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Postoperative radiotherapy alone is as effective as postoperative chemoradiotherapy in patients with pT4aN0 gingival cancer with negative surgical margins

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ABSTRACT

Background and purpose: This study compared the survival outcomes following postoperative chemoradiotherapy (CCRT) and postoperative radiotherapy (RT) alone for patients with gingival cancer with negative surgical margins and only bone invasion.

Materials and methods: Of the 2579 gingival cancer cases reviewed from 2002 to 2018, 156 were enrolled in the study (CCRT: 63 patients; RT: 93 patients). The primary endpoints were the impact of adjuvant treatment (RT vs. CCRT) on overall survival (OS), locoregional recurrence-free survival (LRRFS), and distant metastasis-free survival (DMFS). Subgroup analyses were conducted based on surgical margins (<5 mm vs. ≥ 5 mm) and different adjuvant treatments (RT vs. CCRT).

Results: Median follow-up time, age, and invasion depth were 88.5 months, 57 years, and 14 mm, respectively. More patients undergoing adjuvant CCRT had surgical margins < 5 mm (47.6% vs. 21.5%, $p < 0.01$) than those undergoing RT. No significant difference was observed in the 5-year OS, LRRFS, and DMFS of patients undergoing adjuvant RT and CCRT. Although adjuvant RT alone and CCRT provided similar local control for patients with surgical margins ≥ 5 mm, worse LRRFS trends were observed in patients with surgical margins < 5 mm (hazards ratio, 6.15, 95% confidence interval 0.92–41.13, $p = 0.06$).

Conclusion: Postoperative RT alone may be effective for patients with gingival cancer with negative surgical margins (≥5 mm) and only bone invasion, while postoperative CCRT may result in better LRRFS than RT alone for patients with surgical margins < 5 mm.

1. Introduction

Approximately 5300 new oral cavity cancer cases are diagnosed annually in Taiwan with 800 cases of gingival origin [1]. The standard treatment for oral cavity cancer is radical surgical resection with or without adjuvant treatment based on postoperative pathologic features. Postoperative adjuvant chemoradiotherapy (CCRT) is recommended for patients with head and neck cancer who had involved surgical margins with or without extranodal extension [2,3]. Postoperative radiotherapy (RT) with or without concurrent chemotherapy is also recommended by the National Comprehensive Cancer Network treatment guidelines of head and neck cancer if adverse pathologic features including close resection margins, pathologic T3 or T4 primary cancer, pathologic N2 or N3 nodal disease, nodal disease in level IV or V, perineural invasion, vascular invasion, or lymphatic invasion are present [4].

Pathologic bone invasion is considered an independent risk factor

Abbreviations: CCRT, chemoradiotherapy; RT, radiotherapy; OS, overall survival; LRRFS, locoregional recurrence-free survival; DMFS, distant metastasis-free survival; HR, hazard ratio; 95% CI, 95% confidence interval.

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(pathologic T4a, pT4a) for oral cavity cancer [5,6], and postoperative CCRT is always recommended for patients with bone invasion [2,3,7]. As only a thin layer of connective tissue separates the gingival mucosa from the mandible/maxillary bone, bone invasion is the most common pathological adverse feature of gingival cancer. A higher incidence of bone invasion (approximately 60%) has been reported in patients with gingival cancer [8]; additionally, patients with gingival cancer and bone invasion have poor survival outcomes [8,9]. Therefore, postoperative adjuvant treatment is indicated for these patients.

Postoperative CCRT is always recommended in clinical practice for patients with gingival cancer with pathologically proven bone invasion; however, information on the outcomes following different adjuvant treatment strategies for these patients is limited. Nevertheless, a retrospective cohort study reported that adjuvant RT improved the overall survival in patients with pT4aN0 oral cavity cancer with negative surgical margins more than adjuvant CCRT [10]. However, only 12% of the enrolled patients received CCRT in this study, which may have led to under-reporting CCRT effectiveness.

Furthermore, the optimal postoperative adjuvant treatment strategy for gingival cancer post-radical surgery with negative surgical margins and only bone invasion (pathological T4aN0, pT4aN0) remains unknown. Therefore, in this study, we focused on patients with pT4aN0 gingival squamous cell carcinoma who underwent radical surgery with negative surgical margins and evaluated the survival differences in patients following postoperative adjuvant RT and CCRT.

