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REVIEW

Otitis media with effusion after radiotherapy of the head and neck: a systematic review

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ABSTRACT

Background: Otitis media (OM) and associated hearing problems may be side effects to radiotherapy of the head and neck region and affect patient quality of life. The condition is associated with the tumor location.

Objective: To perform a systematic review concerning the present knowledge of the risk of OM after radiotherapy of the head and neck.

Methods: A comprehensive search of PubMed and Embase was carried out between 1 October 2015 and 6 February 2017. The search strategy followed the PRISMA guideline for systematic reviews.

Results: Of 597 articles 11 fulfilled the inclusion criteria. Seven were retrospective and four prospective. There were no randomized controlled trials. Eight studies concerned nasopharyngeal cancer. One study concerned cancer of the parotid gland and two studies concerned other locations of head and neck cancer. Meta-analysis could not be done due to heterogeneity between the studies. The incidence of OM varied considerably (range 8–29%).

Conclusions: The incidence of OM is high after radiotherapy of cancer of the upper head and neck area and the Eustachian tube (ET) irradiation dosage seems associated with development of OM, but the literature is poor. Research is needed to designate patients at risk of developing OM after radiotherapy. Preferably through analysis of dosage relationships between the ET and middle ear, and development of OM. Reporting of OM should be per ear and follow standardized protocols of middle ear assessment before and after radiotherapy. Furthermore, there is a need to find new ways to prevent and treat radiation-induced OME, preferably through randomized controlled trials.

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Introduction

Radiation therapy (RT) with or without chemotherapy is one of the first line of treatments when attempting to cure head and neck cancer [1]. However, RT and cisplatin can damage the auditory apparatus [2].

Eustachian tube (ET) dysfunction and otitis media (OM) are known side effects of RT among head and neck cancer patients, characterized by earache, chronic purulent secretion, tinnitus, hearing loss and a significant reduction in quality of life [3].

More than 40% of patients with nasopharyngeal cancer have OM with effusion (OME) at the time of diagnosis because of mechanical obstruction and tumor ingrowth into the cartilaginous part of the ET [4,5]. Actually, middle ear problems are often the first symptom that brings the patient to the doctor and is probably the reason why OM is most intensively described for these patients.

RT reduces the incidence of OME in patients with pre-RT OME caused by tumor occlusion of the ET. Nevertheless, many patients without middle ear problems before RT develop OME after the treatment. The reason is that inflammation and fibrosis of the soft tissue in the oropharynx, throat and middle ear leads to dysfunction of the ET and abnormal gas exchange in the middle ear. Overall, the incidence of OME and chronic OM with or without discharge increases after RT [6].

Treatment of RT-induced OME is controversial. Insertion of a ventilation tube into the tympanic membrane (TM) is normally an effective treatment for patients with OME who have not received RT. However, ventilation tube insertion after RT often results in complications such as chronic perforation of the TM and up to 38% develop chronic otitis media with or without suppuration (CSOM) [7]. Tube insertion is therefore not recommended as a standard treatment after RT [4,7–10].

The aim of this study was to systematically evaluate the incidence of RT-induced OME of patients with head and neck cancer using the PRISMA guideline [11].

Material and methods

Search strategy

Studies for this review were identified by a comprehensive search of both PubMed and Embase, 1974–2017, with no language restriction and with help from a librarian.

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The search strategy followed the PRISMA guideline for systematic reviews and included the keywords 'radiotherapy' combined with 'head and neck neoplasms' combined with 'otitis media' and combinations of synonyms of these terms. The search was limited to articles only.

The complete search strategy for MEDLINE in PubMed was: ((('Head and Neck Neoplasms'[Mesh])) AND ('Radiotherapy'[Mesh] OR 'Heavy Ion Radiotherapy'[Mesh] OR 'Radiotherapy, Image-Guided'[Mesh] OR 'Radiotherapy, Intensity-Modulated'[Mesh] OR 'Radiotherapy, Conformal'[Mesh] OR 'Radiotherapy, Adjuvant'[Mesh] OR 'Radiotherapy, High-Energy'[Mesh] OR 'Radiotherapy, Computer-Assisted'[Mesh] OR 'Radiotherapy Planning, Computer-Assisted'[Mesh] OR 'Radiotherapy Dosage'[Mesh])) AND ((((('Otitis'[Mesh] OR 'Otitis Media, Suppurative'[Mesh] OR 'Otitis Media with Effusion'[Mesh] OR 'Otitis Media'[Mesh])) OR ('Hearing Loss'[Mesh] OR 'Hearing Loss, Mixed Conductive-Sensorineural'[Mesh] OR 'Hearing Loss, Unilateral'[Mesh] OR 'Hearing Loss, Sensorineural'[Mesh] OR 'Hearing Loss, High-Frequency'[Mesh] OR 'Hearing Loss, Functional'[Mesh] OR 'Hearing Loss, Conductive'[Mesh] OR 'Hearing Loss, Bilateral'[Mesh])) OR 'Eustachian Tube'[Mesh]).

