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Adjuvant Postoperative Radiotherapy with or without Chemotherapy for Locally Advanced Squamous Cell Carcinoma of the Head and Neck: The Importance of Patient Selection for the Postoperative Chemoradiotherapy

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Purpose
We wanted to evaluate the role of postoperative chemoradiotherapy (CRT) for patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).

Materials and Methods
From March 1993 to July 2008, 101 patients with advanced SCCHN and who had undergone macroscopically complete resection were enrolled. Survival and the cumulative incidence of local or regional relapse, metastasis, and acute toxicity were analyzed.

Results
There was a marginally significant difference of disease-free survival at five years in favor of the CRT arm (51.3% vs. 41.8%, respectively; p=0.10). However, there was no significant difference in overall survival between the two treatment arms (p=0.20). The rate of locoregional failure only for the radiotherapy arm was significantly higher than that for the CRT arm (23.2% vs. 4.4%, respectively; p=0.01). The incidence of grade 3 or 4 hematologic toxicity was significantly higher in the CRT arm than that in the radiotherapy arm (37.7% vs. 1.7%, respectively; p=0.01). In CRT arm, early mortality group within 1 year had low performance status and old age over sixty compared with those of the others.

Conclusion
After curative-intent surgery, adjuvant CRT is more effective in locoregional tumor control than radiotherapy alone for patients with advanced SCCHN. However, compared with radiotherapy alone, this combined modality treatment had no survival benefit, and was significantly associated with increased toxicity. Thus, patients with low performance status and old age must be cautious in selection of toxic trimodality treatment.

Key words
Chemoradiotherapy, Head and neck neoplasms, Prognosis, Radiotherapy

Introduction

Approximately 600,000 patients worldwide are newly diagnosed every year with squamous cell carcinoma of the head and neck (SCCHN). Nearly 60% of this population presents with locally advanced, but nonmetastatic disease. Until recently, primary surgery for locally advanced SCCHN was traditionally followed by postoperative radiotherapy (RT) in most institutions. Despite such a relatively aggressive bimodality treatment, the prognosis of locally advanced SCCHN is poor, and this approach yielded locoregional recurrence, distant metastasis and 5-year survival rates of 30%, 25%, and 40%, respectively [1,2]. Consequently, some physicians have wondered if even more intensive treatment would improve the outcome. The role of chemotherapy for patients who have received primary resection and postoperative RT has been extensively studied. The Intergroup Study 0034 evaluated the issue of postoperative chemotherapy in a trial that randomized patients after surgery to three 21-day

cycles of sequential cisplatin and 5-fluorouracil followed by RT vs. RT alone. However, there was no significant improvement of locoregional control or overall survival (OS) associated with the use of chemotherapy [3].

In contrast to the use of sequential chemotherapy and RT, the European Organization for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group (RTOG) published the results of two randomized trials (EORTC trial no. 22931 and RTOG trial no. 9501) that evaluated the role of concomitant chemotherapy and radiation therapy in the postoperative setting for the patients with locally advanced SCCHN [4,5]. Both trials demonstrated that as compared with postoperative radiation alone, adjuvant chemoradiotherapy (CRT) was more efficacious in terms of locoregional control and disease-free survival (DFS). However, there was some discordance between the trials in terms of OS: the EORTC study revealed a highly significant difference in OS, whereas the RTOG trial showed only marginal improvement of OS. For patients with SCCHN, the major risk factors for local or regional relapse are extracapsular spread of disease and a microscopically involved resection margin, and the minor risk factors are a pathologic tumor stage of III or higher, two or more involved lymph nodes, level IV/V lymph node metastasis in the patients with oral cavity cancer and perineural invasion or vascular embolism [6,7]. Since some randomized trials have reported the superiority of postoperative CRT as compared with postoperative RT alone, our institution adopted postoperative CRT as the adjuvant standard treatment for patients with locally advanced or high-risk SCCHN, and now we report the retrospective and comparative results of postoperative RT and CRT.

