Full-dose re-irradiation using helical tomotherapy as a treatment for recurrent and second primary head-and-neck cancer

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<Title page>

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Directed by Professor Chang Geol Lee

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<Abstract>

Full-dose re-irradiation using helical tomotherapy as a treatment for recurrent and second primary head-and-neck cancer

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Purpose: Limited information regarding re-irradiation (re-RT) for recurrent and second primary head and neck cancer are available until now. Here we studied our initial experience of helical tomotherapy for previously irradiated head and neck cancer.

Patients and Methods: Retrospective review was performed for 36 consecutive patients re-irradiated with helical tomotherapy for head and neck cancer between 2006 and 2012. The re-RT targets encompassed only the recurrent gross tumor with tight margins (5-10 mm).

Results: Twenty-three (64%) patients underwent salvage surgery before re-RT and

26 (72%) patients received concurrent chemotherapy during re-RT. The median time interval between initial RT and re-RT was 34 months and the median cumulative dose of the two irradiations was 125 Gy. The median overall survival was 17 months. Fourteen patients (39%) developed loco-regional recurrences after re-RT (8 in-field, 6 out-field). In multivariate analysis, the higher cumulative RT dose, the longer time interval, and the use of concurrent chemotherapy were associated with improved loco-regional recurrence-free survival (all $p < 0.05$). Additionally, the longer time interval, the smaller gross tumor volume, and the male sex were associated with better overall survival. Ten patients (39%) showed clinically significant late toxicity among 26 evaluable patients but no grade 5 toxicity was observed.

Conclusion: We report moderate safety and acceptable acute and late toxicity after helical tomotherapy re-RT using tight margin and daily image-guidance. The current data showed encouraging local control and survival which is similar with the historical data using 1-2 cm margins.

Keywords: head and neck cancer; radiotherapy; reirradiation; salvage therapy.

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I. INTORDUCTION

Multidisciplinary approach including all three modalities – surgery, radiotherapy, and chemotherapy has become current management of locally advanced head and neck cancer rather than single modality therapy. Radiotherapy plays vital and complementary role as a very effective loco-regional treatment modality. Postoperative radiotherapy with or without chemotherapy has been well proven to enhance local control and improve survival for patients who underwent surgical resection[1,2]. Upfront radiotherapy with concomitant chemotherapy which was originally pioneered for inoperable head and neck cancer patients has also emerged as a curative treatment option comparable to upfront surgery in operable

patients [3,4].

However, for patients with recurrent and second primary head and neck cancer which occurred within previously irradiated areas with full dose, treatment options have been limited traditionally. Majority of the patients presented with surgically unresectable tumors, and many experts consider these tumors incurable with less than 6 months of median survival [5]. Even in surgically resected patients, it needs to be noted that the loco-regional failure rate remains unsatisfactorily high which led to poor survival and deterioration of life quality[6]. In these cases, treatment options have been limited to best supportive care or palliative chemotherapy which yielded a median survival of no more than 8-10 months at best[7-9].

During the last 2 decades, the use of re-irradiation (re-RT) with or without chemotherapy for recurrent and second primary head and neck cancer has steadily become recognized as a relatively safe and effective treatment option for highly selected patients after pioneering studies reported by the University of Chicago and Gustave-Roussy Institute [10,11]. Because of a lack of randomized phase III trials and a paucity of prospective multi-institution studies, limited information regarding re-RT are available on the basis of numerous single institution reports[12-15]. Nevertheless, many significant clinical questions are still unanswered regarding the optimal use of re-RT. Since our institution introduced helical tomotherapy in 2006, re-RT using helical tomotherapy has been applied to patients with recurrent and second primary head and neck cancer. Here we studied the clinical outcomes of this

regimen regarding treatment response, patterns of failure, survival, prognostic factors, and toxicity.

II.MATERIALS AND METHODS

1. Patients

A total of 2413 patients with recurrent and second primary head-and-neck cancer who consecutively received RT at our institution between 1999 and 2012 were identified in our department's database. We then selected 532 patients who treated with re-RT. Among those patients we excluded 380 patients who had distant metastasis at the time of re-RT, 63 patients who did not receive helical tomotherapy, and 53 patients who received re-RT as palliative aim (< 40 Gy). The remaining 36 patients were included in our analysis.

