# Radiation Therapy for Carcinoma of the Oropharynx

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= Abstract =

Purpose : A retrospective analysis for patients with oropharyngeal carcinoma who were treated with radiation was performed to assess the results of treatment and patterns of failure, and to identify the factors that might influence survival.

Materials and Methods : From March 1985 through June 1993, 53 patients with oropharyngeal carcinoma were treated with either radiation therapy alone or combination of neoadjuvant chemotherapy and radiation therapy at the Department of Radiation Oncology, Kyungpook National University Hospital. Patients' ages ranged from 31 to 73 years with a median age of 54 years. There were 47 men and 6 women. Forty-two patients (79.2%) had squamous cell carcinoma, 10 patients (18.9%) had undifferentiated carcinoma and 1 patient (1.9%) had adenoid cystic carcinoma. There were 2 patients with stage I, 12 patients with stage II, 12 patients with stage III and 27 patients with stage IV. According to the TNM classification, patients were distributed as follows: T1 7, T2 28, T3 10, T4 7, TX 1, and N0 17, N1 13, N2 21, N3 2. The primary tumor sites were tonsillar region in 36 patients (67.9%), base of the tongue in 12 patients (22.6%), and soft palate in 5 patients (9.4%). Twenty-five patients were treated with radiation therapy alone and twenty-eight patients were treated with one to three courses of chemotherapy followed by radiation therapy. Chemotherapeutic regimens used were either CF (cisplatin and 5-fluorouracil) or CVB (cisplatin, vincristine and bleomycin). Radiation therapy was delivered 180-200 cGy daily, five times a week using 6 MV X-ray with or without 8-10 MeV electron beams. A tumor dose ranged from 4500 cGy to 7740 cGy with a median dose of 7100 cGy. The follow-up time ranged from 4 months to 99 months with a median of 21 months.

Results : Thirty-seven patients (69.8%) achieved a CR (complete response) and PR (partial response) in 16 patients (30.2%) after radiation therapy. The overall survival rates were 47% at 2 years and 42% at 3 years, respectively. The median survival time was 23 months. Overall stage ($p=0.02$) and response to radiation therapy ($p=0.004$) were significant prognostic factors for overall survival. The 2-year disease-free survival rate was 45.5%. T-stage ($p=0.03$), N-stage ($p=0.04$) and overall stage ($p=0.04$) were

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**significant prognostic factors for disease-free survival. Age, sex, histology, primary site of the tumor, radiation dose, combination of chemotherapy were not significantly associated with disease-free survival. Among evaluable 32 patients with CR to radiation therapy, 12 patients were considered to have failed. Among these, 8 patients failed locoregionally and 4 patients failed distantly.**

**Conclusion : T-stage, N-stage and overall stage were significant prognostic factors for disease-free survival in the treatment of oropharyngeal cancer. Since locoregional failure was the predominant pattern of relapse, potential methods to improve locoregional control with radiation therapy should be attempted. More controlled clinical trials should be completed before acceptance of chemotherapy as a part of treatment of oropharyngeal carcinoma.**

**Key Words : Oropharyngeal carcinoma, Radiation therapy**

## INTRODUCTION

Oropharyngeal carcinomas are generally managed by surgery, radiation therapy or a combination of the two modalities[1]. Radiation therapy alone is an effective method of treatment for early stage. Advanced lesions, however, are treated with combined surgery and preoperative or postoperative radiation therapy which results in no difference in survival and local control rates compared with radiation therapy alone[2]. In many institutions, carcinoma of the oropharynx is treated by definitive radiation therapy alone, and surgery reserved for salvage of failures, since radiation therapy produces less disability[2, 3].

The potential benefit of neoadjuvant or adjuvant chemotherapy combined with radiation therapy in treatment of advanced lesions has not been documented[2, 4].

In this retrospective study, we evaluated the results of definitive radiation therapy for carcinoma of the oropharynx and anaylzed the patterns of failure and the prognostic factors that might affect survival.

