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Management and outcome of middle ear adenomatous neuroendocrine tumours: A systematic review

M.S.D. Engel [a], R.J.L. van der Lans [a], J.C. Jansen [b], C.R. Leemans [a], E. Bloemena [c], B. I. Lissenberg-Witte [d], J.A. Rijken [e], C.F. Smit [a,*], E.F. Hensen [b]

[a] Department of Otolaryngology & Head and Neck Surgery, Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands
[b] Department of Otorhinolaryngology & Head and Neck Surgery, Leiden University Medical Center, Leiden, the Netherlands
[c] Department of Pathology, Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands
[d] Epidemiology and Data Science, Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands
[e] Department of Head and Neck Surgical Oncology, University Medical Center Utrecht, Utrecht, the Netherlands

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ABSTRACT

Middle ear adenomatous neuroendocrine tumours (MEANTs) are rare, unpredictable tumours. Although most MEANTs are characterized by a benign biological behaviour and indolent growth pattern, some studies have reported locally invasive and metastastic disease. Currently, the optimal management strategy for MEANTs remains subject of debate. The aim of this study is to review the literature on MEANTs with focus on its clinical characteristics, treatment strategies and outcome. A systematic review was conducted using PubMed, Embase and Cochrane databases. A total of 111 studies comprising 198 patients with MEANT were included. Treatment modalities comprised surgery (90%), surgery with adjuvant radiotherapy (9%) and palliative (chemo)radiotherapy in (1%). Local recurrence was observed in 25% of the patients and 7% of the patients developed metastasis, over a median period of 5.7 years (range 7 months – 32 years). Twelve of 13 patients (92%) who developed metastases had a local recurrence. Four patients (2%) died of MEANT: three due to distant metastases and one due to extensive local recurrence. Reliable histopathologic predictors of outcome could not be identified. These findings indicate that the clinical presentations of MEANT vary substantially, the overall recurrence rate is considerable and initial local tumour control is paramount. Because of the unpredictable clinical course, prolonged follow-up is warranted.

Introduction

Neuroendocrine neoplasms (NEN) of the head and neck are a diverse and rare group of tumours. Less than 1% of all NENs arise in the middle ear, where they are known as middle ear adenomatous neuroendocrine tumours (MEANTs) [1]. The occurrence of NEN in the middle ear is puzzling, because epithelial cells with neuroendocrine features normally do not reside in the middle ear. It is hypothesized that MEANTs are derived from embryonically enclosed neural crest cells [2]. They demonstrate a histopathological spectrum with glandular and neuroendocrine features. This histologic heterogeneity has led to equivocal terminology, including middle ear adenoma, carcinoid tumour and neuroendocrine adenoma of the middle ear.

Today, recognition is growing that these tumours have strong similarities in phenotype and immunohistochemical profile, which suggests that they represent the same pathologic entity [3,4]. MEANTs commonly have a benign biological behaviour with an indolent growth pattern. However, since 1999 regional and distant metastases have been reported in primary and recurrent MEANTs [5-10].

Currently, an internationally accepted staging system for clinical and surgical decision making in MEANTs is lacking [11]. In 2018, Marinelli et al. proposed a TNMS-classification for MEANTs (S for neuroendocrine secretion) [12]. This classification system can be useful for postoperative tumor staging; however it is relatively complex with dozens of possible TNMS-stages and includes features that can only be assessed during surgery, such as tumor adherence to adjacent structures. As such, it is less suited for preoperative staging and planning.

Partly as a result of the inconsistent terminology in the literature, the

* Corresponding author at: Department of Otolaryngology / Head and Neck Surgery, Amsterdam University Medical Center – Vrije Universiteit Amsterdam, KNO ZH 1D-118, PO Box 7057, 1007 MB Amsterdam, The Netherlands.
E-mail address: cf.smit@amsterdamumc.nl (C.F. Smit).

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Table 1
Classification of the primary tumour extension of middle ear adenomatous neuroendocrine tumours.

Tumour extension	Description
Class 1	Tumour confined to the middle ear cavity
Class 2	Tumour extends beyond the middle ear into the mastoid process
Class 3	Tumour extends beyond the middle ear and mastoid process, but is confined to the temporal bone (e.g. extending into the external ear canal, petrous apex, cochlea, or osseous part of the eustachian tube)
Class 4	Tumour extends beyond the temporal bone (e.g. extending into the dura, temporomandibular joint, parotid gland, or nasopharynx)

lack of clear pretreatment classification and the rarity of the disease, controversy exists regarding the clinical spectrum and the optimal management of MEANTs [7,12,13]. Therefore, we performed a systematic review to gain better insight in the clinical behaviour, histopathologic markers and outcome of MEANT therapy.

Materials and methods

A systematic review of the literature was performed to identify case reports or case series of patients with MEANTs. The literature search was performed with the help of a scientific librarian, using PubMed, Embase and Cochrane databases. The following MESH terms and relevant keywords were used: 'adenoma', 'carcinoid', 'neuroendocrine neoplasm', 'adenocarcinoma', 'amphicrine tumour', 'middle ear', 'tympanic cavity', 'mastoid', 'temporal bone' and 'petrous bone'. All retrieved publications up to January 1st, 2021, were independently screened on title and abstract by two reviewers (ME and RL). Reference lists of eligible publications were checked to identify additional relevant studies.

The inclusion criteria for the systematic review comprised: full-text article written in English; certainty about the middle ear as site of origin; definite histopathology; treatment modality and outcome included in the report. Reviews without information about individual cases were excluded. Duplicates were avoided by: a) excluding duplicate entries from the search retrieval; b) extracting data only once when cases were published twice, identified by overtly overlapping authorship and case description; and c) extracting data only from original published articles and not from review articles, except for cases first published in a review. Disagreements between reviewers were discussed during a consensus meeting.

The following data were extracted, normalized and pooled: patient characteristics, presenting symptoms, extent of disease on presentation, imaging findings, histopathologic features, treatment, recurrence, duration of follow-up and treatment outcome.

To explore the possible relations between tumor extension, biological behavior, choice of treatment and treatment outcome, it was necessary to categorize MEANTs. We opted for a tumor classification based on the extent of the primary tumor only, in four tumor classes (table 1). The tumor class was determined with available information on the extent of disease using clinical and/or radiological data of each reported patient. This allows for tumor classification before surgery and can therefore be used to plan a specific surgical approach, comparable to classifications of other middle ear tumors such as squamous cell carcinomas and jugulotympanic paragangliomas. Cases with insufficient data for classification were defined as unclassified.

