The Role of Radiation Therapy in the Treatment of Adenoid Cystic Carcinoma of the Head and Neck

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Forty eight patients with adenoid cystic carcinoma (ACC) in the head and neck treated between 1979 and 1990 were reviewed according to treatment modalities and clinical courses. The common site of origin was minor salivary gland (69%), mostly hard palate and maxillary sinus. 11 patients received radiation therapy (RT) alone and 37 patients received combined surgery and radiation therapy. The follow-up period of the survivors ranged from 4 to 118 months (median 49. 5 months).

The 5 year local control rate was 69.3%, 67.3% and 83.9% in RT alone, conservative operation (OP)+RT and radical OP+RT group, respectively ($p>0.05$). The control of local disease was best achieved with radical OP+RT. In postoperative RT, high dose ($\geq$60 Gy) and generous field size (>64 cm^2) yielded a better local control rate. Actuarial overall survival rate was 79.0% at 5 years and 19.2% at 10 years. Distant metastases (DM) developed in 40% of patients, mostly in the lung. Disease-free (NED) survival rate was 45.8% at 5 years and significant differences did not exist according to primary sites and treatment options. Survival rate after the onset of DM was 19.5% at 5 years. Occurrence of DM tends to lower survival significantly.

In an effort to find the role of RT in the treatment of ACC, our data suggest that a well-planned postoperative RT employing a high dose and generous field size can produce high local control rate and remaining urgent problem of distant metastasis demands more effective chemotherapy for the purpose of improving survival of ACC patients.

Key Words: Adenoid cystic carcinoma, Radiation therapy, Field size

INTRODUCTION

The adenoid cystic carcinoma (ACC) was first depicted in 1895 by Billoth who referred to the tumor as a cylindroma according to its characteristic histologic appearance and considered it benign tumor[1,2]. This uncommon malignant neoplasms which represent only 10 to 15% of the histology of the head and neck tumors involve chiefly major and minor salivary glands[3,4]. The treatment of ACC has not been definitely confirmed because rarity of this neoplasm excludes randomized trials. Surgical resection with postoperative radiation therapy remains the treatment of choice for operable lesions. For the unresectable lesions, high dose external RT is the alternative option. But treatment result is frequently disappointing due to its peculiar biologic behavior, which is characterized by continual, unpredictable local recurrences and distant metastases. But long term survival is not uncommon, therefore a long period of observation is necessary for an evaluation.

Traditionally these tumors are considered to be radioresistant because of their slow growth rate and slow regression rate after RT. However Baclesse[5] in 1940 achieved local control by using RT and Eby et al[6] concluded that RT is of distinct value providing control of the primary tumor at least as effective as radical surgery.

We will review the data in detail which originate from retrospective evaluation to reveal the course of the disese and try to attain better insights of the role of RT.

MATERIALS AND METHODS

58 patients with ACC of various head and neck origin treated at the SNUH between 1979 and 1990 were retrospectively reviewed. 6 patients received incomplete treatment and 4 patients were treated palliatively. The remaining 48 patients formed the basis of this study. There 26 males and 22 females

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Table 1. Distribution of ACC According to Site

Major gland (N=15)		Minor gland (N=33)	
Parotid	7	Hard palate	9
Submand	6	Max. sinus	7
Sublingual	2	Bucc. mucosa	3
		Nasal cavity	3
		Mouth floor	2
		Nasopharynx	2
		Orbit	2
		Others	5

Table 2. Treatment Modalities

Treatment	Major gland	Minor gland
RT alone	1	10
Op+RT	14	23
conservative op	10	11
radical op	4	12
Total	15*	33**

*includes 4 recurrent cases
**includes 2 recurrent cases

with median age of 43 years (range: 20~72 years). The distribution of patients by primary site is listed in Table 1. Median follow-up for all survivors was 49.5 months (range: 4~118 months).

To analyze with respect to treatment modality, extent of surgery, ultimate survival and development of DM, the patients were divided into three groups: 11 patients who received RT alone, 21 patients who received conservative OP+RT, and 16 patients who received radical OP+RT (Table 2).

All patients received megavoltage radiation therapy using ^{60}Co or 6MV. Multiple fields, often wedged, to include the known extent of the disease with adequate margin were used. In 16 patients, field size was $\leq 64\ cm^2$ and in 32 patients, it was $> 64\ cm^2$. The total dose was 48Gy~72Gy (median 60Gy) in the OP+RT group, 60Gy~72Gy (median 70.2Gy) in the RT alone group.