A similar search strategy was carried out in Embase. The searches were conducted between 1 October 2015 and 6 February 2017.

All retrieved studies were screened for title and abstract. Two independent researchers critically assessed the articles selected for qualitative synthesis. Studies were only included if they reported OM developed after RT. Middle ear examination had to be conducted both before and after RT.

The following exclusion criteria were applied for eligibility during the literature review: languages other than English, intracranial tumors, case reports, reviews, conference letters or abstracts, surgery in the middle ear or ET as part of the treatment, age <18 years, no abstract or full text available, less than 10 patients included, otoacoustic tumors and animal experiments.

Results

Search results and selection

The literature search resulted in a list of 597 records after removal of duplicates. A total of 445 articles were excluded after screening the title. An additional 127 articles were excluded after abstract or full-text screening. Fourteen studies were excluded after more critical appraisal following PICO guidelines from evidence-based medicine, leading to 11 included studies (Figure 1).

Included studies

There were no randomized controlled trials available for analysis. The 11 included studies were all observational cohort studies, seven retrospective and four prospective studies. The number of patients per study ranged from 17 to 175. The mean age varied between studies from 43 years to 56 years. Eight studies included patients with nasopharyngeal cancer, one study included parotid cancer, and two studies included patients with mixed cancer locations in the head and neck area. The follow-up time differed from 3 to 146 months (Table 1).

The reported incidences of RT-induced OME were between 8 and 29%. The studies are summarized below.

Nasopharyngeal cancer

Hsin et al. retrospectively studied 105 patients (210 ears) with nasopharyngeal cancer treated with intensity-modulated RT (IMRT) [4]. All cancer stages were included. Ear examination was done at every second month the first 2 years after treatment. Pure-tone audiometry was conducted every year after treatment and whenever effusion was suspected. If OME was diagnosed, a tympanocentesis or myringotomy was performed to confirm the diagnosis.

After RT treatment, the incidence of OME for ears that were normal before RT (132 ears), was 24/132 ears (18%) and additionally 9/132 ears (7%) developed CSOM. Thus, in total 33/132 new ears (25%) developed OM after RT. It is unclear if CSOM developed secondary to tympanocentesis or myringotomy.

Wakisaka et al. retrospectively reviewed 24 nasopharyngeal cancer patients (48 ears) and studied long-term ipsilateral and contralateral ototoxicity following radiotherapy [12]. Otoscopy and pure-tone audiometry were conducted at intervals of 2–3 months for at least 12 months. OME and CSOM were diagnosed by otoscopy and hearing loss by audiometry.

The investigators found that 7/24 patients (29%) developed OME on the contralateral ear of the tumor and 2/24 of these patients (8%) developed CSOM 1, 3 and 4 years after RT. After treatment, the incidence of conductive hearing loss decreased in ears ipsilateral to the tumor (from 63% to 13%) and increased at contralateral ears (from 0% to 8%).

Wang et al. [13] reviewed 150 (261 ears) nasopharyngeal cancer patients treated with RT. Pure-tone audiometry and tympanometry were conducted 3 months after completion of RT and at yearly intervals thereafter.

Before RT, there were 51/261 ears (20%) with OME. Twenty-nine of them resolved after RT treatment, but additionally 17/210 normal ears (8%) before RT developed OME on average 9.1 months after the treatment.

Kew et al. retrospectively reviewed 32 (64 ears) nasopharyngeal cancer patients and studied pre- and post-RT middle ear effusion by evaluation of magnetic resonance imaging (MRI) before and on average 12.5 months after RT [9]. No audiological or otological assessments were performed. Within a mean period of 13.5 months after RT, 17/64 ears (27%) developed radiologic verified OME after RT.