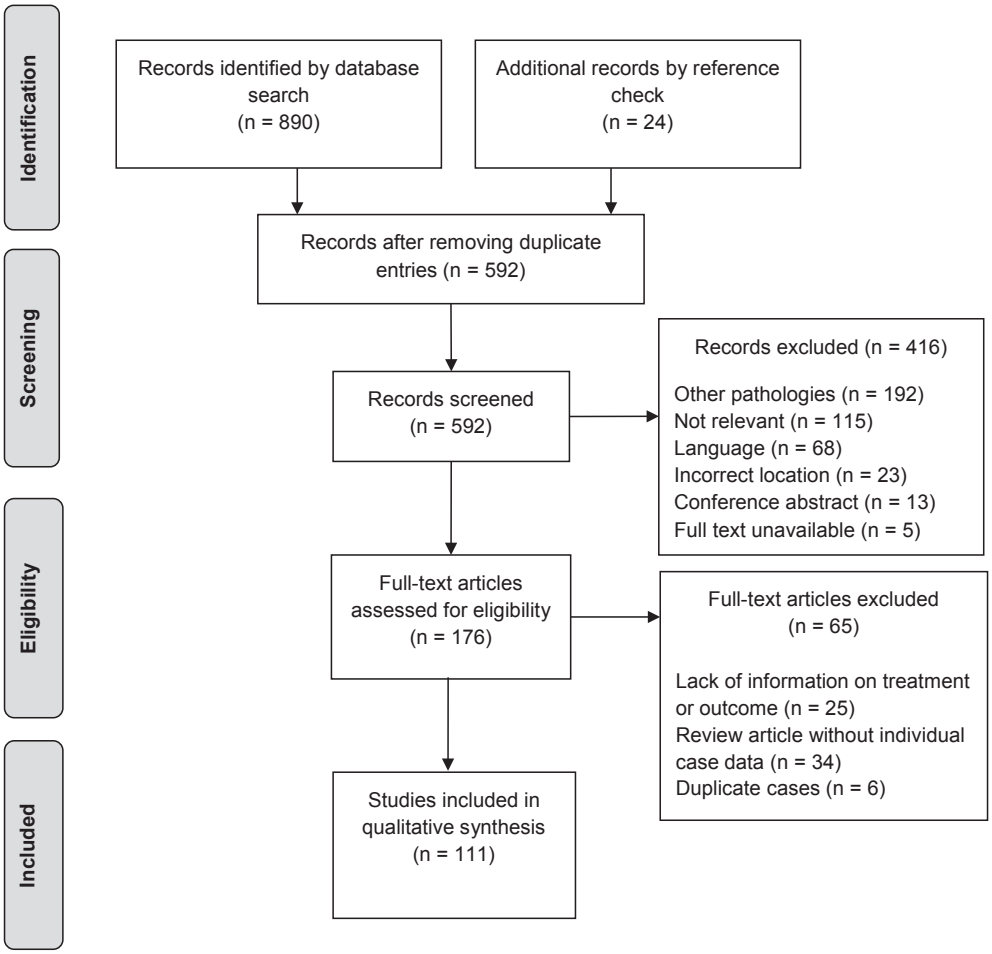

Figure 1. Flow diagram of the literature search.

Table 2
Clinical characteristics of patients with middle ear adenomatous neuroendocrine tumours.

	Number of patients reported characteristics	n	%
Sex	198		
Male		106	54%
Female		90	46%
Unknown		2	
Presenting symptoms	191	185	97%
Hearing loss	178	162	91%
Tinnitus	89	55	62%
Otalgia	76	36	47%
Otorrhea	89	39	44%
Aural fullness	83	64	77%
Vertigo	65	12	19%
Facial nerve paresis	107	39	36%
Carcinoid syndrome[a]	191	4	2%
Tumour classification[b]	176		
Class 1: Tumour confined to the middle ear		60	34%
Class 2: Tumour extending beyond the middle ear into the mastoid process		76	43%
Class 3: Tumour extending beyond the middle ear and mastoid process, but is confined to the temporal bone		35	20%
Class 4: Tumour extending beyond the temporal bone		5	3%
Regional metastases			
At presentation	198	4	2%
During follow-up[c]	191	8	4%
Distant metastases			
At presentation	198	1	0,5%
During follow-up[c]	191	3	2%
Regional and distant metastases			
At presentation	198	0	-
During follow-up[c]	191	2	1%

Time to recurrence was defined as the interval between the date of primary therapy and the date of radiologically or histologically confirmed local recurrence and/or metastasis more than 6 months after surgery. Time to death was defined as the time between the initial therapy and the date of death from any cause. The duration of follow-up was defined as the time from initial treatment to the last outpatient clinic visit.

Statistical analyses were performed using IBM SPSS 26.0. Cumulative recurrence rate and overall survival were estimated with Kaplan-Meier curves and compared with the log-rank test. P-values lower than 0.05 were considered statistically significant.

Results

In all, 914 articles were identified, 890 by searching medical literature databases and 24 by reference checking. After excluding duplicate entries, 592 records were screened on title and abstract. Based on the inclusion criteria, a total of 176 possibly relevant full text articles were identified. After full-text assessment, 65 articles were excluded because of lack of information on treatment or outcome (n = 25), lack of information about individual patients (n = 34) or duplicate cases (n = 6). A total of 111 articles comprising 198 patients with MEANT met the criteria and were included in this systemic review (Figure 1) [2,4-10,14-116].

Clinical characteristics

Clinical characteristics of the included patients are shown in Table 2. Not all characteristics were reported for all patients; ratios are based on the number of patients with known data for the variable. The age at diagnosis ranged from 13 to 83 years, with a median age of 42 years. The median interval between the onset of symptoms and diagnosis was 18 months (range 0–240 months). Clinical presentation was characterized by the occurrence of aspecific otologic symptoms, most commonly hearing loss in combination with aural fullness and/or tinnitus (Table 2). Thirty-nine patients presented with facial nerve paresis; only one patient presented with multiple cranial nerve deficits, i.e. paresis of the facial and trigeminal nerve. In six patients, an asymptomatic MEANT was discovered incidentally during routine physical examination (Table 2). Four patients suffered from concurrent diarrhea, palpitations or flushing, symptoms suggestive of carcinoid syndrome [22,25,67,75].

Information on otomicroscopic findings was available for 123 patients. In most patients a retrotympanal mass (73/123, 59%) or a mass in the external auditory canal (32/123, 26%) was seen.

According to our classification system, the majority of the patients presented with a class 2 tumour (43%; Table 2). Sixty patients presented with a class 1 tumour (34%), 35 patients with a class 3 tumour (20%) and five patients with a class 4 tumour (3%) (Tables 1 and 2). The extent of disease was not reported for 11% of the patients.

Regional metastasis in the neck and/or parotid gland was found in four patients at the time of diagnosis (2%). One patient (1%) presented with distant metastases in the thoracic spine at the time of diagnosis; the primary tumour extended into the external ear canal (class 3). No regional metastases were found in this patient.

Histopathology and immunohistochemistry

Histopathologic features are shown in Table 3. Mitosis and necrosis

Table 3
Histopathologic and immunohistochemical features of middle ear adenomatous neuroendocrine tumours in relation to tumour extension.