Life table method was used for the calculation of survival rate and Logrank test for the comparison of results.

RESULTS

Fig. 1 shows the local control rates for all patients. The local control rate was 71.1% at 5 years and 44.3% at 10 years. 13 patients (27%) had local recurrences. In the RT alone group the 5 year local

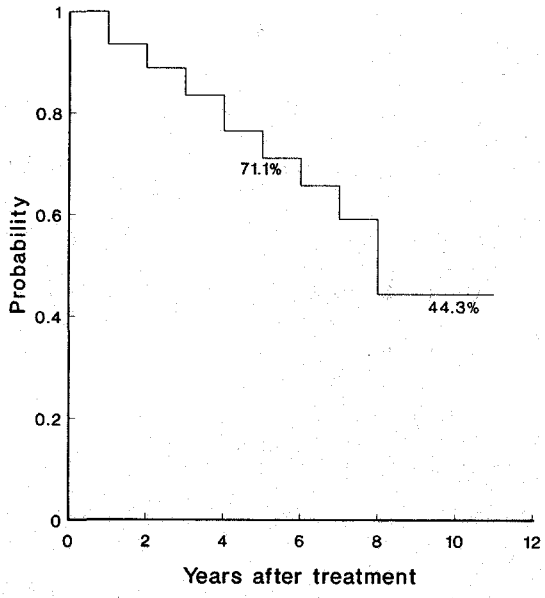

Fig. 1. Overall local control rate.

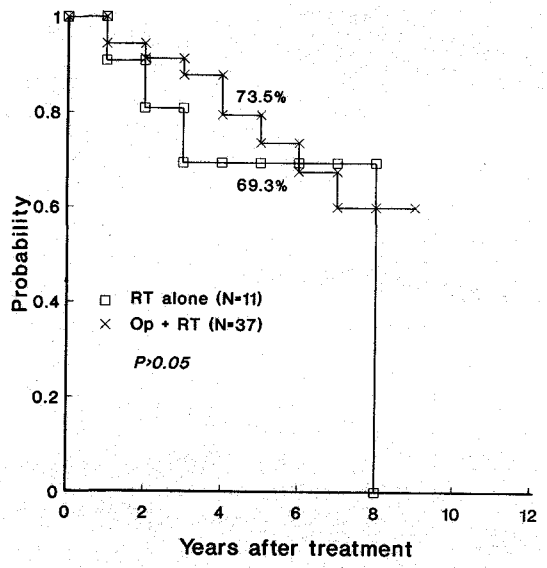

Fig. 2. Local control rate by treatment modality.

control rate was 69.3%. We found 4 established recurrences among these 11 patients. In OP+RT group the 5 year local control rate was 73.5% (67.3% with conservative OP+RT, 83.9% with radical OP+RT). We found 9 recurrences among 37 patients. The above slightly favoring result of OP+RT group was not translated to statistical signifi-

cance (Fig. 2).

We next analyzed the group receiving irradiation postoperatively in an attempt to determine dose-response relationship. Patients were divided into two groups: those who received < 60Gy and those who received ≥ 60Gy. The local control rate was better in the high dose group (at 5 years 87% versus 58%). But this apparent difference was statistically insignificant probably due to small sample size (Fig. 3).

Then we found out field size-response relationship. Patients were divided into two groups: the generous margin group whose field size was > 64 cm^2 and narrow margin group whose field size was ≤ 64 cm^2. Relapse occurred in only 3 of 24 patients with generous margin, compared with 6 of the other 13 patients with narrow margin. The local control rate was statistically higher in the generous margin group (at 5 years 86% versus 54%, $p<0.025$), which explains propensity of infiltration far away from the grossly clear resection margin (Fig. 4).

In the OP+RT group, 32% patients showed pathologically proven presence of perineural invasion which had no statistically significant correlation with locoregional recurrences.

The overall actuarial survival rate was 79.0% at 5 years and 57.7% at 8 years and 19.2% at 10 years. The plateau in survival curve did not exist even after 8 years (Fig. 5). The NED 5 year actuarial survival rate was 45.8% and there was no NED survivor at 9 years (Fig. 5). The NED 5 year survival rate was 37.7% for the RT alone group, 49.7% for the OP+RT group. there was no significant difference (Fig. 6).

