# Post Radiation Middle Ear Effusion in NPC Patients - Analysis of Patient, Tumor and Radiation Factors

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**Abstract**

Introduction: The purpose of this study was to investigate whether patient, tumor and radiation therapy factors are associated with development of middle ear effusion (MEE) in nasopharyngeal carcinoma (NPC) patients. Methods: A retrospective review of NPC patients treated between January 2000 and June 2018 at Rabin Medical Center. Patient factors, tumor factors, radiation doses and radiation fields were collected and outlined if needed (middle ear, eustachian tube (ET), tensor veli palatini (TVP) and levator palatini (LVP) muscles), then analyzed and compared between patients with MEE and those without and between sides in patients with unilateral MEE. Results: 73 patients were enrolled. Most were males (71.2%) with advanced stage diseases (78%). At the time of diagnosis 14 patients (19.2%) presented with MEE and in 18 (24.6%) patients post radiation MEE was observed (15 ipsilateral to the tumor and 3 bilateral). Tumor stage, histology and laterality were not associated with development of MEE. Comparison of mean radiation field dosages including - gross target volume (GTV), clinical target volume (CTV) and patient target volume (PTV) showed no association with post radiation MEE. In addition, no difference was found in the radiation doses to the middle ear, ET or the LVP nor the TVP between ears with and without MEE. Conclusions: Postirradiation MEE remains a common adverse effect in NPC patients. Surprisingly, tumor stage, tumor laterality and histology were not associated with MEE. Similar findings were observed for total radiation doses and specific doses to the middle ear, ET and ET muscles.

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*Key points* –

- This study aimed to investigate whether patient, tumor, and radiation therapy factors are associated with the development of middle ear effusion (MEE) in patients with nasopharyngeal carcinoma (NPC).
- The retrospective review included patients treated between January 2000 and June 2018 at a tertiary medical center. Patient and tumor factors, radiation doses, and radiation fields were collected and analyzed between patients with and without MEE and between sides in patients with unilateral MEE.
- The study found that post-irradiation MEE was a common adverse effect in NPC patients, and tumor stage, histology, and laterality were not associated with MEE.
- Additionally, no difference was found in the radiation doses to the middle ear, Eustachian tube, Levator veli palatine, or Tensor veli palatine muscles between ears with and without MEE.
- The study suggests that IMRT may reduce otologic complications in NPC patients. The study provides important information on risk factors for MEE in NPC patients, which can help inform management strategies.

*Key words* – Nasopharyngeal Carcinoma, Middle ear effusion, Levator veli-palatini, Tensor veli-palatine, Radiotherapy

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## Introduction

Nasopharyngeal carcinoma (NPC) is the most common type of tumor originating in the epithelium of the nasopharynx and a distinct tumor of head and neck region which is primarily treated with external beam radiation therapy, with or without concurrent cisplatin chemotherapy.[1,2] External beam radiation to the head and neck region is notorious for its otologic complications including external otitis, otitis media, sensorineural hearing loss (SNHL) and osteoradionecrosis of the temporal bone.[3,4] Post irradiation middle ear effusion (MEE), is associated with conductive hearing loss. If not identified and managed properly, it may progress to full atelectasis of the ear drum associated ossicular bone erosion, hearing loss deterioration and cholesteatoma.[5,6] Therefore, evaluation of NPC patients for the presence of MEE is mandatory.

In the late 1990's new radiation modalities were introduced to decrease the radio-toxicity related to the radiation therapy (RT), one of which is intensity-modulated radiotherapy (IMRT).[7,8] IMRT is superior to the traditional 2D radiation due to its three-dimensional properties which allow a more precise planning of the irradiated tumor volume, sparing non-involved regions. As such, in patients with NPC it may allow reducing the otologic complications.[9,10] The main structures associated with normal middle ear function are the Eustachian tube (ET), the Levator veli-palatini (LVP) and Tensor veli-palatine (TVP) muscles which function as the ET dilators, and are therefore crucial for its normal function and patency.