Materials and Methods

1. Patient population

From March 1993 to July 2008, 108 patients who had undergone macroscopically complete resection at Seoul St. Mary's Hospital, Seoul, Republic of Korea were enrolled in this study. However, 7 patients were excluded from the study because five patients did not finish RT as scheduled due to the treatment toxicities, and two patients were proven to have lung metastases during the course of RT. Thus, remaining 101 patients were finally analyzed in this study.

They had histologically proven squamous cell carcinoma arising from the oral cavity, oropharynx, hypopharynx, or larynx, with a tumor stage of pT3 or pT4 and any nodal stage (N), or a tumor stage of T1 or T2 with a nodal stage of 2 or 3 and no distant metastasis (M0). The patients with stage T1 or T2 and N0 or N1 and who had unfavorable pathological findings (extranodal spread, positive resection margins, perineural involvement, or vascular tumor embolism) were also eligible, as were those patients with oral cavity or oropharyngeal tumors with involved lymph nodes at level IV or V. The patients who had a history of invasive or synchronous cancer (except nonmelanoma skin cancer), those who had previously received chemotherapy, those who had incomplete treatment or those who had recurred were excluded from the study. This study was approved by the institutional review boards of our institution.

The distribution of postoperative treatment modality was different according to the treatment period in our study. Between 1993 and 2000, 30 patients have received postoperative RT, and only one patient has received postoperative CRT. Between 2001 and 2004, 14 patients have received postoperative RT, and 10 patients have received postoperative CRT, and between 2005 and 2008, 12 patients have received postoperative RT and 34 patients have received postoperative CRT in our study. RT alone was applied to almost all patients who were treated early in the current study since the standard adjuvant treatment was postoperative RT alone at that time. However, after the EORTC and RTOG report (May 2004), cisplatin-based CRT was more frequently done as an adjuvant treatment option.

2. Surgery and pathology review

All the included patients underwent an operation with a curative-intent by one single, very skillful head and neck surgeon. If the tumor was within 5 mm of the surgical margins, the resection margin was considered to be close. The pathologic reports were reviewed by pathologists who had specialized in head and neck pathology.

3. Radiotherapy

All the included patients received postoperative RT that consisted of conventionally fractionated doses of 1.8 to 2 Gy each in five weekly sessions. The treatments were conducted on linear accelerators of 6 to 10 MV with conventional isocentric techniques, which irradiated the upper neck with 2 bilateral portals and the lower neck with one anterior portal.

A large volume encompassing the primary site and all the draining lymph nodes at risk received a dose of 50 to 55 Gy. Regions that had an inadequate resection margin, extracapsular nodal spread or the initially involved lymph node area were boosted up to 65 Gy. The dose to the spinal cord was limited to 45 Gy. Between 1993 and 2000, patients received two-dimensional RT, and after 2000, they received three-dimensional RT.

Table 1. Patient and tumor characteristics (n=101)

Characteristic	RT arm (n=56)	CRT arm (n=45)	p-value
Gender			0.40
Male	54 (96.4)	41 (91.1)	
Female	2 (3.6)	4 (8.9)	
Median age (yr)	58	56	
Tumor stage			0.25
T1	2 (3.6)	3 (6.7)	
T2	28 (50.0)	18 (40.0)	
T3	8 (14.3)	13 (28.9)	
T4	18 (32.1)	11 (24.4)	
Nodal stage			0.03
N0	6 (10.7)	2 (4.5)	
N1	14 (25.0)	1 (2.2)	
N2	35 (62.5)	42 (93.3)	
N3	1 (1.8)	0 (0)	
Resection margin			0.07
Negative	28 (50.0)	15 (33.3)	
Close	15 (26.8)	18 (40.0)	
Positive	7 (12.5)	12 (26.7)	
Unknown	6 (10.7)	0 (0)	
Tumor differentiation			0.58
Well differentiated	16 (28.6)	9 (20.0)	
Moderately differentiated	36 (64.3)	33 (73.3)	
Poorly differentiated	3 (5.4)	2 (4.5)	
Unknown	1 (1.7)	1 (2.2)	
Extracapsular spread			0.22
Negative	14 (25.0)	15 (33.3)	
Positive	17 (30.4)	30 (66.7)	
Unknown	25 (44.6)	0 (0)	
Vascular invasion			0.63
Negative	42 (75.0)	36 (80.0)	
Positive	14 (25.0)	9 (20.0)	
Perineural invasion			0.90
Negative	41 (73.2)	34 (75.6)	
Positive	13 (23.2)	11 (24.4)	
Unknown	2 (3.6)	0 (0)	
Performance status			0.38
ECOG 0	2 (3.6)	1 (2.2)	
ECOG 1	50 (89.3)	37 (82.2)	
ECOG 2	4 (7.1)	7 (15.6)	
Primary tumor site			0.39
Oral cavity	16 (28.6)	11 (24.4)	
Oropharynx	14 (25.0)	17 (37.8)	
Hypopharynx	11 (19.6)	10 (22.2)	
Larynx	15 (26.8)	7 (15.6)	

