DEFINITIVE RADIOTHERAPY WITH OR WITHOUT CHEMOTHERAPY FOR RESECTABLE HEAD AND NECK CANCER

Jason Chia-Hsien Cheng[1], Skye Hongiun Cheng[1], James Jer-Min Jian[1], Lawrence K. Yen[2], Kwan-Yee Chan[3], Cheng-I Hsieh[4]

[1]Department of Radiation Oncology, [2]Department of Head and Neck Surgery and Otolaryngology, [3]Department of Radiology, [4]Department of Medical Oncology, Koo Foundation Sun Yat-Sen Cancer Center

Purpose: To retrospectively analyze the feasibility, toxicity and outcome of definitive radiotherapy with or without chemotherapy for patients with resectable head and neck cancers.

Materials and Methods: Thirty patients with resectable head and neck cancers were treated with definitive split-course radiotherapy with or without concurrent chemotherapy. One patient had stage I, 4 stage II, 3 stage III and 22 stage IV diseases. Radiotherapy was given once daily or twice daily with total dose of 68-74 Gy. Chemotherapy included 2 cycles with CDDP+/-5FU during radiotherapy, and 2 cycles with CDDP+5FU after radiation treatment. Survival outcome was calculated by the Kaplan-Meier method. Prognostic factors were determined by log-rank test.

Results: The median follow-up time was 50.8 months. The 4-year overall survival, disease-free survival and locoregional control rates were 55.7%, 64.9% and 75.8%, respectively. Treatment-related toxicities were tolerable. T1/T2 diseases were associated with better locoregional control (p= 0.03). The presence of residual disease on post-treatment MRI or CT was the prognostic factor for overall survival (p= 0.05), disease-free survival (p= 0.009) and locoregional recurrence-free survival (p= 0.0001).

Conclusion: Definitive radiotherapy with or without chemotherapy can be an alternative to radical surgery for patients with resectable head and neck cancers, with acceptable toxicity and outcome. The presence of residual disease on post-treatment imaging studies demands further investigation and possibly salvage treatment.

[Therapeut Radiol Oncol 1999; 6: 33 - 39]

Key words: Resectable head and neck cancers, Radiotherapy, Chemotherapy, Concurrent

INTRODUCTION

Combinations of surgery and radiotherapy are the standard treatments for patients with locally or regionally advanced head and neck cancer. However, the treatment outcome is not satisfactory, with the survival rate below 40% and locoregional control rate less than 50% [8]. Radical surgery is usually associated with functional or cosmetic compromise in swallowing, respiration, and phonation. Several institutions have tried to preserve both organ and function

Received: 1999, 2, 25. Accepted: 1999, 5, 5.

Address reprint request to: Jason Chia-Hsien Cheng, M. D., Department of radiation Oncology, Koo Foundation Sun Yat-Sen Cancer Center, No. 125, Lih-Der Rd., Pei-Tou, Taipei 112, Taiwan

by the use of non-surgical treatment modalities. With induction chemotherapy followed by radiotherapy [12], concurrent chemotherapy and radiotherapy [13], or hyperfractionated radiotherapy [6], the promising rate of organ preservation has been obtained in selected groups of patients. We reported the experience at Koo Foundation Sun Yat-Sen Cancer Center, in the treatment of resectable head and neck cancers, using split-course radiotherapy with or without chemotherapy.

MATERIALS AND METHODS

From May 1990 through July 1996, 30 patients with resectable head and neck cancer (excluding NPC) were treated with definitive radiotherapy with or without chemotherapy at Koo Foundation Sun Yat-Sen Cancer Center. Twenty-seven patients were male and 3 were female. Age ranged from 25 to 75 years old, with mean age of 56 years old. All patients had the primary tumor at head and neck region, excluding nasopharynx. The locations of the original tumors were listed in Table 1. All patients had biopsy of the primary tumor, and squamous cell carcinoma was confirmed by the pathologist. All the primary tumors and the neck lymphadenopathies were evaluated to be resectable by the otolaryngologist.

The pre-treatment work-up included MRI or CT scan of head and neck, chest radiograph, liver sonography and whole body bone scan. All patients had no evidence of systemic metastasis before the treatment. The stage was based on AJCC classification. One patient had stage I disease, 4 stage II, 3 stage III and 22 stage IV. T and N stages were listed in Table 2.