The primary objective of this study was to perform a comprehensive analysis of patient, tumor and treatment parameters as risk factors for post radiation MEE in NPC patients. Specifically, irradiation parameters of the middle ear, ET, TVP and LVP regions were investigated as well as potential contributors.

## Methods

*Patients*

The study was reviewed and approved by the local Institutional Review Board (IRB). We conducted a retrospective review of the medical database of our tertiary medical center for all patients treated for NPC

between 2000-2018.

Inclusion criteria were adult patients (age>18 years) who had at least one year of follow up. Patients with primary sinonasal malignancies were excluded.

Data retrieved included patient demographics as well as treatment modalities, imaging, tumor pathology and follow up data.

*Treatment protocol*

The treatment protocol in our institution for patients with NPC includes radiation or chemoradiation therapy (CRT) according to the NCCN guidelines. Until 2008 2D/3D -CRT was the radiation modality available in our institution. Since 2008, intensity modulated radiation therapy (IMRT) has been the modality of choice.

A computed tomography simulation was used to plan treatment in all cases. Tumor volumes were outlined, and a computed tomography–based display of the isodoses was recorded to confirm adequate target coverage. The radiation field included the gross tumor in the nasopharynx and neck, elective nodal stations, with a planning target volume (PTV) of a 0.3-cm margin. In our study we examined in particular the radiation doses of the middle ear, Eustachian tube, Levator veli palatine and Tensor veli palatine muscles. Each radiation plan was accessed in Aria$^{TM}$ radiation planning software and the studied structures were delineated on each axial section of the simulation imaging. Corrections were later made on the sagittal and coronal sections of the imaging for a more precise outlining of the structures. (Figure 1.)

*Otitis media with effusion diagnosis and follow up*

Middle ear fluids were observed either by otoscopic examination - oromicroscopy or imaging (CT scan or MRI) follow up. MEE was suspected when otoscopy discovered a decreased motility of the tympanic mebrane, an air-fluid level or amber color change within the middle ear cavity which were confirmed by detecting opacification of the middle ear and mastoid air cells on imaging of the patient which were also examined.

*Statistical analysis*

Data was analyzed using the SPSS statistical software version 25.0 (SPSS Inc., Cary, NC, USA). Data distribution was analyzed using Shapiro-Wilk Test to determine whether the data had a normal distribution. For the analysis of continuous data, Student's t-test was used for normally distributed variables and Kruskal-Wallis for non-parametric variables. Chi-Square or Fisher's test were utilized for analysis of categorical variables. A two-sided p value $<0.05$ was considered statistically significant. All presented means are accompanied by their respective standard deviations.

**Results**

*Patients and clinical features*

A total of 140 patients with NPC were treated in our hospital throughout the study period. Of them, only 73 patients had detailed documentation of their clinical and radiographic examination of their middle ear status on presentation and follow up and were thus included in our study. The mean age of patients was 54.92 (range 18.8 to 79.67 years) and the majority were male (71.2%). 32 patients were smokers (43.8%). Most patients had an advanced disease at primary site at presentation with 31 patients (42.5%) presenting as T4 and 16 as T3 disease (21.9%). Fifty-eight (79.5%) patients presented with nodal disease (79.5% were N1 and greater) and five patients (6.8%) presented with a metastatic disease as presented in Table 1. The median follow-up time was 4.98 years (range 1-16.8 years) following completion of treatment.

Out of the 73 patients, 17 were treated using 2D/3D-CRT and 56 with intensity-modulated radiation therapy (IMRT). The mean radiation dose delivered to the primary site was 68.99 Gy (range 60 to 72 Gy). 70 patients (95.9%) received concurrent chemotherapy. The remaining 3 patients presented with an early-stage disease (2 patients with T1 and one with T2) with N0 and were treated with definitive RT with no chemotherapy.

