대한두경부종양학회지
제 30 권 제 1 호 2014

Predictors of Distant Metastasis in Adenoid Cystic Cancer of Salivary Gland

Kang Woo Kim, MD, Yeon Soo Kim, MD, Kyoung Ho Oh, MD, Min Woo Park, MD, Jae-Gu Cho, MD, PhD, Seung-Kuk Baek, MD, PhD, Jeong-Soo Woo, MD, PhD, Kwang-Yoon Jung, MD, PhD, Soon Young Kwon, MD, PhD

Department of Otorhinolaryngology-Head and Neck Surgery, College of Medicine, Korea University, Ansan, Korea

타액선 선양낭성암종의 원격 전이 예측인자에 관한 연구

고려대학교 의과대학 이비인후과학교실

김강우 · 김연수 · 오경호 · 박민우 · 조재구 · 백승국 · 우정수 · 정광윤 · 권순영

= **국문초록** =

배경 및 목적

타액선 선양낭성암종은 느린 성장 속도와 늦은 원격 전이를 특징으로 하는 드문 상피성종양이다. 본 연구는 다양한 임상 병리학적 변수를 통해 선양낭성암종의 원격 전이에 영향을 주는 인자를 조사하고자 하였다.

대상 및 방법

1999년 10월부터 2011년 12월까지 본원 이비인후과에서 타액선 선양낭성암종으로 진단되어 치료 받은 44명(남자 19명, 여자 25명)을 대상으로 원격전이를 유발하는 위험 인자를 조사하였다. 8명의 환자는 배제 기준에 따라 제외하였다. 환자의 평균 연령은 54세였다. 환자의 병리 보고서, 종양의 크기, T 병기, 수술 절제연의 종양 존재 유무, 신경 조직 침습, 림프절 전이가 조사되었다.

결 과

15명의 환자가 원격전이가 있었으며 21명은 원격 전이가 없었다. 원격 전이를 유발할 수 있는 여러 인자들을 비교하였을 때, 원격 전이는 수술 절제연의 종양 세포 잔존(p=0.014), 종양의 크기(p=0.038), 진행된 T 병기(p=0.024) 가 통계적으로 유의하게 연관성이 있었다. 림프절 전이와 신경 조직 침습은 원격 전이와 연관이 없었다.

결 론

종양의 크기, 진행된 T 병기, 수술 후 절제연의 종양 세포 잔존은 원격 전이의 예측 인자로 생각된다. 따라서 이에 해당하는 환자의 경우 더욱 철저한 관리 및 경과 관찰을 요한다.

중심 단어 : 선양낭성암종 · 원격 전이 · 예측 인자.

Introduction

Adenoid cystic carcinoma(ACC) is not a common tumor that originates within the major and minor salivary glands, accounting for 1–2% of all head and neck malignancies.[1,2] However, ACC is the second most common malignant tumor(30%) of the major salivary glands.[3] The most prominent histopathologic feature is a pseudocyst that is a rounded extracellular space containing basal lamina.[4] ACC has been known to have a delayed clinical course with a slow growth and a late development of metastasis.[2,5] In contrast to squa-

Received : December 11, 2013 / **Revised** : April 1, 2014
Accepted : April 1, 2014
교신저자 : 권순영, 425-707 경기도 안산시 단원구 적금로 123
고려대학교 의과대학 안산병원 이비인후과학교실
전화 : (031) 412-4920 · 전송 : (031) 412-5174
E-mail : entkwon@korea.ac.kr

mous cell carcinoma, lymphatic and local spreads are rare. However, perineural invasion, tendency of distant metastasis(DM) and ability of recurrence over a prolonged period have been noted.[6)]

The treatment of ACC is surgical excision with free margin. The efficacy of postoperative radiation therapy has not yet been fully defined, and indications for its use vary depending on the institutes. Recent studies have suggested that combined therapy of surgery followed by radiation is considered to be the standard of treatment for ACC.[7,8)] The overall 5-year survival for ACC patients was 90.3%.[1)] The overall 10-year and 15-year survival rates were only 79.9% and 69.2% as DM can develop more than 10 years after the initial treatment.[1)] Therefore, long term follow-up should be done, and factors that predict the recurrence are needed.

The purpose of the present study was to investigate the factors that influence DM in ACC with multiple clinical and pathological variables retrospectively.

