Analysis of prognostic factors in malignant external otitis

Kim, Bo Gyung

Department of Medicine

The Graduate School, Yonsei University

Analysis of prognostic factors in malignant external otitis

Directed by Professor Lee, Won-Sang

The Master's Thesis
submitted to the Department of Medicine,
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree
of Master of Medicine

Kim, Bo Gyung

June 2011

This certifies that the Master's Thesis
of Kim, Bo Gyung is approved.

Thesis Supervisor : Professor Lee, Won-Sang

Professor Chung, Myung-Hyun

Professor Nam, Jeong Mo

The Graduate School
Yonsei University

June 2011

ACKNOWLEDGEMENTS

First of all, I want to thank my thesis supervisor, Professor W.S.Lee, who watched over me, gave me close attention, and made me to understand the importance accomplishing this degree in my residency throughout the course. Because his scrupulous interests to my course, I finished the degree with great pleasures.

I also wish to express my graduates to Professor M.H. Chung, Professor J.M. Nam. They taught me from the basis to the final revision of the report.

I want to send my greatest respects to my parents. They guided the way how I should live my life and taught me most important things in life which I could not learn forever without them. For last, I want to send very special thanks my husband, who was my boyfriend when I wrote the master’s thesis. He provided the greatest motivation for me to study and proceed my master’s degree with all my efforts.

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<ABSTRACT>

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The Graduate School, Yonsei University

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Malignant external otitis (MEO) is a potentially fatal infection of the external auditory canal, temporal bone, and skull base. Despite the treatment with modern antibiotics, MEO can lead to skull base osteomyelitis, but until now there have been few studies on prognostic factors in MEO. And there are debates that the factor previously considered to be a prognostic indicator was not actually related to the outcome of MEO. We performed a retrospective study to identify prognostic factors and a meta-analysis of other articles on MEO. Based on disease progression, the 28 patients were divided into the ‘controlled’ and ‘uncontrolled’ groups, with 12 and 16 patients, respectively. We identified three categories of prognostic factor: factors relating to patient, disease, and treatment. We compared prognostic factors between the controlled and uncontrolled groups. In our series, the duration of diabetes mellitus (DM), inflammatory markers (C-reactive protein and erythrocyte sedimentation rate), and computed tomography (CT) or magnetic resonance imaging (MRI) findings did influence the prognosis of MEO. In contrast, prognosis was unrelated to age, gender, mean glucose level, HbA1c, pathogen,

comorbidity, or cranial nerve involvement. There was no factor relating to treatment correlated to the prognosis, such as surgery, steroid therapy, or the interval to the first proper treatment. Cranial nerve involvement is associated with disease progression, but cranial nerve involvement and the prognosis of MEO remain controversial. We also conducted a meta-analysis of cranial nerve involvement as a prognostic factor. Our results showed that cranial nerve involvement has a statistically significance on the prognosis of MEO.

Therefore, we found that glucose control in diabetes mellitus, cranial nerve involvement and disease extent in imaging modalities that were controversial previously were related to the prognosis of MEO. We suggest that significant prognostic factors should be monitored to anticipate the prognosis of patients with MEO.

Key words : malignant external otitis, MEO, prognostic factor, meta-analysis

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I. INTRODUCTION

Malignant external otitis (MEO) is a potentially fatal infection of the external auditory canal, temporal bone, and skull base. In 1838, Toulmouche described a case of osteomyelitis of the temporal bone that was probably the first reported case of MEO[1]. In 1959, Meltzer and Keleman described a case of *Pseudomonas* osteomyelitis of the temporal bone and skull base in a diabetic patient and recognized MEO[2]. Chandler named the disorder 'malignant external otitis' because of its high mortality, and presented a case series of MEO in 1968 [3].

Malignant external otitis tends to affect the elderly, and patients with diabetes mellitus or other immunocompromised conditions, like human immunodeficiency virus (HIV) infection and chemotherapy. The most common causative organism is *Pseudomonas aeruginosa* (> 90%) [4]. Clinical manifestations include deep otalgia for longer than 1 month, persistent otorrhea, headache, and cranial nerve involvement. MEO had a mortality rate of up to 50% before the development of effective antibiotics, but since the introduction of ciprofloxacin and other oral

antipseudomonal agents in the 1990s, survival rate is better [5]. Nevertheless, despite modern antibiotics treatment, MEO can be fatal if the disease progresses.

Malignant external otitis begins in the external auditory canal, and spreads to the skull base and jugular bulb via the fissures of Santorini and stylomastoid foramen. Venous channels and fascial planes facilitate the spread of infection along the dural sinuses, eventually extending to the petrous apex [6]. Many studies have shown that cranial nerve involvement, mostly the facial nerve, is associated with advanced infection and progression of the disease. Cranial nerve involvement occurs when the infection spreads towards the exit of a nerve. The stylomastoid foramen is closest to the external auditory canal, so the facial nerve is the most commonly involved cranial nerve [3]. As the disease advances to the medial skull base, it involves the jugular foramen, affecting the glossopharyngeal, vagus, and spinal accessory nerves [7]. The hypoglossal nerve may be involved within the hypoglossal canal and with progression of the infection, the nerves in the cavernous sinus could be affected. Severe complications, such as cranial nerve involvement and skull base osteomyelitis, are associated with mortality.

