

# Clinical effectiveness, toxicity, and failure patterns of helical tomotherapy for postoperative oral cavity cancer patients

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**Background:** The outcome of postoperative high- and intermediate-risk oral cavity cancer (OCC) patients receiving helical tomotherapy (HT) remains limited.

**Materials and methods:** Between November 2006 and November 2012, 53 postoperative high- and intermediate-risk OCC patients treated with HT were enrolled.

**Results:** The 4-year locoregional, local, and regional control rates were 66%, 76.4%, and 94.3%, respectively. The 4-year locoregional control rates of oral tongue and buccal mucosa cancer were 88.3% and 37.1%, respectively ( $P=0.012$ ). Eleven (20.8%) patients experienced locoregional failure. In-field failure occurred in six of 53 (11.3%) in the primary area and three of 53 (5.7%) in the regional lymph-node area. No marginal failure was noted. Two of 53 (3.8%) experienced out-of-field failure. The rates of grade 3 dermatitis, mucositis, and dysphagia were 11%, 34%, and 13%, respectively. No grade 3 xerostomia was noted. Grade 2 xerostomia was 33% at month 6 and declined to 0 at month 48. A rate of 56% of grade 2 trismus at month 6 was noted, and declined to around 30% after 2 years. No grade 3 trismus was noted after 2 years.

**Conclusion:** HT as a postoperative modality provided satisfying results, especially for xerostomia and trismus, and was impressive in high- and intermediate-risk OCC patients receiving postoperative HT.

**Keywords:** concurrent chemoradiation, helical tomotherapy, locoregional control rate, oral cavity cancer, trismus

## Background

Extensive data suggest that intensity-modulated radiation therapy (IMRT) is safe and efficacious in the adjuvant setting for oral cavity cancer (OCC).<sup>1-4</sup> Helical tomotherapy (HT) is conceptually regarded as image-guided IMRT. HT was designed and developed with advantages of sharper dose gradients and better normal-tissue sparing compared with step-and-shoot IMRT. According to previous reports, HT plans compared favorably with step-and-shoot IMRT plans regarding sparing of organs at risk and keeping equivalent target-dose homogeneity.<sup>5,6</sup> Our and other clinical experience of using HT for locally advanced head and neck cancer achieved encouraging results along with less toxicity.<sup>7-9</sup>

Recently, a Phase III trial showed parotid-sparing IMRT caused better recovery of saliva secretion than conventional RT.<sup>10</sup> In our previous report, HT provided encouraging clinical results for acute xerostomia.<sup>8</sup> Additionally, Hsiung et al<sup>11</sup> and Chen et al<sup>12</sup> confirmed that radiation-induced trismus progressed over time and was improved by IMRT. However, the longer follow-up data of treatment results and side effects for OCC receiving HT as adjuvant modalities are insufficient.

Here, we analyze our clinical experience of postoperative OCC patients treated with HT, focusing on locoregional failure patterns, clinical outcome, and toxicity.

## Materials and methods

### Patient characteristics

Between December 2006 and November 2012, 53 patients with oral cavity squamous cell carcinoma (SCC) who had undergone surgery followed by postoperative HT were retrospectively enrolled. Patients treated for recurrences of OCC (including neck recurrences) were excluded from this analysis. Retrospective patient data were collected with the approval of the Institutional Review Board of Far Eastern Memorial Hospital. Staging investigations included complete history and physical examination, fiber-optic endoscopic evaluation, complete blood counts, comprehensive metabolic panel, bone scans, chest X-ray, and computed tomography (CT) or magnetic resonance imaging (MRI) of the head and neck region, which was done before surgery, and a dental evaluation. The disease was staged according to the American Joint Committee on Cancer Staging Classifications, sixth edition, which is based on pathological findings after radical surgery.

### Radiation therapy

RT or concurrent chemoradiation therapy (CCRT) was initiated within 4–6 weeks after operation using 6 MV photons. HT with daily fractions of 1.8 or 2 Gy on 5 consecutive days was prescribed. The frame, fusing, and planning system were applied as per a previous report.<sup>8</sup> CT scans with 3 mm slice thickness were done for treatment planning.

### Delineation of target volumes

The clinical target volumes (CTVs) were determined according to the incidence and location of metastatic neck nodes from various head and neck subsites.<sup>13</sup> According to the location of the gross tumor and the postoperative flap confirmed using preoperative MRI fused with CT images, CTV1 was defined as the area encompassing both preoperative gross tumor and postoperative flap plus a 0.8–1 cm margin, which included the resection bed with soft-tissue invasion by the tumor or extracapsular extension (ECE) by metastatic neck nodes truncating air, and uninvolved bones. CTV2 was defined as a high-risk subclinical area, primarily including the pathologically uninvolved cervical lymph nodes, deemed as elective nodal regions, or prophylactically treated neck areas. CTV3 was designated as the low-risk area of potential subclinical disease.

