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Oral cavity cancers treated with superselective intra-arterial chemoradiotherapy with radiation doses less than 60 Gy: implications for dose reduction from a propensity score-matched analysis

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► ***Original article***

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ABSTRACT

Background: The optimal radiation dose for oral cavity cancers treated with retrograde superselective intra-arterial chemoradiotherapy (SIACRT) is unclear. The aim of the present study was to evaluate the treatment outcome and toxicity in patients treated with <60 Gy compared with those treated with ≥60 Gy to provide evidence for determining the optimal dose. ***Materials and Methods:*** Between January 2009 and December 2013, 159 oral cavity cancer patients were treated with SIACRT with curative intent at a single institution. One hundred and twenty-nine patients received ≥60 Gy and 30 received <60 Gy. Local control (LC), disease-free survival (DFS), overall survival (OS), and toxicity were compared. Propensity score matching was performed to reduce bias. ***Results:*** The median follow-up period was 48 months (range, 2–88 months). LC (<60 Gy vs. ≥60 Gy, 81.5% vs. 86.1% at 3 years, p = 0.534), DFS (68.8% vs. 72.4% at 3 years, p = 0.816), and OS (85.9% vs. 72.3% at 3 years, p = 0.132) were comparable between the two groups. There was also no difference in toxicity. However, the median overall treatment period was significantly shorter in the <60 Gy cohort (39 days vs. 49 days, p < 0.0001). ***Conclusion:*** The radiation dose may be reduced to <60 Gy when treating oral cavity cancers with SIACRT.

Keywords: *Catheterization, chemoradiotherapy, oral cancer, survival rate, toxicity.*

INTRODUCTION

Oral cavity cancers are some of the most common malignancies worldwide [1]. In Western countries, the age-standardised incidence of oral cavity cancers is approximately 6.9 per 100,000 in men and 2.4 per 100,000 in women [2]. Primary surgical resection with or without postoperative adjuvant therapy is regarded as the standard of care [1]. The National Comprehensive Cancer Network guidelines list several treatment options for these cancers, with resection of the primary lesion as the first-line consideration [3]. However, patient quality of life often deteriorates because of impairments in swallowing and speech function after surgery. Superselective intra-arterial chemoradiotherapy (SIACRT) has been proposed with the aim of preserving organ function [4]. The advantage of this modality is that it enables delivery of high concentrations of anti-tumoural agents, resulting in improvement of local control (LC) and mitigation of toxicity. We previously observed excellent treatment outcomes by adopting retrograde SIACRT, a major method in this modality [5]. At our institution, we generally deliver 60 Gy for the gross tumour volume (GTV), which is less than the recommended dose

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to control gross disease in the head-and-neck region [3]. However, we frequently experience cases that do not complete the standard treatment course for various reasons including infection, myelosuppression, or patient refusal. Treatment outcome and incidence of toxicity in such cases has not been sufficiently described to date. The aim of the present study was to evaluate the treatment outcome and toxicity in patients with oral cavity cancer treated with <60 Gy SIACRT compared with those treated with ≥60 Gy to provide evidence for determining the optimal dose. To the best of our knowledge, the present study is the first to examine whether the radiation dose can be reduced when oral cavity cancers are treated with SIACRT.

MATERIALS AND METHODS

Patients

The present study was approved by the Institutional Review Board of Yokohama City University (Identification Number: B170800007). All patients provided written informed consent before initiation of treatment. Patients with oral cavity cancers were treated with SIACRT with curative intent at a single institution between January 2009 and December 2013. Patients with low performance status, myelosuppression, or severe comorbidity (e.g. renal failure) were deemed ineligible for the treatment modality. Patients who received <40 Gy radiotherapy (RT) or those receiving proton therapy were excluded. The characteristics of the 159 eligible patients are summarised in table 1. Tumour stage was classified by the Union for International Cancer Control TNM classification for head-and-neck tumours, 7th edition [6]. All patients underwent contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET)-CT examinations before treatment unless contraindicated. The patients with clinical stage I disease (1.3%) refused surgical treatment. All patients had histologically confirmed carcinomas. Twenty-two (14%) patients developed double cancer, defined as diagnosis of another cancer at their primary evaluation for oral cavity cancer (synchronous) or during their follow-up period (metachronous). One hundred and twenty-nine patients received radiation doses ≥60 Gy, and 30 received <60 Gy. The proportions of patients with T4 disease and primary lesion located in the tongue were significantly higher in the ≥60 Gy cohort. Furthermore, the median age of the patients in that cohort was significantly younger. Other characteristics were well balanced between the <60 Gy and ≥60 Gy cohorts.

