Zagazig University Medical Journal
www.zumj.journals.ekb.eg

https://dx.doi.org/10.21608/zumj.2021.91112.2319 Volume 28, Issue 5, September 2022(1118-1126)

Manuscript ID ZUMJ-2108-2319 (R2)
DOI **10.21608/zumj.2021.91112.2319**

ORIGINAL ARTICLE

Prospective Study on the Dose Distribution to the Middle-ear Structures during 3D Conformal Radiotherapy for Head and Neck Tumors and Dose Effect on Middle-ear Toxicity: Zagazig University Hospitals Experience.

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Submit Date 2021-08-17
Revise Date 2021-08-28
Accept Date 2021-08-29

ABSTRACT

Background: Head and neck cancer (HNC) is a significant public health problem over the world. Head and neck squamous cell carcinomas (HNSCCs) are the sixth most common malignancy worldwide. Radiation therapy (RT) is a cornerstone in the treatment of HNSCCs**.** The aim of this study was to analyse the dose distribution in the middle ear structures in patients with HNC after RT and to evaluate the dose effect on the occurrence of middle ear toxicity. M**ethods:** This prospective study was carried out at Clinical Oncology and Nuclear Medicine Department at Zagazig University Hospitals. It included 24 patients with HNC treated with RT. Dose distribution to the middle ear was calculated using dose volume histogram parameters to detect the correlation between the dose and the toxicity. **Results:** Patients with HNC treated with RT are associated with an incidence of middle ear toxicity in the form of otitis media with effusion and eustachian tube dysfunction depending on the mean dose to middle ear and dose to 30% of Eustachian tube volume (ET D30). The toxicity is associated with middle ear mean dose ≥40 Gy and ET D30 >52.75 Gy. Head and neck tumors above the larynx are associated with a higher mean dose to middle ear than tumors of larynx and hypopharynx. **Conclusion:** RT in cases of HNC is associated with middle ear toxicity and the incidence of the toxicity depends on the dose of radiation to middle ear. And the dose depends on the site of the tumor.

Keywords: Head and Neck Cancers; Radiotherapy; Middle Ear Dosimetry; Otitis Media with Effusion; Eustachian Tube Dysfunction.

INTRODUCTION

Head and neck cancer (HNC) is a significant public health problem allover the world with a significant mortality and morbidity despite early diagnosis and treatment **[1].** HNC is an epithelial malignancy that arise from the epithelial lining of the paranasal sinuses, nasal cavity, oral cavity, pharynx, larynx, and salivary glands. Most of these malignancies are squamous cell carcinomas **[2].** In Egypt the incidence of head and neck squamous cell carcinomas (HNSCCs) is 17–20% of all cancers **[3].**

Radiation therapy (RT) is widely used for the treatment of head and neck cancers as definitive or adjuvant treatment either alone or with chemotherapy. Due to early detection, increased awareness and great development in treatment options, the proportion of patients who survive the disease has increased. Therefore, physicians should consider the side effects caused by radiation therapy on their patients **[4].**

The effect of radiation on middle ear and eustachian tube (ET) in the form of eustachian tube dysfunction (ETD) and otitis media with effusion (OME) is a known adverse effect that occurs due to fibrosis of the adjacent muscles and inflammation, oedema of the lining epithelium of ET and middle ear leading to impairment of ET function. This impairment leads to the development of negative pressure inside middle ear and retraction of tympanic membrane and if not resolved will lead to the development of

middle ear effusion due to transudation of fluid from lining mucosa **[5].**

The dose of radiation to the middle ear structures and ET can vary according to the site of the primary tumor and the site of lymph node metastasis therefore, it's important to compare the radiation dose to middle ear and ET with the incidence of OME and ETD **[6].**

Aim of the Study

The aim of this study was to analyse the dose distribution in the middle ear structures in patients with HNC after radiotherapy and to evaluate the dose effect on the occurrence of middle ear toxicity and the correlation between the site of the tumor and the middle ear dose distribution.

METHODS

This Prospective study was conducted on 24 patients (19 males, 5 females) of histopathologically proven head and neck malignancies (48 ears). The study was conducted at Clinical Oncology and Nuclear Medicine Department at Zagazig University Hospitals from September 2019 to December 2020. Written informed consents were obtained from all participants, the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion Criteria:

Histopathologically proven malignancy of head and neck, age: 38 – 85 years old, normal hematological, renal and liver functions, normal middle ear examination prior to RT, performance status ≤ 2 by Eastern Cooperative Oncology Group (ECOG) scale.