		Tumour classification[a]				
Characteristics		1 (n = 60)	2 (n = 76)	3 (n = 35)	4 (n = 5)	Unclassified (n = 22)
Mitosis, n/n (%)	14/96 (15%)	4/22 (18%)	4/42 (10%)	3/19 (16%)	1/3 (33%)	2/10 (20%)
Necrosis, n/n (%)	5/63 (8%)	0/13 (-)	2/30 (7%)	1/10 (10%)	1/3 (33%)	1/7 (14%)
Ki-67 staining, n (%)	40[b] (20%)	12 (20%)	16 (21%)	8 (23%)	2 (40%)	2 (9%)
Ki-67 labeling index, mean (range)	5.3 (0–20)	2.5 (0–7.5)	3.1 (1–20)	16.1 (0–95)	3.0 (3–3)	3.0 (3–3)
Immunohistochemical staining, n (%)	135[b] (68%)	42 (70%)	46 (61%)	24 (69%)	4 (80%)	19 (86%)
Immunohistochemical markers, n/n (%)						
Cytokeratin	92/95 (97%)	27/29 (93%)	31/31 (100%)	13/14 (93%)	3/3 (100%)	18/18 (100%)
Epithelial membrane antigen	11/19 (58%)	3/5 (60%)	5/6 (83%)	2/6 (33%)	0/1 (-)	1/1 (100%)
Chromogranin A	94/112 (84%)	30/34 (88%)	30/36 (83%)	17/21 (81%)	4/4 (100%)	13/17 (76%)
Leu-7 (CD 56)	22/29 (76%)	6/9 (67%)	7/8 (88%)	3/5 (60%)	–	6/7 (86%)
Synaptophysin	83/91 (91%)	22/26 (85%)	27/30 (90%)	16/16 (100%)	2/2 (100%)	16/17 (94%)
Neuron-specific enolase	45/62 (73%)	15/25 (60%)	17/24 (71%)	7/7 (100%)	1/1 (100%)	5/5 (100%)
Vimentin	34/34 (100%)	15/15 (100%)	11/11 (100%)	2/2 (100%)	1/1 (100%)	5/5 (100%)
Serotonin	25/34 (74%)	8/12 (67%)	9/10 (90%)	6/7 (86%)	0/1 (-)	2/4 (50%)
Pancreatic polypeptide	21/23 (91%)	10/12 (83%)	5/5 (100%)	4/4 (100%)	–	2/2 (100%)
S100	9/48 (19%)	6/17 (35%)	1/17 (6%)	2/8 (25%)	0/2 (-)	0/4 (-)

Table 4
Treatment strategy in patients with middle ear adenomatous neuroendocrine tumours according to tumour extension category.

		Tumour classification[a]				
	n	1 (n=60)	2 (n=76)	3 (n=35)	4 (n=5)	Unclassified (n=22)
Treatment modality						
Surgery	179	58 (97%)	72 (95%)	25 (71%)	4 (80%)	20 (91%)
Surgery with adjuvant RT	17	2 (3%)	4 (5%)	8 (23%)	1 (20%)	2 (9%)
Palliative treatment[b]	2	0	0	2 (6%)	0	0
Surgical treatment						
Tympanotomy	45	30 (50%)	6 (8%)	7 (21%)	0	2 (9%)
CWU	61	15 (25%)	35 (46%)	7 (21%)	0	4 (18%)
CWD	49	15 (25%)	24 (32%)	6 (18%)	0	4 (18%)
Subtotal petrosectomy	7	0	3 (4%)	0	3 (60%)	1 (5%)
Lateral temporal bone resection	6	0	4 (5%)	1 (3%)	0	1 (5%)
Subtotal temporal bone resection	1	0	0	1 (3%)	0	0
Total temporal bone resection	1	0	1 (1%)	0	0	0
Translabyrinthine craniotomy	3	0	0	3 (9%)	0	0
Transcochlear craniotomy	1	0	0	1 (3%)	0	0
Retrosigmoid and middle fossa craniotomy[c]	1	0	0	0	1 (20%)	0
Unknown surgical approach/extent	21	0	3 (4%)	7 (21%)	1 (20%)	10 (45%)

was seen in 15% and 8% of the patients, respectively. The Ki-67 labeling index, which indicates the proliferation rate, was investigated in 40 patients (40/198, 20%). It varied widely between MEANTs, ranging from less than 1% to 95%, irrespective of tumour extension.

Immunohistochemistry was performed using a variety of neuroendocrine markers, in 135 tumours (135/198, 68%). Neuroendocrine differentiation was confirmed in 133/135 tumours (99%). In the two tumours in whom immunohistochemistry showed no neuroendocrine differentiation, only chromogranin A and Neuron-specific enolase were tested. The immunohistochemical markers that demonstrated the highest expression in MEANT are vimentin (34 of 34 tested tumours; 100%), cytokeratin (92 of 95 tested tumours; 97%), synaptophysin (83 of 91 tested cases; 92%) and pancreatic polypeptide (21 of 23 tested cases; 91%).

Although most studies (92) report data on histopathologic evaluation and markers, the heterogeneity in the reported markers is substantial (Table 3). The association between specific histopathologic features and tumour extension, biological behaviour, and outcome could therefore not reliably be evaluated.

Treatment

Table 4 summarizes the treatment modalities and surgical approaches used in MEANT patients, stratified by tumour extension category. In the majority of the patients, the primary treatment modality was surgery (196/198, 99%). Surgery was not performed in two patients, both were treated with palliative intent: one patient with neck metastases received chemotherapy and one patient with distant metastases in the thoracic spine received chemoradiotherapy.

The most commonly used surgical approach was canal wall-up tympanomastoidectomy (31%), followed by canal wall-down tympanomastoidectomy (25%) and tympanotomy via either transcanal or endaural approach (23%) (Table 4).

All of the 60 tumours limited to the middle ear (class 1) were removed via either a tympanotomy or tympanomastoidectomy. As expected, more extended surgical approaches were used in patients with more extensive disease (class 2 – 4 tumours (Table 4)).

In all three patients with lymph node involvement at first presentation, the removal of the primary tumour was combined with selective neck dissection and/or parotidectomy, followed by locoregional adjuvant radiotherapy in two of them.

In all, 17 patients (9%) received local adjuvant radiotherapy for various reasons, including positive surgical margins and tumour extension into the skull base.

Recurrence

Forty-eight patients (48/196, 25%) experienced recurrent disease after surgery. Most patients with recurrent disease presented with a local recurrence only (35/48, 73%). One in four patients with recurrent disease developed metastases in addition to the local recurrence (12/48, 25%). In one patient (1/48, 2%), the recurrence presented as a metastasis only (i.e. without local recurrence). The median time to recurrence after surgery was 5.7 years (range 7 months – 32 years). Recurrences were asymptomatic in 17 patients (17/48, 35%). Of note, two of these 17 asymptomatic patients presented with regional metastases. Recurrences in these asymptomatic patients were either identified at the outpatient clinic by otoscopic examination, with radiologic imaging (CT, MRI and/or PET-scan), or during second look surgery. Recurrences were found both in patients that had received adjuvant radiotherapy (n = 4) as well as patients that had not (n = 44).

In all, 13 patients (13/196, 7%) developed regional and/or distant metastases after surgery. There was no difference in duration of follow-up after between the patients who developed metastases (median 3.0 years, interquartile range 1.0 – 10.0 years) and the patients who did not develop metastases (median 3.5 years, interquartile range 1.3 – 9.3 years). Of the 13 patients who developed metastases, one had a class 2 tumour (8%), three had a class 3 tumour (23%), two had a class 4 tumour (15%) and in seven patients the extent of disease at first presentation was unknown (54%).