To account for organ motion and patient-setup errors, the planning target volume (PTV)-1 encompassed CTV1 plus a margin of 3 mm, while PTV2 and PTV3 included CTV2 and CTV3 plus a margin of 5 mm, respectively. CTV1 received 60–66 Gy in 30–33 fractions, 64–66 Gy was delivered to high-risk OCC patients, and 60 Gy was delivered to intermediate-risk OCC patients. For CTV2, 59.4–60 Gy/30–33 fractions were delivered, and for CTV3 51.2–54 Gy/30–33 fractions were delivered. Additionally, no more than 20% of the PTV received more than 110% of its prescribed doses, and no more than 1% of any PTV received less than 93% of its prescribed doses.

The dose constraints for organs at risk were: 1) brain stem maximum dose 54 Gy; 2) spinal cord maximum dose 45 Gy; 3) optic chiasm and optic nerve maximum dose 45 Gy; 4) bilateral parotid glands mean dose <30 Gy, median dose <26 Gy, and whole parotid gland volume with <20 Gy for that larger than 20 cc; 5) two-thirds of glottal larynx <50 Gy; 6) inner ear mean dose <50 Gy; and 7) mandible maximum dose 70 Gy.

### Chemotherapy

ECE and/or microscopically involved surgical margins were the risk factors for which the impact of CCRT was significant in the two randomized trials (European Organization Research and Treatment of Cancer and Radiation Therapy Oncology Group). There was also a trend in favor of CCRT in the group of patients who had stage III–IV disease, perineural infiltration, vascular embolisms, and/or clinically enlarged level IV–V lymph nodes secondary to tumors arising in the oral cavity or oropharynx.<sup>14</sup> Therefore, patients with those criteria received concurrent chemotherapy. In addition, if a patient could tolerate chemotherapy, as defined by a Karnofsky performance score of at least 60, a white-cell count of at least 3,500/mm<sup>3</sup>, a platelet count of at least 100,000/mm<sup>3</sup>, and a creatinine clearance of more than 50 mL/minute, then chemotherapy would be prescribed.<sup>15</sup> During RT, patients who received chemotherapy were treated with cisplatin (30 mg/m<sup>2</sup>) plus fluorouracil (425 mg/m<sup>2</sup>) and leucovorin (30 mg/m<sup>2</sup>), both intravenously each week.

### Definition of relapse and delineation of locoregional failure

When available, imaging studies delineating the site of locoregional failure were fused with the treatment-planning CT scan. Otherwise, anatomic landmarks were used to determine the failure site. If >95%, 20%–95%, and <20% of volume of recurrent tumor fell within the CTV, the failure was defined as infield, marginal, and out of field, respectively.<sup>16</sup>

## Follow-up

All patients were evaluated at least once a week during RT. Upon completion of radiation, patients were then evaluated every 3 months for the first 2 years. At each follow-up visit, a complete evaluation, including clinical examination, bimanual palpation of the oral cavity, and neck palpation, was performed. Posttreatment MRI of the oral cavity and neck was done 1, 3, and 6 months after completion of RT. Acute toxicities (occurring <90 days after initiation of RT) and late toxicities (occurring >90 days after initiation of RT) were defined and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3. The earliest date of detection of grade 3 or worse toxicity was recorded.

## Statistical methods

Descriptive statistics were calculated to characterize the patients, diseases, and treatment features, as well as toxicities after treatment. Overall survival (OS), disease-free survival (DFS), locoregional control (LRC), and metastasis-free survival (MFS) rates were estimated using the Kaplan–Meier product-limit method and log-rank tests. Durations were calculated from the date of pathologic proof. All analyses were performed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA).

## Results

### Patient characteristics

Fifty men and three women were enrolled in the study. The mean age was  $51 \pm 10.5$  years (range 24–73 years). The dominant subsets were oral tongue (53%) and buccal mucosa cancer (34%). Thirty-six percent experienced closed or positive surgical margin, and 26% were ECE<sup>+</sup>. The other risk factors of lymphovascular space involvement (LVSI), perineural involvement (PNI), lymph-node involvement  $\geq 2$ , and clinical stage are listed in Table 1.