2. Materials and methods

2.1. Patients

From April 2002 to May 2018, a total of 2579 patients with gingival cancer were retrospectively reviewed. The medical records of enrolled patients were reviewed, and the study was approved by the Institutional Review Board. The eligibility criteria were as follows: (1) age $\geq$ 20 years old; (2) histologically proven squamous cell carcinoma of upper or lower gingiva; (3) Eastern Cooperative Oncology Group (ECOG) performance status 0–3; (4) received radical surgery with tumor excision, marginal/segmental mandibulectomy, and ipsilateral/bilateral neck dissection; (5) pathologically proven bone invasion, negative surgical margins, and no lymph node metastasis (pT4aN0) according to the American Joint Committee on Cancer TNM staging system of head and neck cancer, 8th edition; and (6) patients received postoperative adjuvant RT of>4500 cGy with or without concurrent chemotherapy. The exclusion criteria were as follows: (1) recurrent or second primary gingival cancer, (2) not pT4a primary cancer, (3) patients received radical surgery alone without postoperative adjuvant treatment, (4) surgical margins involved, (5) insufficient adjuvant radiation dose, (6) pathologically proven lymph node metastasis, and (7) incomplete medical records. A total of 156 patients were enrolled, and a detailed flow chart of enrollment is presented in Supplementary Figure S1. Overall, 63 patients received postoperative adjuvant CCRT, and 93 patients received postoperative adjuvant RT.

2.2. Treatment

All patients underwent radical surgery including tumor wide excision, marginal/segmental mandibulectomy, and ipsilateral/bilateral neck dissection followed by adjuvant RT or CCRT. Adjuvant RT was delivered by a 6 MV photon beam with a median radiation dose of 6080 cGy (range, 4600–7000, 180–200 cGy per fraction, once daily, 5 fractions per week). The radiation field included a post-op tumor bed with or without the ipsilateral/bilateral neck lymph node area as per physician's discretion. For concurrent chemotherapy, a platinum-based regimen (most common regimen: weekly 30–40 mg/m^2 cisplatin) was used.

2.3. Study endpoints and statistical analysis

The primary endpoints of this study were the impact of adjuvant treatment (RT vs. CCRT) on overall survival (OS), locoregional recurrence-free survival (LRRFS), and distant metastasis-free survival (DMFS). The secondary endpoint was the impact of surgical margins on survival outcomes in subgroup analysis (surgical margin $<$ 5 mm vs. $\geq$ 5 mm). The OS was calculated from the first day of surgical resection to the date of death or last follow-up. The LRRFS and DMFS were calculated from the first day of surgical resection to the date of locoregional recurrence and distant metastasis, respectively.

For patients' characteristics, mean values with standard deviations and patient numbers with percentages are presented for continuous and categorical data, respectively. Fisher's exact test and Wilcoxon rank sum test were used to evaluate the differences between CCRT and RT groups. The survival difference between patients undergoing adjuvant RT and CCRT was compared by Kaplan–Meier survival curve analysis and log-rank test. The univariate Cox analysis was also used to generate hazard ratios (HR) with 95% confidence intervals (95% CI) between different adjuvant treatments (RT vs. CCRT). All statistical analyses were calculated using SAS version 9.4, and a 2-sided p value $<$ 0.05 was considered statistically significant.

3. Results

3.1. Patients' characteristics

The patient characteristics are presented in Table 1. All enrolled patients were male, and the median age at diagnosis was 57 years (range, 35–85 years). The majority of patients (82%) had tumors at the lower gingiva. Ninety-eight patients had primary tumors $<$ 4 cm in size, and 58 patients had tumors $\geq$ 4 cm in size. More patients with surgical margins $<$ 5 mm underwent adjuvant CCRT than patients with surgical

Table 1
Patient characteristics.