Exclusion Criteria:

Middle ear disease prior to radiotherapy, previous head and neck radiotherapy, previous or concurrent ototoxic chemotherapy, nasopharyngeal and parotid cancers, presence of ET obstruction prior to RT.

All patients received either definitive or adjuvant conformal three-dimensional RT with or without concurrent chemotherapy. All patients were simulated before treatment with head and neck fixation using thermoplastic head and neck mask. Three dimension external-beam radiation therapy was administered to patients using linear accelerator, Elekta Precise Release 2.12 powered by Precise PLAN Release 2.12 - 477.08 silicon graphic workstation (CPU ID: 1762688860), using energy 6-15 MeV. Phase I included primary site and all neck nodal levels; receive 50 Gy by conventional fractionation (1.8-2 Gy per fraction, 1 fraction per day, 5 fractions per week), (50 Gy/25 fractions). Phase II included the primary site or tumor bed and any positive neck nodes; receive a boost dose 16 Gy by conventional fractionation (1.8-2 Gy per fraction, 1 fraction per day, 5 fractions per week), (16 Gy/8 fractions). Patients who received chemotherapy concurrently with RT, received weekly carboplatin. Middle ear was contoured using the bone window (1400-1600/400-600 HU or 3000-4500/600-800 HU). The ET, tympanic cavity and the mastoid air cells were contoured separately based on the CT anatomy. The dose volume histogram (DVH) parameters for each component of the middle ear were collected. The middle ear toxicity was assessed by middle ear examination and tympanometry pre and post RT. Typical tympanogram is classified into types depending on the shape of the peak: (**A**) Curve is within normal measurement parameters, (**B**) Curve indicates OME, (**C**) Curve indicates ETD, (**As**) Curve indicates thickened TM due to post RT inflammation.

Statistical Analysis

All data were collected, tabulated and statistically analyzed using SPSS 22.0 for windows (IBM Inc., Chicago, IL, USA). Continuous Quantitative variables were expressed as the mean ± SD or median (range). Categorical qualitative variables were expressed as absolute frequencies (number) and relative frequencies (percentage).

RESULTS

This study was conducted on 24 patients (19 males and 5 females) with male to female ratio 4:1 who were proved pathologically to have head and neck cancer except nasopharyngeal and parotid cancer with age ranging from 38 to 85 years. Sites of the tumors were (15 larynx, 1 hypopharynx, 3 oral cavity, 5 nasal cavity and paranasal sinuses). The majority of the tumors (91.7%) were squamous cell carcinoma, 1 case only had adenocarcinoma and one case had undifferentiated sarcomatoid carcinoma. Three cases were of grade I, 10 of grade II, 7 of grade III and in 4 cases grade was unknown. T stage was 8, 11, 1, 4 cases for T1, T2, T3, T4 respectively. N stage was 19, 0, 4, 1 cases for N0, N1, N2, N3 respectively. The American Joint Committee on Cancer (AJCC) staging of the tumors were equal for stage I and II by 8 cases, one case only was of stage III and 7 were of stage IV. Weekly carboplatin was given concurrently in 9 cases.

The DVH parameters of the studied ear structures (table 1) show that, the average mean doses to the

middle ear, ET, tympanic cavity, mastoid process were 13.67+/-16.89 Gy, 15.3+/-20.87 Gy, 14.24+/-19.72 Gy, 12.46+/-14.26 Gy respectively and the mean dose (range) to the ET was (0.01-65.26 Gy)

The DVH parameters of the studied ear structures (table 2) illustrate that, 41 ears (85.4%) had mean dose to middle ear less than 40 Gy and 44 ears (91.7%) had dose to 30% of eustachian tube volume (ET D30) less or equal to 52.75 Gy.

Table (3) shows that there is a significant correlation between the mean dose of middle ear and the occurrence of middle ear toxicity in the form of OME as indicated by (B) curve in tympanogram as (B) curve was found only when mean dose to middle ear was ≥40Gy. But table (4) shows significant correlation between the total prescribed dose of RT and the occurrence of middle ear toxicity.

As demonstrated in table (5), in tumors above the larynx, 7 out of 16 studied ears had mean dose to middle ear ≥40Gy and 4 out of 16 studied ears had ET D30 >52.75Gy, while in laryngeal and hypopharyngeal tumors, none of the studied ears had mean dose to middle ear ≥40Gy and none of them had ET D30 >52.75Gy.