## MATERIALS AND METHODS

Fifty-three patients with oropharyngeal carcinoma treated at the Department of Radiation Oncology, Kyungpook National University Hospital, between March 1985 and June 1993, were reviewed.

All patients had previously untreated, histologically proven carcinoma of the oropharynx and measurable local disease without distant metastasis.

Patients were staged according to criteria recommended by the American Committee for Cancer Staging. Performance status was graded by the Eastern Cooperative Oncology Group (ECOG) scale from 0 to 4. Initial examination included history, clinical examination, endoscopy, complete blood count, extended serum chemistry, chest X-ray, bone scan, and CT scan. The patient characteristics are summarized in Table 1. Patients' ages ranged from 31 years to 73 years, median age of 54. There were 47 men and 6 women, a sex ratio of 8:1. Most patients had a performance status of 0 (83%) or 1 (15%) and only 1 patient had a performance status of 2. Forty-two patients (79.2%) had squamous cell carcinoma, 10 patients (18.9%) had undifferentiated caicinoma, and 1 patient (1.9%) had adenoid cystic carcinoma. The primary tumor sites were tonsillar region in 36 patients (67.9%), base of the tongue in 12 patients (22.6%), and soft palate in 5 patients (9.4%). Two patients presented with stage I, 12 patients with stage II, 12 patients with stage III, and 27 patients presented with stage IV. The distribution of patients according to tumor and nodal

**Table 1. Patients Characteristics**

| Characteristics | |
|---|---|
| No. of patients | 53 |
| Age (in years) | |
| Median | 54 |
| Range | 31~73 |
| Sex | |
| Male | 47 |
| Female | 6 |
| Performance status (ECOG) | |
| 0 | 44 |
| 1 | 8 |
| 2 | 1 |
| Histology | |
| Squamous | 42 |
| Undifferentiated | 10 |
| Adenoid cystic | 1 |
| Primary site | |
| Tonsil | 36 |
| Base of tongue | 12 |
| Soft palate | 5 |
| Stage of disease | |
| I | 2 |
| II | 12 |
| III | 12 |
| IV | 27 |
| Treatment group | |
| RT alone | 25 |
| CT + RT | 28 |
| Follow-up (months) | |
| Median | 21 |
| Range | 4~99 |

RT : Radiation therapy
CT : Neoadjuvant chemotherapy

status is shown in Table 2. Twenty-five patients were treated with radiation therapy alone, and twenty-eight patients were initially treated with one to three courses of neoadjuvant chemotherapy followed by radiation therapy. The chemotherapeutic regimen used in this study was either CVB or CF. Ten patients received CVB; cisplatin (80mg/m$^2$) on day 1, vincristine (1.4mg/m$^2$), and bleomycin 10mg for day 2 to day 3, and 18 patients received CF; cisplatin (100mg/m$^2$) on day 1 and day 3, respectively, and 5-fluorouracil (1000mg/m$^2$) infusion for 24 hours on day 2 and day 4, respectively. Cycles were repeated every 3 week. Radiation therapy was treated with 6MV X-ray. The upper neck and primary tumor were treated by two parallel opposed portals. At 4000 cGy, the lateral fields were reduced and electrons were used to protect spinal cord. The supraclavicular area was treated via a single anterior field. All patients received 180-200 cGy per day, five times a week using 6 MV X-ray with or without 8-10 MeV electrons. A tumor dose of 4500-7740 cGy with a median dose of 7100 cGy was given to the region of primary tumor and positive neck disease, and a dose of 4500-5000 cGy was delivered to clinically negative neck.

For those patients treated with radiation therapy alone, the response rate of the patients was assessed at 4 weeks after radiation therapy, and for those patients treated with neoadjuvant chemotherapy and radiation therapy, the response rate was assessed at two points. Within two weeks of completing chemotherapy, patients were evaluated to determine chemotharapy response, and another evaluation was undertaken at 4 weeks after radiation therapy to assess response. Response was evaluated clinically and/or radiologically. A complete response (CR) was defined as complete disappearance of all clinically detectable disease, and a partial response (PR) was defined as a more than 50% reduction of the diameter of all measuable disease. No responce was defined as a less than 50% reduction of the perpendicular diameter of any measurable disease.