Many factors were believed to be related to the prognosis of MEO, such as diabetes mellitus, glucose level, cranial nerve involvement and the disease extent in imaging modalities. But, some studies showed that the factor previously considered to be a prognostic indicator was not actually related to the outcome of MEO. For example, Mani N. *et al.*[8] reported that the cranial nerve involvement did not affect the patient survival rate under an optimized medical treatment. In addition, as reported by Soudry[9], facial nerve involvement was a sign of progression of MEO, it did not, by itself, worsen prognosis. There is ongoing debate regarding the various factors predicting the outcome of MEO. It is unclear which factor(s) lead to disease progression. If we address provocative factors earlier, disease progression should be controlled and we may expect a better prognosis. Thus, we analyzed prognostic factors in the hope of optimizing the treatment of this disease. This study investigated the controversial prognostic

factors in various aspects and a meta-analysis of other articles on malignant external otitis retrospectively.

II. SUBJECTS AND METHODS

We retrospectively identified all cases of MEO diagnosed and treated in our otolaryngology department between January 2000 and March 2011. The criteria on which the diagnosis of MEO was based were those of Cohen and Friedman [10]. We reviewed the records of 28 patients who met these criteria (Table 1). We reviewed, the patients' basic data, including the interval to first treatment, hospitalization duration, underlying disease, ear-nose-throat examination, neurological examination, imaging studies, including CT and MRI, blood glucose levels and strict hyperglycemia control, treatment regimen, surgery performed, and the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels for monitoring of the effectiveness of therapy. We divided the patients into two groups, based on the treatment outcome: the controlled and uncontrolled groups.

Table 1. The diagnostic criteria of malignant external otitis (Cohen et al, 1987)

Major (Obligatory) signs:
1) Pain
2) Exudate
3) Edema
4) Granulations
5) Microabscesses
6) Positive Tc99 scan or failure of local treatment after more than 1 week
Minor (occasitional) signs
7) *Pseudomonas*
8) Positive radiograph
9) Diacetes mellitus
10) Cranial nerve involvement
11) Debilitating conditions
12) Old age

The controlled group contained patients who entered complete remission. The uncontrolled group included the patients who died from the disease or were alive with the disease. Statistically, the two groups were compared using Student's *t*-test, Fisher's test, and the chi-squared test, as appropriate (SAS, ver. 9.2; SAS Institute, Cary, NC, USA and Microsoft Office Excel 2003).

We also performed a meta-analysis of other articles on MEO. For the meta-analysis, several accepted sources were searched to identify primary studies published from 1974 to 2011, primarily using the Medline database, using the search terms "malignant external otitis," "malignant otitis externa," "skull base osteomyelitis," "necrotizing otitis externa," and "infective external otitis," using alternate spellings and an explicit search strategy for each source used. The terms were searched in English.

The literature search was extensive and was designed to obtain a large number of hits for MEO. In total, 368 articles were identified. After removing duplicates and subjects obviously different from MEO, 342 publications remained for the period January 1974 to April 2011 (Table 2). Most studies of the prognosis of MEO were retrospective studies, so that meta-analysis was conducted on retrospective studies. After removing articles because of methodological restrictions and data limitations, we could use only the data on cranial or facial nerve involvement as a prognostic factor and six articles met our major demand on study design(retrospective study, a complete reporting, and complete outcome data dichotomously). We compared the outcome of MEO using dichotomous data (controlled vs. non-controlled group) from the retrospective trials.

TABLE 2. Search Procedure

Step of Evaluation	No. of References
Initial search	369
After removal of duplicates and articles on obviously different subjects	342
Case reports	209
Retrospective studies	20
Prospective studies	30
Reviews	83
After removing articles because of methodologic restrictions, regardless of study design	6

The data were analyzed using Stata statistical software. Our analysis was based on a random-effects model, which generates a wider 95% confidence interval (CI) for the pooled result. The relationship between cranial nerve involvement and the prognosis of MEO effect sizes were calculated as the natural log of the odds ratio (OR). Effect sizes are depicted with their respective 95% CI.

III. RESULTS

We identified 28 patients with a diagnosis of MEO. There were 22 males (78.6%) and six females (21.4%), with a mean age of 65.4±12.6 (range, 33–81) years. Twelve patients (42.9%) entered complete remission from the MEO and were classified as the controlled group. Sixteen patients (57.1%) remained alive with disease(12 patients, 42.9%) or died from the disease(4 patients, 14.3%) and were classified as the uncontrolled group. Basic data at presentation and statistical analysis are summarized in Table 3.

Table 3. Characteristics of the MEO patients

Characteristic	Controlled group(12 cases)	Uncontrolled group(16 cases)
Gender		
Male	9	13
Female	3	3
Age(years)	61.9±15.7	68.1±9.4
Skull base osteomyelitis	3	16
Hospitalization(days)	26.4±15.5	54.2±30.7
Diabetes mellitus	7	16
Comorbidity	4	12
Cranial involvement	6	7
Interval to first treatment(days)	29.0	32.6
Steroid therapy	8	12
Surgery	3	6

Significant differences were found in skull base osteomyelitis, hospitalization, and diabetes mellitus. No significant differences were found for any other comparision.