Table 1. The sites of the original head and neck cancers

Site	No.	Percent
Oral tongue	5	17
Base of tongue	2	7
Tonsil	10	33
Oropharyngeal wall	2	7
Palate	3	10
Hypopharynx	5	17
Buccal mucosa	1	3
Maxillary sinus	1	3
Supraglottic larynx	1	3

The treatment was split-course radiotherapy with or without chemotherapy. The radiation ports included the gross tumor and neck nodal regions. The primary tumor and upper neck were treated with bilateral opposed ports, while lower neck and bilateral supraclavicular fossae with anterior-posterior port. The radiation dose was 70 Gy for the gross primary tumor and neck lymphadenopathies, 50 to 60 Gy for the neck and bilateral supraclavicular fossae with risk of microscopic spread. The fraction size was 2 Gy for once daily and 1.2 Gy for twice daily treatment. One-week rest was prescribed after 44 Gy for once daily and 43.2 Gy for twice daily radiation treatment.

Cisplatinum (CDDP) was administered in bolus intravenously with 60 mg/m^2 on day 1, and 5-FU (5-fluorouridine) in continuous infusion with 600 mg/m^2/day from day 1 to 5. The second cycle of chemotherapy was given after 1-week rest on week 5, with the same regimen and dosage. CDDP alone was given for patients treated with hyperfractionated radiotherapy to avoid severe mucositis. Two cycles of chemotherapy were given 1 and 2 months after completion of radiotherapy, with the dose escalation of CDDP 80 mg/m^2 on day 1 and 5-FU 800 mg/m^2/day from day 1 to 5.

MRI or CT scan of head and neck was performed 3 months after completion of radiothera-

Table 2. T and N stage

	T1	T2	T3	T4	Total
N0	1	4	0	3	8
N1	0	1	2	1	4
N2	2	7	5	4	18
Total	3	12	7	8	30

py to evaluate the treatment response. The patients were followed at out-patient clinic every 3 months for 2 years and every 6 months for 3 years. Chest radiograph and liver sonography were performed every 6 months for 3 years. MRI or CT scan of head and neck was performed once a year for 3 years.

Locoregional recurrence was defined as the presence of any biopsy-proved recurrence at head and neck region. Distant metastasis was defined as the disease recurrence outside head and neck region. Second malignancy was defined as new development of malignancy of different histology from the original head and neck tumor. The patients were followed until the last visit or death. Survival was calculated with Kaplan-Meier method. Prognostic factors were analyzed by log-rank test. Significance level was defined as $p < 0.05$.

RESULTS

The medium follow-up is 50.8 months, ranging from 38.5 to 88.5 months. Twenty-five patients received conventional once daily radiotherapy. Four patients had hyperfractionated radiotherapy, and 1 patient had combination of once-daily and twice-daily treatment. The radiation dose to the primary tumor ranged from 68 to 74 Gy with mean dose of 70.72 Gy. Five patients had radiotherapy alone. One patient had 1 cycle, 9 had 2 cycles, 6 had 3 cycles and 9 had all 4 cycles of chemotherapy. Fourteen patients were alive and 16 dead. Seven patients had locoregional recurrence. All of them died of primary disease. Six patients had distant metastasis, 5 of them had lung metastasis and 1 had both lung and bone metastases. Thirteen patients were alive and disease-free. Nine patients died of primary disease, including 7 patients with local recurrence and 2 with distant metastasis. Five patients died of non-cancer disease, including 3 of pneumonia, 1 of UGI bleeding, and 1 of hepatocellular carcinoma. Three patients had secondary lung cancer and 2 of them died of disease. The treatment-related toxicities were tolerable (Table 3).

The 4-year overall survival, disease-free survival, and local control rates were 55.7%, 64.9%, and 75.8%, respectively. The survival curves were shown in Fig 1-3. By log-rank test, the presence of residual disease on the post-treatment MRI or CT scan of head and neck was the significant factor for worse overall survival (4-year 22% v.s. 70%, p= 0.05), disease-free survival (4-year 33% v.s. 79%, p= 0.009) and locoregional recurrence-free survival (4-year 33% v.s. 95%, p= 0.0001). T1/T2 disease was the significant factor for better locoregional recurrence-free survival (4-year 93% v.s. 57%,

