Comparison between Surgical and Non-Surgical Treatment of Squamous Cell Carcinoma of Tonsil : Retrospective Analysis of 87 Patients

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편도 편평상피암의 수술적 치료와 비수술적 치료의 비교 : 87명 환자의 후향적 분석

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연구목적 :

국소적 진행성 편도암환자에서 수술적치료와 비수술적치료의 결과를 비교 분석하고자 하였다.

연구방법 :

수술 후 보조방사선요법을 시행한 군과 유도화학요법 시행 유무에 상관없이 근치적 방사선 치료 또는 항암화학-방사선 동시치료를 받은 비수술군의 임상결과를 후향적으로 분석하였다.

연구결과 :

52.4개월의 중앙 추적기간결과, 대상환자의 중앙 연령은 53세 이었다. 대상 환자 중 병기 Ⅲ, Ⅳ기 환자는 72명(82.8%)이었고, 49명(56.3%)이 수술적 치료를, 38명(43.7%)명이 비수술적 치료를 받았다. 방사선 조사량외에 양군간의 차이는 없었다 (수술군 : 60.4Gy, 비수술군 : 70.2Gy, p=0.02). 비수술군의 전체 생존율은 81.6%이었다. 수술군의 8명(16.3%), 비수술군의 6명 (15.8%)에서 재발이 발생하였다. 흥미로운 사실은 원격재발은 2명 모두 수술군에서 발생하였다. 병기 Ⅲ, Ⅳ기의 5년 무병생존율과 전체생존율은 수술군이 각각 82.1%, 86.9%이고, 비수술군이 각각 83.3%, 83.1%이었다(p=0.96, p=0.96).

결 론 :

수술적 치료에 비해 비수술적 치료가 활동능력이 불량한 환자에게 선호되었을 가능성이 있었음에도 불구하고, 치료성적은 비슷하였다. 편도암에서 수술적 치료와 비수술적 치료의 전향적 무작위 비교연구가 필요하다.

중심 단어 : 편도암 · 수술 · 화학요법.

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Introduction

The traditional treatment of locoregionally advanced squamous cell carcinoma of the head and neck (SCCHN) is a surgery with or without postoperative radiotherapy (RT). However, the surgical approach has potential limitations. If the extent of surgery for patients with SCCHN is minimized, functional and anatomical sequelae are diminished but treatment outcome would be poor. Therefore, induction chemotherapy has been investigated to preserve organ especially in laryngeal or hypopharyngeal cancer. But survival benefit was not demonstrable or rather debatable[1)2)].

Concurrent chemoradiotherapy (CCRT) in SCCHN was introduced to maximize synergic effect. After a number of randomized studies had compared CCRT with RT alone in stage III, IV disease of SCCHN, the survival results in CCRT group showed benefit over RT alone group[3)5)]. Moreover, meta-analyses have demonstrated survival outcome similar to that which would be expected with surgery plus postoperative RT in locally advanced resectable disease[6)7)]. Since then, a number of studies have been conducted utilizing CCRT as an alternative for surgery in patients with resectable advanced SCCHN with a major goal of organ preservation.

Recently, the first randomized trial for comparing surgery plus RT with CCRT was published in advanced non-metastatic SCCHN[8)]. This trial showed comparable 3-year disease free survival and overall survival. However, to our knowledge, no group has undertaken a randomized trial to compare surgery with non-surgical treatment specifically in patients with advanced resectable carcinoma of tonsil. We investigated the treatment outcome of the patients with locally advanced tonsil cancer and compared outcome of surgical treatment with that of non-surgical treatment.

Patients and Methods

1. Patients

We reviewed retrospectively the medical records of patients who newly diagnosed tonsillar carcinoma at Asan Medical Center from March 1990 to January 2005. The eligibility criteria for enrollment to this study were (1) histologically proven squamous cell carcinoma, (2) resectable nonmetastatic lesion, (3) no coexisting malignancy, (4) no history of previous chemotherapy, (5) performance score of 0−2 according to the Eastern Cooperative Oncology Group scale, (6) adequate bone marrow, renal and hepatic function in order to tolerate CCRT. Patients were staged according to the AJCC/UICC system (6th edition, 2002).