Table 1. Patient characteristics in the total cohort before propensity score matching.

Characteristic		<60 Gy (*n*=30)	≥60 Gy (*n*=129)	*p*-value
Follow-up period (months)	Median	44	49	0.655
	Range	2–83	4–88	
Age (years)	Median	72	62	0.024
	Range	40–88	32–87	
Sex	Male	16 (53%)	83 (64%)	0.263
	Female	14 (47%)	46 (36%)	
Performance status (ECOG)	0	10 (33%)	25 (19%)	0.097
	1–2	20 (67%)	104 (81%)	
Primary location	Tongue	10 (33%)	78 (60%)	0.007
	Others	20 (67%)	51 (40%)	
T stage	T1–T3	24 (80%)	78 (60%)	0.044
	T4a/T4b	6 (20%)	51 (40%)	
N stage	N0/N1	21 (70%)	94 (73%)	0.752
	N2/N3	9 (30%)	35 (27%)	
Stage	I–III	16 (53%)	63 (49%)	0.657
	IVA/IVB	14 (47%)	66 (51%)	
Histology	Squamous cell carcinoma	29 (97%)	124 (96%)	0.888
	Others	1 (3%)	5 (4%)	
Double cancer	Yes	3 (10%)	19 (15%)	0.499
	No	27 (90%)	110 (85%)	
Systemic chemo-therapy	Yes	15 (50%)	76 (59%)	0.376
	No	15 (50%)	53 (41%)	
Hyperthermia	Yes	6 (20%)	23 (18%)	0.782
	No	24 (80%)	106 (82%)	

Abbreviations: ECOG = Eastern Cooperative Oncology Group; RT = radiotherapy.

RT

All patients received CT-based 3D conformal RT by X-ray treatment 5 days per week using a

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conventional 2-Gy fractionation regimen. The initial treatment field encompassed the GTV with a margin of ≥2 cm. Prophylactic lymph node (LN) areas were also included depending on the disease extent. The GTV was based on visual examination and palpation alongside diagnostic imaging examinations like CT, MRI, and PET-CT. The prophylactic LN areas were bilateral if the primary tumour was located across or adjacent to the midline, or if it was N2/N3 stage. In N0 cases, levels 1–3 were encompassed and the field was expanded to the lower neck in N-positive cases. Following initial irradiation of 40 Gy, the GTV generally received a boost. Twenty-nine (18%) patients concurrently underwent hyperthermia for lesions near the skin surface.

As mentioned above, 129 patients received a total dose of ≥60 Gy and 30 received <60 Gy. The most common reason for reducing the total radiation dose was infection/fever, followed by myelosuppression. However, multiple reasons were present in the majority of cases.

Retrograde SIA infusion procedure

All patients received retrograde SIA chemotherapy concomitant with RT. The SIA infusion technique was performed as described previously [5]. After determining the tumour-feeding arteries by 3D CT of the carotid artery, catheters were inserted superselectively via the superficial temporal artery and, if required, via the occipital or contralateral artery, depending on the location and extent of the primary tumour. After the catheter insertion, digital subtraction angiography and angio-CT were performed to confirm the arterial blood flow. The inserted catheters were immobilised to the periauricular skin throughout the treatment course.

Chemotherapy

The regimen for intra-arterial chemotherapy was cisplatin-based, and cisplatin plus docetaxel was adopted for most patients (149/159, 94%). The total doses administered were 150 mg/m^2 cisplatin and 60 mg/m^2 docetaxel. Fifty-two patients (33%) also received induction systemic chemotherapy and 54 (34%) received adjuvant systemic chemotherapy. The regimens for systemic chemotherapy predominantly consisted of tegafur–uracil or S-1.

Follow-up and toxicity assessment

Treatment response at 4 weeks was assessed by physical examination, biopsy, PET-CT, and MRI. Tumour response was evaluated according to the Response Evaluation Criteria in Solid Tumours guidelines version 1.1 [7]. If a residual tumour was detected, primary tumour resection or radical neck dissection (RND) was performed. After treatment, patients were followed up every 1–3 months until 5 years and every 3–6 months thereafter. In a setting of local or regional recurrence, salvage surgery was initially considered.