Skull base osteomyelitis was found in 19 patients (67.9%); of these, nine underwent surgery. The surgery was performed to the patient who was intractable to the medical treatment or performed for the local debridement, and biopsy for histological confirmation.

1. Prognostic factors relating to the condition of patient

The controlled group (12 patients) with a mean age of 61.9±15.7 years recovered fully from the MEO, while the uncontrolled group (16 patients) with a mean age of 68.1±9.4 years remained alive with disease or progressed to death (p = 0.2066). The three patients died in hospital of an aspiration pneumonia attributed to malignant external otitis, the other patient died of sepsis. In both groups, most patients were males (controlled 9:3, uncontrolled 13:3), but this did not significantly affect disease outcome.

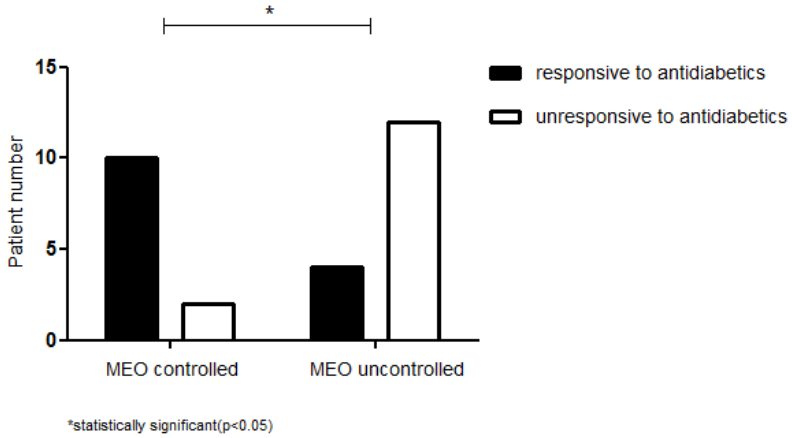
Table 4. Underlying disease of the MEO patients

Patient's underlyng disease	Controlled group(12 cases)	Uncontrolled group(16 cases)	p-value
DM	7	16	**0.0081***
History(years)	7.1	21.8	**0.0010***
HbA1c(%)	6.49±0.97	7.46±1.44	0.0542
glucose level	121.3±39.6	150.8±38.7	0.0533
Comorbidity	4	12	0.0531
Hypertension	2	6	NS
Ischemic heart disease	0	2	NS
Chronic renal failure	0	2	NS
DM retinopathy	1	1	NS
Cerebrovascular accident	1	1	NS

NS indicates not sifnigicant, *statistically sifnificant

Diabetes mellitus (DM) affected 23 patients (82.1%). Diabetes mellitus is a common associating disease in MEO, and was significantly related to the disease progression in seven patients (25.0%) in the controlled group and 16 patients (57.1%) in the uncontrolled group (p = 0.0081) (Table 4). Diabetes mellitus duration also differed significantly between the two groups; it was 7.1 years in the controlled group and 21.8 years in the uncontrolled group (p = 0.001). HbA1c is an indicator of the average blood sugar at the time it is checked and was checked in all patients, but it was not an prognostic indicator of MEO (p = 0.0542). Other underlying diseases included hypertension (8 cases), chronic renal failure (3 cases), ischemic heart disease (2 cases), DM retinopathy (2 cases), and cerebrovascular accident (2 cases). There was no significant difference between the controlled and uncontrolled groups with respect to the comorbidity(p=0.0531).

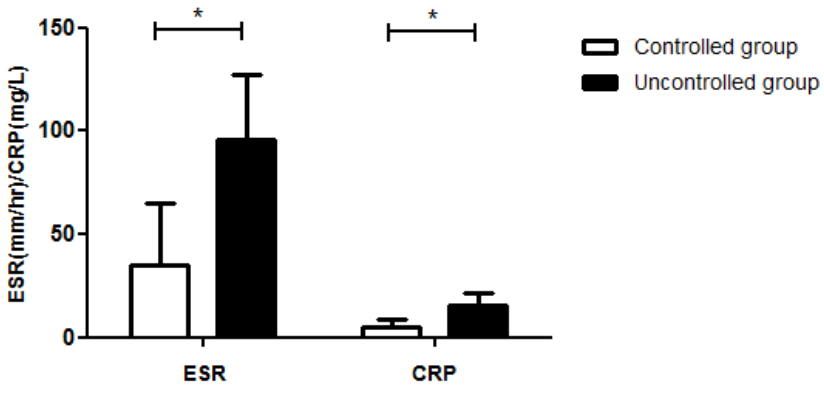
Figure 1. Comparision of sugar control between MEO controlled group and uncontrolled group



*statistically significant($p<0.05$)

All the patients got checked a fasting glucose level in the morning. The patients who were responsive to antidiabetics(<126 mg/dL) and the patients who were unresponsive to antidiabetics(≥126 mg/dL) were compared as regards to the outcome(Figure 1). In MEO controlled group, 10 patients were responsive to antidiabetics and two patients were unresponsive to antidiabetics. In contrast, in MEO uncontrolled group, 12 patients were unresponsive, four patients responsive($p<0.05$).