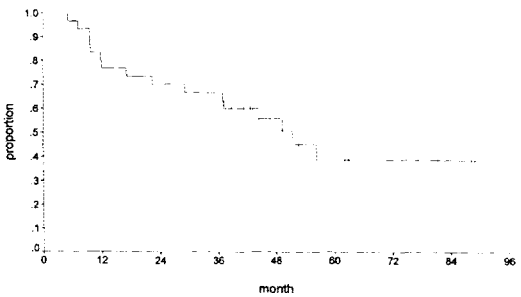

Figure 1. Overall survival

Table 3. Treatment-related toxicity

Toxicity	Gr. 0	Gr. I	Gr. II	Gr. III	Gr. IV	Total
Body weight loss	11 (37%)	12 (40%)	7 (23%)			30
Mucositis			15 (50%)	14 (47%)	1 (3%)	30
Nausea/Vomiting	19 (63%)	3 (10%)	5 (17%)		3 (10%)	30
Anemia	15 (50%)	9 (30%)	4 (13%)	2 (7%)		30
Leukopenia	15 (50%)	11 (37%)	2 (7%)	1 (3%)	1 (3%)	30
Thrombocytopenia	30 (100%)					30

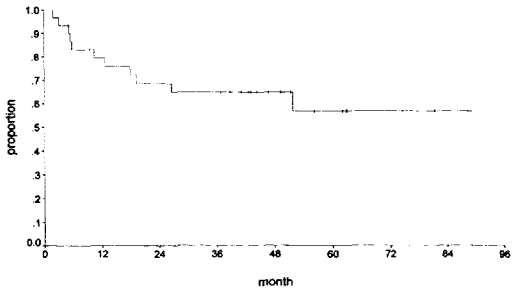

Figure 2. Disease-free survival

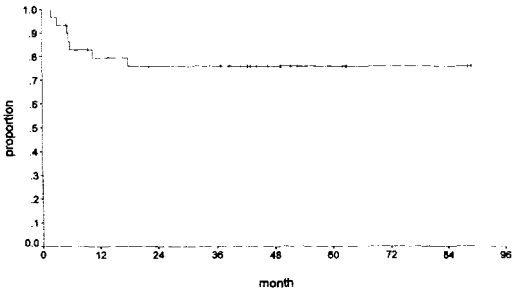

Figure 3. Locoregional recurrence-free survival

Table 4. Analysis of prognostic factors (p value)

	Overall survival	Disease-free survival	Local control
Sex	0.06	0.16	0.34
Age = < 50 v.s. > 50	0.64	0.89	0.84
T1-2 v.s. T3-4	0.34	0.53	0.03
N- v.s. N+	0.99	0.54	0.30
Chemotherapy or not	0.80	0.27	0.36
Tonsil CA or not	0.07	0.83	0.23
Residual disease*	0.05	0.008	0.0001
Local recurrence	0.0000	-	-

Log-rank test

*: presence of residual disease on the post-treatment MRI or CT scan of head and neck

p= 0.03), but not for disease-free survival (p= 0.53) and overall survival (p= 0.34). The locoregional recurrence was associated with the significantly worse overall survival (p= 0.0000). The other factors, including age, sex, N stage, chemotherapy or not, primary tonsillar cancer or not, do not achieve the level with significance (Table 4).

DISCUSSION

Radical surgery followed by post-operative radiation treatment has been the standard treatment recommendation for patients with locally or regionally advanced head and neck cancers. Kramer et al. indicated the 4-year survival rate of 36% and 4-year locoregional control rate of 57% in the final RTOG 73-03 report [8]. Radical surgery is usually associated with the significant functional and cosmetic compromise, including swallow, respiration and phonation. The typical examples are total or near-total glossectomy, partial or total laryngectomy, and tracheostomy. Several study groups have been trying to preserve organ function by the use of induction chemotherapy followed by concurrent chemoradiotherapy [12], concurrent chemoradiotherapy [13], or hyperfractionated radiotherapy [6]. The outcome results are similar to the historical control, but functional preservation and quality of life are a lot better. Our experience indicated the 4-year overall survival, disease-free survival and locoregional control rate of 55.7%, 64.9%, and 75.8%, respectively, which were consistent with the above mentioned study groups.