Table 1: Dose Volume Histogram parameters of the studied ears of head and neck cancer patients (N=48).

DVH parameters	The studied ears of head and neck cancer patients (N=48)			
	Average	±SD	Median	(Range)
Middle ear				
Volume (cc)	9.84	±4.59	9.55	(2.50 – 21.60)
Mean dose (Gy)	13.67	±16.89	5.43	(0.01 – 52.99)
Volume (cc)	0.37	±0.25	0.30	(0.10 – 1.10)
Mean dose (Gy)	15.30	±20.87	2.96	(0.01 – 65.26)
D30 (Gy)	16.57	±21.28	3.30	(0 – 65)
Volume (cc)	1.22	±0.46	1.10	(0.20 – 2.70)
Mean dose (Gy)	14.24	±19.72	2.71	(0.01 – 64.28)
Mastoid process				
Volume (cc)	7.30	±4.19	6.70	(0.70 – 16.50)
Mean dose (Gy)	12.46	±14.26	6.22	(0.01 – 44.15)

Table 2: Comparison between right ear and left ear regarding DVH parameters among the studied head and neck cancer patients (N=24).

DVH parameters	Right ear (N=24)			Left ear (N=24)		Test	p-value (Sig.)
	No.	%		No.	%		
Middle ear							
Volume (cc)							
Average±SD	10.59±4.55			9.10 ± 4.61		1.781*	0.088 (NS)
Median (Range)	10.45 (2.80 – 18.50)			8.50 (2.50 – 21.60)			
Mean dose (Gy)							
Average±SD	12.82 ± 15.57			14.52 ± 18.40		-0.682•	0.495 (NS)
Median (Range)	5.12 (0.01 – 48.10)			5.43 (0.01 – 52.99)			
Dmean <40Gy	21	87.5%		20	83.3%	0.167‡	1.000
Dmean ≥40Gy	3	12.5%		4	16.7%		
Eustachian tube							
Volume (cc)							
Average±SD	0.37 ± 0.27			0.37 ± 0.23		-0.106•	0.915 (NS)
Median (Range)	0.30 (0.10 – 1.00)			0.30 (0.20 – 1.10)			
Mean dose (Gy)							
Average±SD	14.87 ± 19.28			15.74 ± 22.76		-0.958•	0.338 (NS)
Median (Range)	2.96 (0.01 – 53.40)			3.18 (0.01 – 65.26)			
D30 (Gy)							

DVH parameters	Right ear (N=24) No.	%	Left ear (N=24) No.	%	Test	p-value (Sig.)
Average±SD	15.30 ± 19.34		17.84 ± 23.23		-0.991•	0.322 (NS)
Median (Range)	3.11 (0 – 52.20)		3.72 (0 – 65)			
ET D30 ≤52.75Gy	24	100%	20	83.3%	4.364‡	0.109 (NS)
ET D30 >52.75Gy	0	0%	4	16.7%		
Tympanic cavity						
Volume (cc)						
Average±SD	1.27 ± 0.55		1.17 ± 0.35		-0.505•	0.614 (NS)
Median (Range)	1.10 (0.60 – 2.70)		1.10 (0.20 – 1.90)			
Mean dose (Gy)						
Average±SD	12.64 ± 17.14		15.84 ± 22.27		-1.332•	0.183 (NS)
Median (Range)	2.71 (0.01 – 50.20)		3.26 (0.01 – 64.28)			
Mastoid process						
Volume (cc)						
Average±SD	8.05 ± 4.16		6.56 ± 4.18		1.885*	0.072 (NS)
Median (Range)	8.80 (1.00 – 15.20)		5.90 (0.70 – 16.50)			
Mean dose (Gy)						
Average±SD	11.70 ± 13.30		13.23 ± 15.40		-0.438•	0.661 (NS)
Median (Range)	5.51 (0.01 – 40.10)		6.22 (0.01 – 44.15)			

‡ Chi-square test, * Paired Samples t-test, p-value< 0.05 is significant, Sig.: Significance,
● Wilcoxon signed ranks test

Table 3: Relationship between mean dose of middle ear and otological examination at end of radiotherapy among the studied ears of head and neck cancer patients (N=48).