### Treatment outcomes

The mean follow-up time was  $49.8 \pm 4.2$  ms (range 4–70 ms, 95% confidence interval 41.6–57.9). The median dose of radiation was 66 Gy. The actuarial 3- and 4-year OS, DFS, LRC, and MFS rates were 71.5%, 59.0%, 72.1%, and 83.9%, and 59.7%, 59.0%, and 66.1% 83.9%, respectively. (Figure 1A and B) The 4-year LRC rates for oral tongue and buccal mucosa cancer were 88.3% and 37.1%, respectively ( $P=0.012$ ) (Figure 1C). The 4-year LRC rates of infield failure and out-of-field failure were 70.7% and 95.6%, respectively (Figure 1D and E). The 4-year local and regional

**Table 1** Patient characteristics

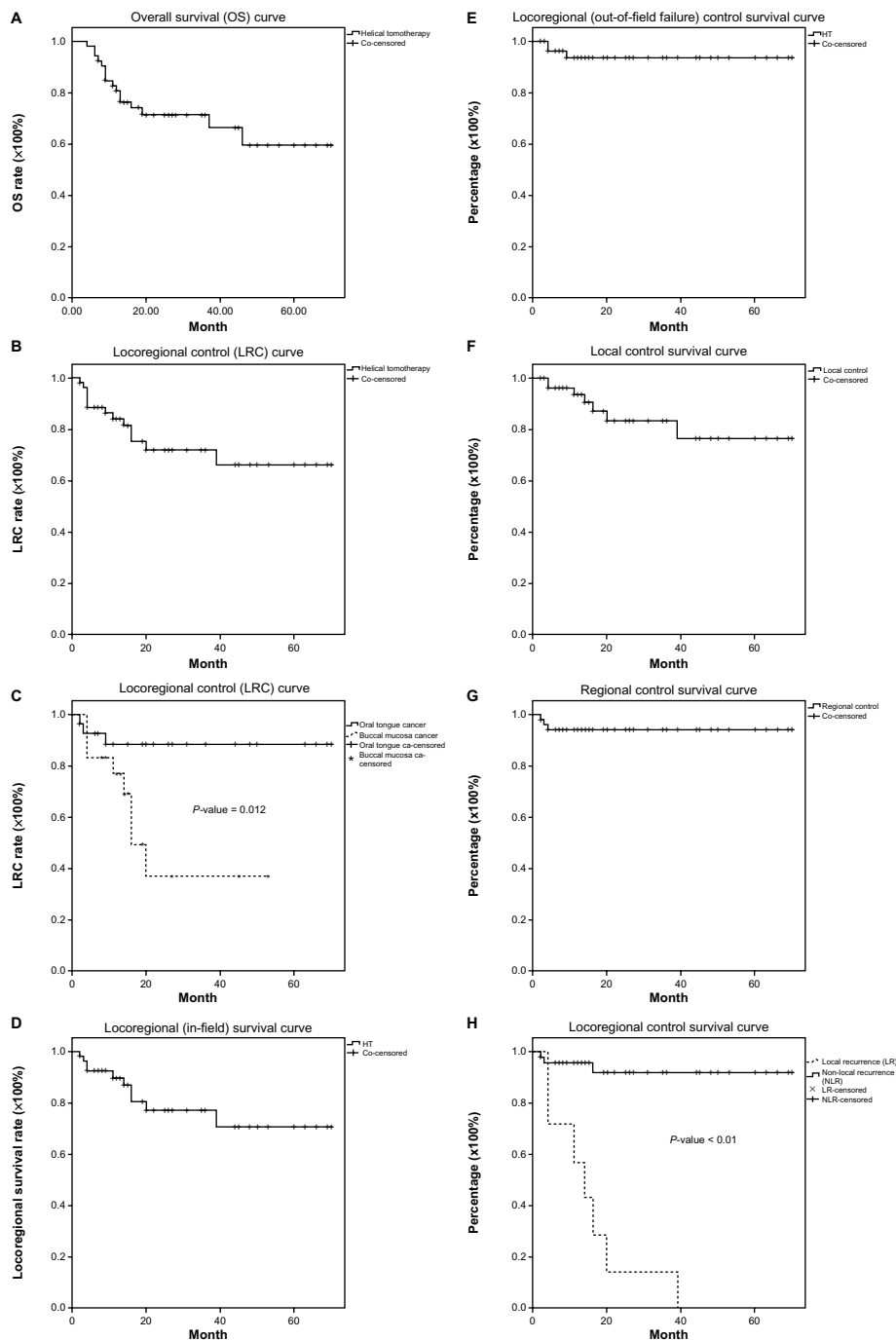
Variable	Helical tomotherapy (n=53) Patients, n
Age (years)	
Mean	51
Range	24–73
Sex	
Male	50 (94.3%)
Female	3 (5.7%)
Subsite	
Oral tongue	28 (52.8%)
Buccal mucosa	18 (34.0%)
Alveolar ridge	5 (9.4%)
Retromolar trigone	1 (1.9%)
Floor of the mouth	1 (1.9%)
Hard palate	0
Lip	0
Pathology	
Squamous cell carcinoma	53 (100%)
Resection-margin status	
Close	19 (35.8%)
Negative	34 (64.2%)
Extracapsular spread	
Positive	14 (26.4%)
Negative	39 (73.6%)
Perineural involvement	
Positive	41 (77.4%)
Negative	12 (22.6%)
Lymphovascular space involvement	
Positive	30 (56.6%)
Negative	23 (43.4%)
Lymph-node involvement $\geq 2$	
Positive	22 (41.5%)
Negative	31 (58.5%)
<b>Pathology stage</b>	
Tumor stage	
Stage I	6 (11.3%)
Stage II	8 (15.1%)
Stage III	10 (18.9%)
Stage IVA	29 (54.7%)
Stage IVB	0
Primary tumor stage	
T1	8 (15.1%)
T2	20 (37.7%)
T3	10 (18.9%)
T4a	15 (28.3%)
T4b	0
Regional lymph-node stage	
N0	23 (43.4%)
N1	5 (9.4%)
N2a	7 (13.2%)
N2b	16 (30.2%)
N2c	2 (3.8%)
N3	0
Adjuvant concurrent chemotherapy	
Yes	49 (92.5%)
No	4 (7.5%)
Radiation-therapy dose	
Median (range)	66 Gy (56–70.2 Gy)