Figure 2. Comparison of inflammatory marker(ESR, CRP) between two groups



*Statistically significant($p<.0001$, $p<.0001$; student's t-test)

The ESR and CRP increased with disease progression and were higher in the uncontrolled group. The ESR level was checked 34.8±30.5mm/hr in controlled group, and 96.1±30.8mm/hr in uncontrolled group ($p < 0.0001$). The CRP level was 5.33±3.21mg/L in controlled group and 15.46±5.70mg/L in uncontrolled group ($p < 0.0001$). Both inflammatory markers were closely related to the outcome of MEO patients(Figure 2). Additionally, they changed with the disease status in individual patient.

Table 5. Microorganisms isolated

Microorganisms	Patient number
Bacteria	
Pseudomonas aeruginosa	13
MRSA	10
Enterobacter	3
Klebsiella pneumonia	2
Proteus	1
Fungi	
Aspergillus fumigatus	2
Polymicrobial infection	4

MRSA indicates methicillin resistant staphylococcus aureus

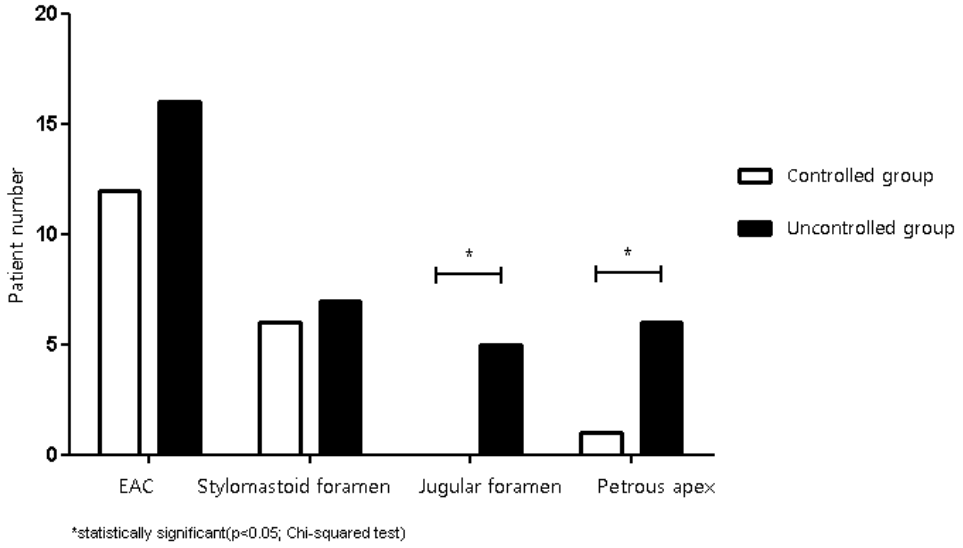
Pseudomonas aeruginosa was the most common iolated bacterial pathogen (13 patients), and then methicillin resistant *staphylococcus aureus*(MRSA, 10 patients). Table 5 provides a detailed followed list of isolated microorganisms. There was no significant difference between the controlled and uncontrolled groups with respect to the infected microorganism.

2. Prognostic factors relating to the disease extent

We classified the disease extent according to the course of disease progression. The infection starts in the external auditory canal (EAC) and spreads to the stylomastoid foramen and then to the mastoid tip and jugular foramen. Then, the septic process extends to the petrous apex and middle cranial fossa[6]. CT or MRI was obtained in all patients. All 28 patients had EAC involvement, 13 patients had stylomastoid foramen involvement(6, controlled; 7 uncontrolled),

and five patients had jugular foramen and lateral venous sinus involvement(0, controlled; 5, uncontrolled). Seven patients had petrous apex involvement(1, controlled; 6, uncontrolled) and one of them had cavernous sinus involvement, presenting as abducens nerve palsy. In five patients, the infection involving the jugular foramen spread to the petrous apex or cavernous sinus. Another two patients had petrous apex involvement, without jugular foramen involvement and these did not follow the typical disease course.

Figure 3. Comparison of disease extent in imaging modalities between controlled group and uncontrolled group



The CT or MRI findings were categorized using the extent of the disease, and the patients who had jugular foramen and petrous apex involvement had a tendency to higher morbidity and mortality than the patients without involvement (p = 0.0451, p = 0.0049). There was no association between the disease extent and glucose level so that the disease extent alone where the lesion was jugular foramen and petrous apex affected the outcome of MEO(Figure 3).

There was cranial nerve involvement in 13 patients (46.4%); all 13 had facial nerve (VII) involvement, four patients also had involvement of lower cranial nerves (IX, X, XI) and

two patients had involvement of hypoglossal nerve(XII). The abducens nerve (VI) was involved in only one patient(Table 6).