2. Re-irradiation

The patients underwent simulation in the supine position and immobilized with an aquaplastic mask device. In obtaining planning CT images, intravenous contrast media was administered. RT was planned using helical tomotherapy Hi-Art System, version 2.0 (TomoTherapy Inc., Madison, WI). The target volumes for helical tomotherapy were defined as follows: the planning target volume 1 (PTV1) encompassed only the gross tumor as suggested in all available images including CT, MRI, and FDG-PET, and PTV2 was defined as the PTV1 plus a 5–10 mm margin. The margin was modified if the adjacent critical organs were abutting GTV, in

which case a tighter margin was used. Three patients received additional elective nodal irradiation. The median PTV1 and PTV2 volume were 46.5 mL (range, 2–540 mL) and 88.0 mL (range, 14–791 mL), respectively. In general, daily fraction doses of 2.0–3.0 Gy and 1.8–2.0 Gy were prescribed to the PTV1 and the PTV2, respectively. The median total dose was 60 Gy (range, 48–78 Gy). To compensate the effect of various dose-fractionation schedules, dose values were biologically normalized to equivalent doses in 2 Gy fractions (EGD2) using a linear-quadratic model. With image guidance system in helical tomotherapy, the setup errors were corrected using megavoltage CT in every fraction of RT. Details of helical tomotherapy are included in our previously published report[16].

3. Response and outcomes assessment

We reviewed all available imaging studies including CT, MRI, ultrasound and FDG-PET and medical records. Tumor response after re-RT was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST criteria). In our study, patterns of recurrence were categorized as local recurrence, regional recurrence and distant metastasis. Local recurrence was defined as the progression of the disease at the primary site. Regional recurrence was defined as the metastasis to cervical lymph node. Distant metastasis was defined as the evidence of metastasis to the distant organs. We defined infield-locoregional recurrence as the recurrence on the re-irradiated site.

4. Toxicity assessment

We defined acute toxicities as events occurring within 3 months from the start of re-RT. Late toxicities were defined as events occurring after 3 months from the start of re-RT. All toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0) and toxicities rated greater than grade 3 were considered as severe.

5. Statistical analysis

The locoregional recurrence-free survival (defined as the length of time from date of first re-RT to locoregional recurrence), progression-free survival (the length of time from date of first re-RT to any recurrence or death), and overall survival (the length of time from date of first re-RT to any cause of death) were estimated by the Kaplan Meier method. Univariate and multivariate analyses were performed with the Cox's regression model. We selected all available variables, and carried out multivariate analysis using backwards elimination with a large alpha level (0.20) to stay in the model. To identify the factors associated with severe toxicity, a Pearson chi-square test or fisher's exact test was used. Statistical analyses were performed using SPSS version 20.0.0 (SPSS, Chicago, IL, USA). P values $\leq$ 0.05 were considered significant.

III. RESULTS

1. Patients

Patient characteristics are listed in Table 1. The median age was 52 years (range, 32–83 years) at the time of re-RT. There were 28 male and 9 female patients. All tumors were confirmed histologically. Twenty-nine patients (81%) had squamous cell carcinomas. The primary tumor originated from the nasopharynx in 10 patients, the maxillary sinus/ nasal cavity/ paranasal sinus in 10, oral cavity in 4, oropharynx in 4, hypopharynx in 3, larynx in 3 and other sites in 3. Most patients had recurrent disease, and 4 patients presented with second primary tumor. Of the 36 patients, 22 had recurrence at the primary site, 9 in the neck, and 6 in the both sites simultaneously. None of the patients showed evidence of metastasis to distant organ, except one patient who had solitary resected lung metastasis. Full-dose irradiation was given in all patients previously. The median time interval between initial RT and re-RT was 34 months (range, 3–204 months). The median dose delivered during the initial course of RT was EQD2 66 Gy (range, 44–82 Gy).

2. Treatment

Twenty-three (64%) patients underwent salvage surgery before re-RT. Twenty-six (72%) patients received concurrent chemotherapy during re-RT, and cisplatin was mostly used. Nine (25%) patients received induction chemotherapy before re-RT. The median dose delivered during re-RT course was EQD2 60 Gy (range, 48–78 Gy). The median cumulative dose of the two irradiations was EQD2

125 Gy (range, 106–148 Gy). Direct comparison of the initial and re-RT plans was performed to determine the overlap of re-RT plan with prior RT treatment areas.

