

Adenoid Cystic Carcinoma of the Parotid and Submandibular Glands : A Comparative Study

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= 국 문 초 록 =

선양낭암은 타액선종양중 비교적 드문 악성종양으로 병리조직학적 및 임상적으로 독특한 양상을 보인다. 병리조직학상 종양세포가 신경주변으로 침범하여 수술당시 적절한 수술연을 얻기 어렵고 이에 따른 국소재발이 거듭되고 임파선전이 및 예측치 않는 원격전이가 생기기도 한다.

지금까지 선양낭암환자의 예후에 영향을 미치는 여러 요인들에 대한 연구들이 이루어지고 있는데 그중 조직학적 분화도, 원발부위, 종양의 크기, 수술연의 상태와 임상적 병기들이 중요시되고 있다.

이에 저자들은 1960년부터 1980년 까지 텍사스대학 M.D. Anderson 암센터에서 치료받은 이하선 및 악하선 선양낭암 각각 13례와 26례를 대상으로 원발부위가 환자의 생존 및 치료에 미치는 영향을 알고자 다른 예후인자로 알려진 조직병리학적 소견들과 함께 통계학적 분석을 실시하였다.

이하선과 악하선에 생긴 선양낭암을 비교한 결과 이하선에 생긴 경우 조직학적 분화도가 더 낮았고 악하선 종양에서 수술연에 종양침범율이 더 적었다. 경부 임파절 전이는 악하선 종양에서 많았으나 반면 원격전이는 이하선 종양에서 더 많이 발생하였다. 그러나 종양의 크기, 신경주위침범 유무, 국소재발과 환자의 생존율사이에는 유의있는 상관 관계는 없었다.

이하선과 악하선에 생긴 선양낭암의 여러 특성들과 생존률간의 univariate 분석결과 악하선에 생긴 선양낭암 환자에서 종양이 크거나 조직학상 분화가 나쁘거나(solid pattern),

경부임파절 전이와 원격전이가 생기면 예후에 나쁜 영향을 끼침이 밝혀졌다. 그러나 이하선에 생긴 경우 분석례가 너무 적어 결론을 내리기에 불충분하였다.

원발부위에 따른 선양낭암 환자들의 특성을 chi-square 검정법을 이용하여 통계학적으로 분석한 결과 이 두군간에는 유의있는 통계학적 차이는 발견할 수 없었다.

KEY WORDS : Adenoid cystic carcinoma · Parotid · Submandibular.

Introduction

Adenoid cystic carcinomas(ADCs) are relatively uncommon malignant salivary gland neoplasms. The tumor accounts for 2-6% of all parotid gland neoplasms, 15% of submandibular gland neoplasms and 30% of minor salivary gland tumors¹⁾. ADCs are characterized by their prolonged clinical course with frequent local recurrences and late distant metastases¹⁾. Evidence exists that histologic features, in addition to primary site, size, and clinical stage, provide prognostically important information in ADC²⁻⁹⁾. An important prognostic parameter is the primary site of the carcinoma. The location of the neoplasm alters survival. Most authors agree that sinonasal ADCs behave more aggressively and are more lethal than those arising in the palate and major salivary glands⁸⁾⁹⁾¹⁰⁾. Among major glands, it has been generally believed that submandibular ADCs have worse prognosis than their parotid counterparts²⁾⁴⁾⁵⁾⁹⁾¹¹⁻¹⁴⁾. However, no difference between these two sites was reported by Perzin et al⁷⁾ and Koka and associates¹⁵⁾.

We have reviewed our material to determine if ADCs of the parotid gland behave less aggressively than their submandibular counterparts. For this purpose we performed a statistical comparison between various histologic parameters in 13 parotid and 26 submandibular ADCs.

Materials and Methods

The study population consists of 13 patients with ADC of the parotid gland and 26 patients

with submandibular gland ADC. These patients were diagnosed and treated at M.D. Anderson Cancer Center between 1961 and 1984. In this study, all patients were observed for a minimum of one to 21 years (average, 6.6 years) after treatment.

A minimum of 2 and an average of 3 (two to five) sections stained with hematoxylin and eosin were examined without previous knowledge of the clinical course. The histologic pattern of the ADCs was classified into 3 grades, in accordance with the criteria used by Batsakis, et al¹⁶⁾. During the histological review, observations were recorded concerning presence of perineural invasion. Extension of the carcinoma to paraglandular structure, status of surgical margins of excision and metastases to regional lymph nodes were also evaluated. Neural invasion was further evaluated according to extension of involvement : 1) extensive when the perineural involvement was multiple and easily identified and 2) non-extensive when it was focal and invaded nerves measuring less than 0.25mm in diameter. The clinical charts were reviewed for patient demographics, size of the lesion, treatment, and follow-up status. Prognosis was evaluated and related to each primary site of tumor by the date of the first treatment to the time of the patient's death or to the date was last seen. Patients who died of disease were considered failures, and survival time was calculated as the length of time between treatment and death. All other patients(including those who died of other causes) were censored, and survival time was calculated as the time from treatment to the last date of contact.

