Re-irradiation Using Intensity-modulated Radiotherapy for Recurrent and Second Primary Head and Neck Cancer

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Abstract. *Background/Aim: Information on re-irradiation (re-RT) for recurrent and second primary head and neck cancer is limited. Herein, a description of our long-term experience of re-RT for previously irradiated head and neck cancer is provided. Materials and Methods: A retrospective review was performed for 73 consecutive patients re-irradiated for head and neck cancer between 2006 and 2015. Re-RT targets encompassed only the recurrent gross tumor and had tight margins (5-10 mm). Results: Salvage surgery was performed on 28 (38%) patients before re-RT and 53 (73%) patients received chemotherapy concurrent with re-RT. The median interval between initial and re-RT was 31 months and the median cumulative dose of the two irradiations was 126 Gy (biologically equivalent to 2 Gy fractionation). With a median survival of 33 months, locoregional recurrence after re-RT developed in 37 patients (51%; 25 infield, 12 outfield). In multivariate analysis, higher re-RT dose (≥66 Gy), longer time interval (>2 years), and use of concurrent chemotherapy were associated with improved locoregional recurrence-free survival (all p<0.05). Additionally, performance status, additional surgical resection, and longer interval were associated with better overall survival (p=0.006, 0.021, 0.004, respectively). Clinically significant acute and late toxicities occurred in 14% and 22% of evaluable patients, but no grade 5 toxicity was observed. Conclusion: Moderate safety and acceptable toxicity was found after re-RT using tight margins, sufficient radiation dose, and daily image guidance. Encouraging local control and survival were obtained, similar to historical data using 1-2 cm margins.*

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Currently, a multidisciplinary approach of surgery, radiotherapy (RT), and chemotherapy rather than single-modality therapy is used to manage locally advanced head and neck cancer. RT is a vital and effective complementary locoregional treatment modality. Postoperative RT with or without chemotherapy has been shown to enhance local control and improve survival for patients who underwent surgical resection (1, 2). Upfront RT with concomitant chemotherapy, which was originally pioneered for inoperable head and neck cancer, has 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 occurring within areas previously irradiated with a full radiation dose, treatment options are limited. The majority of these patients present 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, the locoregional failure rate remains unsatisfactorily high with poor survival and deterioration of life quality (6). In these cases, treatment options are limited to supportive care or palliative chemotherapy with a median survival of no more than 8-10 months (7).

During the past 2 decades, the use of re-irradiation (re-RT) with or without chemotherapy for recurrent and second primary head and neck cancer has become recognized as a relatively safe and effective treatment option for highly selected patients, based on pioneering studies from the University of Chicago and Gustave-Roussy Institute (8, 9). Because of a lack of randomized phase III trials and a paucity of prospective multi-institutional studies, information regarding re-RT is limited and based on numerous single-institution reports (10-14). Many important clinical questions about the optimal use of re-RT are still unanswered. Since the introduction of helical tomotherapy at our institution in 2006, re-RT using intensity-modulated radiotherapy (IMRT) has been actively applied to patients with recurrent and second primary head and neck cancer. Herein, the clinical

outcomes of this regimen for treatment response, patterns of failure, survival, prognostic factors, and toxicity were analyzed.

Materials and Methods

Patients. A total of 2179 consecutive patients with head and neck cancer who received RT at our institution between 2006 and 2015 were identified in our department's database. Overall, 222 patients treated with re-RT were selected. A total of 81 patients who did not receive IMRT, 48 patients who had distant metastasis at the time of re-RT, and 20 patients who received re-RT with a palliative aim (<40 Gy) were excluded. The remaining 73 patients were included in our analysis.

Re-irradiation. Patients underwent simulation in the supine position and were immobilized with an aquaplastic mask device. Intravenous contrast media was administered for planning computed tomography (CT) images. RT was planned using helical tomotherapy Hi-Art System, version 2.0 (TomoTherapy Inc., Madison, WI, USA). Target volumes were as follows: planning target volume 1 (PTV1) encompassed only the gross tumor as suggested by all available images including CT, MRI, and FDG-PET; and PTV2 was defined as PTV1 plus a 5 mm margin. Margins were made tighter if adjacent critical organs abutted the PTV. Six patients received additional elective nodal irradiation. Median volumes were 43 ml (range=2-540 ml) for PTV1 and 101 ml (range=5-791 ml) for PTV2. In general, daily fraction doses were 2.0-3.0 Gy for PTV1 and 1.8-2.0 Gy for PTV2. Median total dose to PTV1 was 60 Gy (range=40-78 Gy). To compensate for effects of varying dose-fractionation schedules, dose values were biologically normalized to equivalent doses in 2 Gy fractions (EQD2, a/b ratio: 10) using a linear-quadratic model. Using the image guidance system, setup errors were corrected using megavoltage CT for each RT fraction. Details of IMRT techniques in our institution are in the previous report (15).