Table 6. Cranial nerve involvement in the MEO patients

Cranial nerve	Controlled group(12 cases)	Uncontrolled group(16 cases)	*p*-value
CN involvement	6	7	0.742
Facial nerve(VII)	6	7	0.742
Lower cranial nerve(IX, X, XI)	0	4	0.1131
IX	0	3	NS
X	0	3	NS
XI	0	2	NS
Hypoglossal nerve(XII)	0	2	NS
Abducens nerve(VI)	0	1	NS
Multiple CN involvement	0	4	0.1131

NS indicates not significant

The facial nerve was the cranial nerve involved most commonly due to its proximity, but there was no significant difference between the controlled and uncontrolled groups (p = 0.7022). The involvement of other cranial nerves was not associated with the outcome of MEO (p = 0.1131). Single or multiple cranial nerve involvement was not related to the prognosis of the patients with MEO in our study.

There is an ongoing debate with respect to the cranial nerve involvement as prognostic factor, so we performed the meta-analysis below. The baseline characteristics of the included trials, such as the study population, cranial nerve involvement, and statistical evaluation by the authors of the trial were comparable (Table 7).

Table 7. Summary of the studies describing cranial nerve involvement in patients with MEO

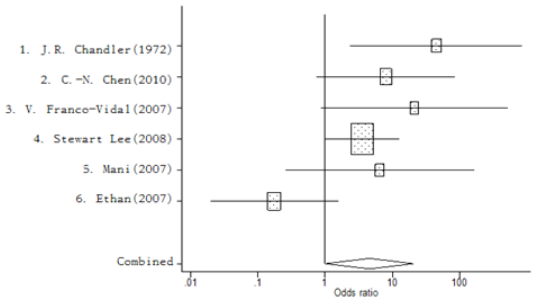
Trial	Cranial nerve involved	Patient No.		Statistical evaluation by the Author of the Trial
Chandler, J.R.[3]		Controlled(n=26)	Uncontrolled(n=12)	
	Facial nerve	8(50%)	8(50%)	
	Multiple cranial nerve	1(20%)	4(80%)	
Chen C.N., et al.[17]		Survival(n= 21)	Mortality(n=5)	
	Single cranial nerve	7	4	0.0577
	Multiple cranial nerve	2	3	0.0335
Franco-Vidal V., et al.[16]				
	Facial nerve	22.20%	77.80%	0.023
Lee S., et al.[12]				
	Cranial nerve	Hazard ratio=0.28 95% CI: 0.03-0.93		P<0.05
Mani N., et al.[8]		Controlled(n=21)	Uncontrolled(n=2)	No significant difference
	Cranial nerve	8	2	found between groups
Soudry E., et al.[9]		Controlled(n=29)	Uncontrolled(n=19)	No significant difference
	Facial N.	7	1	found between groups
Ali T., et al.[11]		n=37		
	Facial N.	15(40%)		
	Multiple CN	9		
	IX	4		
	X	5		
	XI	3		
	XII	3		

All of the included trials mentioned the number of patients in each group, except Ali. T. *et al*[11]. Of the other six articles, four reported significantly different prognoses depending on cranial nerve involvement, while two did not. Three articles described only facial nerve involvement, and the others described multiple cranial nerve involvement (especially the facial nerve and lower cranial nerves).

The outcome of MEO was analyzed in terms of cranial nerve involvement, regardless of the specific cranial nerve. The outcomes are shown in Figure 4. The included studies did not specifically define controlled and uncontrolled groups, but compared mortality. We deduced the complete remission and uncontrolled groups from the papers. A statistical evaluation was not included for all trials, and we based our calculations on the original reported data.

Figure 4. Meta-analysis for the outcome of cranial nerve involvement vs non-cranial nerve involvement in malignant external otitis

Study	Weights Fixed	Weights Random	Study Est	95% CI Lower	95% CI Upper
1. Chandler(1972)	0.44	0.24	45.33	2.39	859.30
2. Chen et al.(2010)	0.68	0.30	8.00	0.75	85.73
3. Franco-Vidal V.(2007)	0.37	0.22	21.14	0.86	520.01
4. Lee S. et al.(2008)	2.38	0.43	3.57	1.00	12.71
5. Mani N. et al.(2007)	0.37	0.22	6.50	0.26	162.96
6. Soudry E.et al.(2007)	0.80	0.32	0.17	0.02	1.55



