Concurrent Cisplatin-Radiation Therapy in Locally Advanced Head & Neck Cancers
- Preliminary Report -

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Purpose : This study tried to evaluate the effectiveness of combined treatment using radiation therapy and concurrent cisplatin as a radiosensitizer in the management of locally advanced head and neck cancer.

Materials and methods : From January 1995 to August 1998, 29 evaluable patients with locally advanced head & neck cancers (AJCC stage II IV) were received curative radiation therapy (total 70 75.6 Gy/35 42 fractions, 1.8 2 Gy/fraction) and concurrent cisplatin chemotherapy (100 mg/m^2, D1, D22, D43). The neck dissections were performed for residual lymphadenopathy. Follow-up ranged from 5 to 55 months (median 24 months).

Results : Twenty-one (72.4%) patients achieved clinical complete responses. The partial response and minimal response rates were 17.2% and 10.4%, respectively. Locoregional failure rate was 27.6%, and included 6 patients with local failures, 4 patients with regional failures, and 2 patients with combined local and regional failures. Four of 29 patients (13.8%) developed distant metastasis. The disease free survival rate at 3 years was 60%. Nasopharyngeal primary tumors or complete responders showed significantly higher disease free survival rate. The grade 3 mucositis and nausea/vomiting was noted in 34.5%, respectively. Major prolongation of radiation therapy duration was inevitable in three patients. Twenty-one patients (72.4%) completed 3 courses of cisplatin and 5 patients received 2 courses of cisplatin. Three patients received only one course of cisplatin due to nephrotoxicity and neurotoxicity, and then changed to 5-FU regimen.

Conclusions : Concurrent cisplatin-radiation therapy in locally advanced head and neck cancer showed high response rate, reasonable locoregional control, and survival rate. As expected, acute toxicities were increased, but compliance to treatment was acceptable. Assessment of the effect of the combination in this setting requires further accrual and follow-up.

Key Words : Cisplatin, Radiation therapy, Head & Neck Cancer

INTRODUCTION

Recent meta-analyses of 63 randomized trials to evaluate the effect of the addition of chemotherapy to local therapy modality on survival of patients with head and neck cancer revealed small but absolute survival benefits at 5 year in favor of the addition of chemotherapy. These benefits of 8% increase in absolute 5 year survival were demonstrated only when chemotherapy was delivered concurrently with radiation therapy, while no benefit was seen in neoadjuvant or adjuvant chemotherapy settings.[1)]

Cisplatin was reported to be effective in patients with squamous cell cancer of the head and neck, and, moreover, to enhance the radiation response when combined with irradiation. In patients with advanced squamous cell carcinoma of head and neck, the Radiation Therapy Oncology Group

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(RTOG) tested the combination of concurrent cisplatin and radiotherapy and reported the promising results with respect to response and survival.[2, 3]

This study tried to evaluate the effectiveness of combined treatment using radiation therapy and concurrent cisplatin as a radiosensitizer. The endpoints included toxicity, response rate, locoregional control and preliminary survival outcomes.

MATERIALS AND METHODS

From January 1995 to August 1998, 31 consecutive patients with locally advanced head and neck cancer were registered and treated with radiation therapy combined with concurrent cisplatin chemotherapy. Eligibility criteria included the followings: histologically confirmed American Joint Committee (AJC) stage III and IV nasopharyngeal, oropharyngeal, hypopharyngeal and laryngeal carcinoma (plus stage II for nasopharynx); absence of systemic metastatic disease; KPS >60; adequate renal function (serum creatinine < 1.7 mg%) and hematologic status (white cell count >3,000/mm^3, platelet >100,000/mm^3).

Radiation therapy was delivered through bilateral parallel opposed portals directed to the primary tumor and upper cervical lymphatics mated with an anterior lower neck field that descended to the level of the clavicles using 6MV photon beam and 9 12 MeV electron beams were used to give additional dose to the posterior neck after 39.6 45 Gy by 6MV photon beam to avoid the spinal cord complication. If clinically evident gross disease was present in the lower neck, AP/PA portals were used. The prescribed dose ranged from 70 to 75.6 Gy in 35 42 fractions to gross disease and 50 to 54 Gy in 25 30 fractions to subclinical disease.

