keywords Cancer · Ear · Hearing · Intensity-modulated radiotherapy · Late complication · Nasopharynx · Radiotherapy

Introduction

Nasopharyngeal cancer (NPC) is mainly located in the Rosenmüller fossa, near the Eustachian tube. The primary modality of treatment of the NPC is radiotherapy (RT) as 95% are undifferentiated squamous cell carcinoma (SCC) which has a high radiosensitivity [1]. Good prognosis and young patient age lead to the frequent occurrence of RT complications. Mainly, these complications rather than cancer affect the patients' quality of life adversely.

The ear is a site that is affected by the tumor of the nasopharynx and the treatment protocols of NPC. Otological complications arising from RT are not less, as a result of being included in the radiation fields. Incidence, type, and severity of these complications are not clear due to the differences in the treatment protocols [dose, fractionation techniques, the combination with chemotherapy (CT), etc.]. As irradiation treatment in all types of cancer, it is crucial maintaining surrounding non-target structures while delivering effective RT for the eradication of tumor [2].

RT-induced damage affects all parts of the auditory pathway; from the external ear to the central auditory system. Therefore, all types of hearing loss (HL) as conductive, sensorineural, or mixed type may be seen in these patients with NPC [3]. Post-irradiation otitis media and sensorineural hearing loss are the most common complications of RT. Middle ear effusion is not only a finding of

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the NPC at diagnosis but also a complication of RT; as a result of Eustachian tube (ET) dysfunction [2].

In general, older RT techniques as 2D conventional RT (2D-RT) were known to produce serious adverse effects. These effects are reduced with the current techniques as 3D conformal RT (3D-RT) and intensity modulated RT (IMRT) [3]. As its proximity, it is controversial that the new RT techniques reduce the ear complications. The research question of this study was whether the current RT technique (IMRT) prevents the ear complications in this close site.

This study aimed to provide insight into the course of late ear complications of RT of the patients with NPC, and enlighten the main and common mechanisms of the pathology.

Materials and methods

Cases

The patients histopathologically diagnosed of NPC in The Departments of Otorhinolaryngology, Head and Neck Surgery, Medical and Radiation Oncology of a tertiary referral center (between the years 1996 and 2015) were included in the study according to the following criteria:

1. The patients over 18 and under 55 years old (to decrease the effect of age-related sensorineural hearing loss and presbyacusis).
2. No history of chronic otitis media and/or audiometric detection of hearing loss or lack of ear pathology prior to NPC diagnosis and treatment.
3. No additional disease or drug use which may cause ear and/or hearing pathology other than NPC and the treatment of NPC.
4. Exclusion criteria were: (1) the detection of recurrence or metastasis in the follow-up period, (2) systemic disease such as hypertension, diabetes mellitus, etc., (3) missing data of RT dose, and (4) surgical treatment of the ear during the follow-up period.

NPC treatment

Mainly, the patients with the early (I and II) stage NPC were treated with RT alone, while CT was added to the treatment protocol of the patients with late (III and IV) stages. No standard therapy was present in the CT protocol. In the Radiation Oncology Department of the tertiary referral center which this study was occupied, the radiation technique changed from 2D-RT to IMRT in 2008.

Radiotherapy

The radiotherapy treatment records with curative intent of 52 patients with NPC were evaluated.

Patients in the 2D-RT group were treated with the conventional 3-field technique using two-dimensional computer planning with cobalt-60 or linear accelerator 6 MV photon beams. Treatments were planned in two phases. In the first phase, patients were irradiated by bilateral-opposing photon beams (for the craniocervical field) and anterior beams (for the lower cervical field). Clinically uninvolved lymphatic regions received 50 Gy and the spinal cord was shielded after a dose of 46 Gy. In the second phase, the dose for primary tumor and pathologic lymph nodes was boosted from 66 to 70 Gy. The prescribed irradiation dose was 2 Gy per fraction with 5 daily fractions per week.

