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### **Citation**

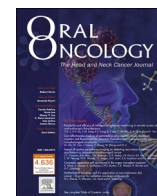
Engel, M. S. D., Lans, R. J. L. van der, Jansen, J. C., Leemans, C. R., Bloemena, E., Lissenberg-Witte, B. I., ... Hensen, E. F. (2021). Management and outcome of middle ear adenomatous neuroendocrine tumours: a systematic review. *Oral Oncology*, 121. doi:10.1016/j.oraloncology.2021.105465

Version: Publisher's Version

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**Note:** To cite this publication please use the final published version (if applicable).



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

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## ARTICLE INFO

### Keywords:

Adenoma  
Neuroendocrine tumor  
Carcinoid  
Middle ear  
Temporal bone

## 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 metastatic 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 post-operative 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

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<https://doi.org/10.1016/j.oraloncology.2021.105465>

Received 22 April 2021; Received in revised form 12 July 2021; Accepted 13 July 2021

Available online 2 August 2021

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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

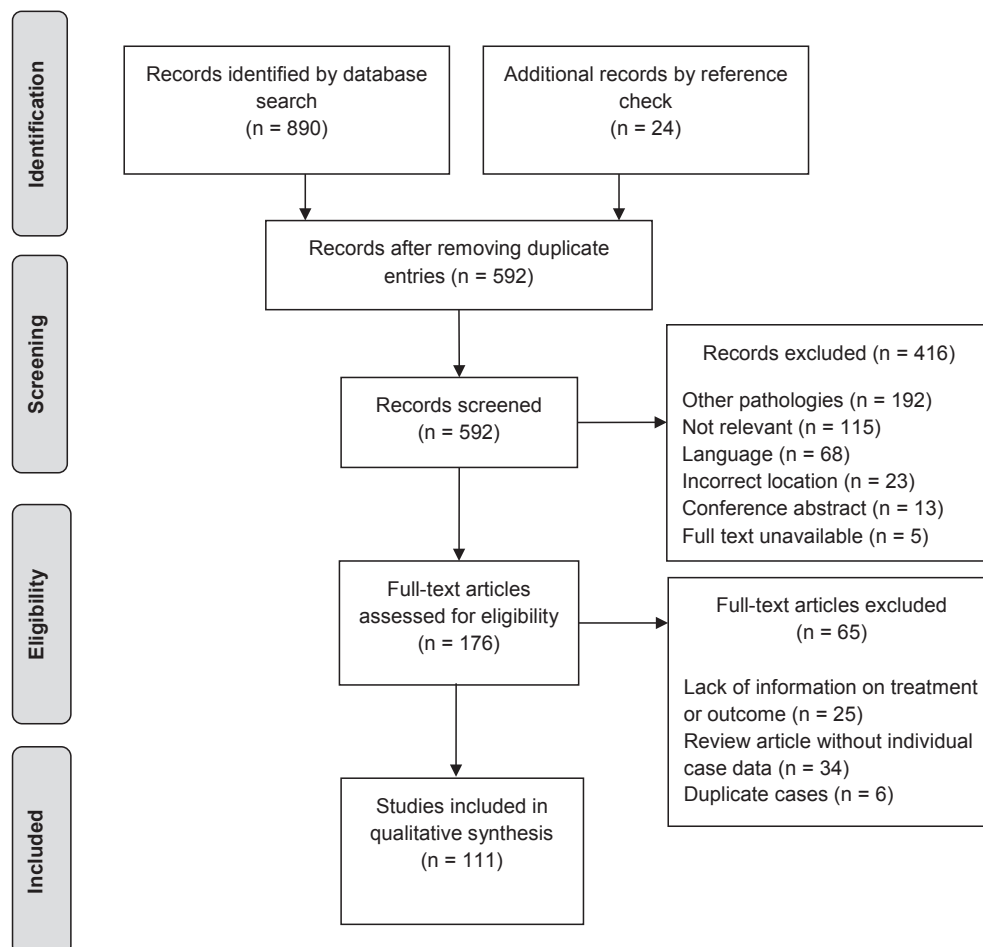
A systematic review of the literature was performed to identify case reports or case series of patients with MEANTs. The literature search was performed with the help of a scientific librarian, using PubMed, Embase and Cochrane databases. The following MESH terms and relevant keywords were used: ‘adenoma’, ‘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<br>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 <sup>a</sup>                                                                           | 191                                            | 4   | 2%   |
| Tumour classification <sup>b</sup>                                                                        | 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 <sup>c</sup>                                                                             | 191                                            | 8   | 4%   |
| Distant metastases                                                                                        |                                                |     |      |
| At presentation                                                                                           | 198                                            | 1   | 0.5% |
| During follow-up <sup>c</sup>                                                                             | 191                                            | 3   | 2%   |
| Regional and distant metastases                                                                           |                                                |     |      |
| At presentation                                                                                           | 198                                            | 0   | -    |
| During follow-up <sup>c</sup>                                                                             | 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.