Response and outcomes assessment. All available imaging studies including CT, MRI, ultrasound, FDG-PET, and medical records were reviewed. Tumor response after re-RT was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST criteria). Complete or partial responses were classified as "responses". Patterns of recurrence were categorized as local, regional, or distant metastasis. Local recurrence was defined as progression of the disease at the primary site. Regional recurrence was defined as metastasis to a cervical lymph node. Distant metastasis was defined as evidence of metastasis to distant organs. We defined infield-locoregional recurrence as recurrence at the re-irradiated site.

Toxicity assessment. We defined acute toxicities as events occurring within 3 months of re-RT start. Late toxicities were defined as events occurring after 3 months from re-RT start. 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 severe.

Statistical analysis. Locoregional recurrence-free survival (LRFS, time from date of first re-RT to locoregional recurrence), progression-free survival (PFS, time from date of first re-RT to any recurrence or death), and overall survival (OS, 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 Cox's regression model. All available variables were selected, and multivariate analysis was carried out using backwards elimination with a large alpha level (0.20) to stay within the model. To identify factors associated with severe toxicity, a Pearson chi-square test or Fisher's exact test was used. The best cut-off value of numerical variables (re-RT dose and interval between initial RT and re-RT) for survival was chosen using Youden's Index. Receiver operating characteristic (ROC) curves and the respective areas under the curves (AUC) were determined, and sensitivity, specificity, positive and negative predictive values were calculated. Statistical analyses were performed using SPSS version 23.0.0 (SPSS, Chicago, IL, USA). *p*-Values ≤0.05 were considered significant.

Results

Patients. Patient characteristics for 56 men and 17 women are shown in Table I. Median age was 57 years at the time of re-RT. All tumors were confirmed histologically. Squamous cell carcinomas occurred in 51 patients (70%). The primary tumor originated from the nasopharynx in 17 patients, maxillary sinus, nasal cavity, or paranasal sinus in 17, oral cavity in 9, oropharynx in 10, hypopharynx in 5, larynx in 9, and other sites in 6. Most patients had recurrent diseases, and 8 patients presented with a second primary tumor. Of the 73 patients, 44 had recurrence at the primary site, 15 in the neck, and 14 in both sites. No patients showed evidence of metastasis to distant organs, except a single patient with solitary resected lung metastasis. All patients had previously received full-dose irradiation. Median interval between initial RT and re-RT was 31 months (range=3-204 months). Median dose delivered during initial RT course was EQD2 66 Gy (range=42-74 Gy).

Treatment. Before re-RT, 28 (38%) patients underwent salvage surgery (complete or partial resection), and 53 (73%) patients received chemotherapy concurrent with re-RT, mostly with cisplatin (72%). Ten (14%) patients received induction chemotherapy before re-RT. The median dose delivered during the re-RT course was EQD2 60 Gy (range=48-78 Gy). Median cumulative dose of the two irradiations was EQD2 126 Gy (range=90-148 Gy). Direct comparison of the initial and re-RT plans was performed to determine the overlap of the re-RT plan with prior RT treatment areas.