2. Treatment and safety

The surgery group consisted of radical surgery followed by adjuvant radiotherapy with or without induction chemotherapy. Surgery included a wide excision of the tumor with or without radical neck dissection as needed. Adjuvant radiotherapy was given to the primary site and neck, 5days a week to a total 60Gy in 30 fractions for 6weeks. Adjuvant radiotherapy was given 4weeks after surgery, and not later than 6weeks. Induction chemotherapy was comprised of FP (5-FU, 1000mg/m^2 IV D2~6+cisplatin, 60mg/m^2 IV D1), DP (docetaxel, 70mg/m^2 IV D1+cisplatin, 75mg/m^2 IV D1) or DFP (docetaxel, 70mg/m^2 IV D1+5-FU, 750mg/m^2 IV D1-5+cisplatin, 75mg/m^2 IV D1). Non-surgery group was planned to given a total 70Gy of irradiation in 35 fractions in 7weeks, and concurrent chemoradiotherapy consisted of radiotherapy with weekly cisplatin (20mg/m^2) ± tegafur/uracil (UFT®) or 3-weekly cisplatin (100mg/m^2). Furthermore non-surgery group received the induction chemotherapy as needed. Response to treatment was assessed 4 weeks after the end of the treatment. The safety was assessed in terms of toxicity, and evaluated based on the CTC (Common Terminology Criteria for Adverse Events version 3.0 [CTCAE v3.0]).

3. End points and statistical consideration

The progression free survival time was calculated from the time of start treatment until the first progression on the treatment, relapse of cancer, death of any cause or last follow-up day. And, disease-specific progression free survival time was calculated from the time of start treatment until the first progression on the treatment or relapse of cancer. The overall survival was calculated from the time of start treatment until death of any cause or last follow-up day. Disease-specific overall survival was calculated from the time of start treatment until death due to disease. Survival curves were estimated using the Kaplan-Meier method. A p value <0.05 was considered statistically significant, and all analyses were performed using SPSS 12.0.

Results

1. Patient characteristics

Between March 1990 and January 2005, a total of 87 patients were newly diagnosed as squamous cell carcinoma of tonsil at Asan Medical Center. Basic characteristics of patients and the TNM stage of the tumor in both treatment arms were outlined (Table 1, 2). Two patients of early tonsil cancer received postoperative radiotherapy because of close resection

margin and incomplete nodal dissection. The median age was 53years (range, 27−90), and the median follow-up time of alive patients was 52.4months (4.8−187.0). The majority of the disease stage was stage IV (69.0%), followed by stage III (13.8%). Forty-nine patients (56.3%) received surgical treatment, whereas non-surgical treatment was given to 38 patients (43.7%).

2. Treatment and outcomes

Treatment methods of each group were summarized (Table 3, 4). When treatment was finished in non-surgery group, 28 patients (73.7%) showed complete response, 3 patients (7.9%) obtained partial response, respectively (Table 5). Salvage surgery was performed in 2 of 7 patients who had failed to respond to the treatment. In addition, relative dose intensity of CCRT group was 0.83.

3. Recurrence

Recurrence was observed in 8 patients (16.3%) of surgery group and 6 patients (15.8%) of non-surgery group. The median time to recurrence was 6.5months (range, 2.0−14.6). The local recurrence occurred in 3 patients (6.1%) in surgery group and 2 patients (5.3%) in non-surgical group, respectively and regional recurrence occurred in 6 patients (12.2%) in surgery group (S) and 4 patients (10.5%) in non-surgery group (NS), respectively. However, the distant recurrence was observed only in the surgery group (2 patients). So, the locoregional control rate was 85.7% in the surgery group (95% CI, 75.9−95.5%) and 81.6% in the non-surgery group (95% CI, 69.3−93.9%), respectively (p=0.31). In the pati-

