Comparison of clinical outcome and quality of life between definitive radiotherapy and postoperative radiotherapy for oral cavity and oropharyngeal cancer patients

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Clinical outcomes and quality of life after definitive radiotherapy in oral cavity and oropharyngeal cancer patients compared with postoperative radiotherapy

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<ABSTRACT>

Comparison of clinical outcome and quality of life between definitive radiotherapy and postoperative radiotherapy for oral cavity and oropharyngeal cancer patients

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Purpose: To evaluate which one is the better treatment strategy by comparing clinical outcome and complication of postoperative radiotherapy (RT) and definitive RT in carcinoma of oral cavity or oropharynx.

Material and methods: Fifty-five patients with oral cavity cancer and 62 patients with oropharyngeal cancer patients treated with definitive or postoperative RT between January 2006 – August 2008 were retrospectively analyzed. The median follow-up time was 34 (range 4-70) months and the median age was 57 (range 26-85). Number of patients with stage IV was 18 of 26 (69%) patients in definitive group and 63 of 91 (69%) in postop group. The portion of intensity-modulated RT was 69% (18 patients) in definitive group and 59% (54 patients) in postop group (p=0.014), but total radiation dose was not significantly different (median dose 70Gy vs. 63Gy, p=0.465). Chemotherapy was applied to 84.6% (22 patients) in definitive group and 8% (7 patients) in postop group. To assess patients' quality of life, information of complaint during treatment and follow-up after the treatment were collected.

Results: Between 2 groups, there were no significant differences in 3-year local control rate (81% vs. 87%, p=0.945) and 3-year progression-free survival (77% vs. 68%, p=0.16). Treatment-related dysphagia (85% vs. 36%, p<0.001) was worse in definitive group significantly and treatment-related xerostomia (35% vs. 56%, p=0.054) tended to be worse in postop group. In late complication, xerostomia (40% vs. 37%, p=0.968) and dysgeusia (19% vs. 7%, p=0.144) showed no difference between 2 groups, but 41% (23 of 56 patients) of patients with reconstruction suffered from flap-related

complication. There was no late dysarthria in definitive group while 12% (8 patients) in postoperative group experienced it.

Conclusions: In oral cavity or oropharyngeal cancer, definitive RT showed comparable clinical outcome and complication rate compared to major surgery and postoperative RT. As non-invasive treatment modality, definitive RT may replace major surgery in oral cavity and oropharyngeal carcinoma.

Key words : head and neck neoplasms, carcinoma of mouth, oropharyngeal neoplasms, radiotherapy

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I. INTRODUCTION

In many cases of carcinomas of oral cavity or oropharynx, the primary treatment is radical surgery. According to clinical cervical lymph node metastatic status, the extent of radical neck dissection is decided.[1,2] When loco-regional advanced disease is suspected, reconstruction should follow the radical surgery. Radiation therapy (RT) must be performed if pathological results confirm the risk factors related to recurrence, as T3/4 disease, positive or close surgical margin, 2 of more metastatic lymph nodes, extracapsular extension or perineural invasion.[3]

Definitive RT with or without concurrent chemotherapy is also considered as organ-preserving treatment for advanced stage carcinomas of oral cavity or oropharynx. In previous studies of its treatment outcome, similar locoregional control rates were reported in T3/4 diseases.[4-11]

And these areas include important structures such as spinal cord, cranial nerves, carotid arteries, mandible, and salivary glands. When these structures are damaged

by the tumor itself or by treatment, respiration, oral intake and cosmesis are going to be impaired. Therefore, the interest to the quality of life (QoL) after the treatment is having been increasing.[10] Comparing with radical surgery, concurrent chemoradiotherapy (CCRT) showed more acute complications but no difference in late complications with more chance to gain better QoL by organ preservation, without statistical significance.[12,13] In addition, rapid development in each field of surgery, RT and chemotherapy turned existing data difficult to apply to current situation.

