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Original Article

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Definitive Radiotherapy versus Postoperative Radiotherapy for Tonsil Cancer

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Purpose
The purpose of this study is to analyze treatment outcome of radiotherapy (RT) in patients with stage III-IV tonsil cancer managed by surgery followed by postoperative RT (SRT) and definitive chemoradiotherapy (CRT), and to thereby evaluate the most feasible treatment modality.

Materials and Methods
Of 124 patients, 67 underwent CRT, and 57 underwent SRT. We compared survival and complication rates in both groups.

Results
The median follow-up time was 57 months (range, 19 to 255 months) for surviving patients. At five years, locoregional progression-free survival (LRPFS) and overall survival (OS) were 88% and 80%, respectively. No significant difference in LRPFS (p=0.491) and OS (p=0.177) was observed between CRT and SRT. In multivariate analysis, old age and higher T stage showed a significant association with poor LRPFS, PFS, and OS; higher N stage showed an association with poor PFS and a trend of poor LRPFS, while no association with OS was observed; treatment modality (CRT and SRT) showed no association with LRFPS, PFS, and OS. Grade 3 or higher mucositis was observed in 12 patients (21%) in the SRT group, and 25 patients (37%) in the CRT group.

Conclusion
Definitive CRT and SRT have similar treatment outcomes for patients with stage III-IV tonsil cancer. Although acute complication rate appears to be higher in the CRT group, it should be noted that not all data on complications were included in this retrospective study. To determine the most feasible treatment modality, not only mucositis and xerostomia, but also emotional aspect and quality of life, should be considered.

Key words
Tonsil neoplasms, Chemoradiotherapy,
Intensity-modulated radiotherapy

Introduction

More than 260,000 new cases of oral cavity and pharyngeal cancers are diagnosed world wide each year [1]. Tumors in the oropharynx most commonly originate in the tonsil. The mainstay of treatment for early stage tonsil cancer is surgery or radiotherapy (RT), and treatment for advanced stage tonsil cancer is definitive chemoradiotherapy (CRT) or primary surgery followed by adjuvant RT. Kramer et al. [2] reported no significant difference in overall survival (OS) or locoregional control (LRC) in patients with squamous cell carcinoma (SqCC) of the oropharynx and oral cavity who were treated with preoperative RT, postoperative RT, or definitive RT. Several recent studies have reported similar efficacy for definitive RT and primary surgery in patients with tonsil cancer [3-6]. Due to a paucity of controlled studies comparing the two

modalities, the relative efficacy of surgery and RT as primary treatment for tonsil cancer remains unknown.

As RT technique has evolved from two-dimensional RT (2D-RT) to intensity-modulated radiotherapy (IMRT), the capacity to achieve conformal target coverage and spare sensitive organs has shown significant improvement. For patients with oropharyngeal cancer, excellent results of LRC of IMRT with or without chemotherapy have been reported [7, 8]. The Radiation Therapy Oncology Group (RTOG) has undertaken the RTOG 0022 protocol for evaluation of the adequacy of the IMRT technique, with particular reference to target coverage and salivary gland sparing in patients with oropharyngeal cancer.

In our institution, the number of patients with tonsil cancer has shown a steady increase, and the importance of definitive RT has been emphasized. Dynamic IMRT, which was first employed in 2003, has been used increasingly. The purpose of the current study was to analyze the outcome for patients with stage III-IV tonsil cancer managed by surgery followed by postoperative RT (SRT) and definitive CRT, and to thereby evaluate the most feasible treatment modality for patients with stage III-IV tonsil cancer.

Materials and Methods

1. Patients

From January 1979 to September 2009, 235 patients with tonsil cancer underwent RT at the Department of Radiation Oncology, Seoul National University Hospital. Following approval of the Institutional Review Board, we reviewed the medical records of these patients. Seventy one patients were excluded for the following reasons: loss of medical records during conversion from paper-based to electronic storage, two or more primary malignancies, metastatic or recurrent cancer, hematologic origin in pathology, incomplete RT dose, or palliative aim. A total of 32 patients received RT alone. The 132 patients who qualified were restaged according to the 2009 American Joint Commission on Cancer tumor-node-metastasis staging system, and eight patients with stage I-II were excluded. A list of the characteristics of 124 patients is shown in Table 1.