*Pathology and immunohistochemistry*

Thirty-nine (53.4%) patients had a non-keratinizing undifferentiated (WHO- 3 classification) on their pathological examination, followed by 32 (43.8%) patients with non-keratinizing differentiated disease (WHO-2), and only two patients presented with a keratinizing NPC (2.7%) (WHO- 1). EBER staining for the presence of Epstein Barr Virus (EBV) was positive in 38 samples (52.1%). Proliferation marker Ki-67 was 58.6%±22.7% in our study.

*Middle ear status at NPC diagnosis*

At the time of NPC diagnosis 14 patients (19.2%) presented with middle ear effusion. When comparing the T stage at presentation, 85.7% of patients who presented with effusion were with an advanced T stage (stages 3,4) compared to only 60.4% in the non-effusion group (P value of 0.07). Following radiotherapy, 7 patients had a resolution of their MEE. Analysis of histopathological factors between patients with MEE at presentation and those without found no difference in EBV status or Ki-67 between groups.

*Post radiation middle ear status*

Of the 59 patients presenting without effusion, eighteen patients (24.6%) eventually developed unilateral persistent post radiation MEE with only one patient of the 59 who developed bilateral MEE and was excluded. Risk factors for post radiation MEE were investigated and are presented in Table 2. Demographic parameters such as patient sex and age, T stage of primary tumor, pathological characteristics of the tumor and radiation dosage were not associated with the occurrence of post radiation MEE as compared with patients who did not develop MEE.

Interestingly the radiation modality whether 2D/3D-CRT or with intensity-modulated radiation therapy (IMRT) had no correlation with development of MEE.

Similarly, radiation doses to the middle ear, ET, LVP and TVP were also not different between these groups. Furthermore, comparison between ears with MEE to ears without MEE in patients who developed unilateral post radiation MEE, did not reveal any difference in radiation doses to the middle ear, ET, LVP and TVP.

*Discussion*

In this study, no risk factors for post radiation MEE in NPC patients were identified. Including specifically, radiation doses to the eustachian tube, TVP and LVP muscles.

Much progress was made in the last decades in the treatment of NPC. Today the primary treatment is RT, mainly IMRT, for early-stage NPC, and a combination of concurrent platinum-based chemotherapy with RT for locoregional advanced disease.[11]

Since introduced, it is well known that radiation treatment for NPC is associated with various morbidities and in particular otologic complications, due to the inclusion of the temporal bone in the radiation fields.[3,4,12–14]

Previous studies demonstrated a wide range of data regarding the prevalence of MEE in irradiated patients. 8% to 48% of NPC patients undergoing conventional radiotherapy develop persistent or recurrent post irradiation MEE.[4,9,12,15]

In our study fourteen patients (19.2%) presented with MEE at disease diagnosis. Following radiotherapy, in half of these patients a resolution of their MEE was noted. Post radiation persistent MEE was observed in a quarter (24.6%) of patients.

Interestingly, advanced T stage, which has been observed to be risk factor for MEE at presentation due to association with skull base and pterygoid plates invasion adjacent to the ET and its dilating muscles, was not identified to be such a risk factor for post radiation MEE in our study. Similar findings were also observed in the study by Chung-Han Hsin et. al.[18], examining post-irradiated ears in 105 patients with NPC treated with RT.

Unlike previous studies, we also performed an analysis of histopathological factors, including tumor histopathology, EBV tumor staining and Ki-67 marker. We did not identify these features to be risk factors for

post radiation MEE as well as for MEE at NPC diagnosis.

Surprisingly, although modern radiotherapy techniques (IMRT) are considered more precise and with minimized collateral damage, previous studies[16–18] as well as our current study showed no protective effect against post irradiation MEE with IMRT compared to 3D-CRT. 31% of patients treated with IMRT developed MEE similar to 29.4% in the 3D-CRT group (p=0.9).