There was also no significant difference in NED survival rate depending upon initial site of disease, whether it arose in major salivary glands or in the

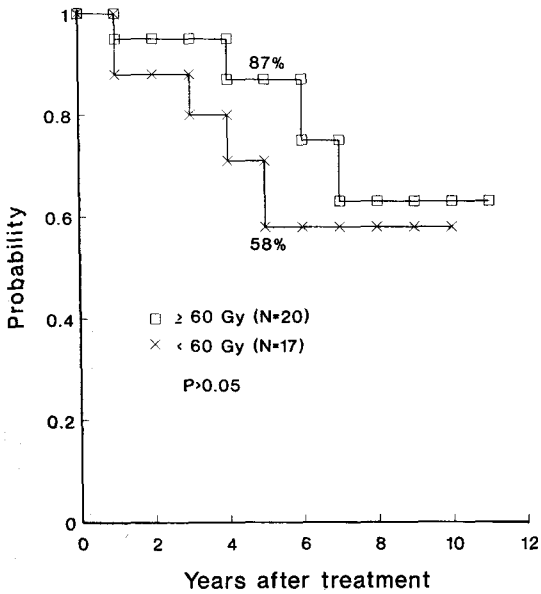

Fig. 3. Local control rate by RT dose in postoperative radiation therapy.

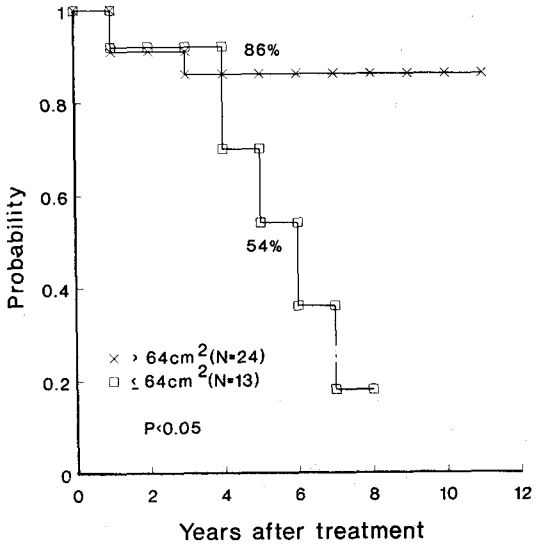

Fig. 4. Local control rate by field size in postoperative radiation therapy.

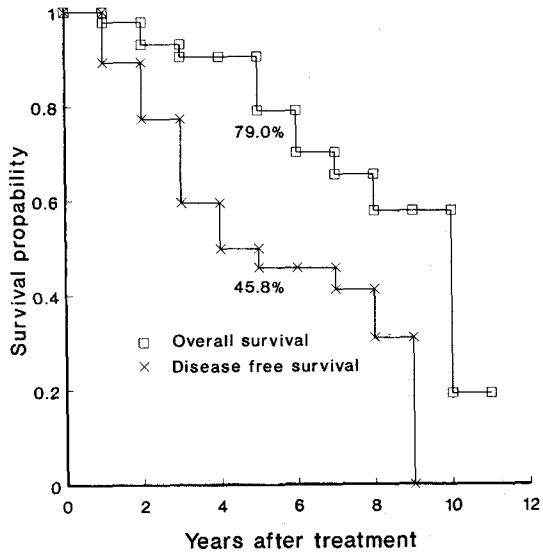

Fig. 5. Overall and disease free survival rate.

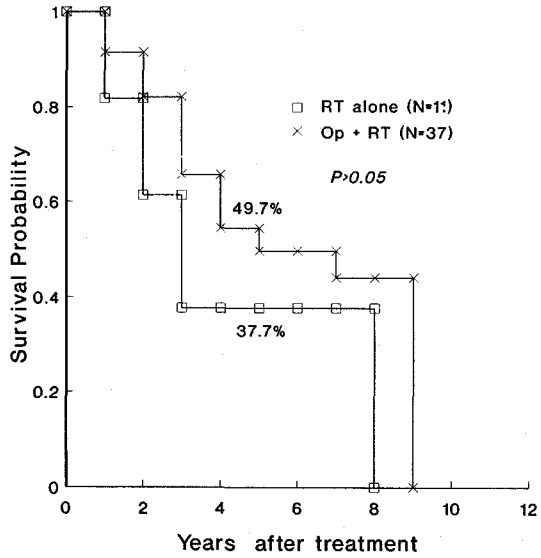

Fig. 6. Disease free survival rate by treatment modality.