Otological examination at end of radiotherapy	Mean dose of middle ear <40Gy (N=41) No.	%	≥40Gy (N=7) No.	%	Test‡	p-value (Sig.)
Ear drum position						
Neutral	34	82.9%	0	0%	19.902	<0.001 (HS)
Retracted	7	17.1%	7	100%		
Ear drum mobility						
Normal	36	87.8%	2	28.6%	32.789	<0.001 (HS)
Move during -ve pressure	5	12.2%	0	0%		
Slight movement	0	0%	5	71.4%		
Ear drum color						
Normal	41	100%	1	14.3%	40.163	<0.001 (HS)
Dull grey	0	0%	6	85.7%		
Ear drum Light reflex						
Normal	41	100%	1	14.3%	40.163	<0.001 (HS)
Lost	0	0%	6	85.7%		
Tympanogram						
A curve	31	75.6%	0	0%	48.000	<0.001 (HS)
AS curve	3	7.3%	0	0%		
B curve	0	0%	7	100%		
C curve	7	17.1%	0	0%		
ETD						
Absent	34	82.9%	7	100%	1.399	0.573 (NS)
Present	7	17.1%	0	0%		

Otological examination at end of radiotherapy	Mean dose of middle ear				Test‡	p-value (Sig.)
	<40Gy (N=41)		≥40Gy (N=7)			
	No.	%	No.	%		
OME						
Absent	41	100%	0	0%	48.000	<0.001 (HS)
Present	0	0%	7	100%		

‡ Chi-square test, p-value< 0.05 is significant, Sig.: Significance.

Table (4): Relationship between total prescribed dose and otological examination at end of radiotherapy among the studied ears of head and neck cancer patients (N=48).

Otological examination at end of radiotherapy	Total prescribed dose				Test‡	p-value (Sig.)
	<66Gy (N=32)		≥66Gy (N=16)			
	No.	%	No.	%		
Ear drum position						
Neutral	26	81.2%	8	50%	5.042	0.042 (S)
Retracted	6	18.8%	8	50%		
Ear drum mobility						
Normal	30	93.8%	8	50%	12.379	0.002 (S)
Move during -ve pressure	1	3.1%	4	25%		
Slight movement	1	3.1%	4	25%		
Ear drum color						
Normal	30	93.8%	12	75%	3.429	0.086 (NS)
Dull grey	2	6.2%	4	25%		
Ear drum Light reflex						
Normal	30	93.8%	12	75%	3.429	0.086 (NS)
Lost	2	6.2%	4	25%		
Tympanogram						
A curve	23	71.9%	8	50%	5.862	0.119 (NS)
AS curve	3	9.4%	0	0%		
B curve	3	9.4%	4	25%		
C curve	3	9.4%	4	25%		
ETD						
Absent	29	90.6%	12	75%	2.091	0.201 (NS)
Present	3	9.4%	4	25%		
OME						
Absent	29	90.6%	12	75%	2.091	0.201 (NS)
Present	3	9.4%	4	25%		

‡ Chi-square test, p-value< 0.05 is significant, Sig.: Significance.

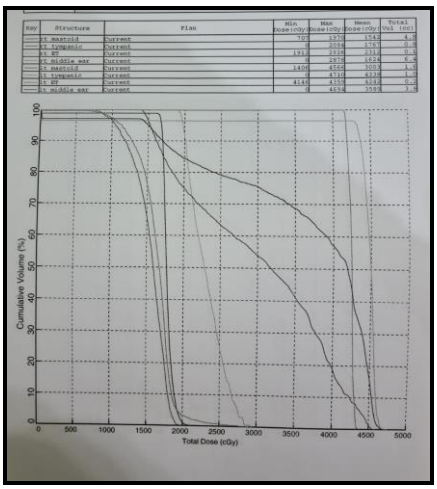
Table (5): Relationship between site of tumor and DVH parameters among the studied ears of head and neck cancer patients (N=48).

DVH parameters	Site of tumor				Test	p-value (Sig.)
	Above the larynx (N=16)		Larynx and hypopharynx (N=32)			
	No.	%	No.	%		
Middle ear						
Volume (cc)						
Average±SD	8.09 ± 4.19		10.72 ± 4.59		-1.958•	0.050 (NS)
Median (Range)	8.50 (2.50 – 16.60)		11 (3.60 – 21.60)			
Mean dose (Gy)						