Response evaluation. Infield lesions were evaluated for response after re-RT completion (Table II). Of the 73 patients, 69 had available data for response evaluation. The complete remission rate was 28% and the partial remission rate was 39% (total response rate 67%) among evaluable patients. Re-RT responses were analyzed by surgical

Table I. *Patient characteristics.*

Variables	No.	%
Age (years)		
Median, range	57 (20-83)	
Gender		
Male	56	77
Female	17	23
ECOG performance status		
0~1	64	88
2~3	9	12
Primary site at initial diagnosis		
Nasopharynx	17	23
Maxillary sinus, Nasal cavity, PNS	17	23
Oral cavity	9	12
Oropharynx	10	14
Hypopharynx	5	7
Larynx	9	12
Other	6	8
Initial treatment		
Surgery + PORT	39	47
RT alone	34	53
Progression type		
Recurrence	65	89
Second primary	8	11
Progression patterns		
Primary site	44	60
Neck nodal site	15	21
Both	14	19
Months from prior RT, months		
Median, range	31 (3-204)	
Prior RT dose, EQD2 (Gy)		
Median, range	66 (42-74)	
Salvage surgery		
Yes	28	38
No	45	62
Re-RT dose, EQD2 (Gy)		
Median, range	60 (48-78)	
Cumulative RT dose, EQD2 (Gy)		
Median, range	126 (90-148)	
Re-RT PTV1 volume (ml)		
Median, range	43 (2-540)	
Re-RT PTV2 volume (ml)		
Median, range	101 (5-791)	
Induction chemotherapy		
Yes	10	14
Concurrent chemotherapy		
Yes	53	73

ECOG: Eastern Cooperative Oncology Group; PNS: paranasal sinus; RT: radiotherapy; PORT: postoperative RT; PTV: planning target volume.

resection before re-RT. Complete response of surgically resected patients was defined as no evidence of disease status after re-RT. For 28 patients treated surgically, the complete remission rate was 42% and partial remission was 69%. Overall, for non-surgical patients, the response rate was 62% and the local control rate was 95%.

Table II. *In-field tumor response.*

Response	All patients (n=73) No (%)	Non-surgically resected patients (n=45) No (%)	Surgically resected patients (n=28) No (%)
CR	19 (26)	8 (18)	11 (39)*
PR	27 (37)	18 (39)	9 (32)
SD	19 (26)	16 (36)	3 (11)
PD	0 (0)	0 (0)	0 (0)
UE	8 (11)	3 (7)	5 (18)

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease; UE: un-evaluable target lesions; %: percentage in all patients of each patient group. *No evidence of disease (NED) status.

Table III. *Failure patterns.*

Failure site	All patients (n=73) No (%)	Non-surgically resected patients (n=45) No (%)	Surgically resected patients (n=28) No (%)
Total failures	45 (62)	27 (60)	18 (64)*
Local only	21 (29)	12 (27)	9 (32)
Regional only	9 (12)	7 (16)	2 (7)
Local and distant only	5 (7)	2 (4)	3 (11)
Distant only	8 (11)	5 (11)	3 (11)
Distant followed by local	2 (3)	1 (2)	1 (4)
Total locoregional	37 (51)	22 (49)	15 (54)
Total infield	25 (34)	15 (33)	10 (36)

%: Percentage in all patients of each patient group. *No evidence of disease (NED) status.

Survival outcomes. At the last follow-up, 42 (58%) patients were alive. Of the 31 patients who died, 55% died of disease progression (13 after locoregional recurrences, 4 after systemic recurrences). The rest died of other medical conditions, sepsis after intensive cancer treatments, or unknown causes. The median follow-up was 28 months (range=6-70 months) after re-RT for surviving patients. Median OS was 33 months and the actuarial 2-year rate was 58% (95%CI=46-70%). A total of 45 subsequent recurrences or disease progression after re-RT occurred during the follow-up period. The median PFS was 8 months and the actuarial 2-year PFS rate was 20% (95%CI=10-30%) (Figure 1).

Locoregional recurrence. Among 45 patients who had a third recurrence, the incidence of overall locoregional recurrence as any component of failure was 82% (37 patients), as shown in Table III. Thirty patients experienced locoregional recurrence without evidence of distant metastasis and 7 had
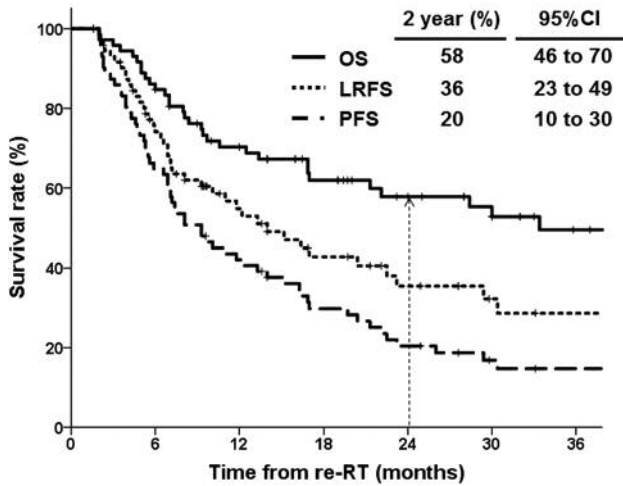
Figure 1. *Overall survival (OS), locoregional recurrence-free survival (LRFS), and progression-free survival (PFS) rates for re-irradiation using helical tomotherapy of recurrent and second primary head and neck cancer (n=73).*