Chemotherapy consisted of three courses of cisplatin administered every 3 weeks, beginning on the day 1 of radiation therapy. Cisplatin 100 mg/m^2 was given by rapid intravenous bolus after forced intravenous hydration. The decision of dose modification or discontinuation of cisplatin were made based on hematologic, renal or neurologic toxicity.

Salvage surgery for residual lymphadenopathy was performed in 2 patients at 8 and 12 weeks after completion of concurrent chemo-radiation therapy.

The endpoints of the study included the initial tumor response, toxicity, locoregional failure rate, distant metastasis rate, preliminary disease free and overall survival rates. The RTOG/EORTC toxicity grading system was used. Evaluation of tumor response was made by physical exam, supplemented by follow-up endoscopic findings and radiographic studies. Biopsy was not routinely done unless obvious persistent lesion was seen in at least 3 months of completion of treatment.

Actuarial disease-free and overall survival rates were calculated by the Kaplan-Meier method. Multivariate analyses using Cox-regression method were performed to evaluate the significance of the prognostic factors.

RESULTS

Of 31 patients registered, 29 were available for analysis. The reasons for exclusion were incomplete information for evaluation (1) and refusal of treatment (1). Duration of follow-up ranged from 5 to 55 months with the median of 24 months, and the mean follow-up period was 37 months.

The characteristics of the patients were summarized in Table 1. The age ranged from 22 to 74 years old with median of 56 years. Sixteen patients had nasopharyngeal primary site and 13 patients had non-nasopharyngeal primary site (oropharynx in 5, larynx in 4 and hypopharynx in 4). Twenty-five of 29 patients had stage III or IV disease. Four

Table 1. Patient Characteristics

Characeristic	Number of patient	%
Primary site		
Nasopharynx	16	55.2
Oropharynx	5	17.2
Larynx	4	13.8
Hypopharynx	4	13.8
Stage (AJCC)		
II	4	13.8
III	6	20.7
IV	19	65.5
Tumor stage		
T1	3	10.3
T2	12	41.4
T3	4	13.8
T4	10	34.5
Nodal stage		
N0	6	20.7
N1	4	13.8
N2	15	51.7
N3	4	13.8
Karnofsky Performance Status		
80	9	31.0
70	14	48.3
60	6	20.7

patients who had stage II disease with bulky primary lesions were included in this protocol. The Karnofsky performance status was 80 in 9 patients, 70 in 14 patients and 60 in 6 patients, respectively.

Table 2 showed the initial tumor response rates. Twenty-one (72.4%) patients achieved clinical complete response (CR). The partial response and minimal response rates were 17.2% and 10.4%, respectively.

Table 3 showed the compliance to treatment. Major prolongation of radiation therapy duration for longer than 2 weeks was inevitable in three patients. Twenty-one patients (72.4%) completed 3 courses of cisplatin and 5 patients received 2 courses. Three patients received only one course of cisplatin due to nephrotoxicity and neurotoxicity, and then changed of regimen to 5-FU was made. Table 4 showed the toxicities of the concurrent treatment protocol according to RTOG/EORTC toxicity grading system. The grade 3 mucositis and nausea/vomiting was noted in 34.5%, respectively. Five patients (17.2%) showed grade 3 leukopenia. The seven of 16 patients with nasopharyngeal cancer showed otitis externa and/or media. The optic neuritis was noted in one of patients with nasopharyngeal cancer involving the orbital apex and the cavernous sinus.

Table 5 showed the pattern of failure. Locoregional failure rate was 27.6% that included 6 patients with local failures, 4 patients with regional failures and 2 patients with combined local and regional failures. Four of 29 patients (13.8%) developed distant metastasis involving the lung and/or the bone. Three of these 4 patients were nasopharyngeal primary. Fig. 1 and 2 represented the disease free and overall survival outcome, respectively. The disease free survival rate at 3 years was 60%. Table 6 indicated the prognostic factors affecting the disease free survivial rate. Complete responders had better disease free survival rate than partial or minimal

Table 2. Intial Tumor Response Rate

Response	Number of patient	%
Complete Response	21	72.4
Partial Response	5	17.2
Minimal Response	3	10.4