Table 1. The basic characteristics of patients

	Surgery group (S) n (%)	Non-surgery group (NS) n (%)	*p value*
No. of Patients	49 (100.0 %)	38 (100.0 %)	
Median follow-up	52.4 months (4.8−187.0)		
Median age (years)	50 (28−68)	58 (27−90)	*0.19*
Male	45 (91.8%)	31 (81.6%)	*0.20*
Initial symptoms			
Foreign body sense	5 (10.2%)	9 (23.7%)	
Sore throat	15 (30.6%)	11 (28.9%)	
Neck mass	28 (57.1%)	15 (39.5%)	
Odynophagia	1 (2.1%)	3 (7.9%)	
Initial imaging W/U			
CT[a]	17 (34.7%)	15 (39.5%)	
MRI[b]	10 (20.4%)	9 (23.7%)	
CT + MRI	13 (26.5%)	8 (21.1%)	
CT + PET[c]	6 (12.2%)	6 (15.7%)	
MRI + PET	2 (4.1%)	0 (0.0%)	
Not available	1 (2.1%)	0 (0.0%)	
Histology			*0.35*
WD[d]	6 (12.2%)	5 (13.2%)	
MD[e]	32 (65.4%)	12 (31.6%)	
PD[f]	11 (22.4%)	12 (31.6%)	
Undiff.[g]	0 (0.0%)	9 (23.6%)	
Stage			*0.38*
I	2 (4.1%)	2 (5.3%)	
II	5 (10.2%)	6 (15.7%)	
III	6 (12.2%)	6 (15.7%)	
IV	36 (73.5%)	24 (63.3%)	

a : Computerized tomography, b : Magnetic resonance image, c : Positron emission tomography, d : Well-differentiated, e : Moderate-differentiated, f : Poorly-differentiated, g : Undifferentiated

Table 2. The TNM stage of the tumor according to treatment groups (AJCC 6th Ed, 2002)

	Surgery group (n=49)				Non-Surgery group (n=38)			
	T1	T2	T3	T4	T1	T2	T3	T4
N0	2	5	0	0	2	6	1	0
N1	3	1	2	0	1	2	2	0
N2	13	12	6	2	4	8	4	3
N3	0	0	2	1	1	2	1	1

Table 3. Treatment methods

Treatment type		No. (%)
Surgery group	Surgery+RT[a]	39 (44.8%)
	Induction CT[b]+Surgery+RT	10 (11.5%)
	CCRT[c]	8 (9.2%)
Non-surgery group	Induction CT+CCRT	10 (11.5%)
	RT alone	12 (13.8%)
	Induction CT+RT	8 (9.2%)

a : Radiotherapy, b : Chemotherapy, c : Concurrent chemoradiotherapy

Table 4. Treatment characteristics

	Surgery group (n=49)	Non-surgery group (n=38)
Wide excision only	8 (16.3%)	−
Wide excision+radical neck dissection	41 (83.7%)	−
RT[a] does (Gy)	60.4 (27.0−75.2)	70.2 (16.0−80.2)
Does ≥ 60Gy (Patients)	42 (85.7%)	33 (86.8%)
RT duration (days)	50 (22−73)	59 (10−79)
RT fraction (number)	33 (17−41)	35 (8−49)
Time to start RT after surgery	4.9weeks (95% CI, 2.4−9.5)	

a : Radiotherapy

Table 5. Treatment outcomes

	Surgery group (n=49)	Non-surgery group (n=38)
Induction chemotherapy		
Overall response	7/10 (70.0%)	18/18 (100.0%)
Median No. of cycles	3 (1−5)	3 (1−3)
Overall response after treatment	−	31 (81.6%) (95% CI, 69.3−93.9%)

ents with progression or recurrence (n=18), the salvage treatment consisted of surgery in 38.9% of patients (4S, 3NS), chemotherapy in 38.9% (4S, 3NS) and irradiation in 11.1% (1S, 1NS) and 5 patients refused further treatment.