Statistical analysis

Differences in the distribution of variables across cohorts were compared by the chi-square test or Fisher's exact test for categorical variables, and the Mann–Whitney U test for continuous variables. All actuarial survival and control rates were calculated from the beginning of CRT using the Kaplan–Meier method. LC was defined as time to first relapse of the primary lesion, disease-free survival (DFS) as time to first failure, and overall survival (OS) as death from any cause. LC, DFS, and OS were compared by the log-rank test. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events version 4.0 [8]. Acute toxicity was defined as occurring within 3 months after initiation of CRT, and late toxicity as occurring later than 3 months. The incidence of mandibular osteoradionecrosis was plotted using the Kaplan–Meier method and compared by the log-rank test.

Propensity score matching was performed to reduce selection bias. Propensity scores were calculated by a multivariable logistic regression model with preselected covariates: location of primary tumour, age, sex, histology, T stage, N stage, Eastern Cooperative Oncology Group performance status, presence of double primary cancer, use of systemic chemotherapy, and use of hyperthermia. The calliper value was set at 0.2. After one-to-one matching by the

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nearest-neighbour method, a well-balanced cohort of 58 patients (29 pairs) was generated.

Values of $p < 0.05$ were considered statistically significant. All statistical analyses were performed using JMP 11.0.0 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

LC, survival and failure patterns

The median follow-up period was 48 (median, 2–88) months in the total cohort and 44 (median, 2–88) months after propensity score matching. After initial treatment, 146/159 (92%) patients achieved complete response of the primary lesion, while 9 (6%) showed partial response and 4 (3%) showed stable disease. One patient showed complete response of the primary tumour and partial response of cervical LN metastases. All primary tumours in the 30 patients who received <60 Gy achieved complete response, while 116/129 (90%) patients who received ≥60 Gy achieved complete response. However, the difference was not significant (p = 0.130). Among those who showed partial response of the primary tumour or stable disease, 4 underwent resection, 4 underwent re-irradiation (stereotactic RT or proton therapy), 2 received systemic chemotherapy, and 3 received best-supportive care. Forty-five patients underwent RND after CRT, because they were considered to have residual disease in the neck.

Among the total cohort of 159 patients, the 3-year/5-year LC, DFS, and OS rates were 83.7%/79.3%, 67.7%/63.3%, and 77.1%/75.3%, respectively. Fifty-two patients (33%) presented with tumour recurrence: 9 (30%) in the <60 Gy cohort and 43 (33%) in the ≥60 Gy cohort. The most common first recurrence site was the primary tumour location (n = 29), followed by distant sites (13 lung, 7 bone/muscle, 5 thoracic LN, 2 liver, 1 skin) and cervical LNs (n = 6). Among the 29 patients who developed local recurrence as the first recurrence, 15 underwent tumour resection, 4 received stereotactic RT, and 3 received proton therapy. In total, local recurrence was observed in 6 patients (20%) in the <60 Gy cohort and 25 (19%) in the ≥60 Gy cohort.

Statistical comparisons of treatment outcomes

Prior to matching, the 3-year/5-year treatment outcomes in the <60 Gy and ≥60 Gy cohorts were as follows: LC, 82.2%/77.3% vs. 84.0%/79.9% (p=0.923); DFS, 69.8%/65.5% vs. 67.2%/62.9% (p=0.764); and OS, 86.4%/86.4% vs. 75.0%/72.8% (p=0.139). None of the differences were significant.

The patient characteristics after propensity score matching are shown in table 2. The characteristics were well balanced and no significant differences were observed between the cohorts. The 3-year/5-year LC rates in the <60 Gy and ≥60 Gy cohorts were 81.5%/76.4% and 86.1%/86.1%, respectively, with no significant difference (p=0.534). Similarly, there were no significant differences in the DFS or OS rates (3-year/5-year DFS, 68.8%/64.2% vs. 72.4%/68.2%, p=0.816; 3-year/5-year OS, 85.9%/85.9% vs. 72.3%/68.0%, p=0.132). The LC, DFS, and OS curves for each cohort are shown in figure 1.

Toxicity

The crude incidences of acute and late grade ≥3 toxicity are summarised in table 3. Overall, the most common acute non-haematological grade 3/4 toxicity among the 159 patients was mucositis, observed in 144 (91%) patients, followed by dysphagia (52%, n=82) and dermatitis (36%, n=57). The most common acute grade 3/4 haematological toxicity was lymphocytopaenia, observed in 152 (96%) patients, followed by leukocytopaenia (52%, n=83) and neutropenia (37%, n=59). One patient died from enteritis at 3 weeks after CRT, and the death was not obviously related to treatment.