Statistical Analysis

Statistical comparisons of ADC by primary sites were made with Fisher's Exact Test (two-tailed) to calculate the significance of values. The Kaplan-Meier method¹⁷⁾ was used to plot survival curves, and the prognostic effect of a variable was tested using the log-rank test.

Results

The parotid ADC comprised of 8 males and 5 females. At the time of histopathologic diagno-

sis, the patients' age ranged from 16 to 79 years (median, 53 years). Tumor size ranged from 1.0 to 6.0cm (median, 3.0cm). Based on the histologic criteria of Batsakis et al(1990), four patients (31%) had grade II tumors while the remaining had grade III neoplasms. Perineural invasion was present in 12 of 13 ACC. In 7 carcinomas, the perineural invasion was extensive and involved numerous small and occasionally large nerves. The surgical margins were free for 7 patients(54%) and involved for 6 patients(46%). Extraglandular extension was present in the majority(85%) of the tumors, while regional lymph node metastases were noted in only 2 patients(Table 1).

Table 1. Clinicopathologic summary of adenoid cystic carcinoma of the parotid and submandibular gland

Characteristics	No. of patients(%)	
	Parotid gland	Submandibular gland
Patients	13	26
Sex, M : F	8 : 5	13 : 13
Median age at diagnosis, years(range)	53(16-79)	58(11-87)
Median size of neoplasm, cm(range)	3.0(1.0-6.0)	3.2(1.5-6.3)
Tumor size, cm		
<4cm	9(69%)	15(58%)
≥4cm	4(31%)	11(42%)
Histologic Grade		
I	0	4(16%)
II	4(31%)	12(46%)
III	9(69%)	10(38%)
Surgical Margins		
Free	7(54%)	20(77%)
Involved	6(46%)	6(23%)
Perineural Invasion		
Extensive	7(54%)	12(46%)
Non-Extensive	5(39%)	13(50%)
No Invasion	1(8%)	1(4%)
Extra-glandular Extension		
Present	11(85%)	23(88%)
Absent	2(15%)	3(12%)
Regional Lymph Node Metastases		
Present	2(15%)	7(27%)
Absent	10(77%)	19(73%)
Unknown	1(8%)	0

Local Recurrence		
Present	2(15%)	3(12%)
Absent	11(85%)	23(88%)
Distant Metastases		
Present	8(62%)	10(38%)
Absent	4(31%)	16(62%)
Unknown	1(8%)	0
Metastatic Site		
Liver	1(8%)	1(4%)
Lung	6(46%)	5(23%)
Brain	1(8%)	0
Bone	0	2(12%)
Lung & bone	0	1(4%)
Overall Status		
Living without evidence of carcinoma	2(15%)	11(42%)
Median, mo(No. of mo alive)	(144, 254)	73(39-214)
Dying of other causes(DOC)	3(23%)	3(12%)
Median, mo(mo of death)	174(140,167,215)	43(12,59,60)
Living with carcinoma(LWD)	2(15%)	3(12%)
Median, mo (No. of mo alive)	89,211	53(48,51,60)
Dying of Carcinoma(DOD)	6(46%)	9(35%)
Median, mo(range)	69(20-145)	35(11-60)
Survival Status		
Alive or DOC	5(39%)	14(64%)
DOD or LWD	8(61%)	12(46%)

Total or subtotal parotidectomy was performed in each of the 13 patients. Eight patients received radiation postoperatively. Eleven patients underwent neck dissection. Follow-up information was available for all patients. Median follow-up from the date of diagnosis is 140 months for all thirteen Pavotid & ADC patients. Two patients (15%) are living with no evidence of disease and have been followed for 144 and 254 months from the time of initial treatment. These patients had grade II carcinoma with pushing pattern. Their carcinomas were confined within the gland at the time of superficial parotidectomy. Irradiation was administered postoperatively.

There was no recurrence or distant metastases thereafter. Two patients are living with disease and have follow-up of 89 and 211 months; three (23%) died of causes unrelated to their ADC at

140, 167 and 215 months; and 6 (46%) died of disease after surviving from 20 to 145 months (median 69 months). Two patients had local recurrences and 8 had distant metastases (six to lungs, one to the brain, and one to the liver).