simultaneous or subsequent locoregional recurrence with distant metastasis. Twenty-five locoregional recurrences occurred within the high-dose irradiated areas and 12 were outside these areas. Patterns of failure were analyzed by surgical resection. Of the 18 patients who failed after being treated surgically, 83% experienced locoregional recurrence with 67% occurring within the high-dose irradiated areas. Similarly, in 27 patients treated non-surgically, 81% experienced locoregional recurrence with 68% occurring within the high-dose irradiated areas. Median locoregional recurrence-free survival was 23 months and the actuarial 2-year LRFS rate was 36% (95%CI=23-49%), as shown in Figure 1.

Prognostic factors. The following potential prognostic variables were examined in univariate and multivariate analyses: 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, or paranasal sinus *vs.* other), recurrence pattern (primary, neck *vs.* both), surgical resection (yes *vs.* no), re-RT dose (EQD2, ≥66 Gy *vs.* <66 Gy), time between first RT and re-RT (>2 years *vs.* ≤2 years), tumor volume (≥median volume *vs.* <median), and concurrent chemotherapy (yes *vs.* no). The most significant cut-offs for disease progressions or deaths were 66 Gy and 2 years for re-RT dose (p=0.039 (95%CI=0.148-0.495)) and time interval (p=0.013 (95%CI=0.196-0.464)), respectively.

In univariate analysis, re-RT dose≥66 Gy, time interval >2 years, and use of concurrent chemotherapy were associated with LRFS (all p<0.05). Performance status, re-RT dose ≥66 Gy, and time interval >2 years were
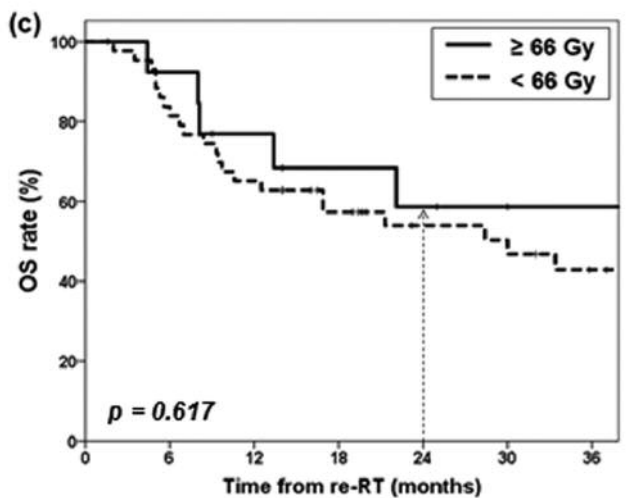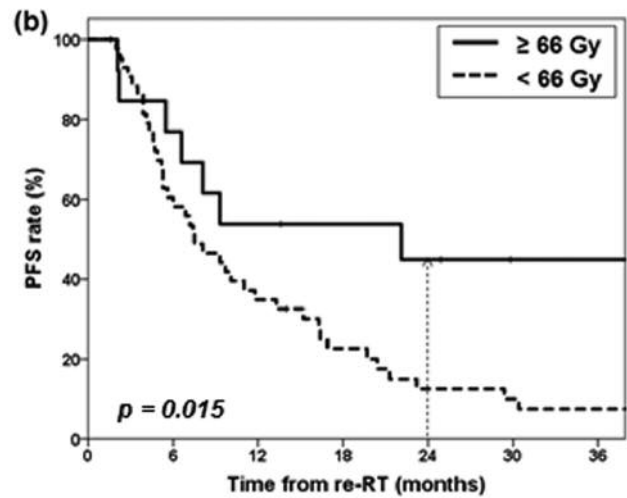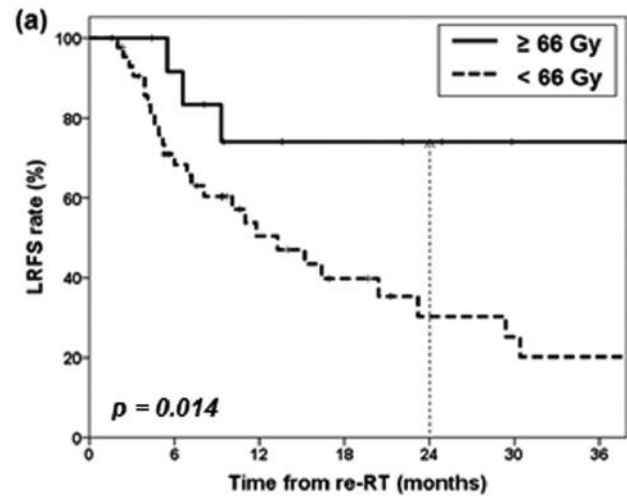