In the late phase, grade 3/4 mucositis (22%, n=35) and dysphagia (17%, n=27) were most commonly observed, and persisted from the acute phase. The incidence tended to be lower in the <60 Gy cohort, but the differences were not significant (<60 Gy vs. ≥60 Gy: 13% vs. 24% for mucositis, p=0.233; 10% vs. 19% for dysphagia, p=0.417). Grade 3 mandibular osteoradionecrosis was observed in 7 patients (4%). The incidence was similar between the cohorts (<60 Gy vs. ≥60 Gy: 5% vs. 6% at 5 years,

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p=0.694).

After propensity score matching, the incidences of acute grade ≥3 mucositis, dermatitis, and dysphagia in the two cohorts (<60 Gy vs. ≥60 Gy) were as follows: mucositis, 86% vs. 90%, p = 1.000; dermatitis, 48% vs 45%, p = 0.792; and dysphagia, 45% vs 59%, p = 0.293. None of the differences were significant. Regarding late toxicity, there were no differences in the incidence of mandibular osteoradionecrosis (grade ≥2, 23% vs. 13% at 5 years, p=0.538; grade ≥3, 5% vs. 0% at 5 years, p=0.329), grade ≥3 mucositis (14% vs. 21%, p=0.730), or grade ≥3 dysphagia (10% vs. 28%, p=0.179). The comparative results for mucositis, dysphagia, and acute dermatitis are summarised in table 4. The incidence of grade ≥3 mandibular osteoradionecrosis for each cohort is shown in figure 2. The median overall treatment period was significantly shorter (p<0.0001) in the <60 Gy cohort (median, 39 days) compared with that in the ≥60 Gy cohort (median, 49 days).

Table 2. Characteristics of the 58 patients after propensity score matching.

Characteristic		<60 Gy (*n*=29)	≥60 Gy (*n*=29)	*p*-value
Follow-up period (months)	Median	44	46	0.635
	Range	2–83	4–83	
Age (years)	Median	70	71	0.686
	Range	40–88	48–86	
Sex	Male	16 (55%)	16 (55%)	1.000
	Female	13 (45%)	13 (45%)	
Performance status (ECOG)	0	9 (31%)	10 (35%)	0.780
	1–2	20 (69%)	19 (66%)	
Primary location	Tongue	10 (35%)	9 (31%)	0.780
	Others	19 (66%)	20 (69%)	
T stage	T1–T3	23 (79%)	21 (72%)	0.539
	T4a/T4b	6 (21%)	8 (28%)	
N stage	N0/N1	20 (69%)	25 (86%)	0.207
	N2/N3	9 (31%)	4 (14%)	
Stage	I–III	15 (52%)	19 (66%)	0.285
	IVA/IVB	14 (48%)	10 (35%)	
Histology	Squamous cell carcinoma	28 (97%)	29 (100%)	1.000
	Others	1 (4%)	0 (0%)	
Double cancer	Yes	3 (10%)	2 (7%)	1.000
	No	26 (90%)	27 (93%)	
Systemic chemotherapy	Yes	15 (52%)	17 (59%)	0.597
	No	14 (48%)	12 (41%)	
Hyperthermia	Yes	6 (21%)	2 (7%)	0.253
	No	23 (79%)	27 (93%)	

Abbreviations: ECOG = Eastern Cooperative Oncology Group; RT = radiotherapy.