2. Surgery

A total of 57 patients underwent surgery: six patients underwent tonsillectomy, 22 underwent neck dissection, and 29 underwent both tonsillectomy and neck dissection. Tonsillectomy included extended tonsillectomy (n=23), wide tonsillectomy (n=9), en-bloc tonsillectomy (n=1), and resection of the tonsil and soft palate (n=2). Neck dissection included radical neck dissection (n=10) and modified radical neck dissection (n=41). Tonsillectomy, as a diagnostic procedure followed by RT, was classified as definitive RT rather than SRT. Treatment methods are shown in Table 2.

3. Radiotherapy

Our institution has used three-dimensional conformal RT (3D-CRT) and IMRT since 2002 and 2003, respectively. Currently, we recommend IMRT to all patients with tonsil cancer. However,

Table 1. Patient characteristics (n=124)

Variables		Total	CRT	SRT	p-value[a)]
Age (yr)	≤60	Median 54	43 (64)	50 (88)	0.003
	>60	(range, 26-78)	24 (36)	7 (12)	
Gender	Male	109 (88)	60 (90)	49 (86)	0.542
	Female	15 (12)	7 (10)	8 (14)	
Performance	ECOG 0	18 (15)	15 (22)	3 (5)	0.007
	ECOG 1-2	106 (85)	52 (78)	54 (95)	
T stage	T1-2	79 (64)	37 (55)	42 (74)	0.033
	T3-4	45 (36)	30 (45)	15 (26)	
N stage	N0-1	35 (28)	19 (28)	16 (28)	0.972
	N2-3	89 (72)	48 (72)	41 (72)	
Stage	III	25 (20)	13 (19)	12 (21)	0.820
	IV	99 (80)	54 (81)	45 (79)	
Histology	SqCC	118 (95)	61 (91)	57 (100)	
Differentiation	WD/MD	57 (46)	17 (53)	40 (80)	0.010
	PD/UD	25 (20)	15 (47)	10 (20)	

Values are presented as number (%). CRT, definitive chemoradiotherapy; SRT, surgery followed by postoperative (chemo) radiotherapy; ECOG, Eastern Cooperative Oncology Group; SqCC, squamous cell carcinoma; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; UD, undifferentiated. [a)]By Pearson's chi-square test.

Table 2. Treatment methods

Variables		No. of patient	%
Radiotherapy technique	2D-RT	57	46
	Definitive	29	23
	Postoperative	28	23
	3D-CRT	42	34
	Definitive	25	20
	Postoperative	17	14
	Intensity-modulated radiotherapy	25	20
	Definitive	13	10
	Postoperative	12	10
Neck irradiation	Ipsilateral neck nodes	21	17
	Bilateral neck nodes	103	83
Treatment modality	Radiotherapy+chemotherapy	67	54
	Surgery+radiotherapy	57	46
	Surgery+radiotherapy+chemotherapy	17	14
Surgery	Tonsillectomy	6	5
	Neck dissection	22	18
	Tonsillectomy+neck dissection	29	23

2D-RT, 2-dimensional radiotherapy; 3D-CRT, 3-dimensional conformal radiotherapy.

Table 3. Target definition and dose prescription

	CTV1	CTV2	CTV3
Target delineation	Primary tumor or tumor bed with 5-mm margin	Oropharynx Parapharyngeal space Retropharyngeal lymph nodal region Level of involved neck node	Next echelon of involved neck node
3D-CRT			
Definitive (35 fractions)	70 Gy	54 Gy	44 Gy
Postoperative (33 fractions)	66 Gy	54 Gy	44 Gy
IMRT			
Definitive (30 fractions)	67.5 Gy	54 Gy	48 Gy
Postoperative (28 fractions)	63 Gy	54 Gy	48 Gy

CTV, clinical target volume; 3D-CRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy.

for economic reasons, many patients chose 3D-CRT, as, at the time of their treatment, the National Health Service of Korea provided reimbursement for 3D-CRT but not for IMRT.