Low and Fong retrospectively reviewed 35 (70 ears) patients with nasopharyngeal cancer and studied long-term post-RT OME [14]. The middle ear was evaluated by tympanometry. Follow-up was between 2 and 8 years. The incidence of OME was not listed in the paper but could be calculated from data within [14]. Sixteen out of 70 ears (23%) had OME before RT and 7/54 ears (13%) developed OME after.

Low and Fong prospectively evaluated 33 patients (66 ears) with nasopharyngeal cancer who received

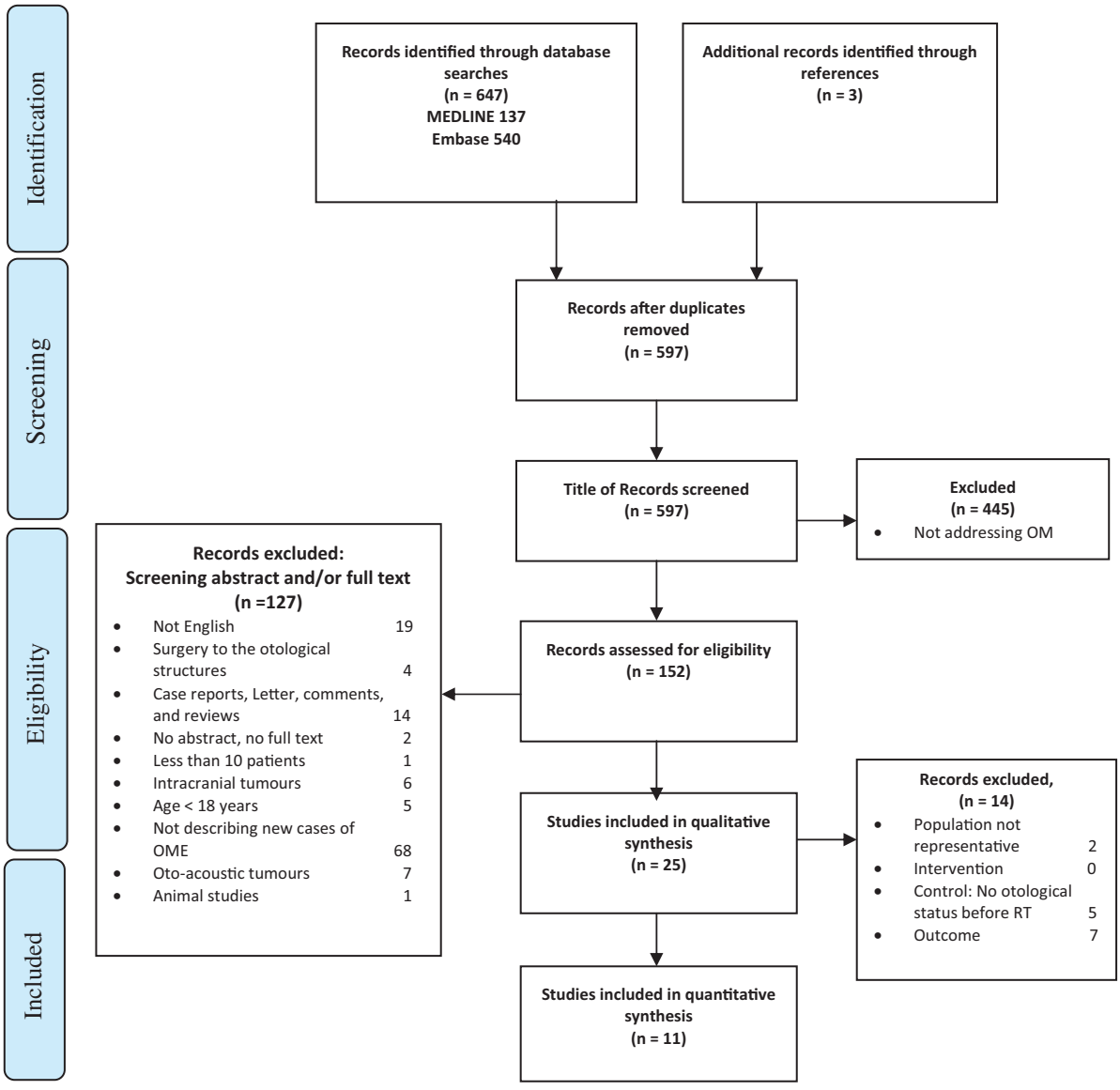

Figure 1. PRISMA 2009 flow diagram.

megavoltage irradiation [15]. Otoscopy and pure-tone audiometry were performed on average 6.5 months after RT. If OME was suspected after otoscopy or pure-tone audiometry, the diagnosis was confirmed by tympanometry.