The treatment-related toxicities were tolerable and manageable. All patients completed the radiation treatment without major deviation or interruption. However, the compliance to

chemotherapy was unsatisfactory. Thirty percent of patients completed 2 cycles of concurrent chemotherapy and another 30% had all 4 cycles of chemotherapy as designed originally. Al-Sarraf et al. reported the compliance rate of 63% and 55% for the concurrent and the adjuvant chemotherapy, in the randomized trial of chemoradiotherapy for nasopharyngeal cancer [2]. Chemotherapy has been widely applied in the neoadjuvant and adjuvant treatment for head and neck cancers. The benefit in the overall survival [2], locoregional control [2], metastasis-free survival [9] and survival parameters in the meta-analysis of randomized trials, has been confirmed [5]. Adelstein et al. reported better relapse-free survival and less systemic metastasis for patients with concurrent chemotherapy and radiotherapy, as compared to radiotherapy alone in their randomized trial for resectable head and neck cancers [1]. Further effort to improve the compliance to chemotherapy is demanded.

In the analysis of prognostic factors, the patients with T1/T2 tumors had better locoregional control as compared to T3/T4 tumors. Furthermore, the presence of residual disease on the post-treatment MRI or CT scan of head and neck bore the significant factor for worse locoregional control, disease-free survival and overall survival. Tumor size has been identified to be one of the most important factors in the treatment of head and neck cancers. Janot et al. indicated that T stage was the only significant factor associated with locoregional failure, in their detailed and prospective analysis of clinicopathological parameters [7]. Tumor response to induction chemotherapy or concurrent chemoradiotherapy is an important indicator in the survival analysis. Spoulding et al. reported that patients with no histologic evidence of tumor had a better disease-free survival than those with persistent disease, in VA Laryngeal Cancer Study Group with induction chemotherapy [11]. They also indicated that patients with complete response had better disease-free survival than partial responders. The most common policy for organ preservation with the non-surgical treatment is to determine the tumor response after induction chemotherapy, or concurrent chemotherapy and radiotherapy with 40-50 Gy [1, 10, 12, 13]. Our result was consistent with these findings, indicating that the presence of residual disease on post-treatment imaging studies was associated with the worse outcome. However, we did not have the biopsy of the corresponding lesion for the tissue diagnosis of residual disease. Further investigation and possibly salvage surgery might be indicated for these patients at completion of concurrent chemoradiotherapy.

Currently reported series with non-surgical modalities for organ preservation have made a lot of progress in the treatment of head and neck cancers. The VA (Veterans Affairs) Laryngeal Cancer Study Group reported the 2-year survival rate of 68% and larynx-preserving rate of 64%, with the induction chemotherapy followed by definitive concurrent chemoradiotherapy if CR or PR obtained [12]. Brizel et al. indicated the 3-year survival rate of 55% and locoregional control rate of 70%, with the concurrent chemotherapy and hyperfractionated radiotherapy, for both resectable and unresectable head and neck cancers [4]. EORTC conducted a phase III randomized trial for larynx preservation in pyriform sinus cancer, comparing induction chemotherapy followed by definitive radiotherapy if CR (complete response) or PR (partial response) achieved, with the traditional radical surgery and post-operative irradiation [10]. The 3-year locoregional control rate was 57% and median survival was 44 months for patients with chemoradiotherapy. The other EORTC (European Organization for Research and Treatment of Cancer) randomized trial reported the 5-year locoregional control rate of 59% for patients with oropharyngeal carcinoma treated with hyperfractionated radiotherapy [6]. In

comparison with RTOG 88-24 report, the 3-year overall survival, disease-free survival and locoregional control rate were 48%, 57%, and 81%, respectively, for patients with stage III and IV resectable head and neck cancers treated with radical surgery and postoperative concurrent chemoradiotherapy [3]. The Cleveland group reported the 3-year relapse-free survival of 67% and organ-preserving survival of 57%, in their randomized trial for patients with resectable stage III/IV squamous head and neck cancers treated with concurrent chemoirradiation [1]. Most of the update results are encouraging and indicate that definitive radiotherapy or combination of chemotherapy and radiotherapy can be an alternative treatment modality to radical surgery in the selected group of patients. It also demands the comprehensive team work in the design of treatment combination and the detailed patient care.