The etiology of post radiation MEE is hypothesized to be associated with either obstruction or functional impairment of the eustachian tube; and/or middle ear mucosal injury.[14,19,20] Middle ear mucosal injury is thought to be related to radiation-induced toxicity leading to impairment of the mucosal and ciliary function.[14,21,22] Radiation injury to the cartilaginous eustachian tube may cause synechia formation and fibrosis, leading to physical obstruction of the ET. Alternatively, irradiation of the muscles involved in the patency and dilatation of the ET – Levator veli palatini and more importantly the Tensor veli palatini may lead to their atrophy or fibrosis. Previous studies focused on radiation doses to the NP, the middle ear itself and the ET[16-18] as risk factors for post radiation MEE, but none thus far examined radiation doses to the ET muscles.

In this study, analysis of radiation doses showed no correlation or difference between the delivered dose to the ET, LVP and TVP and development of MEE.

Previous studies suggested that radiation doses of 80Gy and higher are associated with middle ear injury[21,22]. However, these doses exceed the conventional therapeutic doses. In our study, examination of the radiation doses delivered to the middle ear itself demonstrated no difference between patients who developed MEE and those who did not. In addition, the doses delivered to the middle ears in this study were far from the toxic level reported in previous publications.

Of note, our study results may be limited due to our cohort size and the study's retrospective nature with the inherent biases. Nonetheless, it provides a comprehensive analysis of patient, tumor and treatment factors and their association with the development of post radiation MEE, and the first to our knowledge, to examine tumor parameters and the radiation doses delivered to the muscles involved in the patency of the ET.

In conclusion, no risk factors for postirradiation MEE were identified, including total radiation doses and specific doses to the middle ear, ET and ET muscles. Thus, all NPC patients receiving treatment should be evaluated for post radiation MEE and receive appropriate treatment when necessary. Further studies are needed to understand the risk factors and pathophysiology of post radiation MEE in NPC patients.

**Author Disclosure Statement**

No competing financial interests exist.

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Table 1 – Demographic and clinical data

| **Parameter** | **Mean/%** |
|---|---|
| Total number of patients | 73 |
| Age (Mean, Years) | 54.88 (18.8-79.67) |
| Gender (Male) | 52 (71.2%) |
| Smokers (Yes) | 54 (43.8%) |

| **Parameter** | **Mean/%** |
|---|---|
| T Classification | |
| 1 | 10 (13.7%) |
| 2 | 16 (21.9%) |
| 3 | 16 (21.9%) |
| 4 | 31 (42.5%) |
| N Classification | |
| 0 | 15 (20.5%) |
| 1 | 29 (39.7%) |
| 2 | 21 (28.8%) |
| 3 | 8 (11%) |
| M Classification | |
| 0 | 67 (93.2%) |
| 1 | 5 (6.8%) |
| Stage | |
| 1 | 2 (2.7%) |
| 2 | 14 (19.2%) |
| 3 | 23 (31.5%) |
| 4a | 29 (39.7%) |
| 4b | 5 (6.8%) |
| EBV | |
| Positive | 38 (52.1%) |
| Negative | 35 (47.9%) |
| WHO Classification 1 – Keratinizing<br>2 – Non-Keratinizing Differentiated<br>3 – Non-Keratinizing Undifferentiated | 2 (2.7%) 32 (43.8%) 39 (53.4%) |
| MEE | |
| At presentation | 14 (19.18%) |
| Post irradiation (Excluding MEE at presentation) | 18 (24.66%) |
| Radiation type | |
| IMRT | 56 (76.7%) |
| EBR | 17 (23.3%) |
| Follow-up time (Median, Years) | 4.98 (1-16.8) |

* Numbers are presented as means, (corresponding percentage)

** Abbreviations – EBV – Epstein-Barr Virus; WHO - World Health Organization; MEE – Middle ear effusion; IMRT - intensity-modulated radiotherapy; EBR – External Beam radiation;