In the IMRT group, International Commission on Radiation Units and Measurements Report 62 guidelines (ICRU 62) [4] was used as the reference for target volume delineations. Gross tumor volume (GTVtm) and cervical lymph-node tumor volume (GTVln) were delineated by PET-CT/MRI. Clinical target volume (CTV) included the GTV with a 1–1.5 cm margin, the entire nasopharyngeal space, and the positive lymph-node regions. Planning target volumes (PTV) were created from CTV with 0.5 cm margin. The prescribed irradiation dose was 69.96 Gy (2.12 Gy/F/QD) for GTV and 54–60 Gy (1.63–2 Gy/F/QD) for CTV. In addition, brain stem, spinal cord, parotid gland, eyes, optic chiasma, optic nerves, cochleas, and ear structures were contoured through the planning tomography. IMRT planning was performed with simultaneous integrated boost technique. Mean and maximum RT doses of cochlea were recorded for each patient.

Chemotherapy

Mainly, chemotherapy was added to the treatment protocol of the patients with the late-stage (stages 3 and 4) NPC.

- Chemoradiotherapy protocol: 40 mg/m^2 cisplatin weekly with RT varied between 5 and 7 weeks according to the toxicity and follow-up period. Approximately 240 mg/m^2 cisplatin was administered throughout the protocol.
- Induction or adjuvant chemotherapy was given to the patient in three different cures. DCF (60 mg/m^2 docetaxel + 60 mg/m^2 cisplatin + 600 mg/m^2 5-fluorouracil at 21 days) or CF (80 mg/m^2 cisplatin + 4000 mg/m^2 5-fluorouracil, once in 21 days) was preferred.

Ear and hearing assessment

Fifty-two patients with NPC were retrospectively reviewed. At 2–21 years after the end of NPC treatment,

104 ears of 52 patients were evaluated with the otoscopic examination, pure tone audiometry test, and tympanometry by being blinded to the radiotherapy technique. Pure tone air-conduction (AC) and bone-conduction (BC) were recorded at 500, 1000, 2000, and 4000 Hz. Otoscopic examination and an average of threshold levels of pure tone AC and BC at 500–4000 Hz were recorded in a scale to assess external, middle, and inner ear function, respectively (Table 1) [5].

The results of the tympanometry were recorded as three types (type A, B, and C). Subjective ear complaint score (SECS) was calculated by the presence of the following complaints: hearing loss, aural fullness, tinnitus, and itching. These symptoms were graded by 1 when they exist for each ear and the sum was calculated as SECS.

The approval was taken from the local institutional research committee and informed consents were obtained from the patients. The research was conducted in compliance with the Ethics Principles of the Declaration of Helsinki.

Statistical analysis

In descriptive statistics related to continuous data; mean, standard deviation, median, minimum, maximum values; number and percentage values are given.

The continuous data were evaluated by visual (Histogram) and statistical methods (Shapiro–Wilk and Kolmogorov and Smirnov tests), and it was seen that the data did not follow a normal distribution. Thus, non-parametric tests were used. The results were evaluated statistically using Mann–Whitney *U* test.

Chi-square/Fisher's exact test was used for comparison of nominal variables in two groups.

The Spearman correlation coefficient was used to evaluate the correlation between the hearing parameters of the patients and the cochlear doses of RT.

SPSS for Windows, Version 11.5 Chicago, SPSS Inc. program was used in the statistical analysis and the statistical significance limit was accepted as $p < 0.05$.

Results

Fifty-two patients (104 ears) were included in the study, 36 were men (69%), and 16 were women (31%). According to the 8th AJCC staging system, 25 patients (48%) were stage I, 18 patients (35%) were stage II, 6 patients (11.5%) were stage III, and 3 patients (5.5%) were stage IV.

There were 20 patients (38.5%) in the 2D and 32 patients (61.5%) in the IMRT group. The mean age of the patients in the 2D group was 42.80 ± 8.89, and the mean age of the patients in the IMRT group was 44.25 ± 10.70. No age-related difference was found between two groups ($p > 0.05$).

The stages (0, 1, 2, 3, and 4) of the pathology of the external ear were 7.5%, 85%, 2.5%, 5%, and 0% in the 2D group; 4.7%, 95.3%, 0%, 0%, and 0% in the IMRT group, respectively. The stages (0, 1, 2, 3, and 4) of the pathology of the middle ear were 35%, 32.5%, 12.5%, 17.5%, and 2.5% in the 2D group; 35.9%, 28.1%, 23.4%, 12.5%, and 0% in the IMRT group, respectively. The stages (0, 1, 2, 3, and 4) of the pathology of the inner ear were 47.5%, 35%, 10%, 5%, and 2.5% in the 2D group; 46.9%, 35.9%, 14.1%, 3.1%, and 0% in the IMRT group, respectively. There were no differences in terms of the pathology of the external, middle, or inner ear between two groups ($p > 0.05$) (Table 2).