Table 1. Patient characteristics

Variables	No. of Patients	%
Age, years		
Median	52	
Range	32–83	
Sex		
Male	28	(76)
Female	9	(24)
ECOG performance status		
0-1	29	(78)
2-3	8	(22)
Primary site at initial diagnosis		
Nasopharynx	10	(27)
Maxillary sinus, Nasal cavity, PNS	10	(27)
Oral cavity	4	(11)
Oropharynx	4	(11)
Hypopharynx	3	(8)
Larynx	3	(8)
Other	3	(8)
Initial treatment		
Surgery + PORT	16	(43)
RT alone	21	(57)
Progression type		

Recurrence	33	(89)
Second primary	4	(11)
Progression type		
Primary recurrence	22	(60)
Neck nodal recurrence	9	(24)
Both recurrence	6	(16)
Months from prior RT, months		
Median	34	
Range	3–204	
Prior RT dose, Gy		
Median	66	
Range	44–82	
Salvage surgery		
Yes	13	(36)
No	23	(64)
Re-RT dose, Gy		
Median	60	
Range	48–78	
Re-RT PTV1 volume (mL)		
Median	47	
Range	2–540	
Re-RT PTV2 volume (mL)		
Median	88	
Range	14–791	
Induction chemotherapy		
Yes	9	(25)
Concurrent chemotherapy		
Yes	26	(72)

Abbreviations: PORT = postoperative RT; PTV = planning target volume.

3. Survival

At the last follow-up visit, 21 (59%) were alive. The median follow-up was 10 months (range, 1–68 months) for the surviving patients. The median overall survival was 17 months (95% confidence interval [CI], 8–26 months) and the actuarial 1-year survival rate was 63% (95% CI, 46%–81%), as shown in Fig. 1. A total of 17 subsequent recurrences after re-RT occurred during the follow-up period. The progression-free survival was 7 months (95% CI, 5–10 months) and the actuarial 1-year progression-free survival rate was 34% (95% CI, 16%–51%).

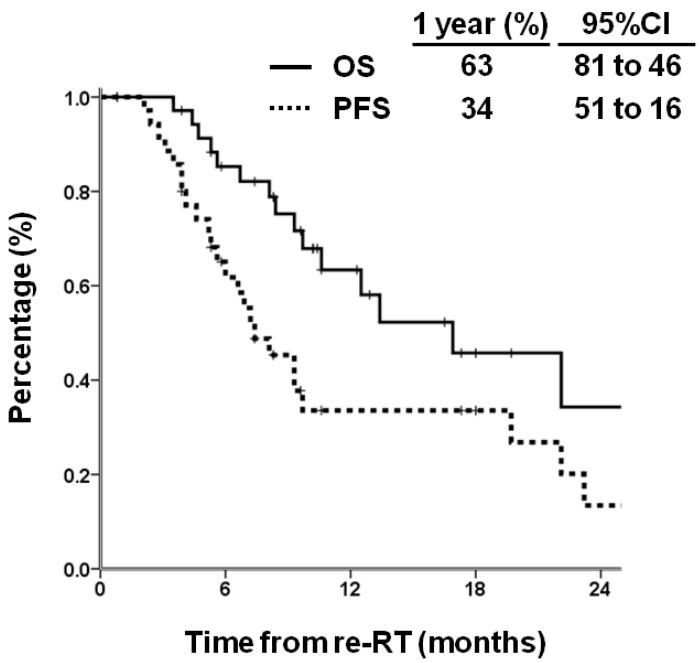

Fig. 1. Overall survival (OS) and progression-free survival (PFS) for helical

tomotherapy as re-irradiation for recurrent head and neck cancer.

4. Response evaluation

The infield lesions were evaluated for response after the completion of re-RT (Table 2). Thirty-one of the 36 patients had available data to evaluate the response. Complete remission and partial remission rates were 33% and 28%, respectively. The total response and local control rates were 61% and 86%, respectively. The re-RT responses were analyzed by surgical resection before re-RT. In 13 patients treated surgically, complete remission and partial remission rates were 46% and 31%, respectively. Overall, response and local control rates of non-surgical patients were 52% and 91%, respectively.

Table 2. In-field tumor response

	All patients (*n* = 36)		**Nonsurgically resected patients**		**Surgically resected patients**	
CR	12	(33)	6	(26)	6	(46)
PR	10	(28)	6	(26)	4	(31)
SD	9	(25)	9	(39)	0	(0)
PD	0	(0)	0	(0)	0	(0)
UE	5	(14)	2	(9)	3	(23)

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; UE = un-evaluable target lesions.