From these diverse aspects, the best treatment modality in locally advanced carcinoma of oral cavity or oropharynx is still controversial.[14]

The aim of this study is to evaluate which one is the better treatment strategy by comparing clinical outcomes and complication affecting QoL of definitive and postoperative RT in carcinoma of oral cavity or oropharynx. It is a retrospective analysis of locoregional recurrence-free survival rate (LRFS), progression-free survival rate (PFS) and incidence of treatment-related complications.

II. MATERIALS AND METHODS

1. Patients

This study is a retrospective analysis of 117 patients with squamous cell carcinoma of oral cavity or oropharynx treated with definitive RT or surgery and postoperative RT at the Severance hospital, Seuol, Korea, from January 2005 to

August 2008.

In patients treated with definitive RT (definitive group), stage was determined based on computed tomography (CT) or magnetic resonance imaging (MRI). In patients treated with surgery and postoperative RT (postop group), surgical staging was done. American Joint Commission on Cancer (AJCC) 7th edition was used.

2. Follow-up

During the RT, every patient had weekly examination to detect treatment-related complication. After completion of RT, patients visited outpatient clinic of radiation oncology, otorhinolaryngology or plastic surgery depending on the treatment they had received.

In definitive group, CT or MRI for evaluation of treatment response were done at 1 to 3 months after completion of RT. Besides, periodic image studies were performed in all patients during their follow-up.

To compare the QoL between 2 groups, complaints of complication were checked. During the RT, oral mucositis, radiation dermatitis of neck, dysphagia, and xerostomia were checked. After the treatment, xerostomia, dysgeusia, dysarthria were checked and other complaints from patients were collected. Late complication is defined as complication observed after 1 year later of treatment. To decide the degree of complication, Common Terminology Criteria for Adverse Events version 3.0 was used.

3. Statistical analysis

Survival times were calculated from the day of pathologic diagnosis. Locoregional recurrence was defined as tumor recurrence or distinct progression in primary area and cervical lymph node area. Progression was defined as recurrence or distinct progression at any site.

For comparison of categorical variables, the chi-squared test and Fisher's exact test were used. LRFS and PFS was calculated using Kaplan-Meier method and compared using the log-rank test. All data were analyzed using SPSS software (SPSS Inc., Chicago, IL, USA.

III. RESULTS

1. Patients characteristics

The median age of patients was 57 (range: 26-85) years. Male patients were dominant (male:female=98:19). Primary site in oral cavity was in 55 patients, oropharynx was in 62 patients.

There were 26 patients in definitive group and 90 patients in postop group.

There was no difference in age and sex between 2 groups, while definitive group showed worse performance status than postop group.

The stage and N classification showed no difference between 2 groups, but there were more T 4 patients in postop group than definitive group (Table 1).

In postop group, the number of patients with negative surgical margin, close

less than 0.5cm and positive margin were 20 (22%), 46 (51%) and 24 (27%), respectively.

Table 1. Patients characteristics

	Definitive group		Postop group		p-value
	No. of pateients	(%)	No. of pateients	(%)	
Age (Year)					0.812
<55	9	(35)	42	(46)	
≥55	17	(65)	49	(54)	
Sex					0.18
Male	24	(92)	74	(81)	
Female	2	(8)	17	(19)	
Performance status (ECOG*)					0.027
0	6	(23)	25	(27)	
1	16	(62)	64	(65)	
2	4	(15)	2	(8)	
Stage					0.961
I & II	3	(12)	9	(10)	
III	5	(19)	19	(21)	
IV	18	(69)	63	(69)	
T classification					0.009
T1	4	(15)	20	(22)	
T2	12	(47)	33	(36)	
T3	6	(23)	11	(12)	
T4	4	(15)	27	(30)	
N classification					0.355
N0	5	(19)	18	(20)	
N1	4	(15)	26	(29)	
N2, N3	17	(66)	47	(51)	
RT modality					0.014
3D CRT†	8	(31)	54	(59)	
IMRT‡	18	(69)	37	(41)	