4. Survival

The 5-year PFS rates were 81.1% for surgery group (95% CI, 70.1−92.1%) and 70.6% for non-surgery group (95% CI, 56.1−85.1%) (p=0.37), and 80.1% for surgery group and 69.3% for non-surgery group in stage III−IV disease (p=0.29). Disease-specific 5-year PFS rates were 82.9% for surgery group and 82.5% for non-surgery group (p=0.89) and 82.1% (95% CI, 71.4−92.8%) and 83.3% (95% CI, 71.4−95.1%) in stage III−IV disease (p=0.96), respectively (Fig. 1). At the time of analysis, 18 patients (9S, 9NS) were dead and disease-associated death occurred in 6 patients (12.2%) in surgery group, and 4 patients (10.5%) in non-surgery group. The 5-year OS rates were 84.3% for surgery group (95% CI, 74.1−94.5%) and 68.2% for non-surgery group (95% CI, 53.4−83.0%) (p=0.32), and 84.2%, and 65.1% in stage III−IV disease, respectively (p=0.36). Disease-specific 5-year OS rates were 86.5% for surgery group and 82.6% (p=0.96) for non-surgery group, and 86.9% (95% CI, 77.5−96.3%) and 83.1% (95% CI, 71.2−95.0%) in stage III−IV disease (p=0.96), respectively (Fig. 2).

5. Safety and toxicity

In surgery group, postoperative complications (fistula and dehiscence) occurred in 5 patients (10.2%), but wound infection did not occur. In non-surgery group, grade 3 or worse neutropenia and thrombocytopenia were developed in 5 (13.2%) and 1 patient (2.6%), respectively. Febrile neutropenia was noted in a patient and recovered. There was no significant statistical difference in both groups, except a weight loss in which more patients in non-surgery group were observed (Table 6). No treatment related mortality occurred in both groups.

Table 6. Non-hematologic acute toxicities in non-surgery group (CTCAE Ver. 3.0)

	Surgery group		Non-surgery group		
	Grade 1, 2	Grade 3, 4	Grade 1, 2	Grade 3, 4	*p* value
Weight loss	35 (71.4%)	3 (6.1%)	27 (71.0%)	8 (21.1%)	*0.048*
Dysphagia	25 (51.0%)	2 (4.1%)	24 (63.2%)	2 (5.3%)	0.45
Stomatitis	37 (75.5%)	2 (4.1%)	30 (78.9%)	−	0.45
Nausea	4 (8.2%)	−	9 (23.7%)	−	0.07
Fistula	1 (2.0%)	−	3 (7.9%)	−	0.31
Skin	25 (51.0%)	−	14 (36.8%)	−	0.20
Anorexia	5 (10.2%)	−	7 (18.4%)	−	0.35
Asthenia	12 (24.5%)	−	11 (26.3%)	−	0.81
Xerostomia	34 (69.4%)	6 (12.2%)	21 (55.3%)	8 (21.1%)	0.37
Voice change	Not evaluated		2 (5.3%)	−	−

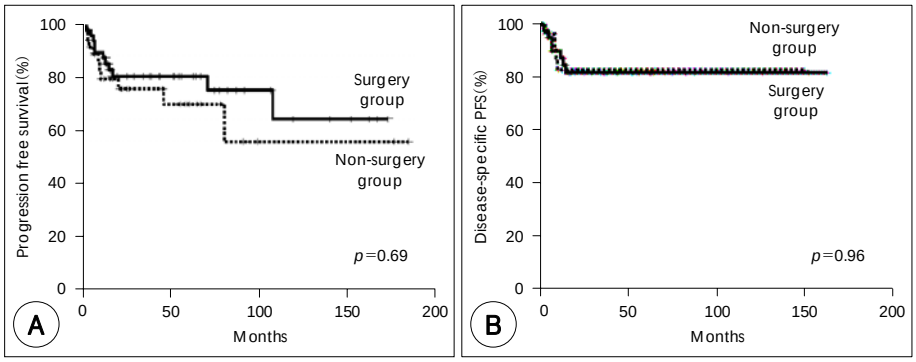

Fig. 1. Survival curves in stage III, IV disease according to treatment. A : Progression free survival. B : Disease-specific progression free survival.