5. Loco-regional recurrence

Among 17 patients who had a third recurrence, the incidence of loco-regional recurrence as any component of failure was 82% (14 patients), as shown in Table 3. Nine patients experienced loco-regional recurrence without evidence of distant metastasis and 5 had simultaneous or subsequent loco-regional recurrence with distant metastasis. Eight loco-regional recurrences occurred within the high-dose irradiated areas except for 6. The patterns of failure were analyzed by surgical resection. In 13 patients treated surgically, 39% experienced loco-regional recurrence and 15% occurred within the high-dose irradiated areas. Similarly, in patients treated non-surgically, 39% experienced loco-regional recurrence and 13% occurred within the high-dose irradiated areas. The median loco-regional recurrence-free survival was 23 months (95% confidence interval [CI], 0–47 months) and the actuarial 1-year loco-regional recurrence-free survival rate was 56% (95% CI, 38%–75%), as shown in Fig. 2.

Table 3. Failure patterns

Failure site	**All patients (*n* = 36)**		**Nonsurgically resected patients**		**Surgically resected patients**	
Total failures	17	(47)	10	(44)	7	(54)
Local only	4	(11)	3	(13)	1	(8)
Regional only	5	(14)	3	(13)	2	(15)
Local and distant only	3	(8)	2	(9)	1	(8)
Distant only	3	(8)	1	(4)	2	(15)
Distant followed by local	2	(6)	1	(4)	1	(8)
Total locoregional	14	(39)	9	(39)	5	(39)

Total infield	8	(22)	6	(13)	2	(15)

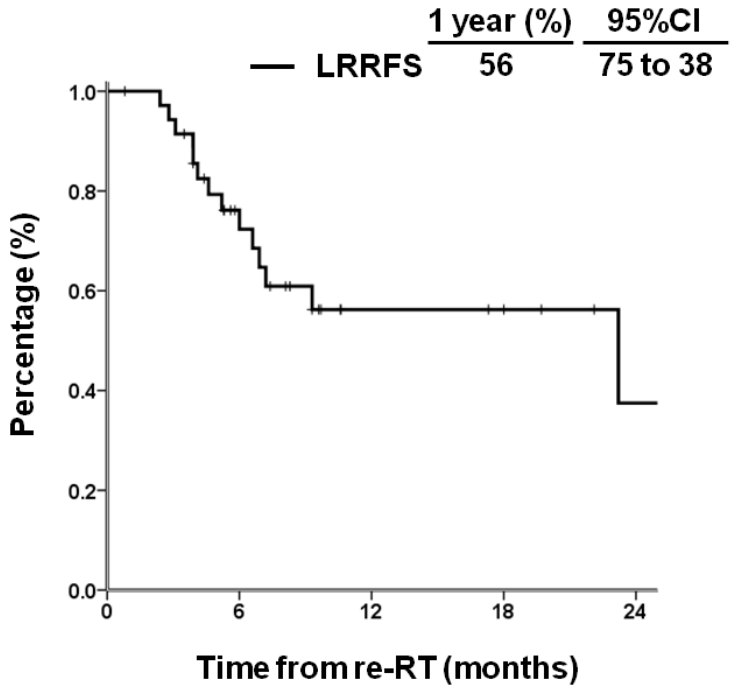

Fig. 2. Loco-regional recurrence-free survival (LRRFS) for helical tomotherapy as re-irradiation for recurrent head and neck cancer.

6. Prognostic factor

The following potential prognostic variables were examined in the univariate and multivariate analyses: sex (male vs. female), age at the time of re-RT (≥ 50 vs. < 50 years), ECOG performance status (2-3 vs. 0-1), disease site

(nasopharynx/ maxillary sinus/ nasal cavity/ paranasal sinus vs. others), surgical resection (yes vs. no), cumulative RT dose to the re-RT area (≥ median cumulative dose vs. < median), the time interval between first RT and re-RT (≥ median time vs. < median), tumor volume (≥ median volume vs. < median), and concurrent chemotherapy (yes vs. no). In univariate analysis, use of concurrent chemotherapy during re-RT was associated with loco-regional recurrence free survival ($p = 0.04$). Performance status and the time interval between initial RT and re-RT were associated with progression-free survival (both $p < 0.05$). Performance status, use of surgical resection, the time interval, and gross tumor volume were associated with overall survival (all $p < 0.05$).

In multivariate analysis, the higher cumulative RT dose, the longer time interval, and the use of concurrent chemotherapy were associated with improved loco-regional recurrence-free survival (Table 4). The time interval and use of concurrent chemotherapy were remained independent prognostic factors in progression-free survival. Additionally, the longer time interval, the smaller gross tumor volume, and the male sex were associated with better overall survival.

