PRIMARY RADIOTHERAPY TREATMENT RESULTS OF MAXILLARY SINUS SQUAMOUS CELL CARCINOMA

Chih-Chiech Hsu[1], Louis Tak Lui[1], Na-Na Chung[1], Lai-Lei Ting[1], Wen-Yi Shau[2]

[1] *Department of Radiotherapy, National Taiwan University Hospital*
[2] *Graduate Institute of Epidemiology, Collage of Public Health, National Taiwan University*

Purpose: Evaluating 5-year survival rates of maxillary sinus squamous cell carcinoma treated by different methods.

Materials and Methods: From 1977 to 1991, 61 patients of maxillary sinus squamous cell carcinoma were included in our study. There were 11 patients with T3 (18%) disease and 50 patients with T4 (82%) disease. Eighteen patients (29.5%) were treated by radiotherapy alone (RT), 32 patients (52.5%) by combined surgery and radiotherapy (SRT) and 11 patients (18.0%) by combined radiotherapy with intra-arterial 5-FU infusion chemotherapy and antrostomy drainage (CRT).

Results: Five-year survival rates were 5.6%, 34.4% and 54.5% in RT, SRT and CRT groups, respectively. Statistical significant difference ($p<0.05$) of survival rates was noted. Regional neck nodal metastasis at initial diagnosis carried significant worse survival results than initial N0 state (7.1% vs. 36.2%, $p=0.0003$). Multivariate analysis revealed that treatment methods, sex and N stages significantly influenced the 5-year survival rate.

Conclusion: Combined treatment was superior to radiotherapy alone in 5-year survival rates.

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Key words: Radiotherapy, Combined treatment, Maxillary sinus, Squamous cell carcinoma.

INTRODUCTION

Squamous cell carcinoma (SCC) of maxillary sinus often presents with advanced stage because the early stage disease may mimic benign process such as sinusitis. Obvious symptoms develop later until the occurrence of invasion to adjacent structures such as nasal cavity, nasopharynx, temporal fossa which often make difficulty in radical surgery. Although many discrepancies exist in management, radiotherapy is frequently given either as an adjuvant role or as a primary treatment under an inoperable situation.

Sixty-one patients in our study received definite primary treatment in our hospital from 1977 to 1991. There were mainly three kinds of different treatment groups. One group of patients received radiotherapy alone (RT) because of their inoperable disease extent or medical conditions, another group of patients received combined radiotherapy with chemo-

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Address reprint request to: Lai-Lei Ting M. D., Department of Radiotherapy, National Taiwan University Hospital, 1, Chang-Te Street, Taipei.

therapy (CRT) and the final group of patients, accounting for more than 50%, received radiotherapy following either radical or debulking surgery (SRT). The treatment results of these three groups were calculated respectively.

MATERIALS AND METHODS

From 1977-1991, 68 patients of maxillary sinus SCC with pathological proof received definite primary RT, CRT and SRT in our hospital. Seven patients were lost to follow-up after treatment and were excluded in our study. Sixty-one patients with at least 5-year follow-up at clinics or through communication by letters were included in analysis. The median follow-up interval was 47.3 months (range from 2 to 198 months). After staging work-up, none of them had evidence of distant metastasis at diagnosis. Twenty-three patients had CT scan examination of local extent. Staging was re-evaluated according to the publication of 1992 AICC TNM system. The characteristics of patients, including age, sex and histology according to different treatment modalities were tabulated at Table 1. All of them were advanced T3 or T4 diseases.

Eighteen patients of the RT alone group received 60-70 Gy (mean 66.3 Gy) to tumor bed via wedge-pair portals or three-fields technique (anterior and two lateral wedged fields) by ^{60}Co machine with 2 Gy per fraction.

Eleven patients received CRT. Most of them had intra-arterial 5-FU infution with combination of radiation and antrostomy drainage. Daily temporal arterial injection of 250 mg/M^2 5-FU was given with RT up to a total dose of 2500-6000 mg/M^2 (mean 3860 mg/M^2). Since antrostomy drainage was considered as a part of treatment, this management was also named as "trimodal therapy" by Japanese author [13]. Radiation technique was the same as the RT group with dose of 52-64 Gy (mean 55.7 Gy).