The treatment method of 2D-RT has been described previously [4]. In brief, most patients were treated with a 4-MV photon beam or Co-60, and with parallel opposed lateral fields with a matched anterior lower neck portal using midline shielding. Median dose was 70.2 Gy in 39 fractions for definitive RT and 66.6 Gy in 37 fractions for postoperative RT.

For 3D-CRT,we used the XiO RT planning system (Elekta CMS, Stockholm, Sweden). Definitions of clinical target volume (CTV) and median dose are shown in Table 3. The next level of involved neck nodes was treated electively. In most cases of ipsilateral neck disease, the contralateral level II with or without level III lymph nodes were irradiated as elective neck nodes. We prescribed a radiation dose to CTV for delivery of more than 97% of the prescribed dose to 97% of the target volumes. Delivered doses were 70 Gy in 35 fractions and 66 Gy in 33 fractionations for definitive and postoperative RT, respectively (Table 3).

Inverse treatment planning with the Eclipse system (Varian Medical Systems, Palo Alto, CA) was used for IMRT with simultaneous use of an integrated boost technique. A six-megavoltage photon beam was delivered to 7-9 fields using a dynamic multileaf collimator. The definitions of CTVs were similar to those for 3D-CRT, while planning target volume (PTV) had a 3-mm margin from CTV. The median dose prescribed to PTV is 67.5 Gy in 30

fractionations and 63 Gy in 28 fractionations for definitive and postoperative IMRT, respectively (Table 3). The following criteria were used for organs at risk: < 20 Gy to half of the parotid gland, < 54 Gy to the brain stem, < 45 Gy to the spinal cord, and < 50 Gy to the optic chiasm and the optic nerve.

Traditionally, elective neck nodal irradiation encompassed the uninvolved contralateral neck nodes; however, in recent practice, patients with well-lateralized tumors underwent ipsilateral neck irradiation only. Detailed information on RT modalities is shown in Table 2.

4. Chemotherapy

Among a total of 67 patients who underwent CRT, 38 received induction chemotherapy, five received concurrent chemoradiotherapy (CCRT), and 24 underwent induction chemotherapy followed by CCRT. Patients undergoing induction chemotherapy received three cycles of cisplatin-based chemotherapy every three weeks. CCRT recipients received cisplatin-based chemotherapy each week. Seventeen of the SRT patients underwent chemotherapy:10 with induction chemotherapy, five with adjuvant CCRT, and two with neoadjuvant chemotherapy and adjuvant CCRT.

5. Statistical analyses

The Kaplan-Meier method was used for calculation of survival rates. The log-rank test and the Cox's proportional hazards model were used in performance of univariate and multivariate analyses. The Pearson's chi-square and the Fisher's exact test were used to compare proportions between subgroups. SPSS ver. 18.0 (SPSS Inc., Chicago, IL) statistical software was used in performance of all statistical analyses. Complications were graded according to the RTOG morbidity scoring system.

Results

1. Treatment outcome

The median follow-up time was 57 months (range, 19 to 255 months) for surviving patients. At five years, locoregional progression-free survival (LRPFS), progression-free survival (PFS), and OS rates were 88%, 84%, and 80%, respectively. Treatment results are shown in Table 4 and Fig. 1. Regarding treatment modality (CRT and SRT), the five-year LRPFS was 83% and 92%; five-year PFS was 78% and 91%; and five-year OS was 76% and 84%, respectively. No significant difference in LRPFS (p=0.491), PFS (p=0.280), and OS (p=0.177) was observed between CRT and SRT. In comparison of CRT and SRT, there were more patients with young age, low T stage, and well-moderate differentiation in the SRT subgroup (Table 1). Because there were an insufficient number of patients whose human papillomavirus (HPV) status was determined, analysis of the association between HPV status and