Table 4. Multivariate analysis

	LRRFS			PFS			OS		
Variable*	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Sex				0.32	0.12-0.90	0.03	0.27	0.07-0.97	0.04
Age									
ECOG PS	4.10	0.83-20.28	0.08	7.56	2.27-25.14	0.001	3.00	0.92-9.78	0.07

Disease site	0.35	0.08-1.43	0.14						
Surgery									
RT dose	0.29	0.08-1.02	0.05						
Time interval	0.27	0.08-0.93	0.04	0.20	0.07-0.54	0.002	0.14	0.03-0.58	0.007
Tumor volume							5.07	1.33-19.37	0.02
Concurrent CTx	0.18	0.05-0.65	0.009	0.31	0.11-0.89	0.03			

Abbreviations: LRRFS = loco-regional recurrence-free survival; PFS = progression-free survival; OS = overall survival; HR = hazards ratio; CI = confidence interval; CTx = chemotherapy.

* Variables included sex (male vs. female), age at the time of re-RT (≥ 50 vs. < 50 years), ECOG performance status (2-3 vs. 0-1), disease site (nasopharynx/ maxillary sinus/ nasal cavity/ paranasal sinus vs. others), surgical resection (yes vs. no), cumulative RT dose to the re-RT area (≥ median cumulative dose vs. < median), the time interval between first RT and re-RT (≥ median time vs. < median), tumor volume (≥ median volume vs. < median), and concurrent chemotherapy (yes vs. no).

7. Toxicity

Four patients (12%) had clinically significant acute toxicity during re-RT among 33 evaluable patients. Two patients had a combination of grade 3 dyspnea and grade 3 aspiration/ laryngeal edema leading to hospitalization for tracheostomy. One patient had developed grade 3 oral pain and grade 2 edema face, and the other had grade 3 dyspnea with grade 2 neck edema. Disease site (nasopharynx/ maxillary sinus/ nasal cavity/ paranasal sinus vs. others) and gross tumor volume (≥ median

volume vs. < median) were determinant of clinically significant acute toxicity (both $p < 0.05$). Ten patients (39%) showed clinically significant late toxicity among 26 evaluable patients (Table 5). No grade 5 toxicity was observed. None of association with severe late toxicity was identified.

Table 5. Late severe complications after re-irradiation using helical tomotherapy

Patient	Diagnosis	Treatment site	Initial treatment	Salvage treatment	Cumulative dose (EQD2)	GTV volume (cc)	ENI	Interval from previous RT (months)	Complication
M/ 45	NPC	Primary	RT	CCRT	122	53	No	32	Middle ear inflammation G3
M/ 66	NPC	Both	RT	IC + CRT	140	35	Yes	204	Trismus G3
M/ 59	MSC	Primary	RT	Op + CRT	118	89	No	62	Hearing impaired G3
M/ 83	MSC	Primary	RT + Op	RT alone	140	48	No	8	Trismus G3, Dry eye G3
M/ 46	OC	Both	Op + RT	CCRT	128	540	No	3	Edema face G3, Facial pain G3
F/ 51	OC	Neck	Op + RT	CCRT	128	64	No	3	Neck pain G3, Neck soft tissue necrosis G3
M/ 55	OPC	Both	RT	IC + CRT	134	60	No	24	Dysphagia G3, Skin ulceration G3
M/ 74	LC	Neck	RT	CCRT	132	13	No	70	Dysphagia G4, Oral pain G3
M/ 83	LC	Primary	RT	CCRT	134	52	Yes	93	Dyspnea G4
F/ 48	SDC	Primary	Op + RT	CCRT	114	30	No	63	Dysphagia G3

Abbreviations: NPC = nasopharynx cancer; MSC = maxillary sinus cancer; OC = oral cavity cancer; OPC = orophaynx cancer; LC = larynx cancer; SDC = salivary ductal cancer; CCRT = concurrent chemo-radiotherapy; IC = induction chemotherapy; CRT = chemo-radiotherapy; EQD2 = equivalent doses in 2 Gy fractions; GTV = gross tumor volume; ENI = elective nodal irradiation.