Thirty-two patients in the SRT group received radiotherapy with a dosage of 60-70 Gy (mean 66.1Gy) following surgery. The procedure of surgery included 13 radical maxillectomy (with or without orbital removal), 6 partial maxillectomy (with or without orbital removal), 5 Denker's procedure and 8 antrostomy Cadwell-Luc's operation. The Cadwell-Luc's surgery might be less radical than previous procedures and was thought to be a "non-radical operation" in our study. Although its main role was for diagnosis, the procedure may have the function of debulking the tumor. In addition, it also played a certain role in the CRT group mentioned above.

Fourteen patients with neck nodal metastasis received radiotherapy alone for treatment with or without previous excision biopsy. Average irradiation doses of 57 Gy, 61 Gy and 65 Gy were given to N1, N2 and N3 diseases through AP-PA field or lateral field.

Survival rates, local control rates and regional neck control rates were calculated by Kaplan-Meier method. Univariate analysis of statistical significance was performed by log rank test. Multivariate analysis by Cox regression model was introduced for calculating the

Table 1. Patients' characteristics

	RT	CRT	SRT
Age	52.7±6.3	53.1±5.4	54.9±4.8
M/F	12/6	8/3	24/8
Histology differentiated			
well or moderate	12	9	25
poorly	6	2	7
T stages			
T3	1	5	5
T4	17	6	27

Table 2. Death causes for different treatment modalities within 5-year follow-up

Death causes	RT	CRT	SRT	Total(%)
Local recurrence	12	2	15	29(67.4%)
Neck recurrence	5	3	2	10(23.3%)
Distant metastasis	0	0	4	4(9.3%)

statistical significance of risk factors for distant metastasis and prognostic factors for survival. Statistical software of SPSS version 6.0 was used for above analysis.

RESULTS

Survival

Summarizing the death causes in Table 2, 3 major causes of death (local failure, neck failure, and distant metastasis) were found. Local failure was 3 times more than neck failure (67.4% vs. 23.3%). The least common cause of death was metastasis (mainly lung metastasis) which accounted for 9.3% of total death. Death caused by reason other than cancer did not exist in our study within 5-year follow-up. Overall 5-year survival of all patients was 29.5%. Figure 1 demonstrated the survival curves for different treatment groups. Five-year survival rates were 5.6%, 34.4% and 54.5% in RT, SRT and CRT groups. Significant difference existed when making comparison between both RT vs. SRT (p=0.003) and RT vs. CRT groups (p=0.002). There was no significant difference in survival rates between SRT and CRT groups (p=0.267). Thus, CRT and SRT had significantly better treatment outcome than RT alone.

Local control

Local failure occurred mostly within 1 year (83.9%) after treatment. Fourteen patients of T4 had local failure within half year after treatment. However, local failure of T3 was found more than 6 months after treatment. The average observed failure intervals after treatment were 4.2 months in RT group, 10.1 months in SRT group and 8.5 months in CRT group, respectively. Combined treatment modalities seemed to delay the onset of local recurrence.

We calculated 5-year local control rates of different treatment methods. Persistent disease after treatment was considered as relapsing at the first month. Local control rates were 0%, 60%, 100% for RT, SRT, CRT in T3; 31.4%, 45.3%, 60% for RT, SRT, CRT in T4; and 29.3%, 48.3%, 80% for RT, SRT, CRT in T3+T4. The curves of 5-year local control rates of different treatment modalities for all patients were demonstrated in Fig. 2. Significant difference (p=0.013) between the 3 kinds of treatment was noted. Either SRT or CRT was superior to RT in local control.