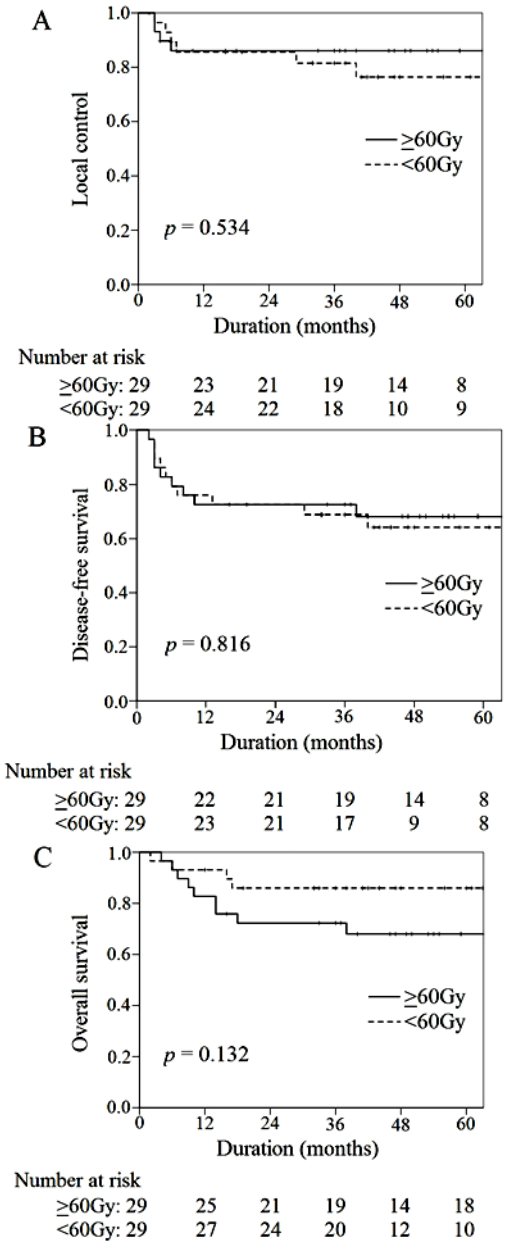

Figure 1. (A–C) Kaplan–Meier curves showing local control **(A)**, disease-free survival **(B)**, and overall survival **(C)** rates stratified by total dose of radiotherapy after propensity score matching. There were no significant differences between the <60 Gy and ≥60 Gy cohorts (3-year/5-year local control: 81.5%/76.4% vs. 86.1%/86.1%, p = 0.534; 3-year/5-year disease-free survival: 68.8%/64.2% vs. 72.4%/68.2%, p = 0.816; 3-year/5-year overall survival: 85.9%/85.9% vs. 72.3%/68.0%, p = 0.132).

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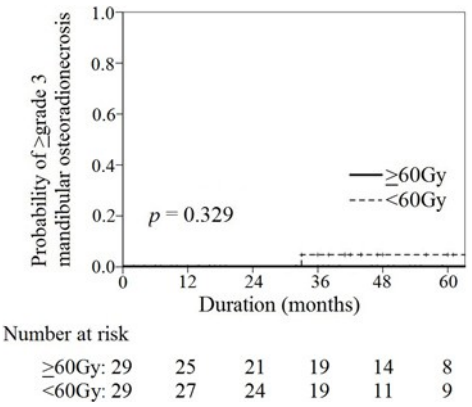

Figure 2. Kaplan–Meier curves showing the incidence of grade ≥3 mandibular osteoradionecrosis stratified by total dose of radiotherapy after propensity score matching. There was no difference in the incidence between the <60 Gy and ≥60 Gy cohorts (5% vs. 0% at 5 years, p = 0.329).

DISCUSSION

Recent studies have shown the potential of SIACRT for oral cavity cancers to preserve organ function, which is crucial for patient quality of life after treatment [4]. Although we previously observed excellent tumour control rates with 60 Gy radiation, the optimal dose for this strategy remains to be determined. The treatment outcomes in the present study were consistent with our previous findings and appeared comparable to the outcomes of strategies involving surgery as the initial treatment [5, 9, 10]. However, statistical analyses revealed no significant differences in LC, DFS, and OS between the <60 Gy and ≥60 Gy cohorts. These results suggest that the radiation dose can be reduced, because patients receiving <60 Gy can be expected to show similarly high therapeutic ratios to patients receiving ≥60 Gy. Although the underlying reason for these findings requires further investigation, it is assumed that the delivery of anti-tumoural agents through intra-arterial catheters leads to high intra-tumoural drug concentrations, thereby enabling comparable efficiency despite lower radiation doses.

The most frequent site of recurrence was the primary tumour location, observed in 29 patients (56% of all recurrences). Probable salvage treatments include tumour resection and re-irradiation such as stereotactic RT or proton therapy. Among the 29 patients who developed local recurrence as the first recurrence site, 15 underwent tumour resection, 4 received stereotactic RT, and 3 received proton therapy. Among them, 13 patients were successfully salvaged. Conversely, the most common site of distant metastasis was the lungs, observed in 13 patients (25% of all recurrences). Although patients with distant metastases are generally incurable, administration of systemic chemotherapy, including targeted therapies like cetuximab, is expected to prolong survival, while in an oligometastatic setting, local therapy at the recurrence site is occasionally beneficial [11, 12].