IV. DISCUSSION

In this study, we explored the treatment outcomes of recurrent and second primary head and neck cancer patients whom their gross tumor volume with a small margin was re-treated with helical tomotherapy using daily image-guidance. Our study showed that the 1-year loco-regional recurrence-free survival and overall survival rates to be 56% and 63% with a median survival of 17 months. Severe late complications occurred in 39% of evaluable patients, but it is noteworthy that most toxicity was manageable and no patient developed treatment related mortality. Additionally, several important clinical parameters were identified as prognostic factors in our material. Use of concurrent chemotherapy during re-RT and sufficient time interval from first RT to re-RT were significantly associated with better loco-regional control. In addition to the time interval, the gross tumor volume was significantly related to dismal survival.

The primary concerns of the physicians in the decision making of the use of re-RT were toxicity and safety. In the French GETTEC study, 39% of patients who underwent surgery plus re-RT and 10% in the surgery alone arm experienced grade 3 or 4 late toxicity ($p = 0.06$)[17]. The main toxicities included osteoradionecrosis, trismus, and sclerosis. In the RTOG 9610 multi-institutional study, the worst late toxicity was grade 3 in 19% of patients and grade 4 in 3%[18]. The majority were associated with re-RT of the pharynx/esophagus. In the RTOG 9911 study, 5% experienced early grade 5 toxicities and the worst late toxicities

were grade 3 in 17%, grade 4 in 17%, and grade 5 in 4%[19]. They estimated 85% of patients experienced grade 3 to 5 toxicity in the first 2 years after re-RT. In other retrospective studies, grade 3 and 4 late toxic effects ranged from 18% to 38%[12-15,20]. Above all things, the rupture of carotid artery is one of the greatest concerns for re-RT related complication. McDonald et al indicated that the incidence was approximately 3% and most were fatal[21].

This severe toxicity could be mainly attributed to re-RT volume. In the above-mentioned GETTECT, RTOG trials and other institutions, the gross disease was encompassed with a minimal margin of 2.0 cm in general. Limiting the re-RT volume to recurrent gross tumor volume with tight margins may help decrease the late toxicity theoretically. Michigan group found all loco-regional recurrences occurred within the re-irradiated infield area, and verified that confining the re-RT targets to the gross tumor only did not compromise tumor control[22]. With the availability of more advanced RT techniques, the use of intensity modulated radiotherapy (IMRT) has been proven effectiveness in sparing normal structures from excessive radiation exposure compared to the conventional RT techniques. M.D. Anderson group reported the outcomes of re-RT using IMRT with 1-2 cm circumferential margins[13]. They concluded morbidity was significant, but may less severe than conventional RT.

In our cohort, the incidence of toxicity after re-RT seems to be in the range reported in other studies, although it is impossible to compare directly. We believed the use of helical tomotherapy with tight margin may affect the results lacking

treatment related mortality in our patients. All potential risk factors were examined in our study, and treatment site and gross tumor volume were identified as clinically relevant predictive factors for acute toxicity. These findings suggest that caution is needed when treating large tumor or located in oral cavity/ oropharynx/ larynx/ hypopharynx. However, like other reports, identification of clinically relevant factors for late toxicity after re-RT remained elusive[23].

In GETTEC trial, 38% of the patients in the surgery plus re-RT arm developed loco-regional recurrences and 1-year loco-regional control rate was approximately 60%[17]. In RTOG 9911 trial, 31% of the patients who received twice-daily re-RT without surgical resection (60 Gy in 1.5 Gy per fraction bid) experienced loco-regional recurrences[9]. In MD Anderson study which included 27% of surgical resected patients, 35% of the re-RT patients had loco-regional recurrences with 64% of 2-year probability for loco-regional control[14]. Our study showed loco-regional recurrence rate of 39% with 1-year loco-regional recurrence free survival of 56% that was similar to previous studies using re-RT. Among 14 loco-regional recurrences, 43% of the patients had an outfield recurrence which remained still outfield if the target was treated with 2 cm margin. Despite relatively small sample size, we observed the similar distribution of failure patterns according to surgical resection. Therefore, this result supports the utility of tight margin.

In MD Anderson study, the multiple covariates were examined in univariate and multivariate analyses, however, only the non-modifiable clinical factors including male gender, age at the time of re-RT was identified as predictors[14].

The modifiable prognostic factors identified in this study were the time interval between two courses of RT and the use of concurrent chemotherapy. The significance remained as predictor of outcome when the analysis was performed with the time interval as a continuous variable, which means the longer time interval the better prognosis. Unlike concurrent chemotherapy, the use of induction chemotherapy was not found to be a significant prognostic factor. Additionally, large volume of gross tumor correlated with decreased overall survival on multivariate analysis. In Gustave-Roussy Institut study, they found that the irradiated volume ($\geq$ 650 cm^3) was the only factor associated with the risk of death (relative risk, 1.8)[4].

