Postoperative Adjuvant Radiotherapy for Adenoid Cystic Carcinoma of the Head and Neck: Treatment Results and Prognostic Factors

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Background: To analyze the treatment results and prognostic factors of patients with adenoid cystic carcinoma (ACC) arising from the major and minor salivary glands of the head and neck, and who received postoperative radiotherapy after radical tumor resection.

Methods: Between October 1987 and December 1999, 25 patients with ACC of the head and neck were treated with radical surgical resection and postoperative adjuvant irradiation without chemotherapy. Using appropriate radiation techniques to the tumor bed, total doses ranged from 44 to 68.4 Gy. All patients had a minimum of 2 years of follow-up.

Results: The 5-year overall survival rate, local control rate, and distant metastasis-free rate were 75%, 83%, and 66%, respectively. To the present, 2 patients had experienced recurrence at the primary sites, and 1 had regional lymph node metastasis. Distant metastases developed in 7 patients (28%), of whom 6 (86%) were disease-free at the primary site. The lung was the most common distant metastatic site. In multivariate analysis, the only statistically significant prognostic factor for a distant metastasis-free rate was the stage at presentation ($p = 0.009$).

Conclusion: Patients with an advanced stage of disease had higher distant metastasis rates even when receiving postoperative radiotherapy. Distant metastasis is still the main problem in the management of ACC of the head and neck. However, more-effective treatment for this problem is still lacking.
(Chang Gung Med J 2003;26:646-53)

Key words: **adenoid cystic carcinoma, postoperative radiotherapy, prognostic factors.**

Adenoid cystic carcinoma (ACC), which accounts for less than 1% of all head and neck malignancies and approximately 10% of all salivary neoplasms,[1,2] was first described by Billroth[3] in 1856 and was called cylindroma because of its unique histologic pattern. ACC of the head and neck shows a long natural course, high recurrence rates, late metastasis, and a tendency for perineural invasion.[4-7] Although surgery is the main treatment for ACC of the head and neck, postoperative radiotherapy is often recommended because tumors without well-defined borders easily infiltrate into adjacent tissues.[8]

In this retrospective study, we reviewed treat-

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Received: Jan. 21, 2003; Accepted: Apr. 30, 2003
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ment results and prognostic factors of 25 patients with ACC of the head and neck treated by radical tumor resection followed by radiotherapy alone at our radiation oncology department in a 12-year period.

METHODS

Patient characteristics and tumor location

Between October 1987 and December 1999, 25 patients with adenoid cystic carcinoma of the head and neck were treated with radical tumor resection followed by postoperative radiotherapy in our department. There were 9 men and 16 women. Their ages ranged from 22 to 72 years, with a median age of 50 years (Table 1). Of the 25 cases of ACC, 14 occurred in the major salivary glands, and 11 occurred in the minor salivary glands. Of the major glands, 8 tumors were located in the parotid glands, 5 in the submandibular gland, and 1 in the sublingual gland. Of the minor glands, 1 tumor was located in the cheek, 1 in the tongue base, 3 in the nasal cavity, 3 in the maxillary sinus, 1 in the external auditory canal, and 2 in the trachea (Table 2).

Table 1. Patient Characteristics

Characteristics	No. of cases
Total cases	25
Gender	
male	9
female	16
Age (years)	
≥ 50	13
< 50	12
Stage	
stage I	8
stage II	10
stage III	4
stage IV	3
Surgical margin	
positive	9
negative	16
Perineural invasion	
positive	11
negative	14
Radiation dose	
≥ 63 Gy	13
< 63 Gy	12

Table 2. Initial Site of Tumor

Site	No. of patients
Parotid gland	8
Submandibular gland	5
Sublingual gland	1
Cheek	1
Tongue base	1
Nasal cavity	3
Maxillary sinus	3
External auditory canal	1
Trachea	2

Staging

Tumors were staged according to the 1997 American Joint Committee on Cancer criteria based on tumor site.[9] ACC of the external auditory meatus was staged according to Arriaga et al.,[10] ACC of the nasal cavity was staged according to the staging system used at the University of Florida,[11] and ACC of the trachea was staged based on Licht et al.[12] The distribution of the 25 patients by the staging system is as follows: 8 were in stage I, 10 in stage II, 4 in stage III, and 3 in stage IV (Table 1).

Surgery

The type of surgery was dependent on the tumor site and extent of disease. Nine patients (36%) had histologically confirmed positive resection margins, and 11 patients (44%) had perineural invasion (Table 1).