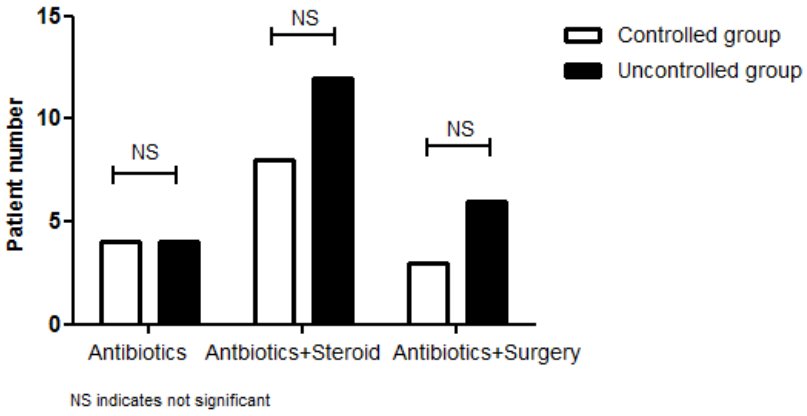
Using the given dichotomous data (controlled vs. uncontrolled groups), the combined OR (random effect model) was 4.537 (1.015–20.277). This suggests that cranial nerve involvement has a statistically significant effect on the prognosis of MEO. However, this result must be viewed with caution. First, the I^2 analysis shows variability of 0.581 and the combined OR (random effect model) showed a trend toward cranial nerve involvement associated with the prognosis of MEO. Second, there is no uniform definition of the outcome in MEO. As mentioned above, another meta-analysis of the "outcome" in the analysis of dichotomous data was not clarified, so we made deductions from the original data and sentences in the studies we reviewed. Third, we calculated the *p*-value if possible, although for Lee[12], statistical significance was deduced from hazard ratio and the *p*-value was presumed to be 0.05.

3. Prognostic factors relating to the treatment

After diagnosing MEO, effective treatment with antibiotics to which the microorganism is susceptible is important, such as quinolone and third-generation cephalosporins for *Pseudomonas aeruginosa* and vancomycin or targocid for methicillin-resistant *Staphylococcus aureus* (MRSA). Intravenous or oral steroid therapy was also used in skull base osteomyelitis or intractable otorrhea, anticipating the anti-inflammatory effect of steroid therapy. With cranial

nerve involvement giving rise to facial or vocal cord palsy, high-dose steroid therapy was also administered for the recovery of cranial nerve function. As most patients had DM, steroid therapy was risky and had to only be given with careful monitoring. Steroid therapy was unrelated to the outcome of MEO (p = 0.6299). Figure 5 provides the comparison of treatment modality between two disease-control groups.

Figure 5. Comparison of treatment modality between controlled group and uncontrolled group



Nine patients underwent surgery: three in the controlled group and six in the uncontrolled group. These were patients who did not respond to medical treatment. In the controlled group, two patients underwent a radical mastoidectomy, facial nerve decompression, and mastoid obliteration and the other patient underwent incision and drainage for a localized mastoid tip abscess. All three recovered from the infection and showed resolution of the disease, although recovery from the facial palsy was not complete. In the uncontrolled group, five patients underwent radical mastoidectomy and facial nerve decompression and the other patient required skull base surgery via an infratemporal fossa approach, type A. The surgery was helpful to the three patients in the controlled group, who were not responded to the medical

treatment, but there was no significant difference between the controlled and uncontrolled groups with respect to surgery(p=0.687).

The duration of hospitalization was 26.4±15.5 days in the controlled group, and 54.2±30.7 days in the uncontrolled group (p = 0.0082). Every patient in the controlled group was discharged within 60 days, while six patients in the uncontrolled group stayed for more than 60 days, and four of them died. The three patients died in hospital of an aspiration pneumonia attributed to malignant external otitis, the other patient died of sepsis.

IV. DISCUSSION

Malignant external otitis has become a treatable infectious disease with the development of new antibiotics. Nevertheless, once it progresses to skull base osteomyelitis or other complications, the prognosis worsens. Further, control of MEO is becoming more difficult with the emergence of resistant microorganisms and in immunocompromised patients, such as those with AIDS and malignancies. There have been cases of malignant external otitis in patients with AIDS, myelodysplasia and neoplasia, and in transplant patients reported[13, 14]. In our series, there were no other immunocompromised patients, except elderly diabetics.

Malignant external otitis arises most often in elderly patients with DM, the most common underlying disease in MEO patients. The duration of DM and the patient's serum glucose level were believed to be related to the prognosis of MEO. As reported by Joshua[15], MEO present of all obligatory clinical and radiological criteria was associated with a higher rate of oral antidiabetic treatment, history of diabetic complications, all of which led to significantly longer treatment and shorter survival. In contrast, Franco-Vidal V. *et al*. [16] reported diabetes was not a significant prognostic factor by itself. Chen [17] also suggested that the duration of diabetes and the degree of glucose tolerance were not factors affecting survival. But, our results

demonstrated that the existence of DM and a history of DM were important prognostic factors in MEO. Although the mean serum glucose level and HbA1c were unrelated to survival, the temporal glucose level was closely correlated with the disease course. Thus, strict sugar control is necessary. There were no significant difference of prognosis between the patients taking oral antidiabetes drugs and insulin-treated patients, which was not shown by our data.

It was not well established why the malignant external otitis involves mostly the diabetic patients but, microangiopathy was presumed to be the predisposing factor. Diabetes mellitus leads to microangiopathy and poor microcirculation and to impaired polymorphonuclear cell function[18, 19]. Furthermore, both chemotaxis of leukocytes and mechanisms of phagocytosis and intracellular digestion are impaired, and the production of antibiotics is reduced[20, 21]. Consequently, the transport of antibiotics to the infected region becomes less effective due to the small vessel obliteration and hypoperfusion. The existence and duration of DM and the ongoing glucose level all affect the progression of MEO in our series. We suggest that rigorous control of the glucose level and administering appropriate antibiotics are key for the treatment of MEO.