All patients have been followed up by personal contact. Survival was estimated from the initiation of treatment to the date of last follow-up or until patients' death. Time to relapse was defined as the time between initiation of treatment and progression of disease. Progression of disease was determined by clinical and/or radiological examination and verified when it's possible by biopsy. The overall and disease-free survival rates were stratified according to tumor parameters.

The survival curves were estimated by Kaplan-Meier method. In addition, logrank test was used to evaluate the prognostic variables for survival. Statistical significance was defined as $p<0.05$.

## RESULTS

### 1. Response to Treatment

Overall response rate to neoadjuvant chemotherapy prior to radiotherapy was analyzed in 28

**Table 2. Pateints Distribution by Tumor and Nodal Status**

| Nodal status | Tumor status | | | | | Total |
|---|---|---|---|---|---|---|
| | T1 | T2 | T3 | T4 | Tx | |
| N0 | 2 | 13 | 1 | 1 | 0 | 17 |
| N1 | 3 | 5 | 4 | 1 | 0 | 13 |
| N2a | 1 | 1 | 3 | 1 | 0 | 6 |
| N2b | 0 | 3 | 2 | 2 | 0 | 7 |
| N2c | 1 | 4 | 0 | 2 | 1 | 8 |
| N3 | 0 | 2 | 0 | 0 | 0 | 2 |
| Total | 7 | 28 | 10 | 7 | 1 | 53 |

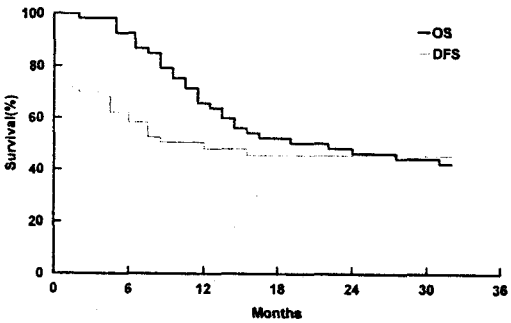


Fig. 1. Overall survival (OS) and disease-free survival (DFS) for all patients.

patients. The response to chemotherapy was evaluated within 2 weeks after the completion of chemotherapy, just prior to radiation therapy. After the completion of chemotherapy, CR was achieved in 3 patients (10.7%), PR in 17 patinets (60.7%), NR in 8 patients (28.6%) for an overall major response rate (CR+PR) of 71.4%. The response rate to chemotherapy according to age, sex, primary site of the tumor or tumor variables was not significantly different. Chemothrapy was generally well tolerated in all patients. Toxicities were predominantly nausea and vomiting, mild to moderate mucositis, and mild myelosuppression. There was no drug-related death.

The response to radiation therapy was assessed at 4 weeks after the completion of radiation therapy. Thirty-seven patients (69.8%) achieved a CR, and a PR in 16 patients (30.2%) after radiation therapy. Age, sex, histology, primary site of the tumor, tumor variables or response to chemotherapy did not affect the response to radiation therapy significantly.

**Table 3. Patterns of Initial Failure in CR Patients (N=32*)**

| Patterns of failure | No. of patients |
|---|---|
| Disease-free | 20 |
| Locoregional failure | 8 |
| Distant failure | 4 |

* : Evaluable patients
CR : Complete response

## 2. Survival and Failure Analysis

Minimum follow-up was 4 months and maximum 99 months, with a median of 21 months at the time of review. Seven patients were lost to follow-up.

The overall survival and disease-free survival rate was 47% and 45.5% at 2 years, and 42% and 45.5% at 3 years, respectively (Fig. 1). The median survival time was 23 months.