	RT (n = 93)		CCRT (n = 63)		p value
variables	n	%	n	%	
Age (years) (Mean)	57.6		55.76		0.28
Age					
<60	53	57.0	43	68.3	0.18
≥60	40	43.0	20	31.8	
Tumor location					
Upper gingival	13	14	15	23.8	0.14
Lower gingival	80	86	48	76.2	
Tumor size					
<4 cm	61	65.6	37	58.7	0.40
≥4 cm	32	34.4	26	41.3	
Surgical margins					
<5 mm	20	21.5	30	47.6	< 0.01
≥5 mm	73	78.5	33	52.4	
Invasion depth					
<14 mm	50	53.8	25	39.7	0.10
≥14 mm	43	46.2	38	60.3	
Perineural invasion					
No	82	88.12	80	79.4	0.18
Yes	11	11.8	13	20.6	
Angiolymphatic invasion					
No	92	98.9	61	96.8	0.57
Yes	1	1.1	2	3.2	
Histology					
Well-moderate differentiation	91	97.9	58	92.1	0.12
Poorly differentiation	2	2.2	5	7.9	
Eastern Cooperative Oncology Group performance status					
0–1	78	83.9	58	92.1	0.15
2–3	15	16.1	5	7.9	
Adjuvant radiation dose (cGy)					
<6000	14	15.1	8	12.7	0.82
≥6000	79	85.0	55	87.3	

CCRT: chemoradiotherapy; RT: radiotherapy.

margins ≥ 5 mm ($p < 0.01$). A higher proportion of patients with pathological invasion depth ≥ 14 mm underwent adjuvant CCRT (60.3% in the CCRT group and 46.2% in the RT group, respectively), and > 80% of patients received a radiation dose of ≥ 6000 cGy.

3.2. Comparison of treatment outcomes between RT and CCRT

Median follow-up time for the patients was 88.5 months (range, 6–209). The 5-year OS, LRRFS, and DMFS for patients who underwent adjuvant CCRT or RT were 77.6% vs. 71.7%, 80.4% vs. 74.5%, and 91.8% vs. 93%, respectively (all log-rank $p > 0.05$) (Fig. 1). Multivariate analysis revealed that the ECOG performance status was an independent factor for predicting OS (HR, 3.53; 95% CI, 1.88–6.66; $p < 0.001$). Age and deep bone invasion were independent prognostic factors for LRRFS ($p = 0.02$ and 0.03, respectively). Other clinicopathological factors (postoperative RT or CCRT, tumor location, tumor size, surgical margins, perineural invasion, angiolymphatic invasion, histology type, and radiation dose) were not significantly different in terms of OS and LRRFS (Table 2) between patients undergoing RT and CCRT. No prognostic factor was found for distant metastasis.

3.3. Impact of surgical margins on survival outcomes

In subgroup analysis for patients with surgical margins < 5 mm, ECOG performance status was associated with a poor prognosis with respect to OS and LRRFS. Additionally, invasion depth and angiolymphatic invasion were worse prognostic factors for LRRFS. Postoperative RT only showed a trend toward a worse LRRFS than CCRT (HR, 6.15; 95% CI, 0.92–41.13; $p = 0.06$, Table 3). The 5-year OS, LRRFS, and DMFS between postoperative adjuvant RT and CCRT for patients with surgical margins < 5 mm were 74.0% vs. 73.3%, 74.7% vs. 81.9%, and 89.4% vs. 89.8%, respectively (all p value > 0.05). For patients with surgical margins ≥ 5 mm, ECOG performance status was associated with poor OS. Tumor location was associated with LRRFS, favoring the lower gingiva. Older age ≥ 60 years had a mild association with improved LRRFS (HR, 0.39; 95% CI 0.14–1.04; $p = 0.06$, Table 4). The 5-year OS, LRRFS, and DMFS of patients with surgical margins ≥ 5 mm undergoing postoperative adjuvant RT versus CCRT were not significantly different. Therefore, postoperative RT could be sufficient for patients with gingival cancer with negative surgical margins and only bone invasion, especially those with surgical margins ≥ 5 mm.

4. Discussion

To the best of our knowledge, this is the first study focusing on patients with pT4aN0 squamous cell carcinoma of the gingiva who underwent radical surgery with negative surgical margins, to evaluate the survival difference between postoperative adjuvant RT and CCRT. This study demonstrates that postoperative RT and CCRT resulted in similar survival outcomes in terms of OS, LRRFS, and DMFS for patients with pT4aN0 gingival cancer and negative surgical margins. Additionally, the ECOG performance status was an independent factor in OS. Furthermore, age and deep bone invasion were independent poor prognostic factors in LRRFS. In subgroup analysis, postoperative CCRT slightly improved the LRRFS (HR, 6.15; 95% CI, 0.92–41.13; $p = 0.06$) compared to RT alone for patients with surgical margins < 5 mm, but no difference was observed in patients with surgical margins ≥ 5 mm, (HR, 1.54; 95% CI 0.61–3.87; $p = 0.36$).