Among all 104 ears, type A, B, C tympanometry were 60%, 27.5%, and 12.5% (*n*: 24, 11, 5) in the 2D group, and 51.6%, 35.9%, and 12.5% (*n*: 33, 23, 8) in the IMRT group, respectively. No difference in terms of tympanometry types was found between two groups ($p > 0.05$) (Table 3).

The AC- and BC-hearing thresholds and the air–bone gap at 500, 1000, 2000, and 4000 Hz of the patients of the 2D and IMRT groups are shown in Table 4.

In the 2D group; the median values of A500, A1000, A2000, and A4000 thresholds were 20, 20, 22.5, and 32.5; the median values of B500, B1000, B2000, and B4000 thresholds were 10, 10, 12.5, and 22.5; the median values of air–bone gap at 500, 1000, 2000, and 4000 Hz were 10, 10, 5, and 10, respectively. In the IMRT group; the median values of A500, A1000, A2000, and A4000 thresholds were 30, 25, 30, and 52.5; the median values of B500, B1000, B2000, and B4000 thresholds were 15, 10, 15, and

Table 1 Late radiation toxicity grading [5]

Grade	0	1	2	3	4
External ear	Normal	Slight skin atrophy, mild cerumen, intermittent hearing loss	Otitis externa	Cerumen impact with loss of skin canal	Bony ear canal necrosis
Middle ear	Normal	Eustachian tube dysfunction, reversed by Valsalva	Mild fluid in middle ear	Mark conductive hearing loss, chronic otitis media	Atelectatic ear, chronic otitis media with complication
Inner ear	Normal	Mild SNHL, 26–40 dB	Moderate SNHL, 41–55 dB	Severe SNHL, 56–70 dB	Profound SNHL, > 71 dB

Table 2 Comparison of the stages of the external, middle, and inner ear pathology of the patients in 2D and IMRT groups

Stage of the pathology	2D		IMRT		*p**
	n	%	*n*	%	
External ear					
0	3	7.5	3	4.7	–
1	34	85	64	95.3	
2	1	2.5	0	0	
3	2	5	0	0	
4	0	0	0	0	
Middle ear					
0	14	35	23	35.9	0.445
1	13	32.5	18	28.1	
2	5	12.5	15	23.4	
3	7	17.5	8	12.5	
4	1	2.5	0	0	
Inner ear					
0	19	47.5	30	46.9	0.773
1	14	35	23	35.9	
2	4	10	9	14.1	
3	2	5	2	3.1	
4	1	2.5	0	0	

*Chi-square test/Fisher's exact test

Table 3 Comparison of right and left ear timpanometry of the patients in 2D and IMRT groups

	2D		IMRT		*p**
	n	%	*n*	%	
Timpanometry					
A	24	60	33	51.6	0.652
B	11	27.5	23	35.9	
C	5	12.5	8	12.5	

*Chi-square test/Fisher's exact test

40; the median values of air–bone gap at 500, 1000, 2000, and 4000 Hz were 10, 10, 5, and 10, respectively. There were no differences in AC- and BC-hearing thresholds and the air–bone gap at 500, 1000, 2000, and 4000 Hz of the patients between the 2D and IMRT groups ($p > 0.05$) (Table 4).

The median follow-up time for all patients was 5.5 years (range 2–21 years). There were no differences in the duration between treatment and ear complaint and subjective ear complaint score (SECS) of the patients between 2D and IMRT groups ($p > 0.05$). There was a statistically significant difference in terms of the duration after treatment between two groups ($p < 0.01$) (Table 5).

The median values of the mean and maximum cochlear RT dose of the patients in the IMRT group were 43.8 (21.2–71.9) and 62.3 (32–75.5) Gy, respectively (Table 6).

There were positive correlations between the values of A500 and A1000 thresholds and mean cochlear RT dose ($r = 0.364$ $p < 0.05$; $r = 0.312$ $p < 0.05$, respectively). No correlation was found between the values of A2000 and A4000, and bone-conduction thresholds and mean cochlear RT dose (Table 7).

There were positive correlations between the values of gap 500 and 4000 and mean cochlear RT dose ($r = 0.405$ $p < 0.01$; $r = 0.302$ $p < 0.05$, respectively). No correlation was found between the values of gap 1000 and 2000 and mean cochlear RT dose (Table 7).