Upto April 1995, 20 patients were alive and free of disease, 2 were alive with recurrent or progression of persistent disease, and 24 had died. The death was accounted for recurrent disease or progression of persistent disease in 22 patients and for other causes in 2 patients. Among the evaluable 32 CR patients after radiation therapy, relapse was first noticed at a locoregional site in 8 patients, at a distant site in 4 patients, and the remaining 20 patients were free of disease. Sites of distant metastasis were lung (2 patients), liver (1 patient), and small bowel (1 patient). Time to relapse ranged from 3 months to 16 months with a median time of 7 months. Patterns of initial failure are indicated in Table 3.

Statistical analysis was used to find out prognostic factors that might predict for overall survival or disease-free survival (Table 4). Overall stage and response to radiation therapy were found to be important prognostic factors for overall survival. The 2-year overall survival rate for stage I-II and stage III-IV was 69.5% and 39.7%, respectively (p=0.02, Fig. 2). Patients with CR to radiation therapy had a better overall survival than patients with PR to radiation therapy (p=0.004, Fig. 3). The 3-year overall survival rate for CR patients to radiation therapy and PR patients to radiation therapy was

**Table 4. Prognostic Factors Predicting Overall and Disease-free Survival**

| Factors | Overall survival (p-value) | Disease-free survival (p-value) |
|---|---|---|
| Age | NS | NS |
| Sex | NS | NS |
| Histology | NS | NS |
| Site of primary tumor | NS | NS |
| T-stage | NS | 0.03 |
| N-stage | NS | 0.04 |
| Overall stage | 0.02 | 0.04 |
| Radiation dose | NS | NS |
| Combination of chemotherapy | NS | NS |
| Response to radiation therapy | 0.004 | - |

NS : Not significant

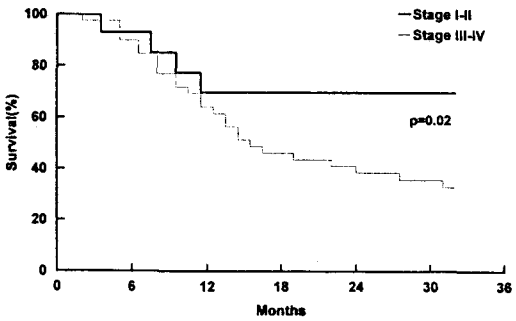


Fig. 2. Overall survival by overall stage.

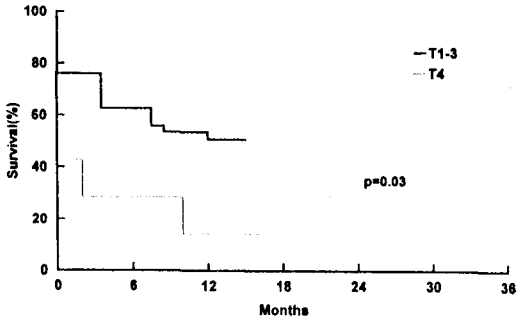


Fig. 4. Disease-free survival by tumor stage.

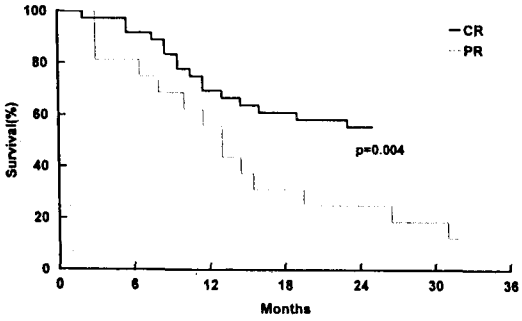


Fig. 3. Overall survival by response to radiation therapy.

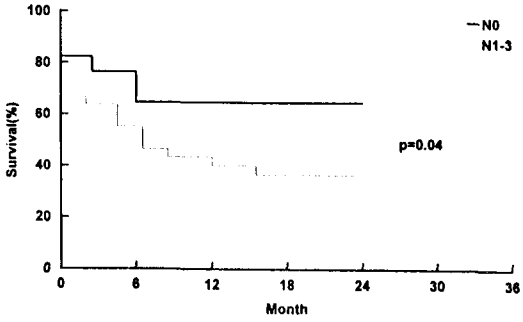


Fig. 5. Disease-free survival by nodal status.