Skull base osteomyelitis is a life-threatening complication of MEO, which begins as a soft tissue infection of the external auditory canal and spreads via the fissures of Santorini and tympanomastoid suture to involve the cranial base[22]. The facial nerve is the most commonly involved cranial nerve due to its proximity to the EAC. As the disease advances to the medial skull base, it involves the jugular foramen and hypoglossal canal, so that the glossopharyngeal, vagus, spinal accessory, and hypoglossal nerves are affected. As Nadol reported, the disease spreads to the central skull base via four checkpoints: the EAC, stylomastoid foramen, jugular foramen, and petrous apex[6]. CT and MRI findings were helpful for diagnosing MEO at admission, but did not predict the prognosis of the MEO, as reported by Sudhoff[23]. In our series, there was a significant difference in outcome when the disease extended to the jugular foramen

and petrous apex. The prognosis was poor when greater disease extension is seen in imaging studies. We suggest that the jugular foramen and petrous apex are checkpoints for predicting the outcome and disease course of MEO from imaging studies. However, Daniel *et al*. reported an atypical presentation of MEO with extensive cranial neuropathy, but no facial paralysis [24]. So the disease does not always spread in the steps mentioned above. In our series, the jugular foramen was also skipped in two patients who had petrous apex involvement, while most of the patients followed the disease course set out above. In some ways, CT and MRI help to predict the prognosis of MEO, and the jugular foramen and petrous apex are critical points in the progression of MEO.

CT and MRI were preferred at initial diagnosis of MEO in our study, but those imaging studies have some limitations of monitoring the course of the disease[23]. In CT scan, the false negative may occur in initial stage of MEO[25, 26]. MRI is helpful for assessing the soft tissue disease and medullary bone involvement, but there is a limitation of assessing the malignant external otitis resolution[13]. There is a debate regarding the best imaging modality for initial diagnosis and monitoring of MEO. Nuclear medicine imaging(Tc-99m or Ga-67 scan) has also been used for the diagnosis and follow up of MEO. Tc-99m provides better information about inflammation and has a high sensitivity for diagnosing MEO and may be useful in early diagnosis. But, it is not specific for infection, it can also detect the malignancy. In addition, it cannot evaluate the precise anatomic location accurately and remain positive after resolution of the disease[23]. In contrast, Ga-67 citrate returns normal after the recovery, and can be useful for assessing the disease activity[27]. But it has also restriction of assessing the anatomical detail, and difficulty in initial diagnosis of MEO. Some authors have recommended Ga-67 citrate scan is a good indicator of resolution, and negativity is the sign to stop the treatment[28, 29].

Cranial nerve involvement was also believed to be related to the outcome of MEO, although cranial nerve involvement is a controversial prognostic factor. Several studies have

suggested that cranial nerve involvement is closely correlated with the outcome of the disease. Franco-Vidal V. *et al.*[16] and Lee S. *et al.*[12] reported that facial paralysis significantly influenced survival, while Mani N. *et al.*[8] reported that cranial nerve involvement did not affect the patient survival rate with optimized medical treatment. Chen reported that in patients with MEO, mortality was not related to involvement of a single cranial nerve, but was related to the involvement of multiple cranial nerves[17]. Soudry reported that although facial nerve involvement is a sign of MEO progression, it did not, by itself, worsen the prognosis in their case series[9]. We found no significant difference in the outcome of MEO with respect to any cranial nerve involvement or multiple cranial nerve involvement. Thus, we performed a meta-analysis of cranial nerve involvement and prognosis, which showed that cranial nerve involvement tended to affect the prognosis of MEO. However, our meta-analysis was limited in that it analyzed the data dichotomously, and only a few articles described cranial nerve involvement and the numbers of survivors and those with disease progression.

An increased ESR was identified as a useful tool when screening for MEO and monitoring the response to therapy[4, 30]. CRP is also an inflammatory marker that reflects the acute phase of inflammation. In our series, disease outcome was closely correlated with both the CRP and ESR. ESR and CRP can help to monitor the response to antibiotics. At admission, once MEO is suspected, laboratory data, including the ESR and CRP, should be checked and followed regularly until complete remission occurs.

Pseudomonas aeruginosa is the most common cause of MEO, although fungal infection and antibiotic-resistant microorganisms are also causes[25, 31]. In our series, MRSA was the second most common pathogen after *P. aeruginosa* and mixed polymicrobial infection was also found. Other studies were similar to our results as above[11, 13, 32]. The other pathogens such as enterococci, klebsiella pneumonia, and fungi were isolated in our series. Combined antibiotics covering polymicrobial infection were administered more frequently than a quinolone alone.

Ciprofloxacin or ceftazidime was used depending on the sensitivity of the organism and vancomycin, targocid, or teicoplanin was administered to patients infected with MRSA. In our series, the pathogen did not affect the prognosis of MEO.