Regional neck control

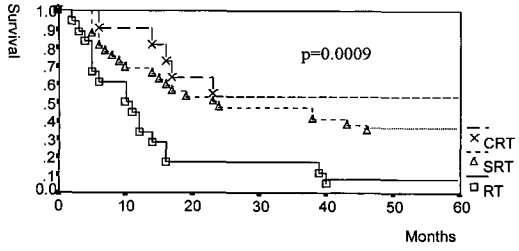

Fig 1. Survival curves for different treatment modalities

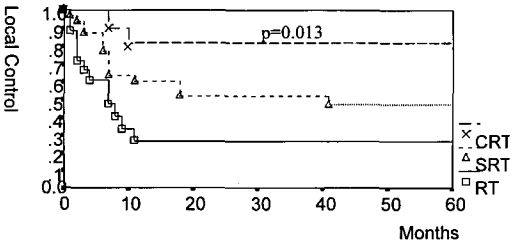

Fig 2. Local control curves for different treatment modalities

Table 3. Initial N stages and metastatic sites of neck at diagnosis

No.	N0	N1	N2	N3	Digastric	Midjugular	Submandibular	Preauricular
T3	10	0	1	0	1	1	0	0
T4	37	8	3	2	8	7	2	1
Total	47	8	4	2	9	8	2	1

6 patients had neck lymph nodal involvement more than 2 sites

There were 23% (14 patients) of neck nodal metastastic rate at initial diagnosis (Table 3). The most common metastatic site was digastric region (45%), followed by midjugular chain (40%). Five-year survival rate of N0 patients was significantly higher than survival rate of patients with positive neck node (36.2% vs. 7.1%, p=0.0003). Five-year regional neck control rates were 70.1%, 29%, 75% and 50% through N0 to N3, respectively. There might be some error existing because 3 of 4 N2 patients and 1 of 2 N3 patients died of local failure or metastasis without regional neck failure observed, which might lead to overestimate the neck control rates of N2 and N3 diseases.

Forty-seven patients without neck nodal metastasis (N0) at diagnosis were noted. Among them, 5 patients had prophylactic bilateral neck irradiation with dose 30-50 Gy (mean 44Gy). Five-year neck control rates were 80% and 75.2% in treated and untreated necks which were statistically non-significant (p=0.89). We also calculated regional neck control rates of different histology in non-irradiated neck of N0. The well and moderately differentiated SCC were considered as "differentiated group" which was in contrast to the poorly or undifferentiated carcinoma. There was also no statistically significant difference existing between the two groups (p=0.96). Five-year neck control rates were 74.8% and 80% for differentiated group and poorly differentiated carcinoma, respectively.

Distant metastasis

As shown by Table 4, 6 patients (9.8%) developed distant metastasis after treatment. Among them, SRT group seemed to have more distant metastasis than the other 2 groups. But multivariate analysis revealed that only the neck control status significantly influenced the future development of distant metastasis (p=0.03) when age, sex, T stages, N stages, local control and regional neck control were taken into analysis. Three over 47 (6.4%) patients without observed neck failure had distant metastasis while 3/14 (21.4%) patients with neck failure had distant failure simultaneously.

Prognostic factors

Results from multivariate analysis for prog-

Table 4. Numbers of distant metastasis according to different treatment modalities

	RT	CRT	SRT	Average duration (months) after treatment
Bone	0	1	1	9.5±1.0
Lung	0	0	4	11.8±14.6

Table 5. Multivariate analysis for prognostic factors of 5-year survival

Factor	p value	Hazard ratio	95% C. I.
Age	0.55	0.99	0.96-1.02
Sex (female vs. male)	0.03	0.27	0.12-0.64
Treatment method			
SRT vs. RT	0.005	0.32	0.14-0.70
CRT vs. RT	0.03	0.28	0.09-0.86
T stages	0.08	2.58	0.88-7.55
N stages	0.001	2.34	1.41-3.88
Histology (poorly vs. differentiated)	0.16	0.56	0.24-1.28