The two patients with local recurrence had tumor with perineural invasion and extraglandular extension. The surgical margin was positive and they received postoperative irradiation. One patient is living with distant metastases after 17 years and the other died of carcinoma 24 months after initial treatment. For patients with distant metastases, median survival was longest with pulmonary metastases (108 months), followed by patients with liver metastases (86 months).

The submandibular ADC comprised of 13 males and 13 females. At the time of histopathologic diagnosis, the patients' age ranged from 11 to

87 years (median, 53 years). The resected primary carcinomas measured from 1.5 to 6.3cm (median, 3.2cm). Four of the primary submandibular gland ADC were grade I, 12 grade II, and ten grade III. Perineural invasion was present in 25 of 26 ADC. In 12 carcinomas, the perineural invasion was extensive. The surgical margins were free for 20 patients (77%) and involved for 6 patients (23%). Extraglandular extension was observed in 23 of 26 ADCs. Lymph node metastases were present in seven patients at the time of the definitive operative procedure.

Submandibular triangle dissection was the primary treatment in each of the 26 patients. Ten patients received radiation postoperatively. Twelve patients underwent neck dissection. Follow-up information was available for all patients. The median follow-up from the date of initial treatment was 49.5 months (range, 12 to 214 months). At the time of the preparation of this report, three patients had local recurrences and 10 had distant metastases (five to lungs, two to the bones, one to the liver, and two to the lungs and bones). Of the three patients with local recurrence two

Table 2. Clinicopathologic characteristics of patients with adenoid cystic carcinoma of the parotid gland and outcome

Group	No. of patients	No. of deaths	Median survival (months)	Log rank P-Value
Overall	13	6	145	
Tumor size				
<4cm	9	4	*	0.66
≥4cm	4	2	*	
Histologic grade				
I	0	0		
II	4	1	*	0.22
III	9	5	86	
Surgical margins				
Free	7	3	*	
Involved	6	3	145	
Perineural invasion				
Extensive	7	3	*	
Non-Extensive	5	3	145	0.66(a)
No Invasion	1	0	*	0.82(b)
Extra-glandular extension				
Present	11	6	145	0.24
Absent	2	0	*	
Regional lymph node metastases				
Present	2	1	*	
Absent	10	4	*	0.97(c)
Unknown	1	1	71	
Metastatic site				
Liver	1	1	86	
Lung	6	4	108	0.65
Brain	1	0		

(a) Extensive vs. Non-Extensive vs. No Invasion

(b) Extensive vs. Non-Extensive

(c) Present vs. Absent

had tumor longer than 4cm, were grade III, exhibited extensive perineural invasion and extraglandular extension, and the lymph nodes were positive. Both patients expired of their tumor 46 and 120 months, respectively, after the initial treatment.

The other patient had a small tumor (less than 2cm) and extensive perineural invasion and extraglandular extension, but the lymph nodes were negative. Patient is alive and well 120 months after resection of recurrence. For patients with distant metastases, median survival was longest for those with pulmonary metastases(60 months), followed by patients with bone metastases(35 months) and liver metastases(11 months). Eleven patients (42.0

%) were alive and without evidence of disease from 39 to 214 months after treatment(median, 73 months). Three patients are living with carcinoma(48, 51, and 60 months). Nine had died of their disease, 11 to 60 months after treatment (median, 35 months). The remaining three patients died of other causes and without clinical evidence of recurrence or metastases at 12, 59, and 60 months.

Comparison of ADCs of the parotid and submandibular glands in the present study(Table 1) revealed that the parotid gland had a higher number of high grade carcinomas than the submandibular gland. Free surgical margin and regional lymph node metastases were higher in the subma-

Table 3. Clinicopathologic characteristics of patients with adenoid cystic carcinoma of the submandibular gland and outcome

Group	No. of patients	No. of deaths	Median survival (months)	Log rank P-Value
Overall	26	9	*	
Tumor size				
<4cm	15	0	*	0.001
≥4cm	11	9	35	
Histologic grade				
I	4	0	*	
II	12	2	*	
III	10	7	37	
Surgical margins				
Free	20	3	*	
Involved	6	4	*	
Perineural invasion				
Extensive	12	6	*	
Non-Extensive	13	3		
No Invasion	1	0	*	
Extra-glandular extension				
Present	23	9	*	0.21
Absent	3	0	*	
Regional lymph node metastases				
Present	7	6	35	0.001
Absent	19	3	*	
Metastatic site				
Bone	3	3	35	
Liver	1	1	11	0.001
Lung	6	4	60	

Table 4. Statistical comparison of adenoid cystic carcinoma of the parotid and submandibular gland