Values are presented as number (%). RT, radiotherapy; CRT, chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group.

4. Chemotherapy

The patients received chemotherapy that consisted of 100 mg cisplatin/m^2 of body-surface area on days 1, 22, and 43 of the course of RT or weekly 30 mg cisplatin/m^2 of body-surface area. The patients received prophylactic hydration and antiemetic agents. If patients were expected to have nutritional problems, then percutaneous gastrostomy or a Levine tube (L-tube) was recommended for nutritional support of the patients.

5. Statistical analyses

The primary end points were the differences of OS and DFS between the RT arm and the CRT arm. OS was defined as the time from RT to death from any cause. DFS was defined as the time from RT to any type of recurrence or death from any cause. Both end points were estimated by means of the Kaplan-Meier method, and the treatment arms were compared by the log-rank test. The cumulative incidence of local or regional relapse, metastasis, secondary primary tumors and acute adverse effects were analyzed as secondary end points, and these were compared by the chi-square test. The early radiation morbidity scoring scheme of the RTOG and the EORTC was used to assess early adverse effects [8]. We investigated prognostic factors such as the primary tumor site, pT and pN stage, performance status, extracapsular spread, perineural invasion, lymphovascular invasion, resection margin status, interval between RT and surgery, and treatment era which could be associated with OS of the included patients by using Cox proportional hazard ratio model.

Results

1. Characteristics of the patients

Between March 1993, and July 2008, 101 patients who were diagnosed as having locally advanced SCCHN were enrolled. Of these 101 patients, 95 (94%) were men. The median ages were 58 years in the RT arm and 56 years in the CRT arm. The primary tumor sites consisted of the oropharynx (31), oral cavity (27), hypopharynx (21), and larynx (22). The baseline characteristics of the two arms were similar and well-balanced, even if this study was not a randomized-controlled study, except that the CRT arm had a more aggressive nodal stage (Table 1).

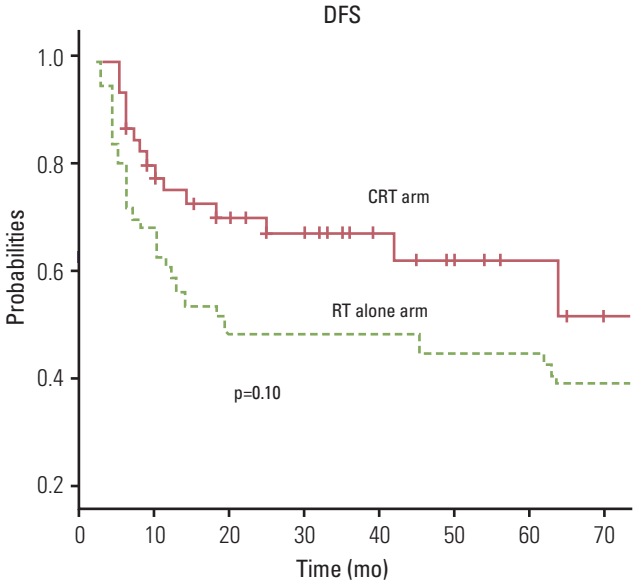

Fig. 1. The Kaplan-Meier estimates of disease-free survival (DFS) at five years were 41.8% in the radiotherapy (RT) arm and 51.3% in the chemoradiotherapy (CRT) arm, respectively. There was a marginal difference in DFS in favor of the CRT group.