There were positive correlations between the values of A500, A1000, and A4000 thresholds and maximum cochlear RT dose ($r = 0.352$ $p < 0.05$; $r = 0.305$ $p < 0.05$; $r = 0.313$ $p < 0.05$, respectively). No correlation was found between the values of A2000, bone-conduction thresholds, and maximum cochlear RT dose (Table 8).

There were positive correlations between the values of gap 500, 1000, 2000, and 4000 and maximum cochlear

Table 4 Descriptive statistics and comparison of air (A)-conduction and bone (B)-conduction hearing thresholds and air–bone gap at 500, 1000, 2000, and 4000 Hz of the patients in the 2D and IMRT groups

	2D		IMRT		*p**
	Mean ± SD	Median (min–max)	Mean ± SD	Median (min–max)	
A500	28.50 ± 21.87	20 (0–85)	29.56 ± 16.23	30 (5–65)	0.356
A1000	27.62 ± 22.87	20 (5–95)	27.81 ± 18.64	25 (0–80)	0.626
A2000	26.50 ± 22.65	22.5 (0–95)	31.56 ± 22.02	30 (0–85)	0.195
A 4000	43.63 ± 31.88	32.5 (0–100)	52.03 ± 27.60	52.5 (0–110)	0.125
B500	16.25 ± 15.22	10 (0–60)	15.23 ± 12.20	15 (0–50)	0.861
B1000	15.00 ± 14.89	10 (0–70)	12.73 ± 15.14	10 (0–70)	0.269
B2000	19.13 ± 18.43	12.5 (0–75)	22.34 ± 18.98	15 (0–80)	0.286
B4000	32.12 ± 24.62	22.5 (0–80)	39.06 ± 25.92	40 (0–80)	0.194
Gap 500	12.25 ± 11.82	10 (0–45)	13.91 ± 14.29	10 (0–50)	0.860
Gap 1000	13.63 ± 13.59	10 (0–45)	14.30 ± 12.72	10 (0–40)	0.663
Gap 2000	8.38 ± 9.29	5 (0–40)	9.30 ± 9.55	5 (0–35)	0.643
Gap 4000	12.25 ± 11.76	10 (0–45)	13.28 ± 12.22	10 (0–45)	0.667

*Mann–Whitney *U* test

Table 5 Comparison of the duration between treatment and ear complaint, duration after treatment, and subjective ear complaint score (SECS) of the patients in 2D and IMRT groups

	2D		IMRT		*p**
	Mean ± SD	Median (min–max)	Mean ± SD	Median (min–max)	
Duration between treatment and ear complaint (month)	21.58 ± 39.69	4.5 (0–120)	5.85 ± 7.51	3 (0–36)	0.411
Duration after treatment (year)	13.11 ± 4.75	12.5 (2–21)	3.41 ± 2.11	3 (2–7)	0.000
SECS		1.5 (0–4)		2 (0–4)	0.217

*Mann–Whitney *U* test

Table 6 Descriptive statistics of cochlear RT dose of the patients in the IMRT group

	IMRT	
	Mean ± SD	Median (min–max)
Kohlea mean	46.11 ± 13.65	43.8 (21.2–71.9)
Kohlea max	58.39 ± 11.29	62.3 (32–75.5)

Table 7 Correlation between mean cochlear doses and air-conduction (A) and bone-conduction (B) hearing thresholds and air–bone gap at 500, 1000, 2000, and 4000 Hz of patients in the IMRT group

Hearing parameters	Mean cochlear doses	
	r^a	*p*
A500	0.364	0.015
A1000	0.312	0.039
A2000	0.147	0.340
A4000	0.261	0.087
B500	0.209	0.173
B1000	0.150	0.332
B2000	0.168	0.275
B4000	0.155	0.314
Gap 500	0.405	0.006
Gap 1000	0.248	0.104
Gap 2000	0.274	0.072
Gap 4000	0.302	0.046

[a]*r*: Spearman correlation coefficient

RT dose ($r = 0.486$ $p < 0.01$; $r = 0.308$ $p < 0.05$; $r = 0.376$ $p < 0.05$; $r = 0.393$ $p < 0.01$, respectively) (Table 8).