* ECOG; Eastern Cooperative Oncology Group, † 3D CRT; 3-dimensional radiotherapy, ‡ IMRT; intensity-modulated radiotherapy

2. Treatments

In definitive group, intensity-modulated radiotherapy (IMRT) was performed in 18 of 26 patients (69%) and three-dimensional conformal radiotherapy (3D-CRT) in 8 of 26 patients (31%, Table 1). The range of total radiation dose was 63-82.5 Gy and fraction size was 1.8-2.5 Gy (Table 2). The number of patients received CCRT and RT alone was 22(84.6%), and 4(15.4%), respectively. Half of the patients with CCRT received induction chemotherapy. Concurrent chemotherapy regimens were as follow; weekly cysplatin in 8 (36.4%), daily cisplatin in 4(18.2%), fluorouracil (5FU) and cisplatin in 5(22.7%), 5FU -docetaxel- cisplatin in 2(9.2%), 5FU – docetaxel in 1(4.5%), 5FU –carboplatin in 1(4.5%), and cetuximab in 1(4.5%). Induction chemotherapy regimens were as follow; docetaxel – TS-1 in 4(36.4%), 5FU - docetaxel – cisplatin in 4(36.4%), 5FU – cisplatin in 2(18.2%), and 5FU – docetaxel in 1(9%).

In the postop group, all 91 patients underwent radical resection of primary lesion and neck dissection. The range of neck dissection was determined by clinical stage and lymphatic drainage of the primary lesion. Reconstruction after the radical dissection was performed in 71 patients (78%). IMRT) was performed in 54 patients (59%) and 3D-CRT in 37 patients (41%, Table 1). The range of total radiation dose was 45-70 Gy and fraction size was 1.8-2.25 Gy (Table 2). Seven patients (7.7%) received CCRT and all of them took cisplatin.

Comparing 2 groups, portion of patients with IMRT was significantly larger in definitive group (69% vs. 41%, p=0.014).

Table 2. Radiotherapy characteristics

	Definitive group		Postop group		
	Median	(Range)	Median	(Range)	P-value
Total dose (Gy)	70	(63-82.5)	63	(45-70)	0.465
Involved neck dose (Gy)	66.6	(59.4-70.2)	63	(45-70)	0.555
Elective neck dose (Gy)	53.4	(27-59.4)	45	(27-57.5)	0.069
Fraction size (Gy)	2.12	(1.8-2.5)	1.8	(1.8-2.25)	0.472
Fraction number	33	(30-39)	33	(24-37)	0.021

3. Recurrence rates, LRFS and PFS

Median follow-up time was 34 (range, 4-70) months. During the follow-up, 19% (5 patients) of definitive group and 34% (31 patients) of postop group showed recurrence. Fourteen percent (15 patients) of postop group showed distant failure, while there was no distant failure in definitive group. This difference was statistically significant (p=0.033). Otherwise, there was no difference in pattern of failure between 2 groups (Table 3).

Table 3. Patterns of failure

	Definitive group		Postop group		Total		p-value
Local recurrence							0.889
No	22	(85)	78	(86)	100	(86)	
Yes	4	(15)	13	(14)	17	(14)	
Regional recurrence							0.334
No	23	(89)	73	(80)	96	(82)	
Yes	3	(11)	18	(20)	21	(18)	
Distant failure							0.033
No	26	(100)	77	(85)	77	(88)	

Yes	0	(0)	14	(15)	14	(12)	
Total recurrence							0.148
No	21	(81)	60	(66)	81	(70)	
Yes	5	(19)	31	(34)	36	(30)	
Final status							0.395
NED*	20	(77)	58	(64)	78	(67)	
ACD†	0	(0)	5	(5)	5	(4)	
DOI‡	2	(8)	5	(6)	7	(6)	
DOD§	4	(15)	23	(25)	27	(23)	

* NED; No evidence of disese, † ACD; Alive with disease, ‡ DOI; Died of intercurrent disease, §DOD; Died of disease

Three-year PFS was 77 % and 69% in definitive group and postop group, respectively (p=0.16, Figure 1) and 3-year LRFS was 81% and 87% in definitive group and postop group, respectively (p=0.945, Figure 2).