Figure 2. *Locoregional recurrence-free survival (LRFS), progression-free survival (PFS) rates, and overall survival (OS) rates according to re-irradiation (re-RT) dose (EQD2<66 Gy vs. ≥66 Gy).*

Table IV. *Univariate and multivariate analysis.*

Variable*	LRRFS				PFS				OS			
	UVA		MVA		UVA		MVA		UVA		MVA	
	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Gender	0.717 (0.351-1.466)	0.362			0.809 (0.436-1.499)	0.500			0.921 (0.397-2.141)	0.849		
Age ≥50 years	0.642 (0.317-1.298)	0.217			0.625 (0.348-1.121)	0.115			1.308 (0.535-3.195)	0.556		
ECOG PS 2-3	1.668 (0.502-5.539)	0.403			3.179 (1.466-6.895)	0.003	3.140 (1.411-6.986)	0.005	4.180 (1.657-10.541)	0.002	3.768 (1.461-9.723)	0.006
Disease site	1.032 (0.888-1.200)	0.679			1.043 (0.921-1.181)	0.509			0.972 (0.818-1.154)	0.745		
Recurrence pattern	1.005 (0.673-1.501)	0.980			1.014 (0.723-1.420)	0.937			1.287 (0.834-1.986)	0.254		
Surgery	0.929 (0.497-1.737)	0.818			0.730 (0.429-1.242)	0.246			0.326 (0.140-0.759)	0.009	0.362 (0.153-0.857)	0.021
re-RT dose 66 Gy	0.275 (0.098-0.773)	0.014	0.341 (0.120-0.967)	0.043	0.393 (0.186-0.833)	0.015	0.502 (0.233-1.081)	0.078	0.797 (0.327-1.943)	0.617		
Time interval >2 years	0.372 (0.199-0.697)	0.002	0.396 (0.209-0.750)	0.004	0.439 (0.261-0.739)	0.002	0.452 (0.266-0.768)	0.003	0.351 (0.168-0.735)	0.006	0.341 (0.163-0.715)	0.004
Tumor volume median ≥43 cc	0.916 (0.494-1.696)	0.779			1.083 (0.649-1.806)	0.760			1.758 (0.856-3.611)	0.124		
Concurrent CTx	0.498 (0.263-0.943)	0.032	0.461 (0.242-0.878)	0.018	0.695 (0.399-1.212)	0.200			1.044 (0.480-2.273)	0.913		

LRFS: Loco-regional recurrence-free survival; PFS: progression-free survival; OS: overall survival; HR: hazards ratio; CI: confidence interval; RT: radiotherapy; CTx: chemotherapy. *Variables included gender (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), Recurrence pattern (primary *vs*. neck *vs*. both), surgical resection (yes *vs*. no), re-RT dose (≥EQD2 66 Gy *vs*. <EQD2 66 Gy), the time interval between first RT and re-RT (>2 years *vs*. ≤2 years), tumor volume (≥median volume *vs*. <median), and concurrent chemotherapy (yes *vs*. no).

associated with PFS (all *p*<0.05). Performance status, use of surgical resection, and interval >2 years were associated with OS (all *p*<0.05). In multivariate analysis, re-RT dose≥66 Gy, time interval >2 years, and use of concurrent chemotherapy were associated with improved LRFS. Performance status and time interval >2 years were remained independent prognostic factors in PFS. Additionally, use of surgical resection was also associated with better OS (Table IV).