Radiotherapy

Twenty-five patients were treated with megavoltage equipment, including ^{60}Co gamma rays, photons at 6-10 MeV, or electrons at 9-12 MeV. The radiation technique used depended on the site of disease. The irradiated fields encompassed the tumor bed and upper neck (10 patients), tumor bed and entire neck (7 patients), and tumor bed (8 patients). The skull base was irradiated in 20 patients. The radiation dose ranged from 44 to 68.4 Gy, at 1.8-2 Gy/fraction, with a median dose of 63 Gy. The duration of the external beam ranged from 34 to 75 (median, 60) days. The interval between surgery and the start of radiation ranged from 15 to 97 (median, 33) days. No patient received chemotherapy before or after the operation.

Follow-up

Patients had follow-up in the Radiation Oncology Department at 1- to 3-month intervals during the first 2 years and every 4 to 6 months between the second and fifth post-treatment years; after 5 years, patients were seen annually. All patients had at least 24 months of follow-up. The range of follow-up for all patients was 24-169 (median, 64) months.

Statistics

We retrospectively evaluated the overall survival rate, local control rate, and distant metastasis-free rate as determined by the Kaplan-Meier method.[13] Several clinical factors including gender, age, stage (early stages I+II vs. advanced stages III+IV), surgical margins (positive vs. negative), perineural invasion (with vs. without), tumor origin (major salivary glands vs. minor salivary glands), and postoperative radiation dose (≥ 63 vs. < 63 Gy) were evaluated. Differences between curves were assessed using the log rank test.[14] Multivariate analysis was performed using the Cox proportional hazards model with a forward step-wise method.[15]

RESULTS

Overall survival rate

The 5-year overall survival rate was 75% (Fig. 1). Since stage, status of resection margin, perineural invasion, and tumor origin from either major or minor salivary glands were reported to be associated with the prognosis, their impacts on the survival of our patients were analyzed. The respective 5-year overall survival rates were 79% and 64% for early stages I+II and advanced stages III+IV ($p=0.350$); 75% and 63% for patients with negative and positive surgical margins ($p=0.552$); 68% and 81% for patients with and without perineural invasion ($p=0.362$); and 80% and 70% for tumor origin from the major and minor salivary glands, respectively ($p=0.451$) (Table 3). Although differences in survival rates existed in patients with and without these risk factors, they did not reach statistical significance for any factor. In the multivariate analysis, no prognostic factor was found to have significantly influenced the overall survival rate.

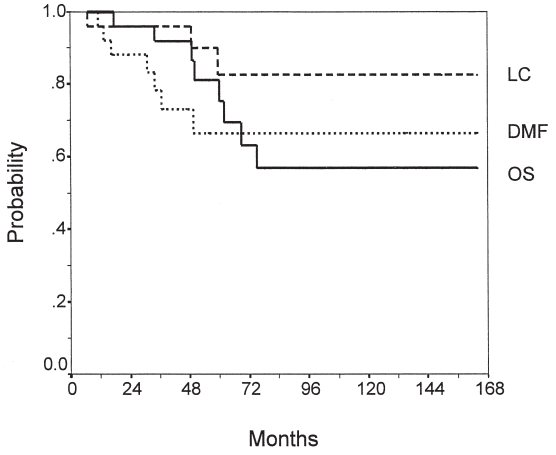

Fig. 1 Overall survival rate (OS), local control rate (LC), and distant metastasis-free rate (DMF) of 25 patients with adenoid cystic carcinoma of the head and neck.

Local control rate

Of 25 patients, 3 patients (12%) had local or regional recurrence. One patient with local recurrence died of cancer, while the other 2 patients died of unknown causes. Two of the patients had local recurrence, and the other had regional lymph node metastasis. All of these recurrences occurred in the irradiated fields within the first 5 years after diagnosis. Isolated local recurrences were observed in 2 patients (8%), isolated metastatic disease without local recurrence in 6 patients (24%), and combined local and metastatic disease in 1 patient (4%). The 5-year local control rate for all patients was 83% (Fig. 1). The respective 5-year local control rates were 92% and 43% for stages I+II and stages III+IV ($p=0.073$); 90% and 74% for patients with negative and positive surgical margins ($p=0.366$); 70% and 93% for patients with and without perineural invasion ($p=0.454$); and 79% and 91% for tumors arising from the major and minor salivary glands, respectively ($p=0.860$) (Table 3). None of the other prognostic factors including gender, age, and radiation dose significantly impacted local control rates (Table 3). In the multivariate analysis, no prognostic factors were found to have significantly influenced the local control rate.

Distant metastasis-free rate

The 5-year distant metastasis-free rate of all patients was 66% (Fig. 1). Both staging and surgical margins were significant prognostic factors for the distant metastasis-free rate. Patients in early stages

Table 3. Results of Univariate Analysis of Different Prognostic Factors

Variables	End point		
	Overall survival *p*	Local control *p*	Freedom from distant metastasis *p*
Gender (male vs. female)	0.265	0.498	0.081
Age (≥ 50 vs. < 50 years)	0.055	0.121	0.144
Stage (I+II) vs. (III+IV)	0.350	0.073	0.009*
Surgical margin (positive vs. negative)	0.552	0.366	0.018*
Perineural invasion (positive vs. negative)	0.362	0.454	0.507
Tumor origin (major salivary glands vs. minor salivary glands)	0.451	0.860	0.856
Dose (≥ 63 vs. < 63 Gy)	0.092	0.513	0.160

* Statistically significant.