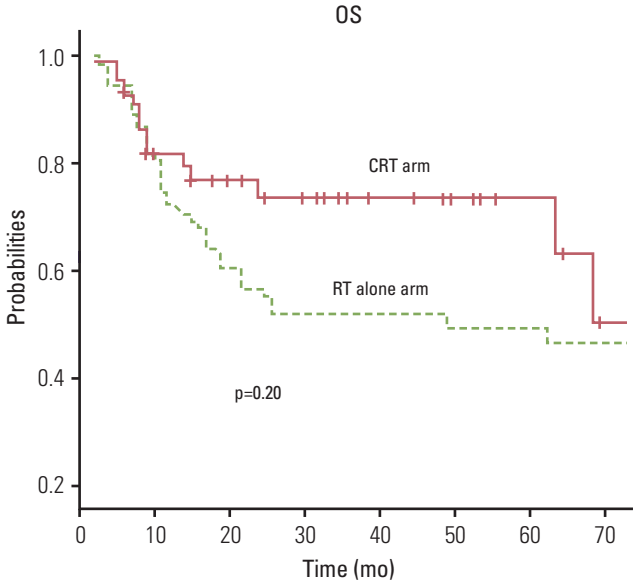

Fig. 2. The Kaplan-Meier estimates of overall survival (OS) at five years were 47.2% in the radiotherapy (RT) group and 63.2% in the combined therapy group, respectively. However, there was no significant difference in OS between two treatment arms. CRT, chemoradiotherapy.

2. Treatment and compliance with chemotherapy

The mean radiation dose was 61.4 Gy in the RT arm and 62.8 Gy in the CRT arm, respectively, and the difference was not significant on the t-test (p=0.13). The median duration of the treatment period was similar between the two arms (RT arm, 51 days; CRT arm, 50 days). In the CRT arm, 6 (13.3%) of 45 patients received three cycles of cisplatin, 100 mg/m^2 at three-week intervals without interruption, and 39 (86.7%) of 45 patients received weekly-scheduled cisplatin, 30 mg/m^2 with 32 (82%) patients receiving the full dose of weekly cisplatin without interruption. Ten patients in the CRT arm had undergone percutaneous gastrostomy and 2 patients in the CRT arm had L-tube feeding for nutritional support.

3. DFS and OS

At the median follow-up time of 65 months, the estimated rates of DFS and OS at 5 years in all patients were 47.5% and 51.8%, respectively. The mean follow-up time of the CRT arm was significantly longer than that of the RT arm (52.3 months vs. 78.2 months; p<0.01). A total of 51 patients died (36 in the RT arm and 14 in the CRT arm). The Kaplan-Meier estimates of DFS at five years were 41.8% in the RT arm and 51.3% in the CRT arm (Fig. 1). There was a marginally significant difference in DFS in favor of the CRT arm (p=0.10). The Kaplan-Meier estimates of OS at five years were 47.2% in the RT arm and 63.2% in the CRT arm (Fig. 2). However, there was no significant difference in OS between the two treatment arms (p=0.20).

4. Failure patterns

Table 2 shows the failure patterns of the treatment arms. There were 37 failures (25 in the RT arm and 12 in the CRT arm). Nearly all of the recurrences occurred within 24 months of diagnosis. The rate of locoregional failure only for the RT arm was significantly higher than that of the CRT arm (23.2% vs. 4.4%, respectively; p=0.01). The rate of distant metastasis only was not significantly different between the two treatment arms (14.2% in the RT arm and 6.6% in the CRT arm, p=0.32).