Characteristic	Parotid Gland	Submandibular Gland	Chi-square P-Value
Total	13	26	
Sex			
Male	8(62 %)	13(50 %)	0.50
Female	5(38 %)	13(50 %)	
Tumor size			
<4cm	9(69 %)	15(58 %)	0.48
≥ 4cm	4(31 %)	11(42 %)	
Histologic Grade			
I or II	4(31 %)	16(62 %)	0.07
III	9(69 %)	10(38 %)	
Surgical margins			
Free	7(54 %)	20(77 %)	0.14
Involved	6(46 %)	6(23 %)	
Perineural invasion			
Extensive	7(54 %)	11(48 %)	0.56
Non-Extensive	5(39 %)	12(52 %)	
Extra-glandular extension			
Present	11(85 %)	23(88 %)	0.73
Absent	2(15 %)	3(12 %)	
Regional lymph node metastases			
Present	2(17 %)	7(27 %)	0.49
Absent	10(83 %)	19(73 %)	
Local recurrence			
Present	2(15 %)	3(12 %)	0.73
Absent	11(85 %)	23(88 %)	
Distant metastases			
Present	8(67 %)	10(38 %)	0.11
Absent	4(33 %)	16(62 %)	
Metastatic site			
Bone	0(0 %)	3(30 %)	Not Calculated
Liver	1(13 %)	1(10 %)	
Lung	6(75 %)	6(60 %)	
Brain	1(13 %)	0(0 %)	
Overall status			
NED	2(15 %)	11(42 %)	Not Calculated
DOC	3(23 %)	3(12 %)	
LWD	2(15 %)	3(12 %)	
DOD	6(46 %)	9(35 %)	
Survival status			
Alive or DOC	5(39 %)	14(54 %)	0.48
DOD or LWD	8(61 %)	12(46 %)	

ndibular gland ADCs, but the distant metastases were higher in the parotid carcinomas. However, there was no significant difference in the tumor size, perineural invasion, local recurrence, and the survival status.

The results of the univariate analyses of survival on parotid ADC and submandibular ADC are presented in Table 2 and 3, respectively.

Among the parotid patients, there was no statistical evidence that any of the characteristics evaluated were of prognostic significance. However, the number of cases involving the parotid gland was too small to draw definite conclusions. Among the patients with submandibular carcinoma, large size of tumor, solid pattern, regional lymph node metastases, and metastases were

found to be the important prognostic variables.

Statistical comparisons of the distribution of various patient characteristics by primary site were made using the chi-square test, and the results are given in Table 4. Pvalues less than some chosen cut-off point (typically 0.05), indicate a skewed distribution, or in statistical terms, lack of independence between the primary site and the variable being tested. With regards to a comparison of survival by primary site, there was no statistically significant difference between the groups ($P=0.74$, Fig. 1). The limited size of the study, particularly with regards to the parotid patient group, limits the power to detect significant differences between groups.