REFERENCES

1. Adelstein DJ, Saxton JP, Lavertu P, et al.: A phase III randomized trial comparing concurrent chemotherapy and radiotherapy with radiotherapy alone in resectable stage III and IV squamous head and neck cancer: Preliminary results. Head & Neck 1997; 19: 567-575.
2. Al-Sarraf M, LeBlanc M, Giri PGS, et al.: Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: Phase III Randomized Intergroup Study 0099. J Clin Oncol 1998; 16: 1310-1317.
3. Al-Sarrah M, Pajak TF, Byhardt RW, Beitler JJ, Salter MM, Cooper JS: Postoperative radiotherapy with concurrent cisplatin appears to improve locoregional control of advanced, resectable head and neck cancers: RTOG 88-24. Int J Radiat Oncol Biol Phys 1997; 37: 777-782.
4. Brizel DM, Albers ME, Fisher SR, et al.: Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. N Engl J Med 1998; 338: 1798-1804.
5. El-Sayed S, Nelson N: Adjuvant and adjunctive chemotherapy in the management of squamous cell carcinoma of the head and neck region: A meta-analysis of prospective and randomized trials. J Clin Oncol 1996; 14: 838-847.
6. Horiot JC, Le Fur R, N'Guyen T, et al.: Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: Final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. Radiother Oncol 1992; 25: 231-241.
7. Janot F, Klijanienko J, Russo A, et al.: Prognostic value of clinicopathological parameters in head and neck squamous cell carcinoma: A prospective analysis. Br J Cancer 1996; 73: 531-538.
8. Kramer S, Gelber RD, Snow JB, et al.: Combined radiation therapy and surgery in the management of advanced head and neck cancer: Final report of study 73-03 of the Radiation Therapy Oncology Group. Head & Neck Surgery 1987; 10: 19-30.
9. Laramore GE, Scott CB, Al-Sarraf M, et al.: Adjuvant chemotherapy for resectable squamous cell carcinomas of the head and neck: Report on Intergroup Study 0034. Int J Radiat Oncol Biol Phys 1992; 23: 705-713.
10. Lefebvre J-L, Chevalier D, Luboinski B, Kirkpatrick A, Collette L, Sahmoud T: Larynx preservation in pyriform sinus cancer: Preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. J Natl Cancer Inst 1996; 88: 890-899.
11. Spoulding MB, Fischer SG, Wolf GT, the Department of Veterans Affairs Cooperative Laryngeal Cancer Study Group: Tumor response, toxicity, and survival after neoadjuvant organ-preserving chemotherapy for advanced laryngeal carcinoma. J Clin Oncol

1994; 12:1592-1599.
12. The Department of Veterans Affairs Cooperative Laryngeal Cancer Study Group: Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. N Engl J Med 1991; 324: 1685-1690.
13. Urba SG, Forastiere AA, Wolf GT, Esclamado RM, McLaughlin PW, Thornton AF: Intensive induction chemotherapy and radiation for organ preservation in patients with advanced resectable head and neck carcinoma. J Clin Oncol 1994; 12: 946-953.

使用放射治療或合併化學治療之方式治療可切除之頭頸部腫瘤

成佳憲[1] 鄭鴻鈞[1] 簡哲民[1] 閻愷正[2] 詹光裕[3] 謝政毅[4]

財團法人辜公亮基金會和信治癌中心醫院
放射腫瘤科[1] 頭頸外科及耳鼻喉科[2] 放射診斷科[3] 腫瘤內科[4]

目的：回顧性分析以放射治療或合併化學治療之方式治療可切除之頭頸部腫瘤的可行性、治療副作用及存活率。

材料與方法：三十位診斷爲可切除之頭頸部腫瘤病人接受根治性放射治療或合併化學治療。一位病人爲第一期，四位第二期，三位第三期，二十二位第四期疾病。放射治療爲一日一次或一日兩次，總劑量爲 68 - 74Gy 。化學治療使用 CDDP 與 5-FU ，包括兩次放射治療中的合併治療，與兩次放射治療後的治療。以 Kaplan-Meier method 分析存活率，以 log-rank test 分析預後因子。

結果：追踪時間之中位數爲 50.8 個月。四年整體存活率、無病存活率及局部控制率分別爲 55.7% 、 64.9% 及 75.8% 。治療相關的副作用屬可忍受。 T1/T2 腫瘤的病人在統計上具有意義的較佳局部控制率 (p= 0.03)。治療結束後的核磁共振或電腦斷層檢查中若有殘存疾病的病人，具統計上有意義的較差整體存活率 (p= 0.05)、無病存活率 (p= 0.009) 及局部無再發存活率 (p= 0.0001)。

結論：放射治療或合併化學治療之方式治療可切除之頭頸部腫瘤可考慮爲根除手術外的一種選擇。它具有可接受的治療相關副作用及存活率。治療結束後的核磁共振或電腦斷層檢查中若有殘存疾病的病人，應接受進一步探查與治療。

[放射治療與腫瘤學 1999; 6: 33 - 39]

關鍵詞：可切除之頭頸部腫瘤、放射治療、化學治療、合併治療