In interpreting our data, the limitations of retrospective analyses including patient and treatment selection must be considered. The reasons why our patients were treated with re-RT using helical tomotherapy were unclear, but the use of this regimen seems to reliably be recommended to patients who have already factors of better outcome. Our cohort also included heterogeneous patients, so the results cannot be directly applied to all recurrent head and neck cancer and encouraging the widespread use of re-RT. Since the cohort was relatively small, there were limitations in conducting a complete statistical analysis. It is necessary to verify the prognostic factors identified in our data. Nevertheless, the strength of our study is that our patients received relatively homogenous treatment including helical tomotherapy re-RT with tight margin, was performed in a single institution.

V. CONCLUSIONS

We report moderate safety and acceptable acute and late toxicity after helical tomotherapy re-RT using tight margin and daily image-guidance. The current data showed encouraging local control and survival which is similar with the historical data using 1-2 cm margins. It seems to be essential that resources be put toward prospective studies of re-RT in this field.

REFERENCES

1. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med.* 2004;350:1945-52.
2. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2004;350:1937-44.
3. Setton J, Caria N, Romanyshyn J, et al. Intensity-modulated radiotherapy in the treatment of oropharyngeal cancer: an update of the Memorial Sloan-Kettering Cancer Center experience. *Int J Radiat Oncol Biol Phys.* 2012;82:291-8.
4. Garden AS, Dong L, Morrison WH, et al. Patterns of disease recurrence following treatment of oropharyngeal cancer with intensity modulated radiation therapy. *Int J Radiat Oncol Biol Phys.* 2013;85:941-7.
5. Taussky D, Dulguerov P, Allal AS. Salvage surgery after radical accelerated radiotherapy with concomitant boost technique for head and neck carcinomas. *Head Neck.* 2005;27:182-6.
6. Temam S, Koka V, Mamelle G, et al. Treatment of the N0 neck during salvage surgery after radiotherapy of head and neck squamous cell carcinoma. *Head Neck.* 2005;27:653-8.
7. Forastiere AA, Leong T, Rowinsky E, Murphy BA, Vlock DR, DeConti RC,

Adams GL. Phase III comparison of high-dose paclitaxel + cisplatin + granulocyte colony-stimulating factor versus low-dose paclitaxel + cisplatin in advanced head and neck cancer: Eastern Cooperative Oncology Group Study E1393. *J Clin Oncol.* 2001;19:1088-95.

8. Gibson MK, Li Y, Murphy B, Hussain MH, DeConti RC, Ensley J, Forastiere AA. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): an intergroup trial of the Eastern Cooperative Oncology Group. *J Clin Oncol.* 2005;23:3562-7.

9. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med.* 2008;359:1116-27.

10. De Crevoisier R, Bourhis J, Domenge C, et al. Full-dose reirradiation for unresectable head and neck carcinoma: experience at the Gustave-Roussy Institute in a series of 169 patients. *J Clin Oncol.* 1998;16:3556-62.

11. Brockstein B, Haraf DJ, Stenson K, et al. Phase I study of concomitant chemoradiotherapy with paclitaxel, fluorouracil, and hydroxyurea with granulocyte colony-stimulating factor support for patients with poor-prognosis cancer of the head and neck. *J Clin Oncol.* 1998;16:735-44.

12. Salama JK, Vokes EE, Chmura SJ, et al. Long-term outcome of concurrent chemotherapy and reirradiation for recurrent and second primary head-and-neck squamous cell carcinoma. *Int J Radiat Oncol Biol Phys.* 2006;64:382-91.

13. Sulman EP, Schwartz DL, Le TT, et al. IMRT reirradiation of head and neck cancer-disease control and morbidity outcomes. *Int J Radiat Oncol Biol Phys.* 2009;73:399-409.

14. Roh KW, Jang JS, Kim MS, et al. Fractionated stereotactic radiotherapy as reirradiation for locally recurrent head and neck cancer. *Int J Radiat Oncol Biol Phys.* 2009;74:1348-55.

15. Rusthoven KE, Feigenberg SJ, Raben D, et al. Initial results of a Phase I dose-escalation trial of concurrent and maintenance erlotinib and reirradiation for recurrent and new primary head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* 2010;78:1020-5.