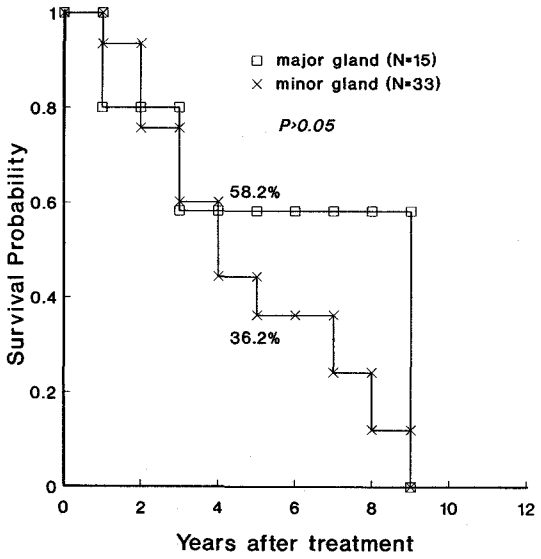

Fig. 7. Disease free survival rate by site.

minor salivary glands (at 5 years 58.2% versus 36.2%), in spite of apparent better result in the major salivary gland tumor (Fig. 7).

Among 48 patients, 25 patients (52%) ultimately failed. Local recurrences were documented in 13 patients (17%). Of those, 6 patients had a local failure only and the other 7 patients had a distant

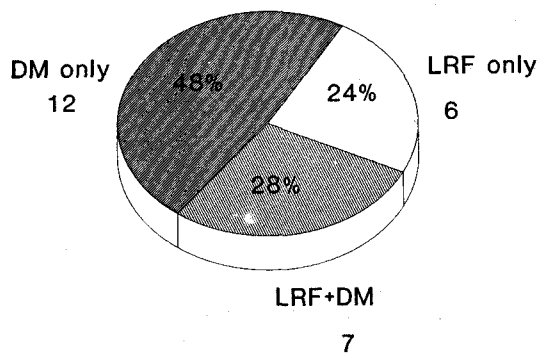

Fig. 8. Failure pattern after treatment.

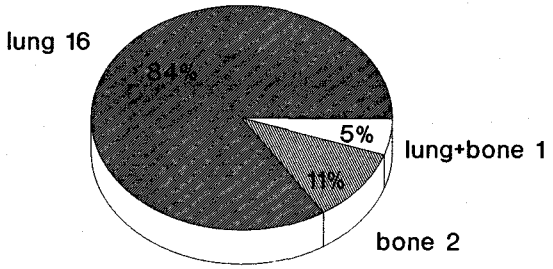

Fig. 9. Sites of distant metastasis after treatment.

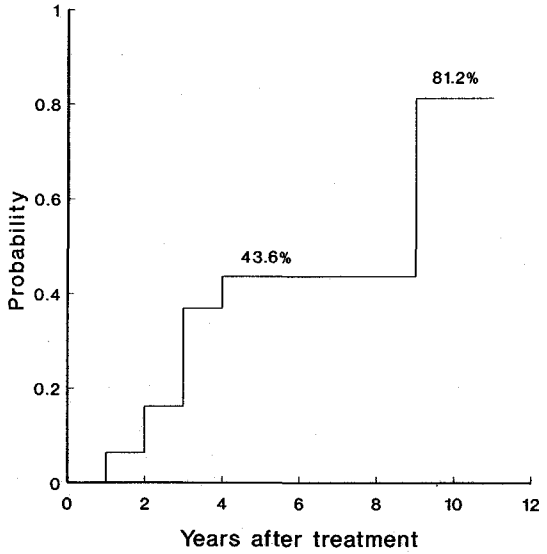

Fig. 10. Cumulative risk of distant metastasis after treatment.

metastasis, too (Fig. 8). Though cervical lymph node involvement was found in 6 patients (13%) at presentation, an isolated lymph node failure occur-

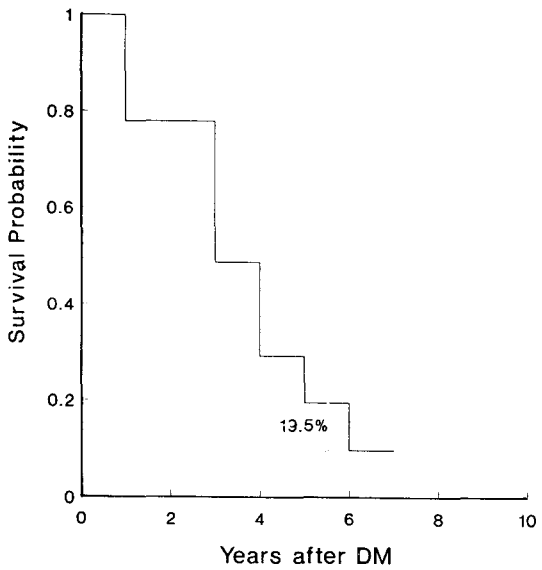

Fig. 11. Survival rate after appearance of distant metastasis.

red in only one case.