An overview of the 5-year cumulative recurrence rate stratified by tumour extension category and treatment modality is shown in Figure 2A and 2B, respectively. Patients with extended MEANTs at first presentation (class 4) had a significantly higher cumulative recurrence rate compared to those with class 1 to 3 tumours (60% vs. 15% – 22%; p = 0.01). All twelve patients with a class 2 tumour who developed recurrent disease, primarily underwent a tympanotomy (n = 2) or mastoidectomy (n = 10). Seven patients with a class 3 tumour developed a recurrence, of which three were primarily treated by tympanotomy, one by subtotal temporal bone resection, one by translabyrinthine craniotomy and two by an unknown surgical approach.

Adjuvant radiotherapy was administered in 17 patients, either local or locoregional. Local adjuvant radiotherapy did not result in a lower recurrence rate compared to patients treated with surgery alone (30% vs. 21%; p = 0.31). Only two patients received adjuvant locoregional radiotherapy, therefore the association between locoregional radiotherapy and recurrence rate could not reliably evaluated.

Outcome and survival

Overall outcome per tumour extension category is shown in Table 5.

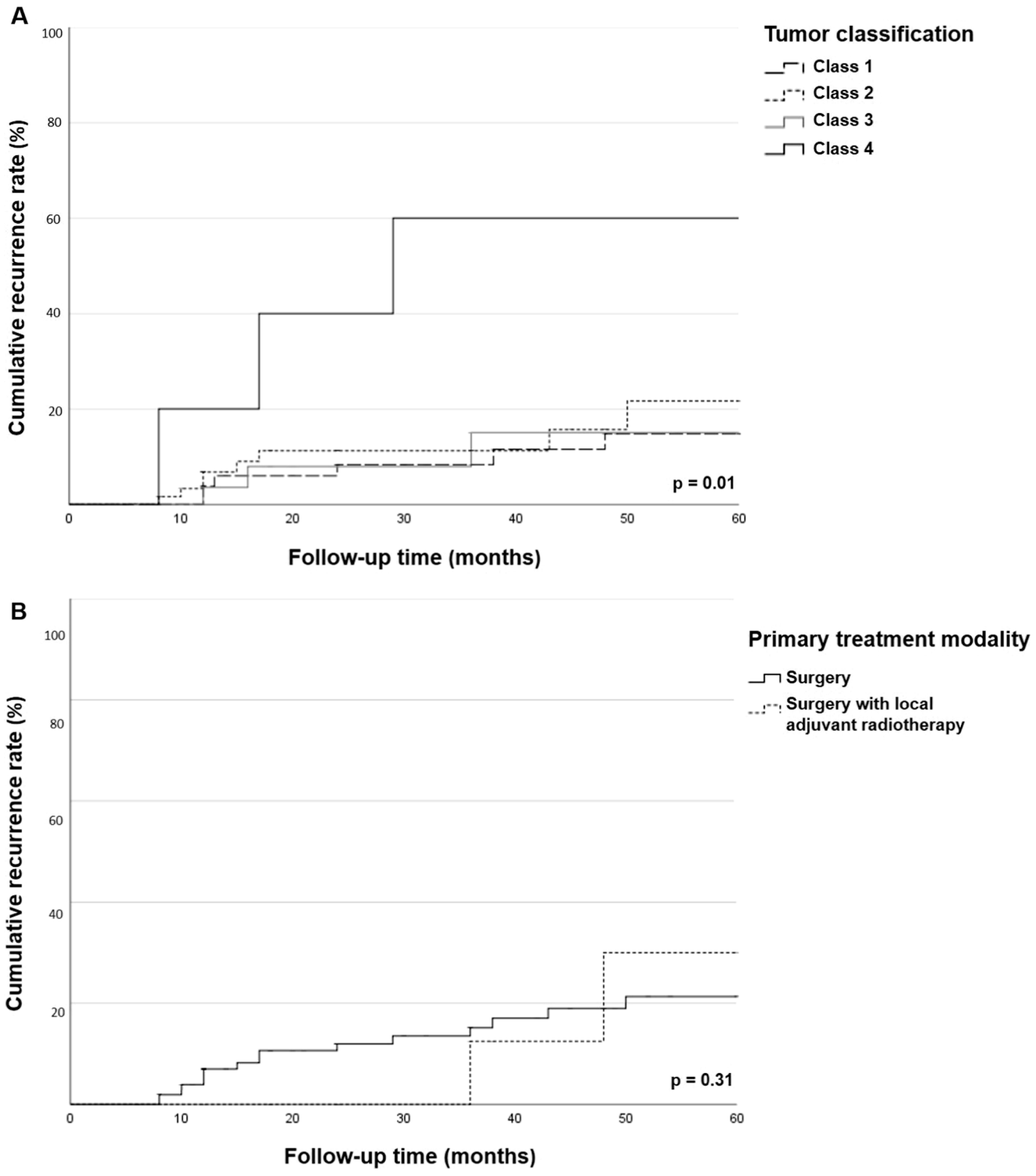

Figure 2. Five-year cumulative recurrence rate for patients with middle ear adenomatous neuroendocrine tumours per (A) tumour extension category as used in this study and (B) primary treatment modality.

The median duration of follow-up was 36 months (range 2 months – 45.0 years). Follow-up was generally performed at the outpatient clinic by symptom evaluation and otoscopic examination. Radiologic imaging (CT, MRI, PET-scan and/or octreotide scintigraphy) was performed in 25% of the patients, 9% of the patients underwent second look surgery.

Eight patients died during follow-up (4%): four patients of MEANT, three patients of unrelated causes and one patient of unknown cause. Of note, one of the two patients who received palliative treatment was alive at the end of the follow-up, six months after therapy. Three of four patients who died of MEANT initially had a stage 3 tumour, and developed progressive bone and liver metastasis 3.5, 4.2 and 10.0 years after the first diagnosis of MEANT. One patient developed a local recurrence with intracranial extension and died 7.0 years after diagnosis, no information was available on primary tumour extension in this case.

The 5- and 10-year overall survival rate in patients with MEANT was 94% (95% CI [88%; 98%]) and 92% (95% CI [86%; 97%]), respectively.

Table 5
Tumour extension and overall outcome in patients with middle ear adenomatous neuroendocrine tumours.

		Tumour classification*				
Outcome	*n*	1 (n=60)	2 (n=76)	3 (n=35)	4 (n=5)	Unclassified (n=22)
NED	167	57 (95%)	64 (84%)	28 (80%)	4 (80%)	14 (64%)
AWD	16	2 (3%)	6 (8%)	3 (8.5%)	1 (20%)	4 (18%)
DOD	4	0	0	3 (8.5%)	0	1 (4.5%)
DID	3	1 (2%)	2 (3%)	0	0	0
DUC	1	0	0	0	0	1 (4.5%)
LTF	7	0	4 (5%)	1 (3%)	0	2 (9%)
Follow-up (median, years)	3.0	4.0	2.5	2.0	3.0	8.5

Since only few patients died, associations between overall survival and clinical or histopathological features of MEANT could not reliably be investigated. In addition, too few events, i.e. death during follow-up (n = 8) or development of metastatic disease (n = 13), occurred to warrant a multivariable analysis to identify prognostic factors for the proposed classification system [117].