There were 16 patients who received higher dose (≥66 Gy) and 57 patients received lower dose (<66 Gy). When the time interval was longer than 2 years, the patients tended to be prescribed higher doses (11/38, 29% *vs*. 5/35, 14% *p*=0.130). The 2-year LRFS rates were 73% and 26% and 2-year PFS rates were 48% and 13% in patients with ≥66 Gy and <66 Gy, respectively (*p*=0.014 and 0.015, respectively) (Figure 2). The overall recurrence rates were significantly lower with higher doses (31% *vs*. 70%, *p*=0.005). The locoregional recurrence rates among them were also significantly lower (19% *vs*. 60%, *p*=0.004). Although it was not significantly different, the number of infield failures among locoregional recurrences was smaller with higher doses (2/3 *vs*. 23/34) (Figure 3). The 2-year OS rates were not significantly different (59% and 58%, *p*=0.617, Figure 2). However, there were only 2 patients who died of locoregional progression among 6 patients who died after receiving ≥66 Gy. If locoregional control was done with sufficient dose of radiation and sufficient re-RT interval, overall survival may have been improved.

Toxicity. Of 70 evaluable patients, 10 (14%) had clinically significant acute toxicity during re-RT. Two patients had a combination of grade 3 dyspnea and grade 3 aspiration or laryngeal edema leading to hospitalization for tracheostomy. One patient developed grade 3 oral pain and grade 2 edema face, and another had grade 3 dyspnea with grade 2 neck edema. The rest 6 patients had grade 3 skin toxicity or mucositis. Poor performance status was the significant determinant of clinically significant acute toxicity (*p*=0.017) and recurrent tumors at oropharynx were the most common (50%) among them. Although it was not statistically different, the volume of gross tumor was larger in patients
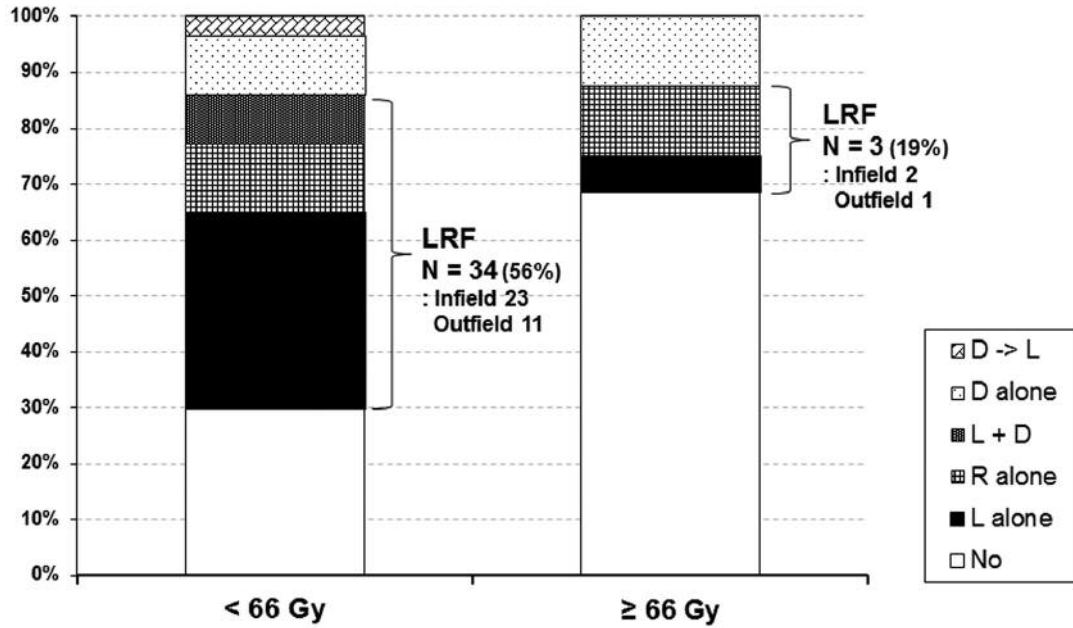
Figure 3. *Pattern of failure according to re-irradiation (re-RT) dose (EQD2<66 Gy vs. ≥66 Gy). LRF: Locoregional failure; D: distant failure; L: local failure; R: regional failure.*