Table 4. Univariate analysis of factors about patients and tumors

Variables		No.	5Y LRPFS (%)	p-value[a)]	5Y PFS (%)	p-value[a)]	5Y OS (%)	p-value[a)]
Age (yr)	≤60	93	93	0.026	89	0.038	83	0.049
	>60	31	70		67		70	
Gender	Male	109	86	0.547	82	0.367	79	0.371
	Female	15	75		100		83	
Performance	0	18	100	0.105	94	0.233	87	0.333
	1-2	106	86		83		78	
T	T1-2	79	91	0.021	90	0.003	91	0.001
	T3-4	45	79		72		59	
N	N0-1	35	97	0.121	97	0.052	82	0.563
	N2-3	89	85		81		79	
Stage	III	25	96	0.247	96	0.135	92	0.167
	IV	99	86		82		76	
Histology	WD/MD	57	86	0.230	84	0.172	74	0.294
	PD/UD	25	80		80		92	
Modality	CRT	67	83	0.491	78	0.280	76	0.177
	SRT	57	92		91		84	

5Y LRPFS, 5-year locoregional progression-free survival; 5Y PFS, 5-year progression-free survival; 5Y OS, 5-year overall survival; W/D, well differentiated; M/D, moderately differentiated; P/D, poorly differentiated; U/D, undifferentiated; CRT, definitive chemoradiotherapy; SRT, surgery followed by postoperative (chemo) radiotherapy. [a)]p-value by log rank test.

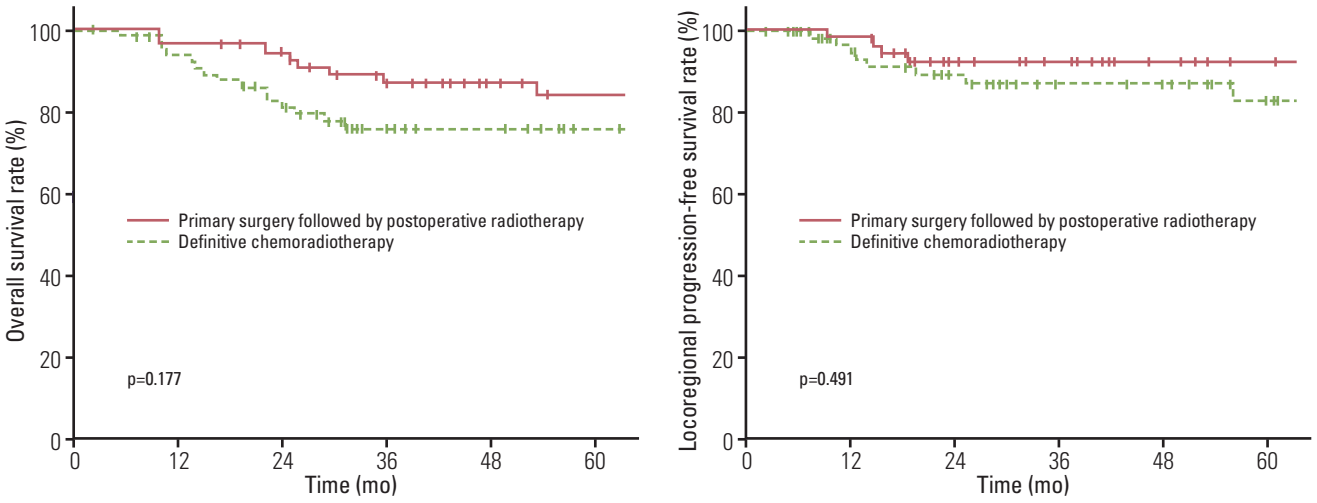

Fig. 1. Survival curves of overall survival and locoregional progression-free survival regarding treatment modality.