Materials and Methods

Medical records of 44 patients with ACC of salivary glands in the departments of otolaryngology at Korea University Anam, Guro, and Ansan Hospitals between October 1999 and December 2011 were retrospectively reviewed. The cohort included 23 females(64%) and 13 males(36%). The age at diagnosis ranged from 28 to 78 years, with a median age of 54 years. The median period of follow-up was 31 months, and the patients were selected who had been visited our hospital at least during 12 months. The maximal period of follow-up was 110 months. Diagnosis of ACC was confirmed by histopathologic evaluation of the specimen obtained during the operation. Pretreatment evaluation included past medical history and physical examination of the patients. Diagnostic imaging of the primary lesion included CT and MRI. Eight patients who did not receive combined therapy of surgery followed by radiation therapy or had incomplete medical records were excluded from the study. When lymph node metastasis was suspected, the neck dissection was performed. The median follow-up period was 45.3 months. Clinical and pathologic data, including age, tumor T stage, tumor size, overall American Joint Committee on Cancer(AJCC 2011) stage, the involvement of resection margin, the sites of metastasis were collected. Primary site of ACC was classified into parotid, submandibular gland, and minor salivary gland. Data regarding the presence of involvement of the resection margin and perineural invasion were obtained from pathology reports. Clinical stage of the tumors was evaluated according to the AJCC. The evaluation for DM was done with imaging studies including Torso PET-CT, chest CT, and bone scan.

Statistical analysis was performed with SPSS(version 12.0, Chicago, IL, USA). One-tailed Mann Whitney U test was used to identify the interrelationship, among age, tumor size, and DM. Correlations between clinical variables(gender, primary site, resection margin, perineural invasion, metastatic node) were assessed via Pearson's chi-square test or, where there are fewer than 10 subjects in any cell of a 2×2 grid, via two-tailed Fisher exact test. A p value$<$0.05 was considered statistically significant.

Results

Characteristics of ACC are presented in Table 1. Most common primary site of ACC is minor salivary gland, our research was so. Because adenoid cystic carcinoma usually was considered as high risk salivary cancer, all patients were undergone surgery followed by radiation therapy. No patients underwent chemotherapy as part of their treatment regimen. Fifteen patients had neck dissection as part of surgery. Histopathological results evaluated included resection margin and perineural invasion. Twenty two patients presented positive resection margin(61.1%). Clear margins were seen in 14 patients(38.9%). Eighteen patients showed positive perineural invasion(50%), and 18 had negative perineural invasion(50%). Fifteen patients developed distant metastasis in spite of de-

Table 1. Characteristics of ACC

Primary site	No.(%)
Parotid	3(8.3)
Submandibular gland	5(13.9)
Minor salivary gland	28(77.8)
T stage	
T1	10(27.8)
T2	6(16.7)
T3	4(11.1)
T4a	11(30.6)
T4b	5(13.9)
Tumor size	
0−1 cm	4(12.5)
1−2 cm	10(31.2)
2−3 cm	4(12.5)
3−4 cm	5(15.6)
4< cm	9(28.1)

Table 2. Correlation of DM with clinical parameters

	DM(+)	DM(−)	p value
Sex			
Female	9	14	0.736
Male	6	7	
*Age(year)	55.98	53.81	0.860
*Tumor size(cm)	3.63	2.55	0.038
Primary site			
Parotid	1	2	0.948
Submandibular gland	2	3	
Minor salivary gland	12	16	
Resection margin			
Positive	13	9	0.014
Negative	2	12	
Perineural invasion			
Positive	10	8	0.176
Negative	5	13	
Lymph node metastasis			
Positive	2	3	1.000
Negative	13	18	
T stage			
T1	1	9	
Advanced T stage	14	12	0.024
N stage			
N0	12	17	1.000
Advanced N stage	3	4	

* : Age and tumor size are continuous variables. One-tailed Mann Whitney U test was used to identify the relationships among age, tumor size, and DM

finitive treatment. The most common site for DM was lung (93.3%), followed by rib(6.7%).

Upon comparison of specific variables with the development of DM, it was found that involved resection margin(p=0.014), tumor size(p=0.038), advanced T stage(p=0.024) had statistically significant correlations with the development of DM(Table 2). Major salivary gland tumor had a lower rate of DM than minor salivary gland tumor, however there was no statistically significant. Lymph node metastasis and perineural invasion had no correlation with DM(Table 2).

Discussion

ACC is a rare and indefinite cancer characterized by a protracted natural history of slow growth, and DM can cause death 1 to 2 decades after definitive treatment.[2,5] Therefore, a further understanding of the progress and biological behavior of ACC is important. Over the last decade, there have been many attempts to find the prognostic factors and the predictors for DM of ACC. Clinical prognostic factors about DM and recurrence include tumor site, increasing size and stage of tumor, solid histological features, positive margins at surgery, and perineural invasion.[2,3,5,9,10] There is no consensus about the key prognostic factors for DM. This study was designed to investigated distant metastatic factors to predict the progress of ACC. In this study, larger tumor size, advanced T stage and involvement of resection margin are thought to be predictors for DM.

Tumor size was analyzed as a continuous variable. It was found to be a predictor of DM. This result was contrary to the previous reports.[11] This study also revealed that advanced T stage contributes to the DM. Larger tumor size and more advanced T stage mean more aggressiveness of the tumors, and it might be more difficult to achieve free resection margin.