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

Patient	Diagnosis	Treatment site	Initial treatment	Salvage treatment	re-RT dose (EQD2)	Cumulative dose (EQD2)	GTV volume (ml)	ENI	Interval from previous RT (months)	Complication
M/45	NPC	Primary	RT	CCRT	52	122	53	No	32	Middle ear inflammation G3
M/66	NPC	Both	RT	IC + CRT	66	140	35	Yes	204	Trismus G3
M/59	MSC	Primary	RT	Op + CRT	50	118	89	No	62	Hearing impairment G3
M/83	MSC	Primary	RT + Op	RT alone	74	140	48	No	8	Trismus G3, Dry eye G3
M/46	OC	Both	Op + RT	CCRT	64	128	540	No	3	Edema face G3, Facial pain G3
F/51	OC	Neck	Op + RT	CCRT	64	128	64	No	3	Neck pain G3, Neck soft tissue necrosis G3
M/55	OPC	Both	RT	IC + CRT	64	134	60	No	24	Dysphagia G3, Skin ulceration G3
M/74	LC	Neck	RT	CCRT	62	132	13	No	70	Dysphagia G4, Oral pain G3
M/83	LC	Primary	RT	CCRT	68	134	52	Yes	93	Dyspnea G4
F/48	SDC	Primary	Op + RT	CCRT	60	114	30	No	63	Dysphagia G3
M/50	OPC	Primary	Op + RT	CCRT	60	127	31	No	113	Dysphagia G3
F/39	NPC	Both	RT	CCRT	45	115	19	No	31	Hearing impairment G3
M/59	NPC	Both	RT	CCRT	67	138	12	No	14	Neck soft tissue necrosis G3
M/50	OC	Neck	Op + RT	Op + CRT	60	124	42	No	13	Xerostomia G3

NPC: Nasopharynx cancer; MSC: maxillary sinus cancer; OC: oral cavity cancer; OPC: oropharynx 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.

who experienced clinically significant acute toxicities (mean 51 ml *vs*. 128 ml, *p*=0.167). Of 63 evaluable patients, 14 (22%) showed clinically significant late toxicity (Table V). No grade 5 toxicity was observed and no association with severe late toxicity was identified.

Discussion

This study explored the treatment outcomes of recurrent and second primary head and neck cancer patients whose gross tumor volume was re-irradiated with small margins using

IMRT and daily image guidance. Our study showed 2-year OS and LRFS rates of 58% and 36% respectively, with a median survival of 33 months. Severe late complications occurred in 22% of evaluable patients, but most toxicities were manageable with no treatment-related mortalities. Additionally, several important clinical parameters were identified as prognostic factors in our cohort. Higher radiation dose, sufficient time from first RT to re-RT, and use of chemotherapy concurrent with re-RT were significantly associated with better locoregional control. In addition to these factors, good performance status, and additional surgical resection were significantly related to improved survival.

The primary concerns of physicians regarding the decision to use re-RT have been 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) (16). The main toxicities included osteoradionecrosis, trismus, and sclerosis. In the Radiation Therapy Oncology Group (RTOG) 9610 multi-institutional study, late toxicity was grade 3 in 19% of patients and grade 4 in 3% (17). The majority of cases were associated with re-RT of the pharynx/esophagus. In the RTOG 9911 study, 5% experienced early grade 5 toxicities and with late toxicities of grade 3 in 17%, grade 4 in 17%, and grade 5 in 4% (18). This study estimated that 85% of patients experienced grade 3 to 5 toxicity within the first 2 years after re-RT. In other retrospective studies, grade 3 and 4 late toxic effects ranged from 18% to 38% (10-13, 19). Rupture of the carotid artery is a major concern with re-RT; McDonald *et al*. found an incidence of approximately 3% and most occurrences were fatal (20).