Table 3. Compliance to Treatment Protocol

Compliance	Number of patient	%
Compliance for Radiation Therapy		
major deviation*	3	10.3
Compliance for chemotherapy		
3 cycles of Cisplatin	21	72.4
2 cycles of Cisplatin	5	17.3
grade 3 leukopenia	3	
poor performance status	2	
cycle of Cisplatin-change to 5-FU	3	10.3
nephrotoxicity	2	
neurotoxicity	1	

*prolonged overall treatment time>2weeks

Table 4. Toxicities

Toxicity	Number of patient	(%)
Acute toxicity*	grade 2	grade 3
Mucositis	19 (66.5)	10 (34.5)
Leukopenia	8 (27.6)	5 (17.2)
Nausea/vomiting	10 (34.5)	3 (10.4)
Laryngeal edema	2 (6.9)	2 (6.9)
Nasopharyngeal ca		
Otitis	7/16	(43.8)
Optic Neuritis	1/16	(6.3)

*RTOG/EORTC toxicity grading system.

Table 5. Patterns of Failure

Pattern of failure	Number of patient	%
Locoregional Recurrence	8	27.6
Local	6	
Regional	4	
Both	2	
Distant Metastasis	4	13.8
Lung	3	
Bone	2	
Both	1	

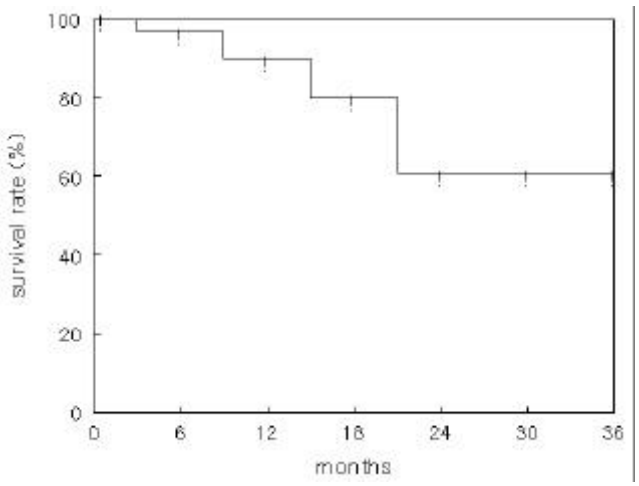

Fig. 1. Overall survival curve.

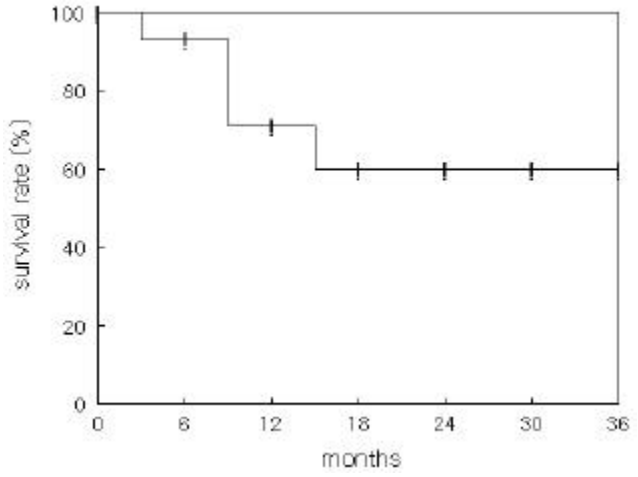

Fig. 2. Disease free survival curve.

Table 6. Prognostic Factors for Disease Free Survival (DFS)

Prognositc factor	No. of patient	3 year DFS (%)	*p*-value
Primary site			*0.005*
nasopharynx	16	87.5	
non-nasopharynx	13	28.8	
Stage			>0.05
T1-2	15	71.4	
T3-4	14	53.9	
N0-1	6	64.0	
N2-3	23	50.0	
Karnofsky Performance Status			>0.05
80	9	77.8	
70	14	57.7	
60	6	31.3	
Overall treatment time			>0.05
≤55 days	18	68.2	
>55 days	11	54.8	
Number of chemotherapy			>0.05
3 cycles	21	69.8	
1 2 cycles	8	53.6	
Initial tumor response			*0.05*
Complete Response	21	72.6	
Partial & Minimal Response	8	25.0	
Anemia			>0.05
(−)	20	67.6	
(+)	9	31.3	

responders (Fig. 3). The patients with nasopharyngeal primary tumors had significantly higher disease free survival rate than those with other primary sites (Fig. 4).