55.7% and 12.5%, repectively. Age, sex, histology, primary site of the tumor, T-stage, N-stage, combination of chemotherapy or radiation dose did not affect overall survival in statistically significant manner.

The T-stage, N-stage and overall stage were significant prognostic factors for disease-free survival (Table 4). All the other parameters, i.e. age, sex, histology, primary site of the tumor, combination of chemotherapy, radiation dose were not significantly associated with disease-free survival. The 2-year disease-free survival for T1-3 and T4 was 50.8% and 14.3%, respectively (p=0.03, Fig. 4). The 2-year disease-free survival for N0 and N1-3 was 64.7% and 36.5%, respectively (p=0.04, Fig. 5). The 2-year disease-free survival according to overall stage was 71.4% for stage I-II and 35.9% for stage III-IV, respectively (p=0.04, Fig. 6).

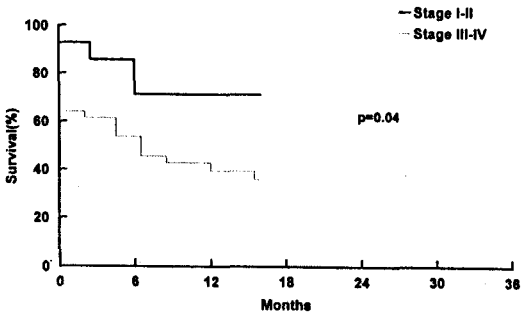


Fig. 6. Disease-free survival by overall stage.

## DISCUSSION

Carcinoma of the oropharynx is the second most frequent form of malignant disease of head and neck following the laryngeal carcinoma. Oropharyngeal carcinoma generally tends to extend into adjacent structures and tends to have high frequency of nodal involvement. In carcinoma of the oropharynx, involvement of cervical nodes has been reported as high as 65 to 70% at diagnosis[5]. Incidence of nodal involvement tends to increase as tumor stage advances. Carcinoma of the oropharynx is often diagnosed when the primary tumor is advanced with nodal involvement[5, 6].

Although it has been generally accepted that radiation therapy would be the treatment of choice for early stage of disease, the treatment of patients with advanced disease is controversial. The control rates for advanced disease are unsatisfactory with either radiation therapy alone or surgery alone. No randomized trial comparing radiation therapy alone with surgery alone, or comparing radiation therapy with combined radiation therapy and surgery has been done. Many authors have advocated combining radiation therapy with a surgical procedure in effort to improve the local and regional control[2, 7, 8]. The rationale is that combined therapy usually decreases the extent of the surgical procedure necessary and also decreases the dose of irradiation necessary to be effective on subclinical disease. Lindberg et al. reported that no difference in local control can be ascertain if the radiation was given preoperatively or postoperatively[2, 7-9]. According to Perez[2], there was no significant difference in survival or recurrence rate in the patients treated with radiation therapy alone or with preoperative radiation therapy and surgery[9]. Other studies also failed to show any advantage for combined preoperative radiation therapy and surgery over radiation therapy alone[10]. Many authors conclude that radiation therapy remains the treatment of choice for all cancers of the oropharynx[9].

The overall and disease-free survival rates for the patients with carcinoma of the oropharynx treated by radiation therapy in this study were comparable with the results obtained in the literature[5]. When radiation therapy failed, the usual site of failure was locoregional, accounting for up to 85% of the failures[11]. Our results were not different from those observed in other studies[11].

It has been well documented that the tumor size, extent of lymph node involvement and overall stage are directly related to prognosis[5, 6, 10-13]. In this study, T-stage, N-stage, and overall stage were statistically significant prognostic factors for disease-free survival. The 2-year disease-free survival for T1-3 and T4 was 50.8% and 14.3%, respectively. The 2-year disease-free survival for N0 and N1-3 was 64.7% and 36.5%, respectively. The 2-year disease-free survival according to overall stage was 71.4% for stage I-II and 35.9% for stage III-IV, respectively. The extent of primary tumor had very clear repercussions on prognosis. All authors agree that the extent of primary tumor influences survival[6, 12, 13]. Tumor stage and possibility of local control or survival are inversely related. This is common to all tumors, regardless of their topography. A common characteristic of oropharyngeal carcinoma is their propensity to harbor a high number of hypoxic tumor cells, that affords considerable radioresistance[6]. This registance rises as tumor volume increases.