Figure 1. Progression-free survival

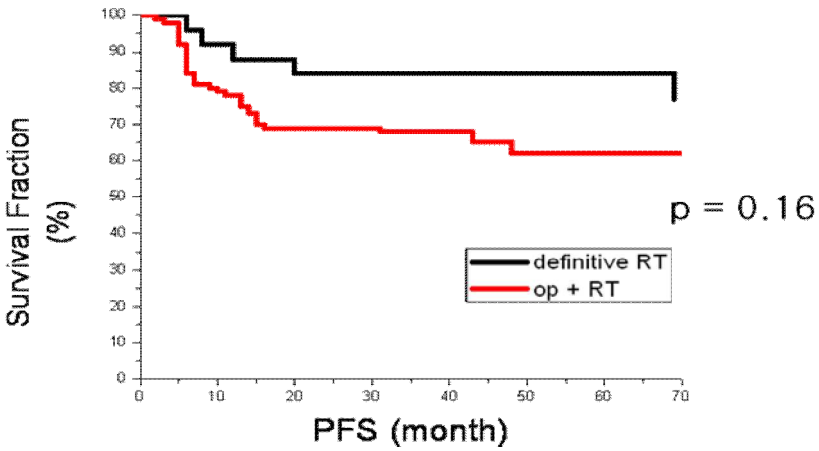
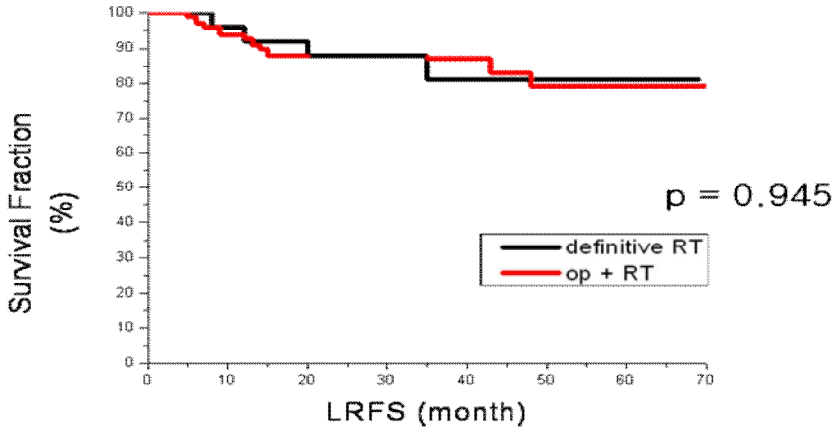


Figure 2. Locoregional recurrence-free survival



4. Quality of Life

A. Acute complication

The portion of patients diagnosed with grade 2 or 3 oral mucositis was 92% (24 patients) and 90% (82%), grade 2 or 3 radiation dermatitis was 54% (14 patients) and 41% (38 patients), xerostomia was 35% (9 patients) and 56% (51 patients), and dysphagia was 85% (22 patients) and 36% (33%) in definitive and postop group, respectively. Comparing the results in 2 groups, incidence of dysphagia showed statistically significant difference ($p<0.001$, Table 4).