DISCUSSION AND CONCLUSION

Enhancing radiation effects by the concurrent administration of chemotherapy is not a new concept. Randomized trials had shown improved disease-free and overall survival for single agent 5-FU, bleomycin, and mitomycin combined with radiation therapy. The major limitation of these agents were the substantial increases in mucosal toxicity caused by themselves.[4-7]

Cisplatin provides a renewed opportunity for testing this strategy because this agent does not cause mucositis as a primary toxicity. The exact interaction of cisplatin and radiation to enhance cytotoxicity is not completely understood. Possible mechanisms for enhancing radiation effects include inhibition of sublethal damage repair, selective radiosensitization of hypoxic cells, and reduction of tumor bulk,

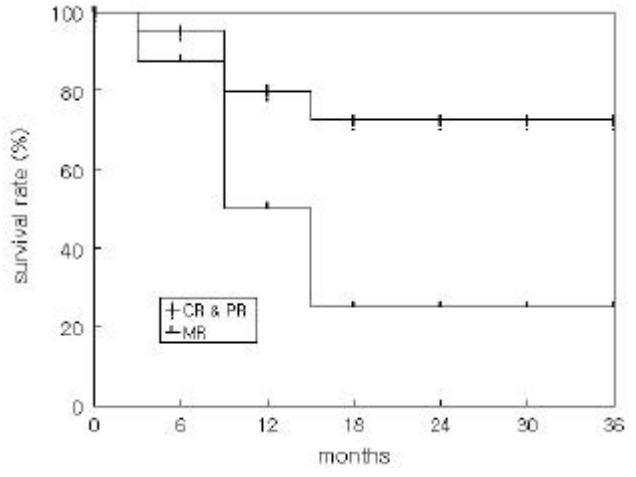

Fig. 3. Disease free survival curve according to tumor response (CR : complete response, PR : partial response, MR : minimal response).

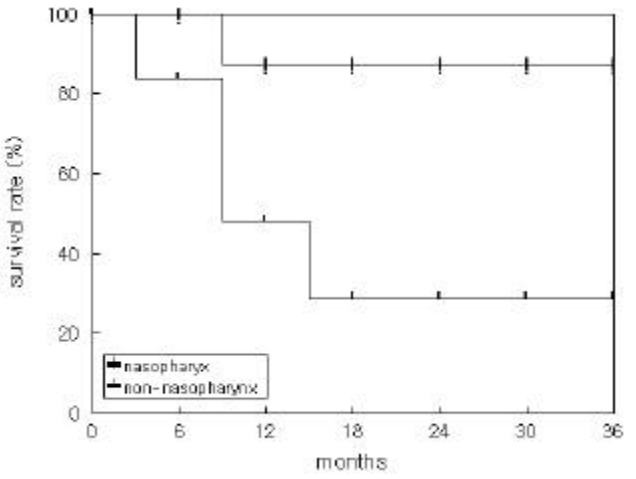

Fig. 4. Disease free survival curve according to primary site.

resulting in improved tumor blood supply, reoxygenation by reduction of tumor mass, and recruitment of cell into a more radiosensitive proliferative phase.[8)]

Concurrent cisplatin chemotherapy combined with radiation therapy was tested primarily in patients with locally advanced, unresectable head and neck cancers. Haselow et al reported the results of an Eastern Cooperative Oncology Group trial randomized patients either to radiotherapy plus weekly cisplatin 20 mg/m^2 or to radiation therapy alone. The overall response rate was significantly higher for concurrent cisplatin plus radiation therapy group (73% versus 59%), but there was no difference in CR rate or survival.[9)] Arlene pointed out that these disappointing results were attributable to the low total dose of cisplatin delivered (120 140 mg/m^2 over 6 to 8 weeks of radiotherapy).[10)]

The Radiation Therapy Oncology Group evaluated an alternative dose and schedule of cisplatin, 100 mg/m^2 every 3 weeks for three doses during conventional radiotherapy. This regimen was quite tolerable; it did not cause significant alteration of radiotherapy delivery.[2)] Long-term results of this RTOG study 81-17 reported that the CR rate in 124 patients was 71% and that the nasopharynx showed the best CR (89%) among the various primary sites. The 4 year locoregional control and survival rates were 43% and 34%, respectively. Compared with historical controls treated with radiation therapy alone, survival rates were improved with concurrent cisplatin chemotherapy.[3)]