Hospitalization duration was significantly correlated with the outcome of the disease in our study. However, this was not because of comorbidity or disease complications, as reported by Rothholtz *et al.* [33]. It was thought that the duration of hospitalization was prolonged by the effectiveness of the treatment. The poorer the response to antibiotics was, the longer the treatment duration and hospitalization were. Although the patients with a poor prognosis were hospitalized longer, a longer hospitalization does not necessarily mean a poorer prognosis.

We performed surgery in nine of our 28 patients. This involved a radical mastoidectomy and facial nerve decompression, or infratemporal fossa or skull base debridement of soft tissue or bone. In the controlled group, one patient underwent an incision and drainage of a mastoid tip abscess; the other two underwent a radical mastoidectomy and facial nerve decompression. In the uncontrolled group, one patient had skull base surgery via a type-A intratemporal fossa approach. Although the necrotic bone and soft tissue were debrided, the infection was not halted in the uncontrolled group. In contrast, the patients in the controlled group recovered fully after surgery, so the surgery helped some patients who had not responded to medical treatment completely and formed localized abscesses. Regardless, surgery was not directly related to the prognosis in the two groups. Any factor relating to the treatment did not affect the prognosis, including surgery, steroid therapy, and interval to the first proper treatment.

In conclusion, the major debating factors; glucose control in diabetes mellitus, disease extent in CT or MRI, cranial nerve involvement were all related to the prognosis of MEO. The prognosis of MEO could be predicted by performing physical examination, laboratary data, and imaging modalities at admission.

V. CONCLUSIONS

To verify the prognostic factor(s) of MEO, we have examined the final outcome related to prognostic factors of MEO. We found that glucose control in diabetes mellitus, cranial nerve involvement and disease extent in imaging modalities that were controversial previously were related to the prognosis of MEO. Glucose control in the patients with diabetes mellitus seems to be a critical factor in MEO. Laboratory data, including the ESR and CRP, as well as glucose level reflects the prognosis of MEO. Cranial nerve involvement was not a significant prognostic factor in our series, while it did predict the prognosis of MEO in the meta-analysis. And we suggest that the jugular foramen and petrous apex be used as checkpoints to identify severe disease progression and the prognosis. We propose that glucose control in DM, cranial nerve involvement, disease extent in imaging findings could be useful to clinically predict the outcome of MEO.

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ABSTRACT (IN KOREAN)

악성 외이도염에서 예후 인자의 분석

<지도교수 이원상>

연세대학교 대학원 의학과

김 보 경

악성 외이도염은 외이도, 측두골과 뇌기저부에 발생하는 매우 치명적인 감염질환이다. 항생제의 발달에도 불구하고 악성외이도염은 병이 악화되어 두개저 골수염으로까지 진행할 수도 있다. 그러나 아직까지 악성외이도염의 결정적인 예후인자에 대한 연구가 많지 않으며 이전부터 예후인자라 믿었던 몇몇 항목은 실제로 예후에 영향이 없었다는 보고도 있어 왔다. 본 연구의 목적은 악성외이도염의 예후인자를 후향적 연구를 통하여 분석하고 다른 연구들 간의 메타 분석을 통하여 예후인자를 규명하고자 하는 것이다. 우선, 본원에서 치료를 받은 총 28 명의 악성외이도염 환자를 후향적 의무기록 조사를 통해 비교 분석 하였다. 병의 진행 정도에 따라 12 명의 ‘controlled’ 그룹과 16 명의 ‘uncontrolled’ 그룹으로 각각 분류하였다. 예후 인자는 세가지 카테고리로 나누어 환자 요인, 질병 요인과 치료 요인으로 분류하였으며 두 그룹간에 각 요인을 비교 분석하였다. 본 연구 결과 당뇨 여부와 당뇨 기간, CRP 나 ESR 과 같은 염증 인자 및 CT 와 MRI 영상 결과는 악성 외이도염의 예후에 영향을 미치는 것을 확인하였다. 그러나 나이와 성별, 평균 당 수치, HbA1c, 병원균, 다른 기저질환, 뇌신경 침범 여부는 악성외이도염의 예후와 관계 없음을 보였다. 또한 수술 시행 여부와 스테로이드 사용 여부, 그리고 적절한 치료 시기까지의 기간과 같은 치료자 요인은 예후와 관련이 없다는 것을 확인하였다.

뇌신경 침범은 질병과 진행과 연관이 있다고 알려져 있으나 악성 외이도염의 예후와 관계 있는지는 아직 논란이 있다. 본 연구에서는 뇌신경 침범 여부가 악성 외이도염의 예후인자로써 의미가 있는지 다른 연구들의 메타분석을 시행하였다. 뇌신경 침범 여부는 질병의 진행뿐만 아니라 악성 외이도염의 예후와도 연관이 있음을 확인하였다. 따라서 본 연구에서는 악성외이도염의 예후인자 중 논란이 있는 당뇨여부와 당뇨 기간, 당 조절, CT, MRI 소견과 뇌신경 침범 여부가 모두 예후와 관계 있음을 확인하였다. 따라서 악성 외이도염의 예후를 평가 하기 위해서 임상적으로 상기 예후인자를 유용하게 사용할 수 있을 것이다.

핵심되는 말 : 악성 외이도염, 예후인자, 메타분석