Discussion

The current review of 198 patients with MEANT supports the view that most of these tumours have an indolent and benign biological behaviour. However, in a subgroup of patients (7%), the clinical course is much less benign. Almost all patients who developed metastases also had a local recurrence (92%). Moreover, one in four patients (25%) with a local recurrence eventually developed metastatic disease. Recurrent disease may manifest without symptoms and can develop more than 30 years after primary surgery [107]. As of yet, it is uncertain whether longstanding primary or recurrent disease increases the risk for metastasis, or that intrinsic primary tumour characteristics impose the risk for both recurrence and metastasis. Either way, these findings underline the utmost importance of complete initial local tumour control and prolonged follow-up.

Surgical resection is the treatment of choice for MEANTs, although there is no consensus on the optimal surgical approach. To explore the potential relation between tumour extension, surgical approach and outcome, we classified MEANTs in four tumour extension categories, based on tumour extension in the temporal bone and surrounding structures (Table 1). Transcanal and transmastoid ear surgery seem suitable for tumours confined to the middle ear and/or mastoid (class 1 and 2), since the majority of these tumours have a benign and indolent clinical course. More extensive surgery, such as subtotal petrosectomy, is warranted in patients with tumour extension beyond the tympanomastoid space (class 3 and 4), as these tumours have a high tendency for malignant progression. Nevertheless, in each individual patient the potential benefit of total eradication of the disease through extensive surgery should be weighed against the inherent morbidity and risk of such a procedure, which may negatively affect the patient's quality of life.

Adjuvant radiotherapy does not seem to reduce the incidence of recurrent disease. Other types of adjuvant therapy are reported in very limited numbers of patients, precluding definitive conclusions.

As of yet, there is no consensus on the optimal follow-up after initial surgery. Several modalities have been reported: clinical follow-up with otoscopy, second look surgery and radiology. The sensitivity for the detection of recurrence of these modalities is unclear. The role of imaging is difficult to define, because MEANT cannot be diagnosed with certainty through specific morphological or functional imaging characteristics. Whereas CT is best suited to evaluate the temporal bone and the involvement or destruction of bony structures by the tumour, MRI is superior in the delineation of the lesion and the differentiation between tumour and inflammatory tissue [118]. In addition, MRI may provide visualization of the intracranial extent of the tumour and regional metastases. Therefore, CT and MRI are complementary techniques for assessing the extent of disease, however, both may be challenging to interpret especially after previous ear surgery [74]. Additionally, since the majority of NEN overexpress somatostatin receptors on their cell surface, nuclear imaging techniques using radiolabeled somatostatin analogues can be performed to identify these tumours [119]. Further research is needed to evaluate the accuracy and role of both morphological and functional imaging in the diagnostic work-up and post-treatment follow-up of MEANTs [74,86,120].

This systematic review has some limitations inherent to the rarity of MEANT. Patients were reported in small patients numbers, with heterogenic diagnostic and outcome parameters and different surgical strategies and follow-up regimens, hampering comparison. Publication bias may have occurred, which on one hand may have inflated success rates of MEANT management and on the other hand may have led to an overrepresentation of more aggressive cases. Additionally, due to the relative small number of patients that developed metastases or died during follow-up, prognostic histopathological factors for the outcome of MEANT could not reliably be evaluated. As with the classification of Marinelli et al, the prognostic value of the proposed classification system could not be determined. Because this is an inherent problem in disease as rare as MEANT, we did not attempt to build a TNM-like classification system, but propose a relatively simple classification that is based on radiological and clinical features of the primary tumor, with the aim of assisting in descriptive statistics and preoperative staging and planning.

As prospective data of sufficient volume to address these issues are nearly impossible to acquire due to the rarity of the disease, a multicenter retrospective study is the best next step in expanding our knowledge and understanding of these rare neoplasms.