These encouraging results of RTOG study 81-17 provided the basis for testing concurrent cisplatin and radiation therapy with specific cisplatin regimens according to specific primary sites in high priority intergroup randomized phase III trials. For advanced stage nasopharyngeal cancer, intergroup study 0099 compared conventional radiotherapy alone versus radiotherapy plus concurrent cisplatin (100 mg/m^2 on day 1, 22, 43) followed by three cycles of adjuvant cisplatin (80 mg/m2 on day 1) and 5-FU (1,000 mg/m^2 on day 1 to 4). Recently, Al-Sarraf et al concluded in the final result report of this trial that concurrent chemoradiotherapy is superior to radiotherapy alone with respect to 3 year progression free survival rate (69% vs. 24%) and overall survival rate (76% vs. 46%). They also mentioned that the addition of effective adjuvant chemotherapy following concurrent chemoradiotherapy was needed to improve the results further based on the high incidence of late systemic failures in advanced nasopharyngeal cancer.[11)] In our study, three of 16 patients (18.8%) with nasopharyngeal cancer developed distant failure. As the intergroup study did not include concurrunt chemoradiotherapy alone arm, the role of adjuvant chemotherapy following concurrunt chemoradiotherapy could not be clearly defined. Recently, our center started randomized phase III trial to define the role of adjuvant chemotherapy following concurrent cisplatin-radiotherapy compared to concurrent ciapltin-radiotherapy alone in advanced nasopharyngeal cancer.

For patients with advanced stage laryngeal cancer that would require total laryngectomy, a three-arm intergroup trial (RTOG 9111, ECOG 9111 and SWOG 9201) is in progress to determine the best organ preservation approach. This trial randomizes patients to receive induction cisplatin and 5-FU chemotherapy followed by radiotherapy; concurrent cisplatin (100 mg/m^2 on day 1, 22, 43) plus radiotherapy; or radiotherapy alone. The other ongoing intergroup trial includes patients with locally advanced, unresectable cancer of hypopharynx, oropharynx, oral cavity or larynx who are randomized to receive conventional radiotherapy; concurrent cisplatin plus conventional radiotherapy; or concurrent cisplatin/ 5-FU chemotherapy plus split-course radiotherapy.[10, 12)] The use of these specific cisplatin regimens at specific primary sites should definitively answer the question of treatment sequence and combined approaches versus radiotherapy alone.

The preliminary results for concurrent cisplatin-radiation therapy in our series of patients with locally advanced head and neck cancers showed high response rate, reasonable locoregional control and survival rates comparable to other reports including RTOG 81-17 study. As expected, acute toxicities were increased, but compliance to treatment was relatively acceptable. Assessment of the effect of the combination in this setting requires further accrual and follow-up and separate analyses according to specific primary sites.

REFERENCES

1. **Pignon JP, Bourhis J, Domenge C, Designe L.** Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma; three meta-analyses of updated individual data. The Lancet 2000;355:949-954
2. **Al-Sarraf M, Thomas F, Pajak TF, et al.** Concurrent Radiotherapy and chemotherapy with cisplatin in inoperable squamous cell carcinoma of the head and neck - An RTOG study. Cancer 1987;15:259-265
3. **Marcial VA, Thomas F, Pajak TF, et al.** Concurrent cisplatin chemotherapy and radiotherapy in advanced mucosal