Eleven out of 66 ears (17%) developed OME and 9/66 ears (14%) developed conductive hearing loss after RT. All patients with abnormal hearing developed hearing loss secondary to OME. No one had abnormal hearing as a result of sensorineural hearing loss before or after RT.

Morton et al. retrospectively evaluated 61 (122 ears) patients with nasopharyngeal cancer [16]. Effusion was diagnosed by otomicroscopy and/or tympanometry.

After RT, 26% developed OME. Forty percent developed otorrhea (CSOM) after insertion of a ventilation tube, and 19% of patients with OME developed otorrhea without insertion of ventilation tubes.

Patients with OME were divided into three groups. Group 1: insertion of ventilation tube before RT, group 2: insertion of ventilation tube after RT and group 3: no insertion of ventilation tube. There was a significant greater incidence of patients with otorrhea and persistent perforation in groups 1 and 2 (53%) compared to group 3 (19%) ($p = .00497$).

Tang et al. retrospectively reviewed records of 175 (350 ears) patients with nasopharyngeal cancer [17]. They all received megavoltage RT. Otoscopy and tympanometry were performed at intervals for up to 24 months. OME was confirmed by myringotomy, with or without insertion of a ventilation tube. After RT, 15/175 patients (9%) developed OME.

Parotid gland cancer

Jereczek-Fossa et al. prospectively studied 17 (34 ears) post-parotidectomy patients who received 3D-conformal radiotherapy as post-surgery treatment [18]. Pure-tone audiometry and tympanometry were performed at 3, 6 and 24 months after RT. Three months post-RT, 3/17 patients (18%) showed transient symptoms of middle ear negative pressure or effusion that resolved completely at the following evaluations at 6 and 12 months. The mean irradiation dosage to the ET and middle ear was 33.0 and 30.9 Gy, respectively.

Table 1. Characteristics of studies included in the systematic review using PubMed and Embase between 1974 and 2017 showing the incidence of OM with effusion, chronic OM and conductive hearing loss after RT.

Author	Study design	Level of evidence	Cancer location	Number patients/ ears	Mean age (years)	Mean follow-up (months)	RT technique	Chemotherapy	Audiological assessment	Total tumor dose (Gy)	Pre-RT OME	Post-RT OME	RT-induced OME	RT-induced CSOM	RT-induced CHL
Hsin et al. [4]	Retrospective cohort	2b	Nasopharynx	105	43.6	61.2 (36–123)	IMRT	No	Otoscopy tympanometry PTA Myringotomy	70	40%	32%	18%	7%	–
Wakisaka et al. [12]	Retrospective cohort	2b	Nasopharynx	24	55.9	78 (12–146)	Co60	37% cisplatin	Otoscopy PTA	60–70	35%	40%	29%	8%	8%
Wang et al. [13]	Retrospective cohort		Nasopharynx	150/261	48.2	43.8 (3–135)	Linear accelerators	Cisplatin	PTA tympanometry	68–70	20%	39%	8%	–	–
Kew et al. [9]	Retrospective cohort	2b	Nasopharynx	32	47.6	12.6 (3–24)	?	?	MRI	66	30%	48%	27%	–	–
Low and Fong [14]	Retrospective cohort	2b	Nasopharynx	35/70	?	24–96	Linear accelerators		Tympanometry	66–70	23%	21%	13%	–	–
Low and Fong [15]	Prospective cohort	2b	Nasopharynx	33	46.3	6.5 (3–12)	Megavoltage	No	Otoscopy PTA Tympanometry	70	23%	32%	17%	–	14%
Morton et al. [16]	Retrospective cohort	2b	Nasopharynx	61	48	44 (12–118)	?	?	Otomicroscopy tympanometry	?	54%	?	26%	–	–
Tang et al. [17]	Retrospective cohort	2b	Nasopharynx	175	46.4	24	Megavoltage	?	Otoscopy Tympanometry Myringotomy	?	38%	?	9%	–	–
Jereczek-Fossa et al. [18]	Prospective cohort	2b	Parotid gl.	17	56	24	3D-CRT	No	PTA Tympanometry	63	0%	18%	18%	–	–
Kaul et al. [19]	Prospective cohort	2b	Mixed	120/240	53	3	Co-60	No	PTA Tympanometry	?	0%	23%	23%	0%	–
Upadhya et al. [20]	Prospective cohort	2b	Mixed	58/70	51–70	6	External beam RT	No	Otoscopy PTA Tympanometry	?	0%	6%	6%	–	20%