**Table 3**

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

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

## 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 retrotympanic 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 4**

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

|                                                       | n   | Tumour classification <sup>a</sup> |          |          |         |                     |
|-------------------------------------------------------|-----|------------------------------------|----------|----------|---------|---------------------|
|                                                       |     | 1 (n=60)                           | 2 (n=76) | 3 (n=35) | 4 (n=5) | Unclassified (n=22) |
| <b>Treatment modality</b>                             |     |                                    |          |          |         |                     |
| 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 <sup>b</sup>                     | 2   | 0                                  | 0        | 2 (6%)   | 0       | 0                   |
| <b>Surgical treatment</b>                             |     |                                    |          |          |         |                     |
| 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 <sup>c</sup> | 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).

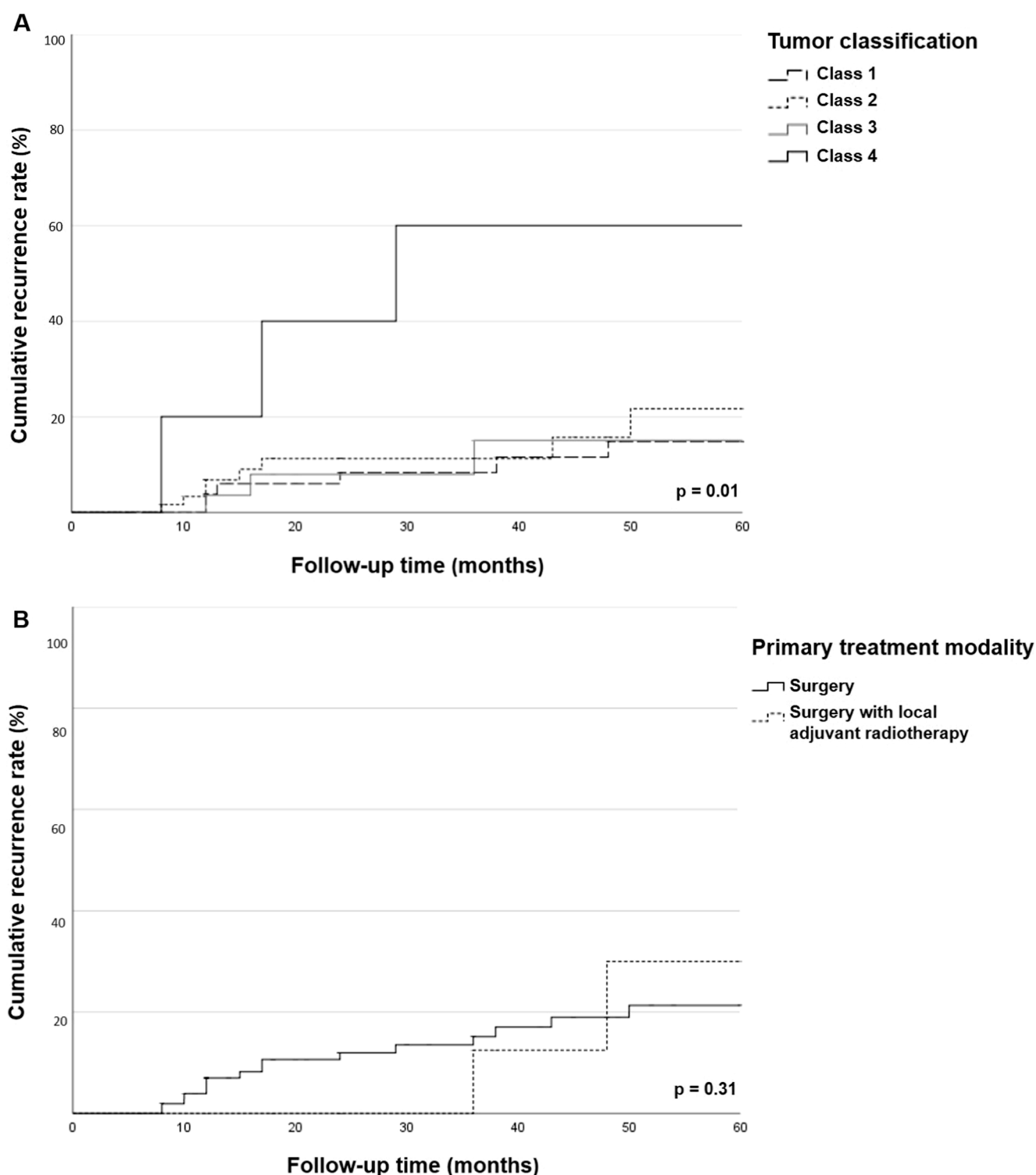
In all, 13 patients (13/196, 7%) developed regional and/or distant metastases after surgery. There was no difference in duration of follow-up after between the patients who developed metastases (median 3.0 years, interquartile range 1.0 – 10.0 years) and the patients who did not develop metastases (median 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 be evaluated.

### Outcome and survival

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



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.

| Outcome                   | n   | Tumour classification* |          |          |         |                     |
|---------------------------|-----|------------------------|----------|----------|---------|---------------------|
|                           |     | 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 tympano-mastoid 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 heterogeneous 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 multi-center 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.

## Acknowledgement

We like to thank Ralph de Vries for his help in conducting the literature search.

Funding: There is no funding source.

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