control survival rates were 76.4% and 94.3%, respectively (Figure 1F and G). Local recurrence primarily influenced the 4-year LRC rate ( $P < 0.01$ , Figure 1H).

## Locoregional failures

Eleven (20.8%) patients experienced locoregional failure. The median time of failure was 7 months. Infield failure was

six of 53 (11.3%) in the primary area and three of 53 (5.7%) in the regional lymph-node area. No marginal failure was noted. Two of 53 (3.8%) experienced with out-of-field failure. Of eleven patients, 63.6% were PNI<sup>+</sup> or LVSI<sup>+</sup>. Moreover, 54.5% were PNI<sup>+</sup> and LVSI<sup>+</sup> simultaneously (Table 2). Patient 10, with right-side oral tongue cancer with operative margin close, ECE<sup>+</sup>, PNI<sup>+</sup>, LVSI<sup>+</sup>, and T2N2b, was treated with



**Figure 1** Kaplan–Meier estimates of (A) 4-year overall survival rate, (B) 4-year locoregional control rate, (C) 4-year locoregional control rate for oral tongue and buccal mucosa cancer, (D) 4-year locoregional (in-field) control survival rate, (E) 4-year locoregional (out-of-field) control survival rate, (F) 4-year local control survival rate, (G) 4-year regional control survival rate, and (H) 4-year regional control survival rate for postoperative oral cavity cancer patients treated with postoperative helical tomotherapy (HT), with or without concurrent chemotherapy.

**Table 2** Patient and disease characteristics of locoregional failures

Patient	Tumor site	T	N	Margin (0= negative, I= close; positive)	ECE (0= no, I= yes)	PNI (0= no, I= yes)	Lysi (0= no, I= yes)	Failure site	Location	Failure pattern	Time to recurrence
1	Right buccal cancer	2	1	0	0	0	1	Left buccal mucosa near retromolar area	CTV1	Infield	20
2	Left buccal cancer	4	2c	1	0	1	0	Left buccal flap	CTV1	Infield	5
3	Left gingival cancer	2	0	1	0	1	1	Left gingiva	CTV1	Infield	8
4	Left buccal cancer	3	0	0	0	1	1	Left buccal mucosa	CTV1	Infield	5
5	Left tongue cancer	1	1	0	0	0	0	Left tongue border near surgical margin	CTV1	Infield	12
6	Left buccal cancer	4a	0	0	0	0	0	Left sphenopterygoid fossa	CTV1	Infield	8
7	Right tongue cancer	4a	2b	1	0	1	1	Left level III	CTV2	Infield	6
8	Left tongue cancer	2	0	1	0	1	1	Left level Ib, II	CTV2	Infield	3
9	Left buccal cancer	2	2c	0	0	0	0	Left level Ib, II, III, and upper part of IV	CTV2 and CTV3	Infield	7
10	Right tongue cancer	2	2b	1	1	1	1	Right level Vb	-	Out of field	9
11	Left buccal cancer	4	2	1	0	1	1	Left retromaxillary fat pad and masticator space	-	Out of field	7