I+II had better 5-year distant metastasis-free rates than patients in advanced stages III+IV (78% vs. 29%) ($p=0.009$) (Table 3) (Fig. 2). The 5-year distant metastasis-free rates for patients with negative and positive resection margins were 87% and 31%, respectively ($p=0.018$) (Table 3). The other prognostic factors were also analyzed. The respective 5-year distant metastasis-free rates were 55% and 77% for patients with and without perineural invasion ($p=0.507$); and 70% and 65% for tumor origin from the major and minor salivary glands ($p=0.856$) (Table 3). In the multivariate analysis, stage (OR 8.50, 95% CI 1.70-42.40, $p=0.009$) was the only statistically significant prognostic factor for the distant metastasis-free rate.

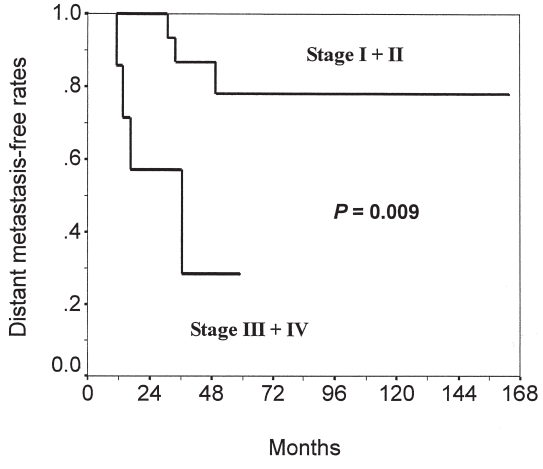

Fig. 2 Distant metastasis-free rates stratified by early stage (I+II) and advanced stage (III+IV).

At the time of this writing, distant metastases had developed in 7 patients (28%), of whom 6 (86%) were disease-free at the primary site. Only 1 of 7 patients had multiple distant metastatic sites including the lung, bone, left supraclavicular lymph nodes, and liver. In the other 6 patients, the lung was the only metastatic site. The time of discovery of distant metastases after treatment ranged from 11 to 50 (median, 31) months.

DISCUSSION

ACC is a relatively rare disease. A unique feature of ACC is its propensity for perineural invasion, even for early stage tumors.[16,17] The pathognomy of the local growth of ACC is its insidious and widespread dissemination through submucosal and fibrous tissue planes around the primary site and its perineural extension through minor and major nerves.[4,18,19] Compared with other cancers of the head and neck, it is more difficult to completely resect ACCs due to the perineural extension to the skull base and proximity to important neural and vascular structures. Therefore, radiotherapy is recommended as an adjunct to surgical resection.[1,20-26] Until now, there has been no clear guidelines on the use of irradiation in the management of ACC. It is necessary to design a controlled, randomized study to address the effects of postoperative radiotherapy in patients with ACC of the head and neck, and define the subgroups of patients who should receive adjunctive radiotherapy. In a review of the literature, patients treated with radiotherapy and surgery obtained better local control of 64-80% compared to 40-44% for patients treated with surgery alone (Table

Table 4. Treatment Results of ACC of the Head and Neck in Other Institutions

Authors	Treatment methods	Local control rate	*p*
Prokopakis et al.[16]	OP	40%	$p = 0.16$
	OP+RT	64%	
Kim et al. [26]	OP	40 % (5-year)	$p < 0.05$
	OP+RT	80 % (5-year)	
Miglianico et al. [21]	OP	44 % (5-year)	$p < 0.01$
	OP+RT	77.8% (5-year)	

Abbreviations: OP: operation; RT: radiotherapy.

4).[17,22,27] Although local control appears to be higher, a survival benefit has not been demonstrated.[20,24] In our retrospective study, a combination of surgery and postoperative radiotherapy resulted in a 5-year overall survival rate, local control rate, and distant metastasis-free rate of 75%, 83%, and 66%, respectively. Our data show that local control rates were comparable to those of other series, but that distant metastasis was still high. Determining a way to decrease the distant metastatic rate is our main strategy for the future.