The adequacy of surgical resection did seem to influence distant metastatic spread. Though several studies were reported no statistically significant correlation between resection margin and DM,[2,7,11] it was not same in this study. Microscopic remnant tumor might affect the DM. Adam et al.[8] recommended a dose of 66 Gy radiotherapy with positive resection margin. Allen et al.[7] reported that combined therapy with surgery followed by radiotherapy in doses more than 60 Gy should be considered the standard treatment for ACC. Therefore, further comparative analysis of relationship between radiotherapy dose and DM is needed.

Correlation between perineural invasion and DM is still controversial. Rapidis et al.[11] suggested that perineural invasion facilitates distant metastatic spread. But Van der Wall[12] reported that there seems to be no statistically significant correlation between the two parameters. It seems not to be perineural invasion correlate with DM in this study. Although the proportion of patients who had DM was higher in patients with perineural invasion, the result was not statistically significant. Some reports suggested that perineural invasion in local control is more significant than those with distant control.[8]

This study has a limitation due to its small numbers of patients. Multivariate analysis could not be done due to small numbers of patients. ACC is need to follow up during long period. Mean follow-up period was 41 months in our study. Survival analysis due to the short follow-up period was difficult. There are wide variations in follow-up periods, and patients who were diagnosed recently had short follow-up periods. Tumor size and T stage, however, were found to be important to predict the progress of ACC. The adequacy of surgical resection is also significant.

Conclusion

Patients with risk factors such as large tumor size, advanced T stage and involved resection margin are more likely to develop DM. Therefore more comprehensive managements should be recommended in these situations.

References

1) Ellington CL, Goodman M, Kono SA, Grist W, Wadsworth T, Chen AY, et al. *Adenoid cystic carcinoma of the head and neck: Incidence and survival trends based on 1973-2007 Surveillance, Epidemiology, and End Results data. Cancer; 2012.*
2) Oplatek A, Ozer E, Agrawal A, Bapna S, Schuller DE. *Patterns of recurrence and survival of head and neck adenoid cystic carcinoma after definitive resection. The Laryngoscope. 2010;120 (1):65-70.*
3) Bhayani MK, Yener M, El-Naggar A, Garden A, Hanna EY, Weber RS, et al. *Prognosis and risk factors for early-stage adenoid cystic carcinoma of the major salivary glands. Cancer. 2012;118 (11):2872-2878.*
4) Lawrence JB, Mazur MT. *Adenoid cystic carcinoma: A comparative pathologic study of tumors in salivary gland, breast, lung, and cervix. Human Pathology. 1982;13(10):916-924.*
5) Fordice J, Kershaw C, El-Naggar A, Goepfert H. *Adenoid cystic carcinoma of the head and neck: Predictors of morbidity and mortality. Archives of Otolaryngology--Head & Neck Surgery. 1999;125(2):149-152.*
6) DeAngelis AF, Tsui A, Wiesenfeld D, Chandu A. *Outcomes of patients with adenoid cystic carcinoma of the minor salivary glands. International Journal of Oral and Maxillofacial Surgery. 2011;40(7):710-714.*
7) Chen AM, Bucci MK, Weinberg V, Garcia J, Quivey JM, Schechter NR, et al. *Adenoid cystic carcinoma of the head and neck treated by surgery with or without postoperative radiation therapy: Prognostic features of recurrence. International Journal of Radiation Oncology, Biology, Physics. 2006;66(1):152-159.*
8) Garden AS, Weber RS, Morrison WH, Ang KK, Peters LJ. *The influence of positive margins and nerve invasion in adenoid cystic carcinoma of the head and neck treated with surgery and radiation. International Journal of Radiation Oncology, Biology, Physics. 1995;32(3):619-626.*
9) Barrett AW, Speight PM. *Perineural invasion in adenoid cystic carcinoma of the salivary glands: a valid prognostic indicator? Oral Oncology. 2009;45(11):936-940.*
10) Sequeiros Santiago G, Rodrigo Tapia JP, Llorente Pendas JL, Suarez Nieto C. *[Prognostic factors in adenoid cystic carcinoma of salivary glands]. Acta Otorrinolaringologica Espanola. 2005; 56(8):361-367.*
11) Rapidis AD, Givalos N, Gakiopoulou H, Faratzis G, Stavrianos SD, Vilos GA, et al. *Adenoid cystic carcinoma of the head and neck. Clinicopathological analysis of 23 patients and review of the literature. Oral Oncol. 2005;41(3):328-335.*
12) van der Wal JE, Snow GB, van der Waal I. *Intraoral adenoid cystic carcinoma. The presence of perineural spread in relation to site, size, local extension, and metastatic spread in 22 cases. Cancer. 1990;66(9):2031-2033.*