Conclusion

The majority of MEANTs have an indolent and benign biological behaviour. However, in a subgroup of patients the course of the disease is much less benign: 25% develop a local recurrence, 7% develop metastasis and 4% die of the disease. These findings suggest that complete initial local tumour control is important in patients with MEANT. Prognostic histopathological/immunohistochemical biomarkers for recurrence or malignant progression of MEANTs have not yet been identified. However, the risk of regional and distant metastasis seems especially high in patients who present with a local recurrence. This suggests that prolonged clinical follow-up is indicated, however the optimal follow-up strategy has yet to be defined.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Soga J. Carcinoid and their variant endocrinomas. An analysis of 11842 reported cases. J Exp Clin Cancer Res. 2003;22:517–30.
[2] Ruck P, Pfisterer EM, Kaiserling E. Carcinoid tumor of the middle ear. Path Res. Pract. 1989;185:496–503.
[3] Torske KR, Thompson LDR. Adenoma versus carcinoid tumor of the middle ear: a study of 48 cases and review of the literature. Mod Pathol. 2002;15:543.
[4] Agaimy A, Lell M, Schaller T, Märkl B, Hornung J. 'Neuroendocrine' middle ear adenomas: consistent expression of the transcription factor ISL1 further supports their neuroendocrine derivation. Histopathology 2015;66(2):182–91.
[5] Bell D, El-Naggar AK, Widley PW. Middle ear adenomatous neuroendocrine tumors: a 25-year experience at MD Anderson Cancer Center. Virchows Arch. 2017;471:667–72.
[6] Mooney EE, Dodd LG, Oury TD, Burchette JL, Layfield LJ, Scher RL. Middle ear carcinoid: an indolent tumor with metastatic potential. Head Neck. 1999;21:72–7.
[7] Ramsey MJ, Nadol JBJ, Pilch BZ, McKenna MJ. Carcinoid tumor of the middle ear: clinical features, recurrences, and metastases. Laryngoscope. 2005;115:1660.
[8] Pellini R, Ruggieri M, Pichi B, Covello R, Danesi G, Spriano G. A case of cervical metastases from temporal bone carcinoid. Head Neck. 2005;27(7):644–7.
[9] Fundakowski CE, Chapman JR, Thomas G. Middle ear carcinoid with distant osseous metastasis. Laryngoscope. 2013;123:779–82.
[10] Gaafar A, Ereno C, Ignacio Lopez J. Middle-ear carcinoid tumor with distant metastasis and fatal outcome. Hematol Oncol Stem Cell Ther. 2008;1:53–6.
[11] Michaels L, Soucek S, Barnes L, et al. Middle ear. Pathology and genetics of head and neck tumors (WHO classification of tumours). Lyon, France: IARC Press; 2005. p. 342–50.
[12] Marinelli JP, Cass SP, Mann SE. Adenomatous neuroendocrine tumor of the middle Ear: a multi-institutional investigation of 32 cases and development of a staging system. Otology & Neurotology. 2018;39:71–721.
[13] Saliba I, Evrard AS. Middle ear glandular neoplasms: adenoma, carcinoma or adenoma with neuroendocrine differentiation: A case series. Cases J. 2009;2:6508.
[14] Abbassi C, Natt R, Tahery J. A rare mass in the middle ear. The Journal of Laryngology & Otology. 2018;E1:1.
[15] Albritton F, Lenis A. Mixed adenoma of the middle ear. ENT Journal. 1994;73:882.
[16] Almuhanna K. Neuroendocrine adenoma of the middle ear with the history of otitis media and carcinoma of the cheek: a case report. BMC research notes. 2014;7:532.
[17] Alsalman H, Crowther JA, McLellan D, Kontorinis G. Temporal bone adenoma: a comprehensive analysis of clinical aspects and surgical outcome on a very rare entity. Journal of Neurological Surgery Part B: Skull Base (IF 1.397): 2020-10-05.
[18] Arnold B, Zietz C, Muller-Hocker J, Wustrow TP. Adenoma of the middle ear mucosa. Eur Arch Otorhinolaryngol. 1996;253(1–2):65–8.
[19] Ayache S, Braccini F, Fernandes M, Homassin JM. Adenoma of the middle ear: a rare and misleading lesion. Otology & Neurotology. 2002;23(6):988–91.
[20] Azzoni C, Bonato M, D'Adda T, et al. Well-differentiated endocrine tumours of the middle ear and of the hindgut have immunocytochemical and ultrastructural features in common. Virchows Arch. 1995;426:411–8.
[21] Bailey QR, Weiner JM. Middle ear adenoma: a case report with ultrastructural findings. The Journal of Laryngology and Otology. 1986;100:467–70.
[22] Bajaj Y, Thevasagayam M, Sotres M, Oates J. Carcinoid tumour of the middle ear and mastoid. The Otorhinolaryngologist. 2007;1(3):154–7.
[23] Bakhos D, Lescanne E, Fetissof F, Robier A, Morinière S. Neuro-endocrine adenoma of the middle ear: a case study. Eur Arch Otorhinolaryngol. 2007;264:1525–8.
[24] Baku M, Ueda H. A rare case of middle ear adenoma. Nagoya J Med Sci. 2014;76(3–4):355–60.
[25] Bates GJ, Luscombe FE. Carcinoid metastasis in the middle ear: anaesthetic and surgical management. J R Soc Med. 1989;82(3):171–2.
[26] Benecke Jr JE, Noel FL, Carberry JN, House JW, Patterson M. Adenomatous tumor of the middle ear and mastoid. Am J Otol. 1990;11(1):20–6.
[27] Bittencourt AG, Tsuji RK, Cabral J, et al. Middle ear adenoma with neuroendocrine differentiation: relate of two cases and literature review. International Archives of Otorhinolaryngology 2013;17(3):340–3.
[28] Bläker H, Dyckhoff G, Weidauer H, Otto HF. Carcinoid tumor of the middle ear in a 28-year-old patient. Pathol Oncol Res. 1998;4(1):40–3.
[29] Chan KC, Wu CM, Huang SF. Carcinoid tumor of the middle ear: a case report. Am J Otolaryngol. 2005;26(1):57–9.