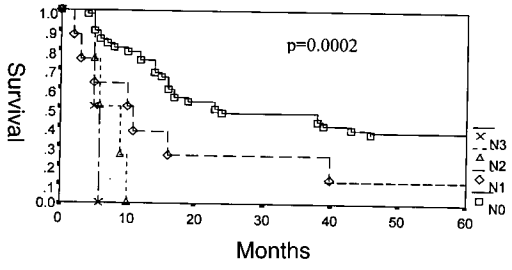

Fig 3. Survival curves of different N stages

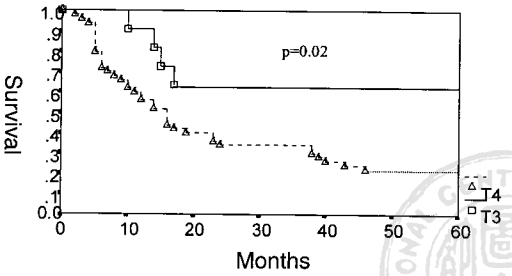

Fig 4. Survival curves of different T stages

nostic factors of 5-year survival were calculated when taking age, sex, treatment methods, T stages, N stages and pathology into consideration (Table 5). Parameters of sex, treatment methods and N stages had $p<0.05$ and were considered as significant prognostic factors. Survival results of different N stages were demonstrated in Fig. 3 where univariate analysis showed $p=0.0002$. Five-year survival rates were 36.2%, 12.5%, 0% and 0% through N0 to N3. T stages had marginal significance with $p<0.1$. We also plotted survival curves of different T stages in Fig. 4. Five-year survival rates were 63.6% and 22% for T3 and T4, respectively. Female patients had the superior 5-year survival rates (47.0%) to those of male patients (22.7%).

Late complication

Two patients without previous orbital removal developed radiation keratitis 3 and 45 months after irradiation. One patient had osteoradionecrosis and 7 had bare bone from 9 to 127 months (mean 44.1 months) after irradiation. Four patients had either oro-antral or antro-cutaneous fistula. One patient developed trismus 75 months after irradiation.

DISCUSSION

Squamous cell carcinoma made up 84% of neoplasm in maxillary sinus at our hospital. The second common histology was adenocystic carcinoma (6%) which was excluded in our analysis because it had longer survival duration even after development of distant metastasis. Other histology types such as sarcoma, neuroendocrine carcinoma, malignant schwanoma and malignant mixed tumor accounted for 10%. Maxillary sinus cancer tends to be advanced stage with invasion to adjacent structure at diagnosis. As other reports, more than 90% of the patients have clinically and roentgenographic evidence of various degrees of bone destruction [5]. It was not surprising that all of our patients were advanced stage diseases (T3: 18% and T4: 82%). Because of its advanced nature, combined treatment modalities rather than radiotherapy or surgery alone is suggested for management [16]. According to our results, we observed that either CRT or SRT had significant advantage in survival and local control.

As reported by other studies [1,7], the 5-year survival rates of T2-4 are 0-44% (mainly 35-40%) and the 5-year local control rates of T2-4 were 14-40% when treated by radiotherapy alone. By using radiotherapy alone in unresectable T3 and T4, the 5-year survival rates are limited to 10-15% [8]. Our study revealed inferior 5-year survival and local control rates (5.6% and 27.2%) in RT group than those of the other two treatment groups because of many inoperable advanced diseases existed in RT group. Treatment dose greater than 65Gy for achieving well local control has ever been suggested by Giri et al [2], but it is often hard to be delivered when taking the tolerance of brain and eye into consideration. To solve this problem, three-dimensional planning system for sparing critical organ is designed to deliver higher dose to tumor bed in order to increase local control [10].

Better treatment outcome of combined surgery and radiotherapy than those of radiotherapy alone are demonstrated by many authors [2,6,7,14]. In general, 5-year survival rates of such combination range from 35% to 50%. However, there is no consensus as to the best timing of radiotherapy before or after surgery. Hu et al [4] have demonstrated better 5-year survival rates of 64% by using preoperative radiotherapy than 26% by postoperative radiotherapy ($p=0.05$). However, Lavertu et al [6] do not have the same conclusion in their 10-year experience's study. In contrast, they demonstrated mild better 5-year survival rates of 53% in postoperative radiotherapy than survival rate of 49.5% in preoperative radiotherapy. The role of preoperative radiotherapy is to reduce the dis-

semination of malignant cells during surgical manipulation and to make surgical removal of tumor easier. Besides, peripheral infiltrated malignant cells rather than main bulky mass may be eliminated by preoperative radiotherapy. The advantage of postoperative radiotherapy is to treat possible small or undetected residual foci after surgery and make no delay of radical surgery [5,16]. Thus, both kinds of treatment methods are reasonable and need large control study to determine which one is better.