Although Wang[14] and Vallis et al.[10] reported no significant difference in survival for N0 compared to N1 disease, many authors would agree with our findings that the extent of lymph node involvement was directly related to prognosis[6, 11]. Mantravadi et al.[15] reported a 42% survival at 5 years for patients

with no initially palpable lymph node and 20% survival for metastatic nodes. Meos-Mendez et al.[16] reported a more favorable prognosis for patients with no initially palpable node; this was associated with lower lymph node recurrence (12.5%) compared with 35% for patients with initially palpable nodes.

Some authors reported that relation was found between age and survival or between sex and survival. Others, however, observed that age and sex were of no prognostic significance[5, 12, 13]. Age and sex had no prognostic value in this study presented as in most other studies.

Histological differentiation has long been disputed, having been to be good prognostic index in some series and not a useful prognostic index in others[10]. In this study, the degree of histological differentiation did not affect survival. Perez et al.[17] found that well differentiated tumors were associated with a 50% survival at 5 years compared with 35% for poorly differentiated tumors. Montravadi et al.[15] observed that patients with well differentiated carcinomas had a better 5-year survival rate than patients with less differentiated carcinomas. However, careful analysis of their data revealed a possible explanation of this observation. The proportion of patients with lymph node metastasis in the group with well differentiated carcinomas was much lower than in the group with moderately and poorly differentiated carcinomas.

Although some authors observed a distinct influence of initial tumor site on prognossis, others reported that initial tumor sites were of no prognostic significance[4, 9, 12]. We did not observe that initial primary site of disease was associated with survival.

Radiation dose was not associated with survival in the range utilized in this study. This can be attributed to several factors. The dose prescribed have been largely dictated by disease extent. The mean tumor dose to the primary site increased according to the T-stage in this study. The dose range in each stage was much smaller than those of other studies[1]. Perhaps more importantly, the dose prescribed to the individual patient was not selected at random, but rather was determined by the bulk of disease and the type of growth (exophytic vs. infiltrative). These factors would obscure the demonstration of dose-response relationships. Garrett et al.[18] did not observe a significant correlation of tumor control in 372 patients treated with irradiation dose ranging from 5000 to 6000 cGy. Noteworthily these authors observed a statistically significant improvement in local control and survival when areas greater than 80 $cm^2$ were treated in T1-2 tumors. Dubios et al.[6] also noted that improved tumor control and survival was correlated with large volume treated but not with increasing doses in patients with carcinoma of tonsillar region. Because of the limited tolerance of the normal tissue, it is not advisable to administer doses greater than 7500 cGy. Furthermore, sparing of normal tissue should be attempted whenever possible.

Brachytheraphy has been advocated by Fletcher et al. and Bloedorn et al. for the treatment of patients with oropharyngeal carcinoma to improve results obtained with external irradiation[2]. On the other hand, Garrett et al.[18] observed no improvement in local control in patients with tonsillar carcinoma in whom an interstitial implant was added to external irradiation.

Several authors have reported increased tumor control in patients with oropharyngeal tumors without enhanced morbidity with multiple daily fractionation[2]. The RTOG failed to demonstrate improved tumor control in a randomized trial for advanced head and neck tumors using hyperfrationation versus conventional irradiation[2, 19].

Since outcome of patients with advanced disease is poor, there has recently been a trend of adding chemotherapy to the treatment[4, 10, 20]. Some of neoadjuvant chemotherapy protocols appeared to be well tolerated and did not increase complications[4, 20]. Despite encouraging overall response rates, the survival rate was not improved in controlled trials[4]. The results of present study did not show that neoadjuvant chemotherapy improved survival. These data were not different from those observed in other studies or in controlled trials. However, longer follow-up is needed to confirm any advantage in the long-term locoregional control and survival of

patients with advanced disease[4, 10, 20].