Distant metastases developed in 19 patients (40%), mostly in the lung (Fig. 8). The distribution of DM is shown in Fig 9. 63% of the DM developed in spite of local control. The cumulative risk of DM was 43.6% at 5 years, 81.2% at 10 years (Fig. 10). Actuarial survival rate after appearance of DM was 48.7% at 3 years and 19.5% at 5 years (Fig. 11). Therefore the fact which most strongly determines the survival time is the appearance of metastasis. But long term survival with coexisting DM, more than 5 years, occurred in two patients.

DISCUSSION

In our study, ACC occurred very frequently in patients between the fourth and seventh decade of life, and was predominant in the fifth decade. It did not occur to patients younger than 20 years and it was slightly more common in man than in woman. The minor salivary gland was the common site of origin, and hard palate was most frequently affected in about 19% of the cases.

Although ACC is known to be not a radiocurable tumor and RT is seldom employed curatively as the initial therapy of choice, RT is often used for ACC and it has proved to be an effective measure in the management of the disease. The local control rate 71.1% at 5 years is in agreement with results obtained with other comparable studies[7~9]. The relatively good result with RT alone (69.3%) leads us to recommend this modality as an intial treatment for large tumors where surgery would be too destructive.

The more favorable local control rate of OP+RT group compared to OP alone group was confirmed by many authors[7,10]. Miglianico et al[10] reported the difference of 5 year local control rate between OP alone and OP+RT was significant (44% versus 77.8%, $p<0.01$). Thus we feel that RT is essential after surgery. In our study, regardless of statistical insignificance, the better result of radical OP +RT group suggests the completeness of surgery which represents a residual tumor burden might be an important factor in predicting the local control and it seems logical to conclude that the surgery confers some benefit and effectiveness of RT directly relates to the amount of tumor present.

In literature dose and field size-response relationship was frequently documented. It appeared that a dose of 55Gy permits the local control of small lesions after incomplete surgery as shown by Cowie and Pointon[11]. Elsewhere Simpson et al[9] pointed out a significant difference in the local control of patients who received ≥ 60Gy and Miglianico et al[10] recommended a dose of more than 50Gy after complete resection, 65Gy after incomplete resection, 65Gy for small lesions, 70 to 75Gy for larger tumors. Virkram et al[12] reported that 5 year NED survival rate was significantly better for the group treated with generous field size (> 64 cm^2) and high dose (>45Gy), compared with group treated with narrow field size or low dose (88% versus 22%). In our 37 patients who received adjuvant RT, those who were treated with dose ≥ 60 Gy or field size > 64 cm^2 had a better local control rates (statistically significant only for field size). The validity of any conclusion drawn from such a small sample is questionable, but if we consider that these tumors have a infiltrative capacity beyond the visible and palpable limits of the lesion, the combination of surgery with a "well planned" RT may have a real potential for improving the survival.

The perineural involvement was found in 12 patients (32%). But its presence or absence does not appear to influence the prognosis as shown in our data[7,8,13].

The NED survival rate varied from 45.8% at 5 years to 0% at 9 years and overall survival rate was 79.0% at 5 years and reached 19.2% at 10 years. The slow evolution of ACC may explain a large

difference between the NED and overall survival and the reason why a long term follow-up is necessary. The apparent poor NED survival in minor salivary gland tumor which was confirmed by others[13] probably reflects the greater chance to infiltrate outside of the confines of the gland and to invade bone and surrounding soft tissue and limited resectability.