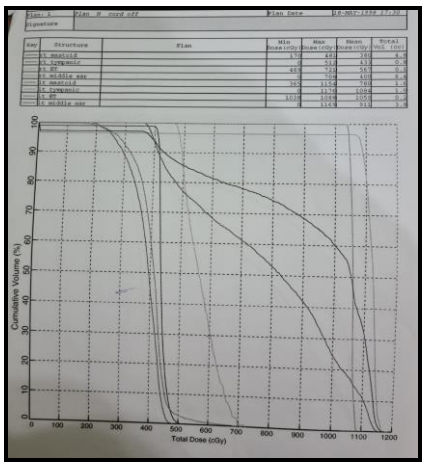
DVH parameters	Site of tumor Above the larynx (N=16)		Larynx and hypopharynx (N=32)		Test	p-value (Sig.)
	No.	%	No.	%		
Average±SD	31.89 ± 17.52		4.57 ± 5.19		-4.988•	<0.001
Median (Range)	24.72 (1.98 – 52.99)		1.73 (0.01 – 19.70)			(HS)
Dmean <40Gy	9	56.2%	32	100%	16.390‡	<0.001
Dmean ≥40Gy	7	43.8%	0	0%		(HS)
Eustachian tube						
Volume (cc)						
Average±SD	0.26 ± 0.11		0.43 ± 0.28		-1.872•	0.061
Median (Range)	0.30 (0.10 – 0.50)		0.30 (0.20 – 1.10)			(NS)
Mean dose (Gy)						
Average±SD	39.01 ± 20.90		3.45 ± 3.78		-4.813•	<0.001
Median (Range)	38.10 (2.23 – 65.26)		1.79 (0.01 – 13.17)			(HS)
D30 (Gy)						
Average±SD	42.01 ± 18.29		3.86 ± 4.23		-4.988•	<0.001
Median (Range)	40.02 (2.30 – 65)		1.92 (0 – 15.25)			(HS)
ET D30 ≤52.75Gy	12	75%	32	100%	8.727‡	0.009
ET D30 >52.75Gy	4	25%	0	0%		(S)
Tympanic cavity						
Volume (cc)						
Average±SD	1.16 ± 0.37		1.25 ± 0.50		-0.781•	0.435
Median (Range)	1.05 (0.70 – 1.90)		1.15 (0.20 – 2.70)			(NS)
Mean dose (Gy)						
Average±SD	36.37 ± 20.25		3.17 ± 3.51		-4.988•	<0.001
Median (Range)	27.80 (1.86 – 64.28)		1.64 (0.01 – 11.98)			(HS)
Mastoid process						
Volume (cc)						
Average±SD	5.59 ± 3.75		8.16 ± 4.19		-1.937•	0.053
Median (Range)	5 (0.70 – 13.10)		8.95 (1.30 – 16.50)			(NS)
Mean dose (Gy)						
Average±SD	27.85 ± 14.06		4.77 ± 5.44		-4.967•	<0.001
Median (Range)	22.81 (1.85 – 44.15)		1.64 (0.01 – 20.63)			(HS)

‡ Chi-square test, ● Mann Whitney U test, p-value< 0.05 is significant, Sig.: Significance.

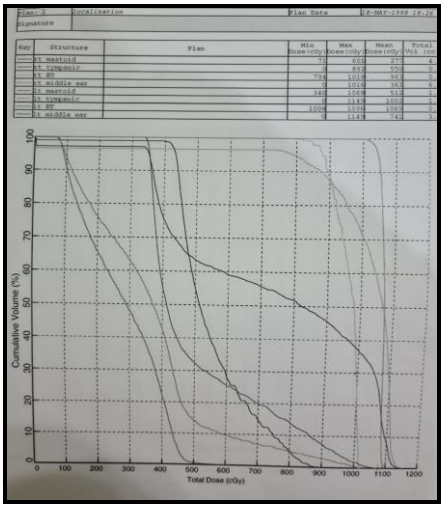
Figure 1: In a case of maxillary cancer, (a) shows DVH parameters during phase I, (b) shows DVH parameters during phase I off-cord, (c) shows DVH parameters during phase II and (d) shows beam eye view.



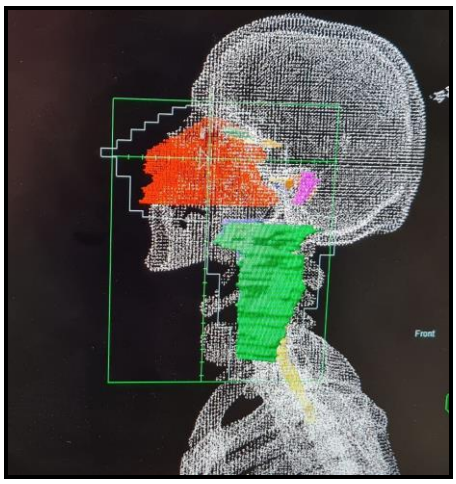
(a)