Severe toxicity could be mainly attributed to re-RT volume. In GETTECT, RTOG trials and other trials, gross disease was generally encompassed with a minimal margin of 2.0 cm. Limiting re-RT volume to recurrent gross tumor volume with tight margins could help decrease late toxicity. A Michigan study found that all locoregional recurrences occurred within the re-irradiated infield area, and verified that confining re-RT targets to the gross tumor did not compromise tumor control (21). With the availability of more advanced RT techniques, the use of intensity modulated radiotherapy (IMRT) has been effective in sparing normal structures from excessive radiation exposure compared to conventional RT techniques (14, 22). An MD Anderson report on the outcomes of re-RT using IMRT (11) found that even though 1-2 cm circumferential margins were used, morbidity was significant, although possibly less severe than conventional RT. In more recent studies using both modern RT and tight margin (23-25), the 1-year local control and OS rates were 71-75% and 50-67%, respectively, with mild toxicity except one paper (24). There was 32% of grade 3 or worse toxicities including six grade 5 toxicities, that required further investigation.

In our cohort, the incidence of toxicity after re-RT was in the range reported in other studies, although direct comparisons are impossible. We believe that our use of IMRT with tight margins might have contributed to the absence of treatment-related mortality. Several potential risk factors were examined and performance status and gross tumor volume were identified as clinically relevant predictive factors for acute toxicity. These findings suggest caution when treating large tumors or tumors in a complicate location. However, similar to other reports, identification of clinically relevant factors for late toxicity after re-RT remains elusive.

In the GETTEC trial, 38% of patients in the arm receiving surgery plus re-RT developed locoregional recurrences, and the 1-year loco-regional control rate was approximately 60% (16). In the RTOG 9911 trial, 31% of patients who received twice-daily re-RT without surgical resection (60 Gy in 1.5 Gy per fraction bid) experienced locoregional recurrences (7). In an MD Anderson study which included 27% of surgically resected patients, 35% of the re-RT patients had locoregional recurrences with a 64% probability of locoregional control for 2 years (12). Our study showed a locoregional recurrence rate of 51% with a 1-, 2-year LRFS rates of 55%, 36%, respectively, similar to previous studies using re-RT. Among 37 locoregional recurrences, 32% of patients had an outfield recurrence that remained outfield if the target was treated with a 2 cm margin. Despite our relatively small sample size, we observed a similar distribution of failure patterns according to surgical resection. These results support the utility of tight margins.

A study examining multiple covariates in univariate and multivariate analyses found that only nonmodifiable clinical factors of male gender, and age at the time of re-RT were predictors of outcome (12). In the Gustave-Roussy Institute study, they found that irradiated volume (≥ 650 cm^3) was the only factor associated with risk of death (relative risk, 1.8) (4). In our study, surgical resection before re-RT which could reduce the irradiation volume, and performance status were correlated with OS on multivariate analysis. Similarly, recent papers (26, 27) also have demonstrated that significant medical comorbidities or poor performance status could influence survival, which means that these are worse candidates for re-RT.

Modifiable prognostic factors in our study were re-RT dose, time between the two RT courses, and use of concurrent chemotherapy. Prediction of outcome remained significant when the analysis was performed with time as a continuous variable and longer time intervals were associated with better prognosis. One French review paper (28) identified that surgical resection, a dose higher than 50 to 60 Gy in a smaller-irradiated volume, and an interval between the two treatments of more than 2 years, were the most commonly

highlighted prognostic factors. Two recent papers (27, 29) also showed that the patients receiving more than 40 Gy in 5 fractions (BED equal to 72 Gy) had significantly higher local control than others. Although more investigation is needed on the optimal dose and fractionation schedule, our study is worth noting in this context.

In interpreting our data, limitations of retrospective analyses and patient and treatment selection must be considered. The reasons that our patients were treated with re-RT using helical tomotherapy were unclear, but the use of this regimen might be reliably recommended to patients who have factors suggesting better outcome. Our cohort was heterogeneous, so the results cannot be directly applied to all recurrent head and neck cancers to encourage the widespread use of re-RT. Since the cohort was relatively small, conducting a complete statistical analysis was limited. The prognostic factors identified in our data must be verified. Nevertheless, the strength of our study is that our patients received relatively homogenous treatment including re-RT with tight margins and sufficient radiation dose, performed at a single institution and were followed-up for a long period of time.

Conclusion

Moderate safety and acceptable acute and late toxicity after re-RT using full radiation dose, tight margins, and daily image guidance is reported. Encouraging local control and survival were obtained similar to historical data using these modern RT strategies. Resources should be directed toward prospective studies of re-RT in this field.

Conflicts of Interest

The Authors declare that they have no competing interests regarding this study.

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