5. Treatment toxicities

Table 3 shows the acute treatment toxicities of the treatment arms. The incidence of grade 3 or 4 hematologic toxicity was significantly higher in the CRT arm than that in the RT arm (37.7% vs. 1.7%, respectively; p=0.01). Grade 3 or 4 nausea and vomiting did not occur in the RT arm. However, 2 patients in the CRT arm experienced severe nausea and vomiting. There was no significant difference in skin problems, mucositis and xerostomia between the two treatment arms in our study. There were two cases of septic shock and one case of severe aspiration pneumonia in the CRT arm, and they were all dead within 3 months after chemoradiation.

Table 2. Failure pattern and second primary cancer (n=101)

Characteristic	RT arm (n=56)	CRT arm (n=45)	p-value
Locoregional only	13	2	0.01
Distant only	8	3	0.32
Locoregional and distant	4	7	0.21
Second primary cancer	4	0	0.12

RT, radiotherapy; CRT, chemoradiotherapy.

Table 3. Acute treatment toxicities (n=101)

Toxicity	RT arm (n=56)		CRT arm (n=45)		p-value
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	
Hematologic	23 (41.0)	1 (1.7)	25 (55.5)	17 (37.7)	0.01
Nausea/Vomiting	6 (10.7)	0 (0)	11 (22.2)	2 (4.4)	0.08
Skin	29 (51.7)	1 (1.7)	16 (35.5)	2 (4.4)	0.38
Mucositis	40 (71.4)	11 (19.6)	25 (55.5)	14 (31.1)	0.21
Xerostomia	36 (64.2)	4 (7.1)	20 (44.4)	7 (15.5)	0.14

Values are presented as number (%). RT, radiotherapy; CRT, chemoradiotherapy.

Table 4. Univariate and multivariate analyses of factors associated with survival

Characteristic	No. of patients	Five-year survival (%)	Univariate analysis (p-value)	Adjusted odds ratio (95% CI)	Multivariate analysis (p-value)
Performance status			0.01		0.01
ECOG 0-1	90	60.5		1.00[a]	
ECOG 2	11	24.2		13.30 (4.05-43.70)	
Resection margin status			0.44		0.61
Negative	19	56.7		1.00[a]	
Positive	76	58.4		1.12 (0.72-1.73)	
Lymphovascular invasion			0.03		0.04
Negative	78	60.9		1.00[a]	
Positive	23	35.2		2.50 (1.00-6.25)	
Perineural invasion			0.16		0.95
Negative	75	62.5		1.00[a]	
Positive	24	42.2		1.03 (0.36-2.89)	
T stage			0.01		0.09
T1-2	51	67.0		1.00[a]	
T3-4	50	46.1		2.12 (0.87-5.14)	
N stage			0.51		0.51
N0-1	23	62.6		1.00[a]	
N2-3	78	54.4		1.51 (0.43-5.26)	
Extracapsular extension			0.17		0.27
Negative	29	68.0		1.00[a]	
Positive	47	52.4		1.78 (0.63-5.00)	
Radiation-operation interval (wk)			0.09		
≤6	62	63.3		1.00[a]	0.22
>6	39	46.8		2.04 (0.93-4.98)	
Treatment era (yr)					
1993-2004	55	51.2		1.00[a]	0.32
2005-2008	46	59.8		0.76 (0.45-2.12)	

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group. [a]Reference.

Table 5. Characteristics of the early mortality group within 1 year in the CRT arm (n=45)

Characteristic	Early mortality group (n=12)	Others (n=33)	p-value
Age (yr)			0.03
0-60	7 (20.0)	28 (80.0)	
>60	5 (50.0)	5 (50.0)	
PS			0.01
ECOG 0-1	7 (18.4)	31 (81.6)	
ECOG 2	5 (71.4)	2 (28.6)	

Values are presented as number (%). CRT, chemoradiotherapy; PS, performance status; ECOG, Eastern Cooperative Oncology Group.

However, there was no septic shock or severe aspiration pneumonia in the RT arm. Four patients in the RT arm had second primary cancers during their follow-up periods. Three cases of non-small cell lung cancer occurred 26, 48, and 61 months, and one case of esophageal cancer occurred 39 months after the completion of RT.