Table 5. Multivariate analysis

Variables	Locoregional progression-free survival			Progression-free survival			Overall survival		
	p-value[a)]	RR	95% CI	p-value[a)]	RR	95% CI	p-value[a)]	RR	95% CI
Age (>60 yr)	0.026	3.371	1.152-9.861	0.032	2.853	1.092-7.448	0.025	2.251	1.105-4.584
T (T3-4)	0.008	4.339	1.474-12.772	0.001	5.159	1.969-13.512	0.001	3.219	1.612-6.427
N (N2-3)	0.086	3.371	0.774-47.175	0.041	8.302	1.090-63.241	-		
Modality (CRT vs. SRT)	-			-			-		

RR, relative ratio; CI, confidential index; CRT, definitive chemoradiotherapy; SRT, surgery followed by postoperative (chemo) radiotherapy.
[a)]p-value by results of Cox proportional hazards model.

prognosis was not possible.

According to results of univariate analysis, old age (>60 years) and higher T stage (T3 and T4) showed a significant association with LRPFS, PFS, and OS. Higher N stage (N2 and N3) showed a trend of poor PFS. In multivariate analysis, old age and higher T stage showed a significant association with poor LRPFS, PFS, and OS; higher N stage showed an association with poor PFS and a trend of poor LRPFS, while no association with OS was observed; treatment modality (CRT and SRT) showed no association with LRFPS, PFS, and OS (Table 5).

2. Patterns of failure

Eighteen patients experienced recurrence, 13 locoregional recurrence, four distant metastasis, and one locoregional recurrence and distant metastasis. The sites of metastases included the lung, liver, and spine. Nine patients had second primary malignancies, including leukemia, non-small cell lung cancer, oral cavity cancer, hypopharyngeal cancer, esophageal cancer, and stomach cancer.

3. Complications

Mucositis was the most common complication of RT, while xerostomia was an important late complication. Grade 3 or higher mucositis was observed in 12 patients (21%) in the SRT group and 25 patients (37%) in the CRT group. A total of 27 patients experienced grade 2 chronic xerostomia, 11 patients belonged to the SRT group (19%), and 16 belonged to the CRT group (24%). In patients treated with IMRT (SRT, n=12; CRT, n=13), four patients (33%) with SRT and 10 (77%) with CRT experienced grade 3 or higher acute mucositis. More than six months of follow-up after treatment, two patients with SRT (17%) and three patients with CRT (23%) had grade 2 chronic xerostomia. Of 29 patients receiving definitive CCRT, 16 patients (55%) had grade 3 or higher acute mucositis, and seven (24%) experienced grade 2 chronic xerostomia. In patients who underwent surgery and adjuvant CCRT (n=7), two patients (29%) were noted with grade 3 or higher acute mucositis, and none of the patients experienced grade 2 chronic xerostomia.

Discussion

Patients with stage III-IV tonsil cancer are treated with CRT or SRT. Controlled studies comparing these modalities are lacking; therefore, we conducted a retrospective analysis in an effort to elucidate the optimal management for patients with tonsil cancer.

Several studies have reported no significant difference in LRC and survival between primary surgery and definitive RT for patients with SqCC of the tonsil [3-6]. Shirazi et al. [3] compared organ preservation and surgical management for advanced-staged SqCC. No statistically significant difference in four-year local control (94% and 86%, p=0.29) and four-year OS (71% and 48%, p=0.27) was observed for surgery and organ preservation groups. Poulsen et al. [9] compared outcomes of primary surgery and definitive RT in patients with stage III and IV SqCC of the tonsil. The surgery group showed a superior five-year OS (69% vs. 41%, p=0.007), a trend of improved LRC (88% vs. 73%; p=0.08), and no significant difference in disease-specific survival (75% vs. 56%, p=0.14). However, in this trial, definitive RT was offered if patients were medically or surgically inoperable, suggesting selection bias.