squamous cell carcinoma of the head and neck - Long-term results of the RTOG study 81-17. Cancer 1990;1:1861-1868
4. **Lo TCM, Wiley AL, Ansfield FJ, et al.** radiation and 5-fluorouracil for advanced squamous cell carcinoma of oral cavity and oropharynx: A randomized study. AJR Am J Rontgenology 1976;126:229-235
5. **Shanta V, Krishnamurthi S.** Combined bleomycin and radiotherapy in oral cancer. Clin Radiol 1980;31:617-620
6. **Fu KK, Phillips TL, Silver LJ, et al.** Combined radiotherapy and chemotherapy with bleomycin and methotrexate for advanced inoperable head and neck cancer: Update of a Northern California Oncology Group randomized trial. J Clin Oncol 1987;5:1410-1418
7. **Weisberg JB, Son YH, Papac RJ, et al.** Randomized clinical trial of mitomycin-C as an adjunct to radiotherapy in head and neck cancer. Int J Radiat Oncol Biol Phys 1989; 17:3-9
8. **Fu KK, Phillips TL.** Biologic rationale of combined radiotherapy and chemotherapy. Hematol Oncol Clin North Am 1991;5:737-751
9. **Haselow RE, Warshaw MG, Oken MM, et al.** Radiation alone versus radiation with weekly low dose cisplatinum in unresectable cancer of head and neck. In: Fee WE, Goefect H, Johns ME, Strong EW, Ward PH, eds. Head and Neck Cancer. Toronto: BC Decker, 1990;279-281
10. **Forastiere AA.** Overview of platinum chemotherapy in head and neck cancer. Seminar in Oncology 1994;21:20-27
11. **Al-Sarraf M, LeBlanc M, Giri PG, et al.** Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: Phase III randomized intergroup study 0099. J Clin Oncol 1998;16:1310-1317
12. **Fu KK, Cooper JS, Marcial VA, et al.** Evolution of the Radiation Therapy Oncology Group clinical trials for head and neck cancer.1996;35:425-438

국문 초록

국소진행된 두경부종양의 Cisplatin-방사선 동시병용치료
- 예비적 임상결과보고 -

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목 적 : 국소진행된 두경부종양 환자에서 방사선감작제로서 cisplatin을 방사선치료와 동시병용하였을때, 반응율과 독성을 알아보고 국소재발율 및 단기생존율을 분석해 보고자 하였다.

대상 및 방법 : 1995년 1월부터 1998 8월까지 AJCC 병기 II-IV의 국소진행된 두경부종양으로 근치적방사선치료중 cisplatin 동시화학요법을 받은 환자 29명을 대상으로 하였다. 비인강암이 16예였고 구인두암이 5예, 하인두암과 후두암이 각각 4예씩이었다. 대상환자의 연령분포는 22세에서 74세로 중앙값은 56세였고 남녀비는 22:7이었다. 방사선치료는 6 MV와 15 MV X선 및 9 14 MeV 전자선을 사용하여 원발병소와 전이된 임파절에 총 7,000 7,560 cGy (중앙값 7,020 cGy)까지 조사하였다. Cisplatin은 100 mg/m^{2}을 방사선치료와 동시에 매 3주 간격으로 3회까지 투여하는 것을 원칙으로 하였다.

결 과 : 치료에 대한 반응율은 완전관해가 21예(72.4%), 부분관해가 5예(17.2%), 경미한 반응이 3예(10.4%)로 나타났다. 치료 후 잔여임파절병변에 대한 경부곽청술이 2예에서 시행되었다. 추적관찰기간(5 55개월, 평균 37개월)중 8례에서 원발병소 혹은 임파절에서 재발하여 국소재발율은 27.6%였고, 원격전이가 4예(13.8%)에서 관찰되었다. 3년무병생존율은 60%였으며 원발병소가 비인강암인 경우나 치료에 완전반응을 보였던 경우가 무병생존율이 유의하게 높은 것으로 나타났다. 치료에 다른 급성독성으로 10예(34.5%)에서 grade 3의 점막염, 5예(17.2%)에서 grade 3의 백혈구감소증이 관찰되었다. 전체 환자 중 21예(72.4%)가 3회의 Cisplatin 화학요법을 완료하였다. 3예에서는 grade 3의 백혈구 감소증, 2예는 전신상태불량으로 cisplatin이 2회만 투여되었고, 다른 3예는 신기능이상 및 신경독성으로 인해 치료중간에 5-FU로 대치되었으며, 전체치료기간이 2주 이상 지연되는 major deviation은 3예(10.3%)에서 관찰되었다.

결 론 : 국소진행된 두경부 종양환자에서 Cisplatin을 근치적방사선치료와 동시에 병용하는 치료전략은 비교적 높은 치료반응율, 국소제어율 및 생존율을 나타내었다. 급성치료독성의 빈도가 높았으나 치료에 대한 순응도는 비교적 양호하였다. 향후 좀더 많은 증례의 수집 및 장기추적관찰과 함께 원발병소에 따른 독립적인 연구가 필요할 것으로 사료되었다.

핵심용어 : Cisplatin, 방사선치료, 두경부종양