In conclusion, T-stage, N-stage, and overall stage were statistically significant prognostic factors for disease-free survival in our series. All the other parameters, i.e., age, sex, histological differentiation, radiation dose, initial site of primary disease, neoadjuvant chemotherapy were not significantly associated with disease-free survival. Since locoregional failure was the predominant pattern of relapse, efforts to improve locoregional control and survival should be attempted. More controlled clinical trials must be completed before acceptance of chemotherapy as a part of treatment of advanced oropharyngeal carcinoma.

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**국문초록 =**

## 구인두암의 방사선치료

경북대학교 의과대학 치료방사선과학교실

박 인 규 · 김 재 철

**목 적** : 구인두암으로 방사선치료를 받은 환자들을 대상으로 후향적 분석을 시행하여 생존율, 치료 실패 양상 및 생존율에 미치는 요인 등을 알아보고자 하였다.

**방 법** : 1985년 3월부터 1993년 6월까지 경북대학교병원 치료방사선과에서 구인두암으로 방사선치료를 시행한 53예의 환자를 대상으로 후향적 분석을 시행하였다. 환자의 연령은 31세에서 73세로 중간값은 54세였으며 남자 47예 여자 6예였다. 조직학적으로 편평세포암종이 42예, 미분화암종 이 10예, 선양 낭성암종이 1예였다. 병기별 분포는 I기 2예, II기 12예, III기 12예, IV기 27예이었다. T1 7예, T2 28예, T3 10예, T4 7예, T병기가 불명확한 경우가 1예이었고, N0 17예, N1 13예, N2 21예, N3 2예였다. 원발병소는 편도 36예, 설기저부 12예, 그리고 연구개 5예였다. 방사선 단독치료가 25예, 유도화학요법 및 방사선치료 병용요법이 28예였다. 유도화학요법은 CF (cisplatin, 5-fluorouracil) 또는 CVB (cisplatin, vincristine, bleomycin) 약제로 1-3회 시행하였다. 방사선치료는 6MV X선 및 8-10MeV 전자선을 이용하였고 방사선 치료선량은 일일 180-200 cGy씩 총 4500-7740 cGy로 중간값은 7100 cGy였다. 환자의 추적기간은 4개월에서 99개월로 중간추적기간이 21개월이었다.

**결 과** : 방사선치료 후 37예 (69.8%) 에서 완전관해를 보였고 16예 (30.2%) 에서 부분관해를 보였다. 전체 환자에서 2년생존율은 47%, 3년생존율은 42%였고 중앙생존기간은 23개월이었다. 치료에 대한 반응 (p=0.004) 및 전체병기가 (p=0.02) 통계적으로 의미있게 생존율에 영향을 미치는 것으로 나타났다. 2년 무병생존율은 45.5%였고 T 병기 (p=0.03), N 병기 (p=0.04) 및 전체병기가 (p=0.04) 의미있게 무병생존율에 영향을 미치는 것으로 나타났다. 환자의 나이, 성별, 조직학적 소견, 원발병소, 방사선량 및 화학요법과의 병합치료는 무병생존율에 영향을 주지 않았다. 방사선치료 후 완전관해를 보인 36예 중 추적조사가 가능했던 32예에서의 치료 실패양상은 국소재발이 8예, 원격전이가 4예로 주된 치료 실패 원인은 국소재발이었다.

**결 론** : 본 연구에서는 N 병기, T 병기 및 전체병기가 무병 생존율에 영향을 미치는 인자로 나타났으며, 국소재발이 주된 실패 요인이 되고 있어 국소완치를 위한 노력이 절실히 요구된다. 현재까지 구인두암의 치료는 방사선 단독치료가 가장 효과적인 치료방법으로 여겨지며 화학요법은 좀더 많은 비교 대조군 연구를 통해서만 역할을 평가할 수 있을 것으로 사료된다.