In our study, 25 patients with ACC of the head and neck were treated by surgery and postoperative radiotherapy. The treatment modalities were identical. Several clinical factors including gender, age, stage (early stages I+II vs. advanced stages III+IV), surgical margins (positive vs. negative), perineural invasion (with vs. without), tumor origin (major salivary glands vs. minor salivary glands), and postoperative radiation dose (≥ 63 Gy vs. < 63 Gy) were evaluated. In the univariate and multivariate analyses, stage was the only statistically significant predictor for the distant metastasis-free rate, but was insignificant for both the overall survival rate and local control rate. Probable explanations for our results include the following. Distant metastases affecting the lung are usually slow growing, sometimes apparently isolated, and frequently surgically resectable.[18] Further analyzing our data, distant metastases developed in 7 patients (28%), of whom 6 (86%) were disease-free at the primary site. Only 1 of the 7 patients had multiple distant metastatic sites. In the other 6 patients, the lung was the only metastatic site. As there is a long natural course in patients who develop lung metastasis, there were no statistically differences in 5-year overall survival rates between patients at stages I+II and those at III+IV. Perhaps, the differences in overall survival rates would show up with longer-term follow-up. However, the reasons for no statistical differences in local control rates between stages I+II and III+IV were not clear. The small case number or other causes are worthy of further investigation.

With regard to surgical margins, Fordice et al.[18] reviewed 160 patients treated at a single institution for ACC of the head and neck (140 patients with a combination of surgery and radiotherapy, 17 with only surgery, and 3 with only radiotherapy) and found that positive surgical margins ($p = 0.003$) were associated with increased treatment failures. Several other authors[5,8,28,29] also demonstrated that positive surgical margins were a strong predictor of outcome. With the advent of cranial base surgery, ACC that extends to the base of the skull can be approached surgically. More-aggressive surgery with attainment of negative margins is key for successful therapy for ACC of the head and neck.

As to staging, Jones et al.[30] reported on 108 patients with ACC of the head and neck who underwent radiotherapy alone (N= 21), local excision (N= 25), palatal fenestration (N= 14), radical excision (N= 42), or no curative treatment (N= 6). Recurrence at the primary site was more likely to occur in patients with advanced disease at the primary site (T3-4, $p = 0.009$), as reported by Spiro et al.[2,31]

None of the other negative clinical prognosticators identified in previous studies such as tumor site within a minor salivary gland[4] and perineural invasion[32] were significant for overall survival rate, local control rate, or distant metastasis-free rate in our study. The reason for this discrepancy is not clear. The small case number may have been the main cause.

There are no definite conclusions about the irradiated fields for ACC of the head and neck. Garden et al.[8] suggested that the base of the skull be treated

electively when a named nerve is involved. In the case of a parotid or paranasal sinus tumor, the nerve pathways are often included by their proximity to the tumor bed; however (e.g., in the case of a submandibular gland tumor), attempting to encompass the base of the skull would require a significant change in volume that they did not feel was warranted in the case of focal perineural invasion without involvement of a named nerve. As to radiation dose, patients who received a dose greater than 60 Gy in addition to surgery had significantly higher local control rates than those who received less than 60 Gy as reported by Simpson et al.[33] However, there were no statistical differences in overall survival rate, local control rate, and distant metastasis-free rate for patients receiving ≥ 63 Gy and < 63 Gy in our study. This is worthy of further investigation.

In conclusion, patients with advanced-stage ACC had higher distant metastasis rates even when receiving postoperative radiotherapy. Distant metastasis is still the main problem in the management of ACC of the head and neck. However, more-effective treatment for this problem is lacking.

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頭頸部腺樣囊狀腫瘤病人接受術後放射線治療之治療結果與預後因子

許軒之 黃英彥 王重榮

背 景： 分析頭頸部腺樣囊狀腫瘤病人接受術後放射線治療之治療結果與預後因子。

方 法： 從1987年10月至1999年12月共25位接受根除性手術的頭頸部腺樣囊狀腫瘤病人前來本科接受術後放射線輔助治療，總劑量爲44-68.4格雷，每位病人均無接受化學治療且至少有2年的追蹤。

結 果： 此25位病人之5年存活率、局部控制率及無遠處轉移率分別爲75%、83%及66%。至今有兩位病患復發於原發部位，1位發生局部淋巴結轉移；共7位 (28%) 病患有遠處轉移病灶，且此7位遠處轉移病患中有6位 (86%) 其原發部位均無局部復發，肺部爲最好發之遠處轉移器官。以多變數分析，本研究發現疾病期別爲無遠處轉移率統計上最有意義之預後因子 ($p=0.009$)。

結 論： 病人爲較晚期之疾病期別 (第三、四期) 即使給予術後放射線治療仍有較高之遠處轉移率，遠處轉移仍然爲治療頭頸部腺樣囊狀腫瘤之主要問題，然而此問題目前仍無解決之道。

(長庚醫誌 2003;26:646-53)

關鍵字： 頭頸部腺樣囊狀腫瘤，手術後放射線治療，預後因子。

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受文日期：民國92年1月21日；接受刊載：民國92年4月30日。
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