In the literature[1,4,7] the incidence of lymph node metastasis is 10~15% at diagnosis and 15~20% during the course of disease. Only 1 patients had a lymph node failure in our study. The patients died eventually of unpredictable DM that was found in 40% of cases, similar to other reported cases[14]. Most of DM developed irrespective of local control. The cumulative risk of DM was 81.2% at 10 years. Pulmonary involvement occurred in 89% of DM. Grahne et al[15] reported that lung metastasis was three times as frequent as lymph node involvement. Pulmonary metastasis was rarely solitary and therefore unresectable. However, some metastasis which localized in one lobe can be cured with segmental resection[16] and some authors[17] reported that ACC seemed to respond to CVF (cyclophosphamide, vincristine, 5-fluorouracil)regimen. But the impact on survival was negligible. Therefore appearance of DM predicts a worse prognosis.

Matsuba et al[7] correlated the histologic type of tumors with prognosis and classified the tumor into tubular with a best prognosis, cribriform with a intermediate prognosis and solid with a worst prognosis. Recognition of tubular pattern is generally easy, but discrimination between cribriform and solid type depends on the pathologist's subjective interpretation. To overcome this uncertainty Santucci et al[18] created a new prognostic criterion in ACC by the number of gland like spaces per square milimeter which can be used as an objective measures for the prognostic evaluations. Subclassification based upon this new criterion is very helpful in the long term follow-up.

Some authors[19,20] presented very high local control rate of a group of a patients with inoperable and unresectable salivary gland tumors using state of the art photon radiation therapy, accelerated hyperfractionated photon with 1.6 Gy per fraction, comparable to those claimed by neutron (high LET) therapy, yet without significant complications. Although the numbers in these series were small and follow-up was relatively short, these new methodology might be a guide for a future trials.

CONCLUSION

ACC is uncommon tumor with a characteristic evolution and carries a dismal ultimate prognosis. It appears that ACC might be more radiosensitive than was presumed before. The combination of RT and surgery can yield a good local control rate, thus we now recommend radiation therapy as an integral part of treatment for ACC in head and neck. In adjuvant RT, a well planned radiation therapy employing a high dose ($\geq$60Gy) and generous field size ($>64\,cm^2$) could yield a better local control rate. But this primary control uncovers the remaining problem of DM from which patients continue to die. Therefore further therapeutic measures using effective chemotherapy shoud be explored in the hope of improving patient survival.

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= 국문초록 =

두경부에 생긴 선양 낭포암의 치료에 있어서 방사선치료의 역할

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1979년부터 1990년 사이에 서울대학교병원 치료방사선과에서 48명의 환자가 두경부에 생긴 선양 낭포암으로 치료를 받았다. 이 환자들을 대상으로 방사선치료의 효과를 알아보기 위해 저자들은 후향성조사를 하였으며 다음과 같은 결과를 얻었다. 15명의 환자는 대타액선의 병변이었고 나머지 33명의 환자는 주로 경구개와 상악동을 침범한 소타액선의 병변이었다. 11명의 환자는 수술이 불가능하여 방사선치료만 받았으며 37명의 환자에게는 수술후 방사선치료를 추가하였다. 이 환자들의 중앙 추적기간은 49.5개월이었다.

모든 환자에 있어서 국소치유율은 5년에 71.1%, 10년에 44.3%였으며 근치적인 수술과 방사선치료를 한 그룹에서 좀 더 좋은 결과를 보였으나 통계학적으로 유의하지는 않았다. 신경주위로의 침범여부는 국소치유율에 영향을 주지 못했다.

수술후 방사선치료를 한 그룹에서는 60 Gy이상의 방사선양과 64 cm^2이상의 field size로 치료한 경우에 좀 더 좋은 국소치유율을 나타내었으며 통계학적 유의성은 field size에 대해서만 나타났다.

원격전이는 환자의 40%에서 일어났으며 주로 폐를 침범하였다. 원격전이 이후의 생존율은 5년에 19.5%로서 원격전이가 생존율을 결정하는 중요한 요인임을 알 수 있었다.

전체생존율은 5년에 79.0%, 10년에 19.2%였으며 8년 이후에도 생존율은 계속 감소하였다. 무병생존율은 5년에 45.8%였으며 수술과 방사선치료를 같이한 그룹과 대타액선의 병변에서 더 좋은 결과를 나타냈으나 통계학적으로 유의한 차이는 없었다.

결론적으로 선양 낭포암의 수술후 방사선치료에 있어서 60 Gy이상의 방사선양과 64 cm^2 이상의 field size로 치료함으로써 좀 더 좋은 국소치유율을 얻을 수 있었으며 환자의 생존율을 높이기 위해서는 좀 더 효과적인 항암제의 개발이 시급하다 하겠다.