The group of intra-arterial 5-FU injection with antrostomy drainage during radiotherapy yielded the best treatment outcome in our study. Sakai et al [11] showed better 2-year local control rate of 50%, and Sato et al [12] revealed 2-year survival rate of 57% by using intra-arterial 5-FU infusion with radiotherapy for maxillary sinus carcinoma. They also claimed that combined treatment would accelerate clearance of tumor cell, required less irradiation dose to yield comparable control rate as done by high-dose radiation and preserved much better cosmetic result. However, Shibuya et al [13] demonstrated the multiplicity of feeding vessels to maxillary sinus by using Tc99m-macroaggregated-albumin intra-arterial injection. Relative fewer branches derived from maxillary artery supplied to anterior and superior part of maxillary sinus were demonstrated in their study. This was also the major reason why we abandoned the clinical trial after 1985. Furthermore, Tsujii et al [15] demonstrate mild inferior but comparable results by using intra-arterial 5-FU infusion with antrostomy drainage during radiotherapy in. survival rates when comparing with the treatment method of combined maxillectomy and radiotherapy (SRT). The 5-year survival rates in their study are little lower in arterial-injection group than the SRT group (42.1% vs. 44.0%). Considering the well treatment results in our study, this kind of management for more chemotherapeutic-sensitive head and neck SCC, as reviewed by other author [3], was appreciated.

Our incidence of neck nodal metastasis at diagnosis (23%) was higher than other series reported [9] (10-20%). This may be due to more advanced local-invasive nature of disease in our patient. We found that positive initial neck nodal status correlated with significantly worse survival results. Whether prophylactic radiotherapy to N0 neck is necessary or not is still controversial. Giri et al [2] do not suggest elective neck radiation because they have only 8% of neck failure in untreated N0. But Paulino et al [9] summarize many other studies as well as theirs, find that various range of 8.6-28.9% neck recurrence rates develop in initial untreated N0 disease. Since the incidence of neck failure is high in their untreated N0 (28.9%), they suggest prophylactic neck irradiation for maxillary sinus SCC. However, our neck control rates of N0 disease was similar in both prophylactic irradiated neck and those without treatment. Since case number of elective neck irradiation was small in our study, it is hard to make definite conclusion. It may still need large control study.

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上頷竇扁平細胞癌之放射治療結果

許智捷[1] 雷 德[1] 鍾娜娜[1] 丁禮莉[1] 邵文逸[2]

[1]台大醫院 放射治療科
[2]台灣大學公衛學院 預防醫學研究所

目的：評估上頷竇癌用不同治療方式後的結果。
材料與方法：從 1977 至 1991 年 61 個上頷竇扁平細胞癌中，有 11 個病人（18 %）是 T3, 50 個病人（82 %）是 T4 。其中 18 個病人只作放射治療， 32 個病人術後追加放射治療， 11 個病人合併放射治療，竇造口術及動脈內注射化學治療。
結果：以上三組病人五年存活率分別爲 5.6 %， 34.4 %及 54.5 %，具有明顯統計差別。在診斷時有淋巴轉移的病人，其五年存活率較無淋巴轉移病人明顯偏低（7.1 %比 36.2 %）。多變數分析得出性別，治療方式，淋巴分期爲顯著的預後因子。
結論：合併治療比只作放射治療有較好的五年存活率。
[放射治療與腫瘤學 1998; 5: 163-170]

關鍵詞：放射治療、合併治療、上頷竇、扁平細胞癌