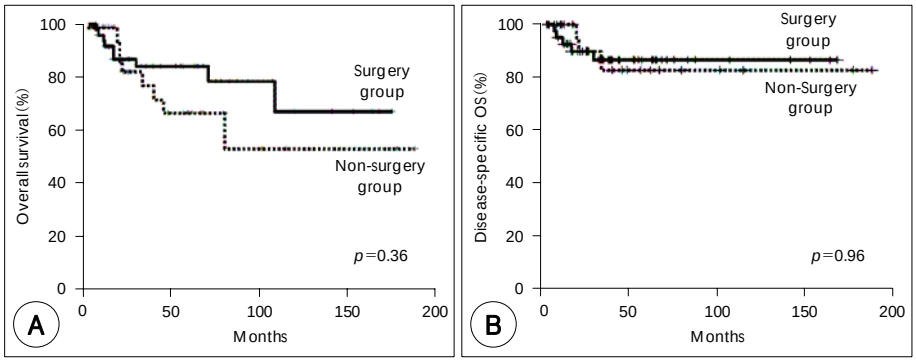

Fig. 2. Survival curves in stage III, IV disease according to treatment. A : Overall survival. B : Disease-specific overall survival.

Discussion

The aim of this study was to evaluate and compare the treatment outcome between surgery group and non-surgery group. The treatment outcome of single modality, that is radiotherapy or surgery, is similar in patients with early stage tonsil cancer[9]. However, the prognosis of advanced disease (stage III or IV) was poor. Patients with advanced disease need to be treated with multimodal combined treatments. Surgery has played important role even in the treatment for advanced head and neck cancer, but it has perioperative morbidity and postoperative anatomical, functional and psychosocial sequelae[10]. Recently concurrent chemoradiotherapy has emerged as a standard treatment for patients who decline surgery or desire organ preservation.

Generally, the treatment outcome for tonsil cancer patients showed that 5-year OS rate was 30−60%, and disease-specific OS rates 20−71%[11-15]. In our study the survival outcome was comparable with that of other studies, and disease-specific survival outcomes were similar in both groups. However, the overall survival rate showed lower trends in non-surgery group as compared with surgery group. It was supposed that our study was not a randomized trial, so there were no definitive criteria of selection which patients would be treated with either surgical treatment or non-surgical treatment. Elderly patients and patients with comorbidies and poor performance were likely to be treated with non-surgical treatment rather than surgical treatment. Therefore, survival rate for non-surgery group was expected to be lower, but there was no significant survival difference between two treatment groups. Disease-specific survival and disease control rate in both groups were comparable.

There had been few randomized study in resectable head and neck cancer, and recently the first attempt was reported to compare the upfront surgery and adjuvant RT with CCRT as primary treatment[8]. In that study, 3-year PFS rates were 43% for CCRT and 54% for surgery, respectively and 3-year OS rates were 40% for CCRT and 50% for surgery group, respectively. They concluded that CCRT was an effective form of treatment with limitation of toxicity and surgery remained an important modality of bulky, yet resectable disease. However, they included broad range of HNSCC. So, their results cannot be compared directly with our results.

Recurrence of the head and neck cancer is seen mainly in locoregional area, but distant recurrence is also the important cause of treatment failure and death[8)16)17]. In this study, there was acceptable result of locoregional and distant recurrence rates. It is notable that distant recurrence occurred only in a surgery group; however, it is difficult to conclude due to small number of patients that surgical treatment seems to be less effective in controlling systemic disease.

Safeties and toxicities were also major concern in the non-surgical treatment of head and neck cancer. Variable toxicity profiles were ascribed to different and various chemotherapy agents and radiation schedule[18]. In our study, toxicity profiles were comparable in both groups.

Conclusion

This study showed that the treatment outcome in non-surgery group was similar to that in surgery group in terms of progression free survival, overall survival and recurrence rates despite patients with poor performance were likely to receive non-surgical treatment. Further prospective randomized clinical trials to compare surgical treatment with non-surgical treatment of concurrent chemoradiotherapy in patients with tonsillar carcinoma are warranted.

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