Postoperative adjuvant RT or CCRT is recommended for patients with oral cavity cancer and adverse pathologic features including close resection margins, pathologic T3 or T4 primary cancer, pathologic N2 or N3 nodal disease, nodal disease in level IV or V, perineural invasion, vascular invasion, and lymphatic invasion [2–4,7]. However, in patients without major risk factors (surgical margins involved and/or extracapsular extension), Trifiletti et al. reported that adjuvant CCRT could improve the OS more than RT alone for patients with increased number

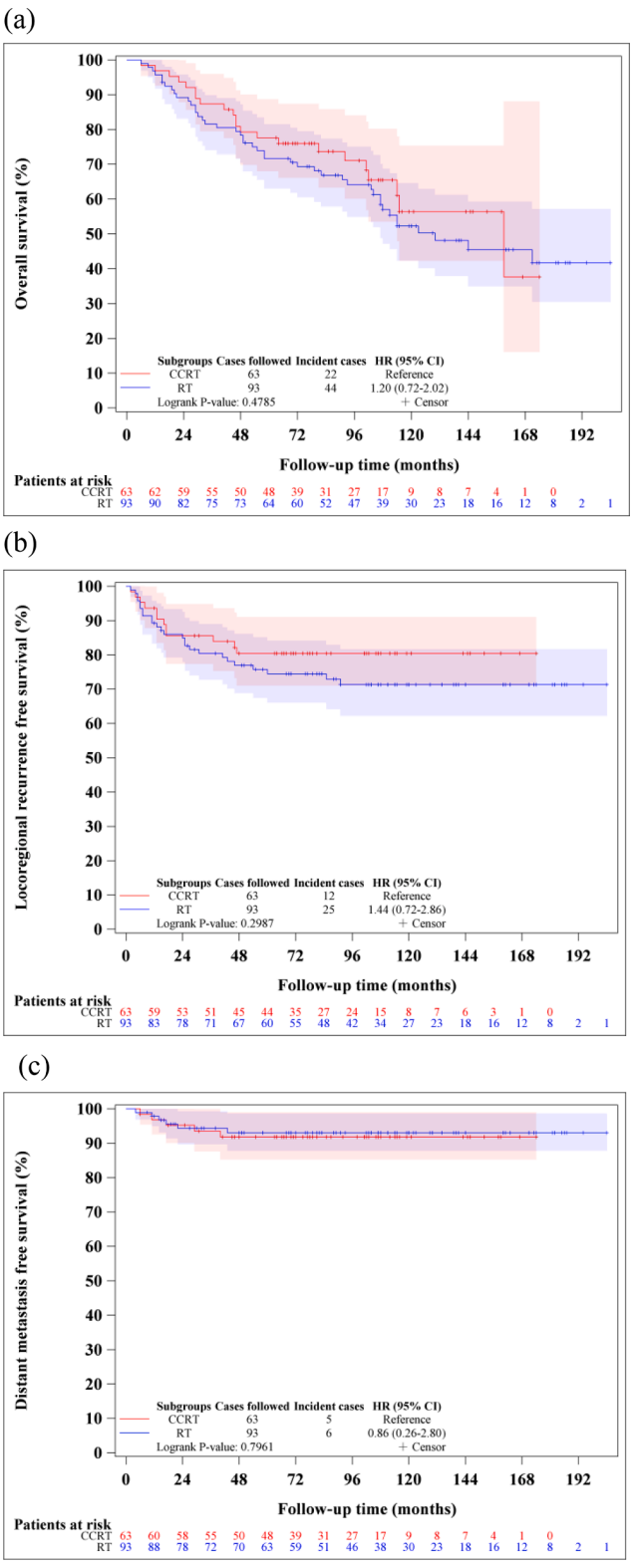

Fig. 1. Overall survival (a), locoregional recurrence-free survival (b), and distant metastasis-free survival (c) of patients who underwent postoperative adjuvant radiotherapy and chemoradiotherapy for pT4aN0 squamous cell carcinoma of the gingiva and negative surgical margins.

of positive lymph nodes [11]. Hence, the routine use of CCRT in patients without major adverse features remains controversial. Moreover, pathologically proven bone invasion is common for patients with oral cavity cancer and the T stage is upstaged to T4a regardless of tumor size. A

Table 2
Cox proportional hazard model for overall survival (OS) and locoregional recurrence-free survival (LRRFS) for patients with pT4aN0 gingival cancer.