Discussion

Otological complications are one of the most common late complications of RT in patients with NPC. There is no consensus on the associated risk factors of ear complications of RT in NPC. Radiation dose and technique, adjuvant therapies (CT, etc.), age, concomitant systemic, and ear diseases are discussed in several studies [1, 3, 6, 7].

Table 8 Correlation between maximum cochlear doses and ear air-conduction (A) and bone-conduction (B) thresholds and air–bone gap at 500, 1000, 2000, and 4000 Hz of patients in the IMRT group

Hearing parameters	Max. cochlear doses	
	r^a	*p*
A500	0.352	0.019
A1000	0.305	0.044
A2000	0.164	0.289
A4000	0.313	0.038
B500	0.004	0.980
B1000	0.007	0.965
B2000	0.087	0.573
B4000	0.130	0.400
Gap 500	0.486	0.001
Gap 1000	0.308	0.042
Gap 2000	0.376	0.012
Gap 4000	0.393	0.008

[a]*r* Spearman correlation coefficient

3D-RT and IMRT are the techniques to effectively target the tumor by reducing the unnecessary radiation exposure to the surrounding structures. Thus, the radiation technique is expected to affect the complication rates. However, the proximity of the ear structures to the nasopharynx makes them sensitive to the damage of RT. Accurate identification of ear structures in imaging studies prior to RT is a prerequisite for dose limitation to these structures in post-treatment sequelae [8].

3D-RT and IMRT were reported not only to increase the tumor control rate but also to prevent radiation-induced complications and improve the quality of life of the patients [2]. In a study by Pow et al. [9], in the 12-month follow-up after completing RT, the quality of life was found to be higher in the IMRT group than 2D-RT group. In a long-term study, the impairment in both AC and BC was found to be less in the IMRT group comparing with the 2D/3D-RT group [10]. The incidence of HL was reported as 26–85% in the patients

treated with the conventional RT versus 16% with IMRT [3, 5, 11–14]. In a study by Hsin et al., chronic otitis media were found to be lower in the IMRT group, compared with the 2D-RT group. However, the incidence of middle ear effusion (correlated with T stage) cannot be reduced by IMRT [15].

In contrast, in a study with 325 patients with head and neck tumor, the incidence of ear disorders following 2D-RT was found to be 41.8% [6]. Zeng et al. [16], Liang et al. [17], Yao et al. [18] reported the rate of otological complications of IMRT in patients with NPC as 46.2%, 52.9%, and 44.3%, respectively. In our study, when all parts of the ear were evaluated separately, the rate of the external, middle, and inner ear pathologies in the IMRT group was found to be 95.3%, 65%, and 53.5%, respectively. The rate of type B and C tympanometry which revealed the presence of the middle ear pathology was found to be 40%. No statistically difference was found in the ear pathologies and tympanometry results between 2D-RT and IMRT groups. The comparative results of SECS, which was depended on the subjective ear complaints, also supported these results.

Yao et al. reported that the medial part of the ET and mastoid was included in the high-risk regions of the irradiation inevitably. Thus, the irradiation dose of the cartilaginous part of the ET and mastoid was assessed to be the same or even higher in IMRT, comparing with 2D-RT [18]. In the pathogenesis of ET dysfunction; the deterioration of the ciliary activity and cellular structure of the mucosa are the main ultra-structural findings at acute phase [19]. Persistence of these findings results in a dysfunction spectrum of Eustachian tube in chronic phase; as the patulous Eustachian tube, adhesion, and obstruction of Eustachian tube [20]. As a result, tubal dysfunction and inflammatory process of the middle ear and mastoid cause the middle ear disorder. The limitation of the irradiation dose in IMRT is not considered sufficient to reduce the otological complications. Our study is consistence with the studies [6, 16–18] which revealed that IMRT was unsuccessful to reduce the occurrence of otological complications in NPC.

As the comparison of AC hearing thresholds and A–B gap in hearing frequencies; no difference was found between 2D-RT and IMRT groups in our study. When AC hearing thresholds were evaluated in two groups; it was seen that, in the 2D-RT group, only the median value of A4000 hearing threshold was deteriorated. In the IMRT group, although the deterioration in A4000 hearing threshold was more, all frequencies were affected. The mechanism under the conductive hearing loss at high frequencies due to middle ear pathology is explained as the "mass effect". One possible cause is that ET dysfunction can lead to negative pressure and transudate in the middle ear; this transudate can be contaminated with bacteria from the nasopharynx. The exudate and glue formation and their persistence may result as the mucosal polyp and granulation tissue formation [3]. Fibrosis at the late stage may add deterioration at low frequencies; this is known as "stiffness effect". The impairment in air-conduction thresholds was found to be more evident and its incidence is higher than that of bone-conduction thresholds as a result of the affected middle ear. This finding is consistent with the studies that reported RT-induced Eustachian tube dysfunction [6, 16–18].