[30] Cruz Toro P, Domenech I, Clemente I, Anna Farre A, Amilibia E. Neuroendocrine Adenoma of the Middle Ear. Otology & Neurotology. 2011;33:e7–8.
[31] Davies JE, Semeraro D, Knight LC, Griffiths GJ. Middle ear neoplasms showing adenomatous and neuroendocrine components. J Laryngol Otol. 1989;103(4):404–7.
[32] Dehner LP, Chen KTK. Primary tumor of the external and middle ear. Benign and malignant glandular neoplasms. Arch Otolaryngol. 1980;106:13–9.
[33] Derlacki EL, Barney PL. Adenomatous tumor of the middle ear and mastoid. Laryngoscope. 1976;86(8):1123–35.
[34] Di Lella FA, Villalta ML, Boccio CM. Middle ear adenoma: a rare location for a benign tumor. J Otolaryngol ENT Res. 2017;7(1):00188.
[35] Dogru S, Wilkinson EP, Robinson RA, Smith RJ. Middle ear adenoma with neuroendocrine differentiation (MEA-ND) in the pediatric population. Int J Pediatr Otorhinolaryngol. 2009;73(6):895–8.
[36] Duderstadt M, Förster C, Welkoborsky HJ, Ostertag H. Adenomatous tumor of the middle ear and temporal bone: clinical, morphological and tumor biological characteristics of challenging neoplastic lesions. Eur Arch Otorhinolaryngol. 2012;269(3):823–31.
[37] Entong W, Weixi G, Jiping D. Carcinoid tumor in the middle ear: a case report and literature review. Journal of Otology 2006;1(1):57–60.
[38] Faverly DR, Manni JJ, Smedts F, Verhofstad AA, van Haelst UJ. Adeno-carcinoid or amphicrine tumors of the middle ear a new entity? Pathol Res Pract. 1992;188(1–2):162–71.
[39] Fedorová K, Formánek M, Zeleník K, et al. Middle ear adenoma imitating late postoperative complication. Ear Nose Throat J. 2020;24. https://doi.org/10.1177/0145561320935846.
[40] Friedmann I, Galey F, House W, Carberry J, Ward P. A mixed carcinoid tumour of the middle ear. The Journal of Laryngology & Otology. 1983;97(5):465–70.
[41] Furstenberg AC. XLII. Primary adenocarcinoma of the middle ear and mastoid. Annals of Otology, Rhinology & Laryngology. 33(3): 677–689.
[42] Girdhar-Gopal HV, Mikaelian DO. Adenoma and adenocarcinoma of the middle ear and mastoid cavity. Transactions - Pennsylvania Academy of Ophthalmology and Otolaryngology. 1990;42:1058–60.
[43] Gobel Y, La Croix C, Mornet E, Marianowski R. Recurrent neuroendocrine adenoma of the middle ear: a case report. Eur Ann Otorhinolaryngol Head Neck Dis. 2014;131(4):267–8.
[44] Gunduz M, Yamanaka N, Saito T, Kuki K, Yokoyama M, Nakamine H. Middle ear adenoma with neuroendocrine differentiation. Auris Nasus Larynx 2000;27(1):73–6.
[45] Hagan WE, Leonard GL, Ichinose H, Cox RH. Primary monomorphic adenoma of the middle ear. Laryngoscope. 1980;90(12):1962–72.
[46] Hale RJ, McMahon RF, Whittaker JS. Middle ear adenoma: tumour of mixed mucinous and neuroendocrine differentiation. J Clin Pathol. 1991;44(8):652–4.
[47] Hardingham M. Adenoma of the middle ear. Arch Otolaryngol Head Neck Surg. 1995;121:342–4.
[48] Hasan Z, McGinness S, Gunaratne DA, Coleman H, Varikatt W, da Cruz M. Neuroendocrine adenoma of the middle ear: a rare histopathological diagnosis. Case Rep Otolaryngol. 2016;9834750.
[49] Hosoda S, Tateno H, Inoue HK, et al. Carcinoid tumor of the middle ear containing serotonin and multiple peptide hormones. Acta Pathol Japon. 1992;42:614–20.
[50] Inoue S, Tanaka K, Kannae S. Primary carcinoid tumor of the ear. Virchows Arch. A Path. Anat. and Histol. 1982;396:357–63.
[51] Isenring D, Pezier TF, Vrugt B, Huber AM. Middle ear adenoma: case report and discussion. Case Reports. Otolaryngology. 2014::1–4.
[52] Isipradit P, Asawavichianginda S, Keelawat S. Carcinoid tumor of the middle ear. J Med Assoc Thai. 2007;90(4):805–8.
[53] Jackson CG, Glasscock 3rd ME. Primary adenoma of the middle ear. Am J Otol. 1980;2(2):105–7.
[54] Jahrsdoerfer RA, Fechner RE, Moon CN, Selman JW, Poxell JB. Adenoma of the middle ear. Laryngoscope. 1983;93:1041–4.
[55] Jones SE, Yung MW, Orrell JM, Norris A. Adenoma in the middle ear: a report of two cases. J Laryngol Otol. 2001;115(3):216–9.
[56] Kacerovska D, Cermak J, Kreuzberg B, Kazakov D. Neuroendocrine adenoma of the middle ear with extension into the external auditory canal. Cesk Patol. 2012;48(1):36–8.
[57] Kambayashi J, Ishidoya M, Urae T, et al. A case of carcinoid tumor of the middle ear producing peptide hormones. Auris Nasus Larynx 1988;15(3):155–63.
[58] Kanaya H, Hirabayashi H, Arakawa K, Fukami S, Okuba M. Middle ear carcinoid tumor : case report and literature review. 2006;33:133–7.
[59] Ketabchi S, Massi D, Franchi A, Vannucchi P, Santucci M. Middle ear adenoma is an amphicrine tumor: why call it adenoma? Ultrastruct Pathol. 2001;25(1):73–8.
[60] Kim YH, Lee SH, Jung DJ. Neuroendocrine adenoma of the middle ear confused with congenital cholesteatoma. Braz J Otorhinolaryngol. 2014;80:180–1.
[61] Knerer B, Matula C, Youssefzadeh S, et al. Treatment of a local recurrence of a carcinoid tumor of the middle ear by extended subtotal petrosectomy. Eur. Arch. Otorhinolaryngol. 1998;255:57–61.
[62] Knight JR, Bowdler DA. A benign middle-ear adenoma producing facial paralysis. J Laryngol Otol. 1985;99(8):809–12.
[63] Kochalis X, Birchall JP, Sloan P. Light and Electron Microscopic Studies of A Case of Middle Ear Adenoma. Laryngoscope. 1984;94:1482–4.
[64] Kodama H, Takezawa H, Suzuki T, et al. Carcinoid tumor of the middle ear. The Journal of Laryngology and Otology. 1989;103:86–91.