(b)



(c)



(d)

DISCUSSION

Irradiation dosage to the otological structures can vary considerably according to the origin of the primary cancer and the location of lymph node metastasis. New RT techniques such as Intensity Modulated Radiation therapy (IMRT) have shown an advantage in sparing non-target organs; however, dosage to the ET and middle ear is still high for most upper HNC **[6].**

This study was conducted on 24 patients (48 ears) who were proved pathologically to have head and neck cancer mostly of squamous cell carcinoma except nasopharyngeal and parotid cancers with age ranging from 38 to 85 years. All patients had RT either definitive or adjuvant with a total dose from 60Gy to 66Gy using 6 Megaelectronvolt or Cobalt^{60}, the DVH parameters were calculated to detect the mean dose to middle ear and the ET D30.

According to the results of our study, 41 ears (85.4%) had mean middle ear dose less than 40 Gy and 44 ears (91.7%) had D30 of eustachian tube less than or equal to 52.75 Gy. The incidence of OME and ETD increased when the mean middle ear dose exceeded 40 Gy and ET D30 was more than 52.75 Gy. We also evaluated the irradiation dose to the Eustachian tube using a primary DVH, which showed that the mean dose (range) to the ET is (0.01-65.26 Gy) compared to 47.4 Gy (4.4–69.0 Gy) reported by **Akazawa et al. [7]. Bhandare et al. [8]** found that, acute otitis media occurred in 12.9 % and chronic otitis media in 22.5% of studied participants at a median dose of 64 Gy to the middle ear which is considered a higher dose when compared to the results of our study. As reported by **Upadhya et al. [9],** dose of radiation was directly proportional to ototoxicity with a minimum of 60 Gys total radiation dose required to produce significant ototoxicity.

In our study, there was no significant correlation between the total prescribed dose of RT and the occurrence of middle ear toxicity. But according to **Evans et al. [10],** the dose of the radiation was proportional to the development of ototoxicity.

Total radiation dose minimum of 60 Gy was required to produce noticeable ototoxic effects. **Hamd et al. [4]** reported that despite there was no statistical difference, higher RT doses cause more side effects. Hence more advanced techniques should be used in order to scale the radiotherapy doses given to advanced tumors while simultaneously reducing the doses to healthy normal tissues.

Moreover, our study showed that there was a significant correlation between the site of the tumor and the mean dose of middle ear and ET and subsequent otoscopic and tympanometry findings. Tumors above the larynx was associated with a higher mean dose to the middle ear (more than 40 Gy) and ET than tumors of larynx or hypopharynx. In a prospective study by **Hamd et al. [4],** they reported that tympanogram findings immediately post radiotherapy at glottic, sub-glottic, supra- glottic, parotid, and tongue tumors revealed a significant increase in ipsilateral ET dysfunction in sub- and supra-glottic groups, compared with the glottic group. No significant difference was present regarding contralateral ET dysfunction. Tympanogram findings after 12 weeks post radiotherapy revealed a non-significant difference concerning ipsilateral and contralateral ET dysfunction. Unlike our study that showed no significant difference relating to either ipsilateral or contralateral ET dysfunction after RT.

Conclusion: Patients with HNC treated with RT either definitive or adjuvant are associated with an incidence of middle ear toxicity in the form of OME and ETD depending on the mean dose to middle ear and ET D30. The toxicity is associated with middle ear mean dose ≥40Gy and ET D30 >52.75Gy. Tumors above the larynx are associated with a higher mean dose to middle ear than tumors of larynx and hypopharynx. There is no significant correlation between the total dose of radiation and developing middle ear toxicity. More advanced techniques of RT as IMRT can provide a better protection for risk structures as middle ear. However, more studies need to be conducted to evaluate the difference between 3-dimensional conformal radiation therapy and IMRT regarding middle ear toxicity.

Conflict of Interest: All authors declared that there is no conflict of interest.

Financial Disclosures: All authors declared that there is no financial disclosure.

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To Cite:

Monged, R., Alhosainy, A., Alattar, A., Balata, S. Prospective Study on the Dose Distribution to the Middle-ear Structures during 3D Conformal Radiotherapy for Head and Neck Tumors and Dose Effect on Middle-ear Toxicity: Zagazig University Hospitals Experience.. *Zagazig University Medical Journal*, 2022; (1118-1125): -. doi: 10.21608/zumj.2021.91112.2319