		OS			LRRFS		
		HR	95% CI	*p* value	HR	95% CI	*p* value
Adjuvant treatment	RT vs. CCRT	1.12	(0.64–1.97)	0.70	2.00	(0.88–4.53)	0.10
Age	≥ 60 vs. < 60	0.96	(0.57–1.62)	0.89	0.38	(0.17–0.84)	0.02
Tumor location	Lower vs. Upper	0.88	(0.45–1.73)	0.72	0.53	(0.23–1.22)	0.14
Tumor size (cm)	≥ 4 vs. < 4	0.73	(0.42–1.27)	0.27	1.06	(0.50–2.25)	0.89
Surgical margin (mm)	≥ 5 vs. < 5	0.80	(0.47–1.38)	0.43	0.98	(0.44–2.18)	0.96
Invasion depth (mm)	≥ 14 vs. < 14	1.27	(0.77–2.10)	0.36	2.29	(1.10–4.79)	0.03
Perineural invasion	Yes vs. No	1.03	(0.47–2.23)	0.95	0.65	(0.20–2.05)	0.46
Angiolymphatic invasion	Yes vs. No				0.98	(0.13–7.50)	0.98
Histology type	PD vs. WD + MD	0.69	(0.16–3.06)	0.63	2.60	(0.51–13.27)	0.25
ECOG performance status	2–3 vs. 0–1	3.53	(1.88–6.66)	<0.01	2.21	(0.94–5.21)	0.07
Radiation dose (cGy)	≥ 6000 vs. < 6000	0.85	(0.43–1.70)	0.65	0.70	(0.28–1.71)	0.43

HR: hazard ratio; CI: confidence interval; RT: radiotherapy; CCRT: chemoradiotherapy; ECOG: Eastern Cooperative Oncology Group; PD: poorly differentiated; WD: well differentiated; MD: moderately differentiated.

Table 3
Cox proportional hazard model for overall survival (OS) and locoregional recurrence-free survival (LRRFS) for patients with pT4aN0 gingival cancer with surgical margins < 5 mm (n = 50).

		OS			LRRFS		
		HR	95% CI	*p* value	HR	95% CI	*p* value
Adjuvant treatment	RT vs. CCRT	1.18	(0.43–3.29)	0.75	6.15	(0.92–41.13)	0.06
Age	≥ 60 vs. < 60	0.54	(0.18–1.60)	0.27	0.41	(0.06–3.08)	0.39
Tumor location	Lower vs. Upper	1.36	(0.44–4.28)	0.59	1.48	(0.26–8.49)	0.66
Tumor size (cm)	≥ 4 vs. < 4	0.52	(0.17–1.59)	0.25	0.10	(0.01–1.28)	0.08
Invasion depth (mm)	≥ 14 vs. < 14	2.28	(0.83–6.29)	0.11	17.98	(1.68–191.95)	0.02
Perineural invasion	Yes vs. No	1.90	(0.63–5.75)	0.25	1.86	(0.28–12.32)	0.52
Angiolymphatic invasion	Yes vs. No				402.27	(2.50–64750.64)	0.02
Histology type	PD vs. WD + MD	0.22	(0.02–2.58)	0.22	0.95	(0.04–23.39)	0.98
ECOG performance status	2–3 vs. 0–1	4.25	(1.30–13.89)	0.02	6.65	(1.13–39.02)	0.04
Radiation dose (cGy)	≥ 6000 vs. < 6000	0.42	(0.09–1.89)	0.26	0.39	(0.03–5.25)	0.48

HR: hazard ratio; CI: confidence interval; RT: radiotherapy; CCRT: chemoradiotherapy; ECOG: Eastern Cooperative Oncology Group; PD: poorly differentiated; WD: well differentiated; MD: moderately differentiated.

Table 4
Cox proportional hazard model of overall survival (OS) and locoregional recurrence-free survival (LRRFS) for patients with surgical margin ≥ 5 mm (n = 106).