6. Prognostic factors associated with OS

We analyzed the prognostic factors such as the performance status, resection margin, lymphovascular invasion, perineural invasion, pT and pN stage, extracapsular extension, interval between RT and surgery, and treatment era

which could be associated with OS of the patients. Performance status (p=0.01), lymphovascular tumor invasion (p=0.03), and T stage (p=0.01) were significant prognostic factors associated with OS on the univariate analyses (Table 4). Additional multivariate analyses confirmed that only performance status (p=0.01) and lymphovascular tumor invasion (p=0.04) were significant prognostic factors associated with OS. In CRT arm, nearly all of the deaths occurred within 2 year of the diagnosis, and 12 patients were dead early during the first year of follow-up. Low performance status (p=0.01) and old age (p=0.03) over sixty were significant prognostic factors for the early death within 1 year (Table 5).

Discussion

For various reasons, the management of advanced head and neck cancer poses a significant challenge to physicians and to society as a whole. This disease tends to occur in the socio-economically deprived portion of the population, and comorbidities such as cardio-vascular disease and chronic obstructive airway disease are frequent in this population due to the pervasive damage from tobacco usage [9-11]. Before the EORTC report, the standard of care for locally advanced SCCHN was total resection of all visible and palpable disease, followed by adjuvant RT [2]. Yet the 5-year cumulative incidence of local or regional relapse was higher than 30% and the 5-year rate of OS was generally lower than 50%. The care of advanced SCCHN has gradually evolved from curative surgery as the mainstay of treatment to RT as the principal treatment. Thereafter, additional effectiveness has been observed with administering altered-fractionation RT (i.e., accelerated fractionation or hyperfractionated RT) and with RT combined with chemotherapy. Local or regional relapse is the most common form of treatment failure. Thus, various strategies have been proposed to improve the outcome among patients who have resectable and locally advanced SCCHN [12-14]. One strategy to improve the outcome is to intensify the effect of postoperative RT by combining it with chemotherapy such as cisplain. Cisplatin has been used in the treatment of SCCHN since the early 1970s. This material has proved to have a radiosensitizing effect, whether it is given in small weekly doses or in higher doses (100 mg/m^2) every three weeks (days 1, 22, and 43 during RT) [15,16]. The EORTC conducted a large scale trial to verify the effects of postoperative concurrent RT and chemotherapy in patients with high-risk SCCHN, and they detected a 11% increase in the rate of progression free survival (36% to 47% at five years) and a 13% decrease in locoregional relapses (31% to 18%) [5]. The RTOG 9501 study also verified the efficacy of combined modality therapy [6]. In the RTOG 9501 trial, the estimated 2-year rate of local and regional control was 82% in the combined-therapy arm, as compared with 72% in the RT arm, and DFS was significantly longer in the combined-therapy arm than that in the RT arm. These studies proved that CRT has been found to improve locoregional control or survival over that with RT alone in a selected group of patients. In our study, the 5-year OS and DFS of the CRT arm were higher than those of the RT arm. However, the benefit for DFS was marginally significant (p=0.10) and the benefit for OS was not statistically significant (p=0.20). Our study has a limitation of a small number of the patients (n=101). Thus, if we could get a larger enrollment, it is likely that the benefit for OS and DFS would attain statistical significance.

Yet such combination regimens are associated with high rates of severe and protracted mucositis and an increased need for nutritional support and invasive procedures for that purpose (i.e., gastroscomy) [17]. Late toxic effects, and particularly swallowing dysfunction, are also common. A considerable proportion of the patients with head and neck cancer have a reduced performance status or co-existing conditions, and these patients may be particularly prone to have such adverse events. In our study, the presence of combined modality increased the incidence of grade 3 or 4 hematologic toxicity (37.7% vs. 1.7%, respectively; p=0.01) and it caused mucositis of grade 3 or higher in 31.1% of the patients. Concurrent RT and chemotherapy is a toxic and risky treatment option, and it must be carefully conducted for older age patients or those with a low performance status.