B. Late complication

Xerostomia was detected in 42% (8 patients) and 35% (24 patients), dysgeusia in 15% (8 patients) and 7% (5 patients) in definitive and postop group, respectively, without statistical significance. However, dysarthria was observed in

Table 4. Acute complication

	Definitive group				Postop group				P-value
	None	Grade 1	Grade 2	Grade 3	None	Grade 1	Grade 2	Grade 3	
Oral mucositis	0 (0)	2 (7)	12 (46)	12 (46)	0 (0)	9 (10)	62 (68)	20 (22)	0.051
Dysphagia	4 (15)	15 (58)	7 (27)	0 (0)	58 (64)	30 (33)	3 (3)	0 (0)	<0.001
Radiation dermatitis	0 (0)	12 (46)	10 (39)	4 (15)	3 (3)	50 (55)	34 (37)	4 (4)	0.193
	No	Yes			No	Yes			
Xerostomia	17 (65)	9 (35)			40 (44)	51 (56)			0.054

Table 5. Late complication

	Definitive group			Postop group			P-value
	None	Grade 1	Grade 2	None	Grade 1	Grade 2	
Xerostomia	11 (58)	7 (37)	1 (5)	45 (65)	19 (28)	5 (7)	0.723
	No	Yes		No	Yes		
Dysgeusia	17 (85)	3 (15)		64 (93)	5 (7)		0.286
Dysarthria	20 (100)	0 (0)		60 (88)	8 (12)		0.108
Overall comlication	10 (47)	11 (53)		27 (36)	49 (64)		0.313

12% (8 patients) in postop group, while none of the patients in definitive group experience it (Table 5). Twenty-seven of 71 patients with reconstruction in postop group experienced flap-related complication.

IV. Discussion

QoL had become an important issue for oncologists as well as cancer patients. Not only the sequela from the disease itself, but also from the treatments for patients may affect patients' QoL, studies about the sequelae from major oncologic treatment modalities are exist. Surgery may leave donor site morbidity, microvascular flap complications, wound infection, shoulder disability, esthetic changes and swallowing and chewing difficulties. Radiation can cause fibrosis, mucositis, dysphagia, and xerostomia. In case of CCRT, patients may experience opportunistic infection, hematopoietic suppression and renal failure.[15]

However, differences in QoL of resectable and advanced oral cavity or oropharyngeal cancer patients treated with surgery and postoperative RT or definitive RT remain largely under-evaluated.[16]

In this study, we reviewed treatment outcomes and complications affecting QoL in radically treated oral cavity or oropharyngeal cancer patients, depending on the treatment modality in relatively large number of patients. In our results about acute complications, oral mucositis and radiation dermatitis developed in similar rate in 2 groups, while xerostomia was more common in definitive

group. The reason for this might be related to the fact that more patients in definitive group received IMRT, because IMRT can reduce the dose to major salivary glands and eventually reduce the possibility of xerostomia.[15] On the other hand, dysphagia was significantly more common in definitive group and it might be due to the high portion of CCRT (84.6%) in definitive group. Only 7% of patients in postop group received CCRT. From the radiosensitizing effect of concurrent chemotherapeutic agents, there might be more disphagia in definitive group despite the similar radiation dose comparing with the postop group.

In our study, we defined late complication as the complication observed after 1 year later of treatment. It is from the findings of previous studies as follow; the scores of QoL affected by the treatment improved until the first year after treatment,[17] and worsened QoL subclasses after extensive surgery and RT returned as pretreatment values at 1 year after the treatment.[18] In a previous study that chose 3 years as the cutoff for defining the late complication, authors declared the risk of positive bias of the selection due to the follow-up loss from death of the patients during the 3 years. [19]

In spite of the 1 year period for function return, 38% of the patients underwent reconstruction complained impairments from the flap. Major complaint was the volume problem and 2 patients finally had second surgery. Otherwise, facial deformities and dysarthria were also common, and 7 of 8 patients with dysarthria were treated with radical surgery and reconstruction.

A weakness in our study comes from its retrospective nature. This study also bases on subjective reports from patients and physical examination, not quantitative questionnaires. Nonetheless, we have attempted to provide useful information of expectable complications depending on the treatment modalities, which might be helpful to make decisions of the treatment.