LOE: level of evidence; RT: radiation therapy; Gy: Gray; OME: otitis media with effusion; CSOM: chronic otitis media with or without suppuration; CHL: conductive hearing loss; 3D-CRT: 3-dimensional conformal radiation therapy; PTA: pure-tone audiometry.

Mixed head and neck cancer

Kaul et al. prospectively studied 120 patients with head and neck malignancies treated with RT [19]. Different cancer locations were included: 17% hypopharyngeal carcinoma, 20% laryngeal, oral cavity and oropharyngeal carcinoma, 13% with salivary gland carcinoma and 10% had paranasal sinus and nasopharyngeal carcinoma. Esophageal, thyroid and occult primary carcinoma were present in 10% of patients. All patients underwent radical RT. Pure-tone audiometry was done during mid-treatment, at the end of treatment and once a month for 3 months afterwards. Tympanometry was done at follow-up if required.

OME developed in 23% of the patients undergoing RT with four patients (3.3%) developing OME during the early phases of treatment while 24 additional patients (20%) developed OME during the middle part of the treatment. None of the patients had OME at follow-up after one month.

Upadhya et al. prospectively included 58 patients with different head and neck cancer locations: laryngopharynx, oropharynx, oral cavity, neck (nodes with unknown primary cancer), maxillary sinus, parotids and thyroid [20].

Patients with nasopharyngeal cancer, hearing loss or abnormal impedance audiometry before RT were excluded. Therefore, the study comprised of total 70 ears. All patients were treated with external beam RT. The patients were exposed to pure-tone audiometry and tympanometry immediately after, 3 months after and 6 months after RT.

Immediately after RT, 18/70 ears (26%) developed OME, which fell to 11/70 ears (16%) and 4/70 ears (6%) 3 and 6 months after RT, respectively. However, 6 months after RT, the incidence of ET dysfunction was still high, 22/70 ears (31%), and conductive hearing loss was found in 14/70 ears (20%).

Patient-related outcomes such as symptoms from the ears, socially significant hearing loss or quality of life before or after RT were not reported in any of the included studies.

Discussion

Even though OM after RT of upper head and neck cancer is well known between clinicians, it is not well documented. The reason might be that follow-up visits have primarily focused on relapse detection and not side effects of the treatment. However, in parallel with better cancer survival, there has been an increased interest in morbidity and late side effects. In particular, dry mouth and swallowing problems are very common after RT of the head and neck. However, less severe side effects such as middle ear problems might not be noticed and detected at follow-up. This might especially be the case for the six retrospective studies included in this systematic review.

Dosage dependency

Irradiation dosage to the otological structures can vary considerably according to the origin of the primary cancer and the location of lymph node metastasis. Therefore, it is most reasonable to compare the incidence of OME for the same

cancer origin or even more optimal to compare the irradiation dosage to the ET and middle ear with the incidence of OME. The dosage dependency was demonstrated by Wang et al. and Yao et al., who found that the incidence of OME was reduced when dosage to the ET and middle ear was below 52 Gy and 46 Gy, respectively [8,21]. Jereczek-Fossa et al. found a similar relationship. When mean dosage to the ET and middle ear was 33.0 and 30.9 Gy, only 18% of the patients had transient ET dysfunction and OME at 3-month follow-up, which completely resolved after 2 years [18]. Furthermore, Upadhya et al. evaluated patients with different cancer origins, which resulted in a lower incidence of 6% at 6-month follow-up. This might reflects the varying irradiation dosages to the nasopharynx depending on the tumor positions [20]. Common to the patients that developed middle ear morbidity after RT was a relatively high dosage to the otological structures.