16. Lee IJ, Seong J, Lee CG, et al. Early clinical experience and outcome of helical tomotherapy for multiple metastatic lesions. *Int J Radiat Oncol Biol Phys.* 2009;73:1517-24.

17. Janot F, de Raucourt D, Benhamou E, et al. Randomized trial of postoperative reirradiation combined with chemotherapy after salvage surgery compared with salvage surgery alone in head and neck carcinoma. *J Clin Oncol.* 2008;26:5518-23.

18. Spencer SA, Harris J, Wheeler RH, et al. Final report of RTOG 9610, a multi-institutional trial of reirradiation and chemotherapy for unresectable recurrent squamous cell carcinoma of the head and neck. *Head Neck.* 2008;30:281-8.

19. Langer CJ, Harris J, Horwitz EM, et al. Phase II study of low-dose

paclitaxel and cisplatin in combination with split-course concomitant twice-daily reirradiation in recurrent squamous cell carcinoma of the head and neck: results of Radiation Therapy Oncology Group Protocol 9911. *J Clin Oncol.* 2007;25:4800-5.

20. Lee N, Chan K, Bekelman JE, et al. Salvage re-irradiation for recurrent head and neck cancer. *Int J Radiat Oncol Biol Phys.* 2007;68:731-40.

21. McDonald MW, Moore MG, Johnstone PA. Risk of carotid blowout after reirradiation of the head and neck: a systematic review. *Int J Radiat Oncol Biol Phys.* 2012;82:1083-9.

22. Popovtzer A, Gluck I, Chepeha DB, et al. The pattern of failure after reirradiation of recurrent squamous cell head and neck cancer: implications for defining the targets. *Int J Radiat Oncol Biol Phys.* 2009;74:1342-7.

23. Wong SJ, Bourhis J, Langer CJ. Retreatment of recurrent head and neck cancer in a previously irradiated field. *Semin Radiat Oncol.* 2012;22:214-9.

<ABSTRACT (IN KOREAN)>

재발성과 이차암성 두경부암에서 토모테라피를 이용한 고선량 재 방사선 치료

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목적: 현재까지 재발성과 이차암성 두경부암에서 재 방사선 치료를 하는 것에 대한 정보는 제한되어 있다. 본 연구에서는 토모테라피를 이용하여 이전에 방사선 조사가 된 부위에 대하여 재 방사선 치료를 한 본원의 첫 임상 경험을 밝히고자 한다.

대상 및 방법: 2006년부터 2012년까지 본원에서 토모테라피를 이용하여 재 방사선 치료를 받은 36명의 환자에 대해서 후향적 분석을 시행하였다. 재 방사선 치료의 치료 표적은 재발한 육안적 종양체적에서 5에서 10mm

의 마진으로 정의하였다.

결과: 전체 환자 중 23명 (63%)의 환자는 재 방사선 치료 전에 구제적 수술을 받았고, 26명 (72%)의 환자는 동시 항암 화학요법을 재 방사선 치료와 시행 받았다. 첫 번째 방사선 치료와 재 방사선 치료간의 기간은 34개월 (중위수)이었고, 누적 선량은 총 125 Gy (중위수)였다. 방사선 재 치료 후 중앙생존기간은 17개월이었다. 14명 (39%)의 환자에서 국소 또는 임파선 재발을 경험하였다 (8명: In-field, 6명: Outfield). 다변량 분석결과에서는 누적선량이 많을수록, 두 방사선 치료간의 기간이 길수록, 동시 항암 화학요법을 할수록 무 국소-임파선 재발 생존일이 유의하게 증가하는 것으로 밝혀졌다 (모든 $p < 0.05$). 추가적으로, 두 방사선 치료간의 기간이 길수록, 재발한 육안적 종양체적이 작을수록, 남성일수록 생존기간이 유의하게 길었다. 평가가 가능했던 26명의 환자 중 10명 (39%)에서 재 방사선 치료 후 장기 중증 부작용이 관찰되었지만 치료로 인한 사망은 관찰되지 않았다.

결론: 이번 연구를 통해 토모테라피를 이용한 재 방사선 치료는 비교적

안전하고 허용 가능한 정도의 부작용을 보인다는 것을 알 수 있다. 또한 종양 체적에 1-2 cm 마진을 주고 치료한 다른 연구들과 비슷한 국소 제어율과 생존율을 보였다.

핵심되는 말: 두경부암; 방사선치료; 재방사선치료; 구제적 치료