Post-irradiation sensorineural hearing loss (SNHL) rates vary between 0 and 60% as a result of the damage of the sensorineural auditory pathways [12, 21–23]. SNHL can be classified as early-onset (hours or days) and late-onset (months or years) [24]. The study by Low et al. proved audiologically that the retro-cochlear auditory pathways were functionally preserved; however, the cochlea and internal auditory canal received significant doses [25]. SNHL following RT was reported to have a higher incidence at high frequencies [23, 26]. In a prospective study, high-frequency SNHL was reported as 95% [12]. Hwang et al. indicated that hearing deterioration started at high frequencies. However, after adjusting for age and with longer follow-up time, this difference in the incidence of HL at varying frequencies disappeared [10]. When BC-hearing thresholds were evaluated in two groups; it was seen that in the 2D-RT group, none of the median value of BC-hearing thresholds was deteriorated. In the IMRT group, only the median value of B4000 hearing threshold was affected. This finding of our study shows that, although the effect of age was minimized as the age of the study groups was under 55 years, high frequencies were affected more in RT-induced SNHL.

The duration after treatment was 12.5 (2–21) years in the 2D-RT group, 3 (2–7) years in the IMRT group, in our study. There was a significant difference in the duration after treatment between two groups, as the 2D-RT was an older RT technique. The mean AC- and BC-hearing thresholds' deterioration was shown to differ significantly, 2–9 years after RT [10]. At least 12 months was reported for SNHL to become evident [26]. The duration between treatment and subjective ear complaint was recorded as 4.5 (0–120) months in the 2D-RT group and 3 (0–36) months in the IMRT group, retrospectively. No difference was detected in this parameter between two groups. One possible cause is that when the depletion of hair cells reaches a critical level, detectable SNHL may become or radiation-induced injury make the hair cells more susceptible to noise and ototoxic medications-induced apoptosis [27]. To our knowledge, the time of subjective ear complaints onset was not present in the literature, which was shown to begin so earlier before being detected audiologically in our study.

Radiation-induced damage was shown to be dose-dependent [24]. In various studies, the higher dose of RT was reported to be related to the higher incidence and severity of HL [22, 28, 29]. However, in the study by Liberman, no significant difference was found in the hearing thresholds

at any frequencies when the mean radiation dose at ear was 42 Gy [30]. In our study, the median values of the mean and maximum cochlear RT dose of the patients in the IMRT group were 43.8 (min–max 21.2–71.9), 62.3 (min–max 32–75.5) Gy, respectively. Cochlear RT doses of this study were above the values that Liberman et al. mentioned.

There were positive correlations between the values of A500 and A1000 thresholds and Gap500 and mean cochlear RT doses in the IMRT. The factor underlying this observation may be interpreted as follows: the mean RT dose mostly shows its effect with fibrosis of the middle ear structures (tympanic membrane, ossicular chain, mucosa of the middle ear, etc.) which may cause stiffness and hearing deterioration at low frequencies. However, maximum cochlear RT dose was correlated positively with Gap at all frequencies and A500, A1000, and A4000 thresholds. This finding may reflect the increasing fibrosis which affects all frequencies as tympanosclerosis.

As the limitation of our study, the impact of CT was not included in the statistical analysis because of the varying doses of Cisplatin. CT protocol including cisplatin was added to the therapy of the patients with the late-stage NPC. Cisplatin is a known ototoxic agent causes hearing loss, especially at high frequencies. The ototoxicity of Cisplatin was reported to be dose-dependent and increases with a total dose more than 600–1050 mg/m^2 [10, 31]. In this study, the dose of cisplatin of the patients with late-stage NPC was below this range. Thus, the ototoxicity of cisplatin may be disregarded.

In conclusion, IMRT was not found to be superior to 2D-RT to prevent RT-induced ear complications. The solution of the middle ear problems must be the goal of the strategies for complication treatment.

Compliance with ethical standards

Conflict of interest None to declare.

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