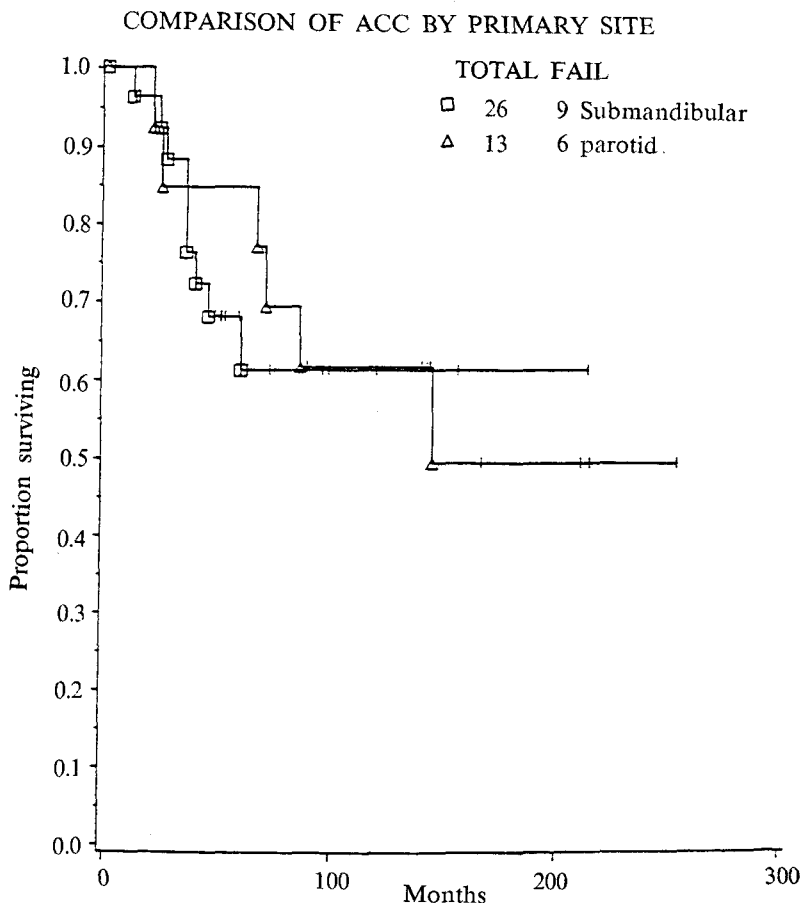


Fig. 1. Comparison of survival in adenoid cystic carcinoma patients by primary site.

Discussion

The clinical behavior of ADC is variable and difficult to predict. Data on local recurrence, spread and survival are somewhat contradictory. The best available predictors of patient outcome are the size of the carcinoma and the clinical stage at presentation²⁾³⁾¹⁸⁾. In addition, several histologic parameters have been employed without uniform results⁴⁻⁹⁾.

The location of the carcinoma is also important as far as the prognosis is concerned¹³⁾. Sinonasal ADCs have an extremely poor prognosis as compared to those occurring in the palate or in the major salivary glands⁸⁾⁹⁾¹³⁾. Although earlier experiences indicate that patients with parotid ADCs had a better survival rate than those with submandibular gland carcinomas, our results indicate that there was no statistically significant differences between these two major salivary glands. This finding is in accord with the finding of Spiro³⁾, Perzin⁷⁾, and Koka¹⁵⁾, but differs from those of Spiro¹²⁾¹³⁾ and Seaver et al¹⁴⁾.

In the current series, we found that the parotid ADCs had a higher frequency of high grade carcinomas than the submandibular counterparts. Free surgical margins and regional lymph node metastases were more frequent in the submandibular ADCs, but distant metastases were higher in the parotid carcinomas. However, there was no significant difference in tumor size, perineural invasion, extraglandular extension, local recurrence, and the overall survival.

As with salivary gland carcinomas of any histologic type, the size of the neoplasm and the clinical stage were the most important prognostic factors. Our findings clearly indicate that tumors 4 cm or larger are particularly ominous. Locoregional control was obtained with much greater frequency in patients with smaller primary neoplasms. These findings are in agreement with those

of Spiro, et al³⁾. In the current series, large tumor size, regional lymph node metastases, and distant metastases were found to be the most important prognostic variables in the submandibular ADCs ($p=0.0001$).

The identification of histologic parameters in predicting the biologic behavior of ADCs is being better defined. Some of the histologic parameters that have been reported to influence prognosis are a dominant morphologic pattern, histologic grading, and perineural invasion.

Until now, two histologic parameters, the predominant morphologic pattern (tubular, cribriform, or solid) and histologic grading, have been the most frequently used to correlate with the prognosis of ADC. Histologic grading, according to the aforementioned architectural patterns, has been attempted by several authors, without uniform results. However, indications are the tubular pattern is associated with a better prognosis and that the solid pattern is associated with a poorer one. Solid pattern ACC has overall worst prognosis in terms of distant metastasis and long-term survival⁶⁾⁷⁾⁹⁾¹⁰⁾¹⁹⁾. Santucci and Bondi¹⁰⁾ proposed neoplastic growth type (pushing/infiltrating) as a new parameter prognostically significant in ADC. The predominant morphologic pattern along with other parameters, such as the type of growth and the perineural invasion, seemed to provide a good basis for evaluating the outcome of ADCs¹⁰⁾. A characteristic feature of ADCs is the perineural invasion. The frequency of perineural invasion is perhaps an important factor in local recurrence²⁰⁾ but, paradoxically, it does not appear to lead necessarily to a reduction in survival prospects. In this study, the perineural invasion, even extensive, did not affect overall survival.

We did not specifically investigate modes of therapy as part of the current study. Our major purpose was to investigate the influence on prognosis of primary site and its relation to various

histologic parameters. However, the local control of ADC was significantly improved with the addition of postoperative radiation therapy following adequate surgical resection⁸⁾¹⁵⁾, but does not alter the survival¹⁵⁾²¹⁾. The incidence of distant metastases remains high after introduction of postoperative radiotherapy and the ultimate outcome is poorly predictable. Distant metastases can develop despite local and regional disease control. The onset of metastases is unpredictable. Distant metastases can occur more than 10 years after the initial treatment⁵⁾.

Currently, distant metastases are poorly controlled and usually implies an exceedingly poor prognosis.

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