Table 2 – Comparison of patients with and without effusion during study period

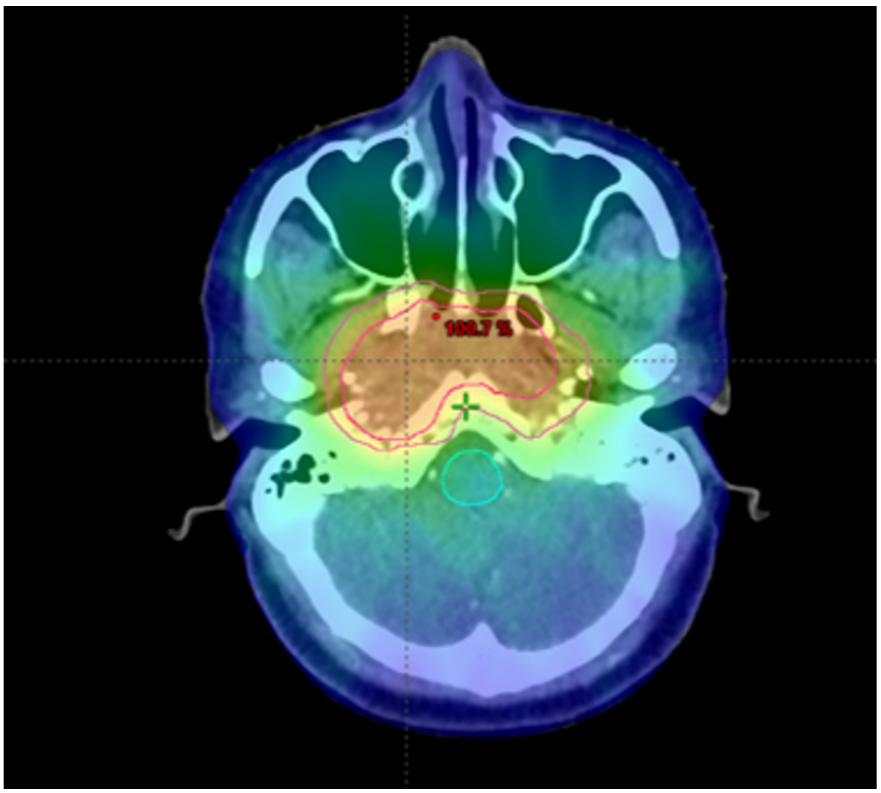
| Parameter | No MEE throughout the study period (n=41) | Post radiation MEE (n=18) | P Value |
|---|---|---|---|
| Age (Years) | 55.37 | 59.21 | 0.29 |
| Sex – Male n(%) | 29 (70.7%) | 12 (66.7%) | 0.77 |
| Advanced T Stage 3-4 n(%) | 27 (65.9%) | 11 (61.1%) | 0.73 |
| Smoker n(%) | 17 (41.5%) | 8 (44.4%) | 0.83 |
| Radiation Treatment - IMRT n(%)*** | 29 (70.7%) | 13 (72.2%) | 0.91 |

| Parameter | No MEE throughout the study period (n=41) | Post radiation MEE (n=18) | P Value |
|---|---|---|---|
| WHO Classification | | | 0.17 |
| Type 1 | 2 (4.9%) | 0 (0%) | |
| Type 2 | 22 (53.7%) | 6 (33.3%) | |
| Type 3 | 17 (41.5%) | 12 (66.7%) | |
| EBV n(%) | 21 (51.2%) | 9 (50%) | 0.93 |
| PTV (Gy) | 64.79 | 64.07 | 0.99 |
| GTV (Gy) | 68.13 | 66.6 | 0.94 |
| CTV (Gy) | 65.09 | 64.84 | 0.78 |
| Middle Ear (Gy) | 42.61 | 45.83 | 0.58 |
| Tensor Veli Palatini (Gy) | 63.7 | 62.5 | 0.81 |
| Levator Veli Palatini (Gy) | 64.26 | 63.54 | 0.52 |
| Eustachian Tube (Gy) | 48.5 | 51.94 | 0.37 |

* Numbers are presented as means, (corresponding percentage)

** Abbreviations – EBV – Epstein-Barr Virus; WHO - World Health Organization; IMRT - intensity-modulated radiotherapy; EBR – External Beam radiation; GTV - gross target volume; CTV - clinical target volume; PTV - patient target volume

*** IMRT data is compared to EBR in the analysis presented in the table.



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