Our results demonstrated an improvement in locoregional only control (23.2% vs. 4.4%; p=0.01) with concurrent postoperative RT and chemotherapy. However, combined therapy did not reduce the probability of distant metastasis, even though almost the patients received a high-dose chemotherapy or weekly full-cycled chemotherapy. This tells us that further adjuvant chemotherapy or more effective chemotherapy regimens are needed to reduce distant relapse in patients with locally advanced SCCHN. Nearly all of the recurrences occurred within 2 year of the diagnosis, and 27 patients recurred early during the first year of follow-up. Head and neck cancers are known to have rapidly proliferating clones and they have a very short potential tumor doubling time (i.e., 4 days) [18]. Sometimes, disease progression during the immediate postoperative period is observed. In patients who had an aggressive tumor stage, immediate CRT could be more effective than curative resection to reduce locoregional recurrence and distant metastasis thereafter [19,20]. In our uninvariate analysis, patients whose interval between surgery and radiation >6 months had poorer survival

outcome than those who had an interval of ≤6 months between surgery and radiation (p=0.09). Peters et al. [21] reported that for the patients who had curative resection, treatment delay of adjuvant RT greater than 6 weeks was associated with a progressively increased risk of recurrence and poor survival. Thus, it is usually recommended that postoperative adjuvant radiation should start within 5 to 6 weeks of operation if there is no postoperative wound problem.

We have failed to verify the significant benefit of survival with CRT compared with RT alone. When we see the survival curves of RT and CRT arm, there is no difference of survival decline within 1 year, and the survival gap has appeared after 1 year. In CRT arm, nearly all of the deaths occurred within 2 year of the diagnosis, and 12 patients were dead early during the first year of follow-up. We found that they had low performance status and old age over sixty compared with those of the others. In our study, patients with low performance status and old age over sixty are high-risk characteristics of early mortality for the trimodality of curative surgery followed by CRT which is intensive and toxic at the same time. Thus, less intensive treatment option such as neoadjuvant chemotherapy followed by surgery or definitive CRT instead of surgery followed by CRT should be considered to them. The sequence of cancer treatment and radiation field design is also very important for the patient's prognosis [22-24].

We analyzed prognostic factors associated with survival of the patients. In many clinical trials, the performance status, the T and N stages, lymphovascular and perineural invasion and the type of treatment (RT or CRT) were the independent prognosticators of OS for patients with locally advanced SCCHN and who were treated with radiation therapy with or without chemotherapy. In our study, the performance status and the lymphovascular invasion were the significant prognostic factors associated with OS on the multivariate analysis.

Despite the significant benefit of postoperative CRT in locoregional tumor control for the locally advanced head and neck cancer patients, our trial has some perspective weak points. First, our study should be understood in view of the inherent biases of a retrospective study design which had enrolled the patients for more than 10 years. The distribution of postoperative treatment modality was skewed across the treatment period in our study. Between 1993 and 2000, 30 (96.7%) of 31 have undergone RT alone after curative surgery, and only one (3.3%) patient has undergone postoperative CRT. Thereafter postoperative CRT was applied to the patients, and mostly after May 2004. Between 1993 and 2000, patients have received two-dimensional RT, and after 2000, they have received three-dimensional RT. Second, neck magnetic resonance imaging has been routinely performed to verify the invasiveness of primary diseases after 1997, not between 1993 and 2000, and positron emission tomography-computed tomography has been routinely performed to verify distant diseases after 2003, not between 1993 and 2002. Thus, the inaccuracy of the clinical tumor-node-metastasis staging before RT could also be a potential bias in our series.

Conclusion

Our study suggests that after surgery with a curative-intent, adjuvant combined RT and chemotherapy with cisplatin is more effective in locoregional tumor control than RT alone for the patients with locally advanced SCCHN. However, compared with RT alone, this combined modality treatment had no survival benefit, and was significantly associated with increased toxicity. Thus, patients with low performance status and old age must be cautious in selection of toxic trimodality treatment.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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