In our study, the five-year LRPFS was 83% and 92%, and OS was 76% and 84%, for CRT and SRT, respectively. These results are favorable, considering the cancer characteristics of our study (stage III-IV). Although the difference between CRT and SRT was not statistically significant, a trend toward better treatment outcome was observed with SRT. These differences may result from between-group variances in patient characteristics; for CRT and SRT, 36% and 12% of patients were over 60 years of age (p=0.003), and T3-4 constituted 45% and 26% of patients (p=0.033), respectively. The CRT subgroup consisted of non-operable patients; this could indicate a selection bias.

In patients with CCRT (n=36), most received a protocol based definitive CCRT regimen (n=29) for treatment of advanced head and neck cancer. In comparison of patient characteristics of definitive CCRT and SRT, no significant difference was observed in proportion of T3-4: 32% and 26% (p=0.575), for definitive CCRT and SRT, respectively. In our subgroup analysis of definitive CCRT and SRT, the three-year LRPFS was 100% and 92% (p=0.150), and three-year OS was 93% and 84% (p=0.492), respectively. A trend toward better LRC and OS was observed with definitive CCRT; however, as the median follow-up time was only 30 months, further follow-up is warranted. Grade 3 or higher acute mucositis was observed in 16 patients (55%) in the definitive CCRT group, nine patients (24%) who underwent sequential chemotherapy and RT, and 12 patients (21%) in the SRT group. The cisplatin-based chemotherapy regimen, which was given concurrently to patients, may have caused the severe toxicity. Alternative systemic agents, such as cetuximab, should be utilized in order to reduce the toxicity related to CCRT.

According to the meta-analysis reported by Pignon et al. [10], 4.5% of absolute benefit in five-year survival was identified when chemotherapy was added to locoregional treatment for head and neck cancers. The benefit was greater for concomitant chemotherapy than for induction chemotherapy. Several studies have reported that RT using concurrent cisplatin improved LRC and survival in patients with oropharyngeal cancer [11,12]. Adelstein et al. [11] compared RT with CCRT using fluorouracil and cisplatin in patients with SqCC of the head and neck. Compared with the RT group, the CCRT group showed longer recurrence-free interval (at five years, 62% vs. 51%; p=0.04) and longer disease-free survival (98% vs. 82%, p=0.02). In the report by Calais et al. [12] on a phase III, randomized, clinical trial for patients with oropharyngeal cancer, the CCRT arm showed better OS (at three years, 51% vs. 31%; p=0.02) and LRC (at three years, 66% vs. 42%; p=0.03), compared with RT alone. However, the rate of grade 3 and 4 mucositis and hematologic toxicity was higher in the CCRT arm. Results of recent randomized trials on the effect of adding concomitant cetuximab to RT showed that use of CCRT resulted in significantly improved OS (at five years, 46% vs. 36%; p=0.018), compared with RT [13], with no significant difference in the incidence of grade 3 or greater toxic effects [14].

In the IMRT group, although the median follow-up time was short (30 months), there was no recurrence or death. Several studies of IMRT have reported approximately 90% LRC [7,8]. Huang et al. [7] reported that definitive IMRT with CCRT for treatment of stage III and IV oropharyngeal carcinoma resulted in a 90% LRC. In a study of patients with stage I-IV oropharyngeal cancer, de Arruda et al. [8] reported two-year local and regional PFS of 98% and 88%, respectively; most of these patients (86%) underwent CCRT. For IMRT, it is possible to delineate the risk area, which varies among patients, and to improve target coverage. In contrast, the dose of 2D-RT cannot be escalated if the target area is close to an organ at risk, such as the spinal cord. This may be one reason why IMRT shows excellent outcomes. Chao et al. [15] analyzed the locoregional failure (LRF) patterns of IMRT for patients with head and neck cancer. In 17 cases of LRF, 11 were in the CTV and only one was marginal to the CTV. LRF within CTV might be overcome by escalation of the radiation dose. In addition, in our study, a high proportion of patients in the IMRT group (17 patients, 68%) received concurrent chemotherapy, which may have contributed to the good LRC achieved with IMRT.