New RT techniques such as IMRT have shown an advantage in sparing non-target organs; however, dosage to the ET and middle ear is still high for most upper head and neck cancers, especially nasopharyngeal cancer, where the ET is part of the planning target volume [4]. A single study comparing IMRT with two-dimensional RT showed that IMRT was able to reduce the incidence of CSOM significantly but had no influence on the incidence of OME [22]. The benefit from IMRT is expected to be greater when the tumor is located farther away from the nasopharynx.

Difference in reported incidences between studies

The reported incidences of RT-induced OME among nasopharyngeal cancer patients varied between 8 and 29%. There can be different explanations for this. For example, the incidences are calculated in different ways. Some studies report the incidence per ear and others per patient. If number of ears is used, the reported incidence will be lower due to twice as many ears than patients. This was the case for Hsin et al. and Low and Fong, who found an OME incidence per ear of 18% (25/136) and 17% (11/66), respectively [4,15]. Wakisaka et al., Kew et al. and Morton et al. reported the incidence of OME per patient resulting in a higher incidence of 29%, 27% and 26%, respectively [9,12,16].

Time and interval of follow-up also influences the reported incidence. Long follow-up times and short follow-up intervals detect more OME cases than short follow-up times and long follow-up intervals [4,12]. This might be the case for the largest study included that had follow-up intervals of up to 24 months and a low OME incidence of 9% for nasopharyngeal patients [17].

Generally, the follow-up time and interval of follow-up varied between studies, with the shortest follow-up time being 3 months and the longest 146 months (>12 years). Therefore, it is difficult to compare the incidences across the studies. The conclusion is that long follow-up with short intervals has the best chance to capture patients with OME after RT.

Another reason could be the relatively small number of patients included in the studies, implying that a relatively low number of OME cases result in a high incidence [12,15,18].

Detection of middle ear morbidity

The techniques applied for establishing the OME diagnosis have an influence on the outcome. An accurate clinical method to detect middle ear effusion is tympanometry [23,24]. The results are presented in a type A curve, suggesting normal middle ear function, type B, suggesting middle ear effusion and type C, suggesting dysfunction of the ET.

Otoscopy is also useful to diagnose OME and CSOM when there is retraction of the TM, entrapment of air bubbles behind the TM, perforation of the TM or chronic discharge from the middle ear. However, these findings are not always evident and patients with OME without noticeable symptoms may therefore not be discovered.

Pure-tone audiometry may also contribute to the diagnosis of OME and ET dysfunction. When a significant conductive hearing loss is present, it can be suggestive of OME [12,15,18]. According to the American Speech Hearing Association definition, a person has a hearing loss if a pure-tone audiometry (in either the high frequency, low frequency or both) in one or both ears is worse than 15 dB [25]. However, conductive hearing loss may be mild and unnoticed by the patient and the clinician, even when middle ear effusion is present.

All included studies performed more than one assessment to detect OME, except for Kew et al., who used MRI [9]. The different methods to detect middle ear morbidity have advantages and disadvantages. To obtain the most accurate evaluation of the middle ear and its consequences, more than one assessment should be used and should include otoscopy or even better otomicroscopy, pure tone and impedance audiometry before and at follow-up after RT and the incidence of OM should be reported per ear. Patient-reported middle ear and hearing problems is also important in the evaluation of the otological side effect after RT. There is a risk of over- or under-diagnosing OME when only one assessment is used. However, MRI, which is an effective way to detect all middle ear effusions, does not explain how it affects the audiological apparatus or the patients [9]. It would have been interesting to compare the results of MRI with an audiological assessment.

Conclusions

OME is seemingly a common adverse event after RT to the upper head and neck area and can be further complicated by CSOM. Post-RT OME is best described for nasopharyngeal cancer but is also observed in patients with other cancers in the upper head and neck area. There seems to be a link between the irradiation dosage to the ET and development of OME; however, more research is required to reveal who is at risk of developing OME after RT through analysis of dosage relationships between irradiation dosage to the ET and middle ear and development of OM. Post-treatment OM should be reported per ear and follow standardized protocols

of middle ear assessment including otological examination, impedance and pure tone audiometry before and at follow-up after radiotherapy. Furthermore, there is a need to find new ways to prevent and treat radiation-induced OME. This could be obtained by randomized controlled trials testing the effect of ventilation exercises of the ET during and after irradiation therapy treatment, for example frequent Valsalva maneuver or daily use of e.g., the Otovent® balloon.

Disclosure statement

No potential conflict of interest was reported by the authors.

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