[65] Krouse JH, Nadol JB, Goodman ML. Carcinoid tumor of the middle ear. Ann Otol Rhinolol Laryngol. 1999;90:547–52.
[66] van der Laan TP, Dikkers FG, van Hemel BM, Dorgelo B, Halmos GB. Carcinoid tumor of the Middle Ear - A Case Report With Review of the Literature van der Laan, TP. Neuroendocrine carcinoma of the head and neck: in search for a better outcome. Rijksuniversiteit Groningen. Part 2017;I:43–50.
[67] Latif MA, Madders DJ, Barton RP, Shaw PA. Carcinoid tumour of the middle ear associated with systemic symptoms. J Laryngol Otol. 1987;101:480–6.
[68] Le Nobel GJ, Lin VY, Iakovlev V, Lee JM. An eustachian tube neuroendocrine carcinoma: a previously undescribed entity and review of the literature. Case Rep Surg. 2016;2016:4643615.
[69] Lee ES, Tang IP. Middle ear carcinoid tumor: a rare case. Arch Otolaryngol Rhinol. 2017;3(3):061–3.
[70] Lee SK, Choe MS. CT and magnetic resonance imaging features of middle ear adenoma of neuroendocrine differentiation: A Case Report. J Korean Soc Radiol 2013;69(3):187–91.
[71] Little FB. Pathologic quiz case 2. Arch Otolaryngol. 1985;111:346.
[72] Liu G, Chen F, Li JN, Liu SX. Carcinoid tumor of the middle ear: a case report and review of literature. Int J Clin Exp Pathol. 2014;7(10):7105–9.
[73] Mahrous A, Tysome J, Marker A, Moffat D. Isolated adenoma with neuroendocrine differentiation involving both the facial nerve and parotid Gland. International Journal of Otolaryngology and Head & Neck Surgery 2014;3:101–5.
[74] Maintz D, Stupp C, Krueger K, Wustrow J, Lackner K. MRI and CT of adenomatous tumours of the middle ear. Neuroradiology 2001;43(1):58–61.
[75] Mandigers CMPW, van Gils APG, Derksen J, van der Mey A, Hogendoorn PCW. Carcinoid tumor of the jugulotympanic region. J Nucl Med. 1996;37:270–2.
[76] Manni JJ, Faverly DRGS, van Haelst UJGM. Primary carcinoid tumors of the middle ear. Arch Otolaryngol Head Neck Surg. 1992;118:1341–7.
[77] Marion RG. Primary middle ear adenoma. Acta OtoLaryngologica. 1983;95(393): 92–5.
[78] McCrary HC, Faucett EA, Reghunathan S, et al. The first reported case of recurrent carcinoid tumor in the external auditory canal. Otol Neurotol. 2017;38 (1):114–7.
[79] McNutt MA, Bolen JW. Adenomatous tumor of the middle ear. An ultrastructural and immuncytochemical study. Am J Clin Pathol. 1985;84:541–7.
[80] Menezes G, Wakely Jr P. Aspiration cytopathology of middle-ear neuroendocrine carcinoma. Diagn Cytopathol. 2001;25:168–71.
[81] Mhawej R, Farah C, Haddad A, Tabchy B. Primary neuroendocrine tumors of the ear, nose and throat: A report of three cases and a review of the literature. Oncol Lett. 2015;10(4):2533–6.
[82] Mills SE. Neuroectodermal neoplasms of the head and neck with emphasis on neuroendocrine carcinomas. Mod. Pathol. 2002;15(3):264–78.
[83] Mori E, Kojima H, Wada K, Moriyama H. Middle ear adenoma diagnosed by recurrent facial paralysis. Auris Nasus Larynx 2009;36:75–8.
[84] Morita M, Mori N, Takashima H, et al. Primary poorly differentiated adenocarcinoma of the middle ear. Auris Nasus Larynx 1994;21:59–63.
[85] Nader ME, Bell D, Ginsberg L, DeMonte F, Gunn GB, Gidley PW. The first reported case of primary intestinal-type adenocarcinoma of the middle ear and review of the literature. Otol Neurotol. 2017;38(9):e364–8.
[86] Nikanne E, Kantola O, Parvianinen T. Carcinoid tumor of middle ear. Duodecim. 2003;119:1081–4.
[87] Nyrop M, Guldhammer Skov B, Katholm M, et al. Carcinoid tumor of the middle ear. Ear Nose Throat J. 1994;73:688–93.
[88] Orendorz-Fraczkowska K, Jaworska M, Gawron W, Badowski R. Middle-ear ceruminous adenoma as a rare cause of hearing loss and vertigo: case reports. Auris Nasus Larynx 2005;32(4):393–7.
[89] Orozco FR, Choi JS, Correa AJ, Voelker CCJ. Temporal bone histopathology case of the month: small cell neuroendocrine carcinoma of the external auditory canal and middle ear. Otol Neurotol. 2020;41(10):e1279–81.
[90] Paraskevakou H, Lazaris AC, Kandiloros DC, Papadimitriou K, Adamopoulos G, Davaris PS. Middle ear adenomatous tumor with a predominant neuroendocrine component. Pathology Aug. 1999;31(3):284–7.
[91] Paulus W, Romstöck J, Weidenbecher M, Huk WJ, Fahlbusch R. Middle ear adenocarcinoma with intracranial extension. J. Neurosurg. 1999;90(3):555–8.
[92] Ribé A, Fernández PL, Ostertarg H, et al. Middle-ear adenoma (MEA): a report of two cases, one with predominant “plasmacytoid” features. Histopathology 1997; 30:359–64.
[93] Riches WG, Johnston WH. Primary adenomatous neoplasms of the middle ear: light and electron microscopic features of a group distinct from the ceruminomas. Am J Clin Pathol 1982;77:153–61.
[94] Riddell DA, LeBoldus GM, Joseph MG, et al. Carcinoid tumour of the middle ear: case report and review of the literature. J Otolaryngol. 1994;23(4):276–80.
[95] Sahan M, Yildirim N, Arslanoğlu A, Karslioğlu Y, Kazikdasş KC. Carcinoid tumor of the middle ear: report of a case. Am J Otolaryngol. 2008;29(5):352–6.
[96] Sakurai M, Mori N, Horiuchi O, et al. Carcinoid tumor of the middle ear: an immunohistochemical and electronmicroscopic study: report of a case. Acta Pathol Japon. 1988;38:1453–60.
[97] Sato K, Mihashi R, Kurita T, et al. Significance of cytodiagnosis in primary carcinoid tumor of the middle ear: A case report. Oncol Lett. 2018;15(5):8062–6.
[98] Shibosawa E, Tsutsumi K, Ihara Y, Kinoshita H, Koizuka I. A case of carcinoid tumor of the middle ear. Auris Nasus Larynx 2003;30:99–102.
[99] Shim MJ, Song CI, Yoon TH. A case of middle ear adenoma. Korean J Audiol. 2012;16(1):27–30.
[100] Shishido T, Ikeda R, Suzuki J, et al. Middle ear adenoma with facial palsy: a case report and a review of the literature: middle ear adenoma with facial palsy. Auris Nasus Larynx 2020 Nov 24;S0385–8146(20):30305–9.
[101] Soni NK, Chatterji P, Solanki RL. Primary benign monomorphic adenoma of the middle ear and mastoid. Indian J Otolaryngol. 1984;36:19–20.
[102] Stanley MW, Horwitz CA, Levinson RM, et al. Carcinoid tumours of the middle ear. Am J Clin Pathol. 1987;87:592–600.
[103] Sterrer E, Windisch F, Frey K, Rettensteiner K, Loader B. Middle ear adenoma with neuroendocrine differentiation: a pediatric case report. Wien Klin Wochenschr. 2017;129(5–6):208–11.
[104] Tabuchi K, Aoyagi Y, Uemaetomari I, et al. Carcinoid tumours of the middle ear. J Otolaryngol Neck Surg. 2009;38:E91–4.
[105] Tomazic PV, Beham A, Lackner A, Ropposch T, Stockreiter U, Walch C. Neuroendocrine adenoma of the middle ear (NAME) mimicking as chronic otitis media with an episode of facial nerve palsy. B-ENT. 2011;7:121–5.
[106] Tsiouvaka S, Papadopoulou I, Lachanas V, Koltsidopoulos P, Skoulakis C. Neuroendocrine adenoma of the middle ear presented as paraganglioma: a case report. Hippokratia. 2017;21(4):201–3.
[107] Van der Lans RJL, Engel MSD, Rijken JA, Hensen EF, Bloemena E, van der Torn M, et al. Neuroendocrine neoplasms of the middle ear: unpredictable tumor behaviour and tendency of recurrence. A single centre experience with nine patients. Head Neck 2021:1–6.
[108] Vilain J, Degols JC, Ledeghen S. Recurrent adenomatous neuroendocrine tumor of the middle ear: a diagnostic challenge. Case Rep Otolaryngol. 2018;2018: 8619434.
[109] Wang L, Ouyang N, Guo HX, Liu QY. Middle ear adenoma with uncommon presentation and literature review. BMJ Case Rep. 2017; 2017:bcr2016216694.
[110] Wassef M, Kanavaros P, Polivka M, et al. Middle ear adenoma. A tumor displaying mucinous and neuroendocrine differentiation. Am J Surg Pathol. 1989;13(10): 838–47.
[111] Woods RH, Moses B, Roa A, Lumpkin S, Pearlman S. Middle ear adenoma: Report of two cases. Otolaryngology – Head and Neck surgery. 1993;108(6):755–9.
[112] Xie B, Zhang S, Dai C, Liu Y. Middle ear adenomatous neuroendocrine tumors: suggestion for surgical strategy. Braz J Otorhinolaryngol. 2020;15(20): 1808–8694.
[113] Zahtz GD, Zielinski B, Abramson AL. Benign adenoma of the middle ear cavity causing facial paralysis. Otolaryngol Head Neck Surg. 1981;89(4):624–7.
[114] Zaman SU, Zakir I, Faraz Q, et al. Neuroendocrine adenoma of middle ear causing acute onset facial palsy- a rare case report. Iranian Journal of Otorhinolaryngology. 2019;31(106):305–10.
[115] Zehlicke T, Punke C, Boltze C, Pau HW. Transient facial palsy in two cases of benign, very rare middle ear tumors (carcinoid tumor and myxoma). Neurologist. 2008;14(1):52–5.
[116] Zagaria A, Nicastro V, Abita P, Freni F, Galletti F. Adenomatous neuroendocrine tumours of the middle ear in a young man with conductive hearing loss. J Craniofac Surg. 2020;19.
[117] ter Wee MM, Lissenberg-Witte BI. A quick guide on how to conduct medical research. Houten: Bohn Stafleu van Loghum; 2019. ISBN: 9789036822473.
[118] Tuan AS, Chen JY, Mafee MF. Glomus tympanica and other intratympanic masses: role of imaging. Operative Techniques in Otolaryngology-Head and Neck Surgery. 2014;25(1):49–57.
[119] Galgano S, Sharbidre K, Morgan DE. Multimodality imaging of neuroendocrine tumors. Radiol Clin N Am. 2020;58:1147–59.
[120] Martinez-Lazaro R, Cortes-Blanco A, Moreno-Selva A, et al. Follow-up of a carcinoid tumor in the middle ear by In-111 pentetreotide scintigraphy. Clin Nucl Med. 2007;32(6):466–7.