In patients who underwent IMRT, 14 (56%) experienced grade 3 or higher acute mucositis, and 14 (56%) had grade 2 acute xerostomia. As mentioned above, a considerable percentage of IMRT recipients underwent CCRT, which contributes to the rate of occurrence of severe complications. Development of less toxic and more targeted systemic agents is needed. Nevertheless, six or more months after completion of IMRT, five patients (20%) had grade 2 xerostomia, with none experiencing a higher grade toxicity of this effect. This is a favorable result, and comparable with results reported by other institutions: the University of California, San Francisco reported 22% grade 2 xerostomia at follow-up of two years or more [7], and the Memorial Sloan-Kettering Cancer Center reported 33%

grade 2 xerostomia at follow-up of nine-month or greater [8]. Although not included in our study, swallowing function is another determinant of quality of life in patients with tonsil cancer who underwent RT [16]. According to recent reports, RT dose of pharyngeal constrictor muscles and larynx is associated with post-RT swallowing function, and, in order to minimize dysphagia and aspiration, IMRT can shield these muscular structures at risk from radiation [17].

Roughly comparing complication rates of CRT and SRT in our study, it appears that more patients who underwent CRT experienced complications. However, it should be noted that our study is lacking in information on complication of CRT or SRT. Due to the retrospective study design, there were some missing and ambiguous reports regarding complication. In addition, information on quality of life, swallowing function, speech, or emotion was absent. Surgery is associated with severe complications, including carotid artery rupture, postoperative pneumonia, oropharyngocutaneous fistula, and severe dysphagia [5,6,18]. Mendenhall et al. [5,6] and Parsons et al. [18] compared severe or fatal complication rates for patients with SqCC of the tonsil who underwent primary surgery and definitive RT. The primary surgery group showed significantly higher rates of severe (23% vs. 6%, $p < 0.001$) and fatal (3.2% vs. 0.8%, $p < 0.001$) complications, compared with the definitive RT group. In addition, more emotional impairment has been demonstrated in patients who underwent surgery for treatment of oropharyngeal cancer: social eating and contact [19]. Transoral robotic surgery for treatment of head and neck cancer has recently shown favorable swallowing outcomes, regarding oral diet without feeding tube and symptoms of aspiration after operation [20]. Despite promising results of transoral robotic surgery, it should be considered that these studies were very small in size and consisted of relatively lower T stage (T1-2, 73-79%). Therefore, further mature data are needed in order to elucidate long term oncologic and swallowing outcomes.

In our study, no significant difference in LRPFS, PFS, and OS for CRT and SRT was observed in patients with stage III-IV tonsil cancer. CCRT showed a trend toward better treatment outcome, compared with SRT; however, long-term follow-up is needed in order to confirm this result. In terms of RT technique, patients receiving IMRT experienced no recurrence or distant metastasis and had less severe chronic xerostomia, comparable with results reported by other institutions. One limitation of this study was its long treatment period, approximately 30 years. Therefore, because a variety of treatment techniques and regimens was used, each subgroup was quite small. Use of positron emission tomography and magnetic resonance imaging may have a significant impact on staging and RT target volume; therefore, development of diagnostic imaging techniques should have been evaluated [21,22]. In addition, our study included the absence of data on quality of life of patients with tonsil cancer; for example, gastrostomy tube insertion during treatment and swallowing function after treatment.

Conclusion

Definitive CRT and SRT have similar treatment outcomes for patients with stage III-IV tonsil cancer. Although acute complication rate appears to be higher in the CRT group, it should be noted that not all data regarding complications were included in this retrospective study. To determine the most feasible treatment modality, treatment related complications, in particular, not only mucositis and xerostomia, but also emotional aspect and quality of life, should be considered.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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