The incidence of adverse events, including grade ≥3 mucositis and dermatitis, was comparable between the cohorts regardless of the total radiation dose delivered. A potential explanation for this observation is that in-field inflammation may have been predominantly dependent on the range of the initial radiation field until 40 Gy, and the shrunken boost field did not contribute to the severity. The wide range of initial field, which often covered the whole oral cavity/cervical skin, and high concentration of chemotherapeutic agents concomitantly administered via the selective catheter may have been adequate to cause severe damage even with 40 Gy. Furthermore, we often made efforts to reduce the oral mucosal volume exposed to radiation during boosting by using multiple (generally 3 or 4) beam angles, leading to a conformal dose distribution. Our efforts may have made boost radiation less likely to cause development of mucositis. Reports regarding dose constraints for the oral mucosa are limited [13]. Shankar *et al.* [14] reported that variables possibly affecting the incidence and severity of oral mucositis during cancer treatment include the type, dose, and schedule of systemic cytotoxic drugs delivered, RT dose and field, and concomitant CRT. Otter *et al.* [13] evaluated 253 head-and-neck squamous cell carcinoma patients treated with intensity modulated radiotherapy (IMRT). They demonstrated that the mean dose to the oral mucosa was the strongest predictor for grade 3 oral mucositis on multivariate analysis. In

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contrast, Yahya *et al.* [15] failed to show a relationship between dosimetric parameters and duration of grade 3 mucositis or opiate use. These inconsistent results suggest the need for further investigation.

We found that the incidence of severe (grade ≥3) mandibular osteoradionecrosis was 4% (n = 7), which was consistent with another study [16]. Mendenhall *et al.* [16] reported on the incidence of severe mandibular osteoradionecrosis in 1,495 patients with head-and-neck squamous cell carcinoma treated with definitive RT at the University of Florida. They found that mandibular osteoradionecrosis occurred most often in patients treated for oral cavity cancers, with rates of 5% in the floor of the mouth and 6% in the oral tongue. Although the development of mandibular osteoradionecrosis is affected by radiation dose and multiple factors including types of treatment and technique [17], the impact of the delivery pathway of chemotherapeutic agents at our institution (i.e. SIACRT) on the incidence of mandibular osteoradionecrosis was unclear.

As all patients in the present study were irradiated with 3D conformal RT, introduction of IMRT has the potential to reduce the incidence of mandibular osteoradionecrosis. Ahmed *et al.* [18] examined 6 patients with advanced oral cavity carcinoma who required bilateral irradiation and compared the dose distributions of 3D conformal RT and IMRT. They reported that mandibular V50, V55, and V60 (defined as percentage of mandible receiving at least 50, 55, and 60 Gy, respectively) were significantly lower for IMRT. Furthermore, Tsai *et al.* [17] observed a trend toward less mandibular osteoradionecrosis among patients treated with IMRT compared with 3D conformal RT, according to a review of 402 oropharyngeal cancer patients treated with RT. Because the incidence is also affected by numerous other potential risk factors, including age, sex, comorbidity, tumour location in relation to mandible, dentition status, smoking, and alcohol [17], more distinct and detailed analyses are required to interpret this issue.

The duration required for initial treatment was significantly reduced in the <60 Gy cohort in the present study. As widely believed by politicians and hospital managers, reducing the time spent in hospital may decrease costs per patient and consequently release capacity to treat more patients [19]. Lagoe *et al.* [20] introduced specific management approaches to reduce length of stay and demonstrated savings of >28,000 patient-days and an average daily census of 96.0 over a 3.5-year period. Moreover, shortening of hospitalization is expected to reduce the mental burden on patients, in addition to mitigating the workload of medical staff.

The limitation of our study was that even though propensity score matching was performed, selection bias was not completely removed. However, our matched analysis suggested that SIACRT enables physicians to control oral cavity malignancies with fewer radiation doses, even for locally advanced lesions such as those at T4 stage. To further clarify this issue, a randomised controlled trial is warranted.

In conclusion, our results suggest that radiation dose may be reduced to <60 Gy when treating oral cavity cancers with SIACRT. A randomised clinical trial is warranted to confirm these results.

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***Conflicts of interest*: Declared none.**

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