V. CONCLUSION

In oral cavity or oropharyngeal cancer, definitive RT showed comparable clinical outcome and complication rate compared to major surgery and postoperative RT. As non-invasive treatment modality, definitive RT may replace major surgery in oral cavity and oropharyngeal carcinoma.

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< ABSTRACT(IN KOREAN)>

구강암과 구인두암에서 수술 후 방사선치료와 근치적 방사선치료의 성적과 부작용에 대한 비교

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차 지 혜

목적: 구강암과 구인두암에서 수술 후 방사선치료를 받은 군과 근치적 방사선치료를 받은 군 간의 임상적 치료 성적을 국소 제어율과 무진행 생존율 측면에서 비교하고 환자의 삶의 질에 대해 수집된 정보를 분석하여 환자에게 더 나은 치료가 무엇인지 밝히고자 한다.

대상 및 방법: 2006년 1월부터 2008년 8월까지 본원에서 근치적 방사선치료 또는 수술 후 방사선치료를 시행받은 구강암 환자 55명과 구인두암 환자 62명(총 117명)을 후향적으로 분석하였다. 추적관찰 기간은 4-70개월(중앙값: 34개월)이었으며 연령분포는 26-85세(중앙값: 57세), 남녀 성비는 98명, 19명이었다. 근치적 방사선치료군 26명 중 1-3기가 8명(31%), 4기가 18명(69%)이었으며 수술 후 방사선치료군 91명 중에서는 각각 26명(31%)과 63명(69%)이었다. 세기조절방사선치료 시행 비율은 근치적 방사선치료군에서 69%(18명), 수술 후 방사선치료군에서 59%(54명)이었으나(p=0.014), 두 군의 총 방사선량은 유의한 차이가 없었다(중앙값 70Gy vs. 63Gy, p=0.465). 근치적 방사선치료군 중 22명(84.6%), 수술후 방사선치료군 중 7명(8%)이 항암화학요법을 함께 시행받았다. 삶의 질에 대해서는 치료 중의 구내염, 경

부 방사선피부염, 연하곤란, 구갈 여부와 치료 종료 후 추적관찰에서 만성 구갈과 미각 장애, 그 외의 호소 사항에 대한 정보를 수집하였다.

결과: 두 군 간의 3년 국소 제어율(81% vs. 87%, p=0.945)과 3년 무진행 생존율(77% vs. 68%, p=0.16)의 의미있는 차이는 관찰되지 않았다. 치료중 연하곤란(85% vs. 36%, p<0.001)은 근치적 방사선치료군에서 의미있게 높게 나타났고, 치료중 구갈(35% vs. 56%, p=0.054)은 수술 후 방사선치료군에서 높은 비율로 나타났으며, 그 외의 치료 중 부작용은 두 군 간의 차이가 없었다. 만성 부작용 중 구갈(42% vs. 35%, p=0.723)과 미각 장애(15% vs. 7%, p=0.286)는 두 군 간에 차이를 보이지 않았으나, 조음장애의 경우 근치적 방사선치료군에서는 보고되지 않은 데 반해 수술 후 방사선치료군에서는 12%(8명)에서 보고되었다. 또한 수술 후 방사선치료군에서 재건술을 시행받은 71명 중 27명(38%)이 피판으로 인한 후유증을 호소하였다.

결론: 구강암과 구인두암의 치료에서 근치적 방사선치료는 수술과 방사선치료 병행요법과 비교했을 때 국소 제어율과 무진행 생존율, 또한 치료 중 부작용과 만성 부작용 측면에서 열등하지 않았다. 따라서 구강암과 구인두암에서 비침습적 치료로서 방사선치료는 수술을 대체할 수 있는 치료방법으로 선택될 수 있으며, 좀 더 많은 수의 환자를 통해 증명되는 것이 필요하다.

핵심되는 말 : 두경부암; 구강암; 구인두암; 방사선치료