		OS			LRRFS		
		HR	95% CI	*p* value	HR	95% CI	*p* value
Adjuvant treatment	RT vs. CCRT	1.11	(0.54–2.30)	0.78	1.54	(0.61–3.87)	0.36
Age	≥ 60 vs. < 60	1.46	(0.78–2.75)	0.24	0.39	(0.14–1.04)	0.06
Tumor location	Lower vs. Upper	0.72	(0.30–1.74)	0.47	0.27	(0.10–0.72)	< 0.01
Tumor size (cm)	≥ 4 vs. < 4	0.76	(0.38–1.51)	0.43	1.69	(0.70–4.08)	0.25
Invasion depth (mm)	≥ 14 vs. < 14	0.92	(0.49–1.74)	0.81	1.83	(0.78–4.28)	0.16
Perineural invasion	Yes vs. No	0.39	(0.09–1.64)	0.20			
Angiolymphatic invasion	Yes vs. No						
Histology type	PD vs. WD + MD	0.66	(0.08–5.71)	0.71	3.23	(0.32–32.56)	0.32
ECOG performance status	2–3 vs. 0–1	3.11	(1.38–7.02)	< 0.01	1.88	(0.63–5.59)	0.26
Radiation dose (cGy)	≥ 6000 vs. < 6000	1.03	(0.41–2.58)	0.96	0.63	(0.20–1.94)	0.42

HR: hazard ratio; CI: confidence interval; RT: radiotherapy; CCRT: chemoradiotherapy; ECOG: Eastern Cooperative Oncology Group; PD: poorly differentiated; WD: well differentiated; MD: moderately differentiated.

higher incidence rate of bone invasion is reported in patients with gingival cancer, owing to its specific anatomic site with only a thin layer of connective tissue between the gingival mucosa and the maxilla/mandible bone [12]. Many studies have demonstrated that medullary bone invasion was an independent poor prognostic predictor for survival in patients with gingival cancer [5,6,9], and postoperative adjuvant treatment was recommended by NCCN guidelines for patients with pT4a gingival cancer.

However, the most effective postoperative adjuvant treatment strategy for patients with T4a gingival cancer remains unknown. Namin et al. investigated the effect of tumor size, subsite, and adjuvant therapy on outcomes for patients with pT4aN0 oral cavity carcinoma and negative surgical margins using the National Cancer Database. The study reports that postoperative adjuvant RT could result in better survival outcomes than surgery alone, but postoperative CCRT could not [10]. However, the therapeutic effect of adjuvant CCRT may be underreported in the study as only 12% of enrolled patients received this treatment. In the current study, postoperative adjuvant RT and CCRT had similar survival outcomes (OS, LRRFS, and DMFS) for patients with pT4aN0 gingival cancer with negative surgical margins. Additionally, we analyzed the subgroups based on surgical margins (<5 mm versus ≥ 5 mm) and showed that adjuvant CCRT could provide a slightly improved LRRFS compared to RT alone only for patients with surgical margins < 5 mm ($p = 0.06$).

Our study also demonstrated invasion depth ≥ 14 mm is an independent factor for poor prognosis in disease control. Although we do not

have actual pathological structures of invaded bone, it is reasonable to assume that the depth of invasion is equal to medullary bone invasion and causes poor disease control. Additionally, patients aged $\geq$ 60 years had a better LRRFS rate than patients aged $<$ 60 years. Of the 60 patients aged $\geq$ 60 years, 40 patients underwent RT alone and 20 patients underwent CCRT. Adjuvant RT alone instead of CCRT is often considered in clinical practice for older patients. The higher treatment-related toxicities of CCRT might lead to interruption of the treatment period and may lead to decreased LRRFS. Moreover, poorer local control of upper gingival tumors was observed in patients with surgical margins $\geq$ 5 mm; thus, increased intensity of adjuvant treatment may be warranted.

Limitations of the current study include its retrospective nature, small sample size, the lack of extensive data on bone invasion (invasion to cortical bone, medullary bone, or mandibular canal), the lack of data on treatment-related adverse effects of adjuvant RT and CCRT, and the lack of data on failure patterns.

4.1. Conclusions

In conclusion, for patients with pT4aN0 gingival cancer with negative surgical margins $\geq$ 5 mm, when compared to CCRT, postoperative adjuvant RT alone can provide equal therapeutic efficacy in terms of OS, LRRFS, and DMFS. Postoperative adjuvant CCRT may be beneficial for LRRFS for patients with pT4aN0 gingival cancer with surgical margins $<$ 5 mm than RT alone. Further randomized studies are needed to compare the survival outcomes between different adjuvant treatment modalities for these patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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