**Abbreviations:** CTV1, clinical target volume (area encompassing both preoperative gross tumor and postoperative flap plus a 0.8–1 cm margin); CTV2, CTV to high-risk subclinical disease area; CTV3, CTV to low-risk subclinical disease area; T, tumor stage; N, nodal stage; ECE, extracapsular extension; PNI, perineural involvement; Lysi, lymphovascular space involvement; HT, helical tomotherapy.

HT and had out-of-field failure in level Vb (Figure 2A). In patient 11, with left-side buccal mucosa cancer with operative margin close, PNI+, Lysi+, and T4N2, out-of-field failure occurred in the left side retromaxillary fat pad and masticator space (Figure 2C).

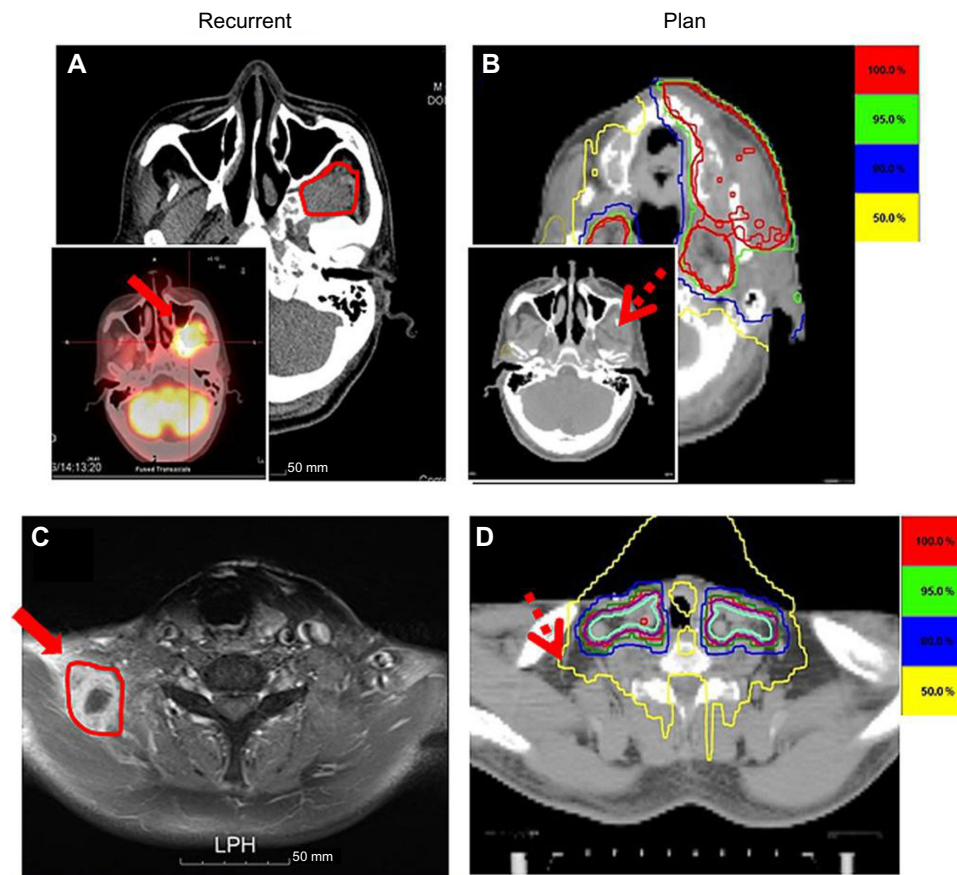
### Toxicities

During CCRT, there was no grade 3 acute toxicity for xerostomia or body-weight loss. The rates of grade 3 dermatitis, mucositis, dysphagia, anemia, leucopenia, and thrombocytopenia were 11%, 34%, 13%, 2%, 9%, and 0%, respectively. The rate of grade 4 leucopenia was 2%. Only two (5%) patients suffered fistula formation after treatment (Table 3). The incidence of trismus and xerostomia at posttreatment 6 months versus 12 months versus 24 months versus 36 months versus 48 months was grade 1 (30.8% versus 40.0% versus 70.0% versus 69.2% versus 71.4% and 66.7% versus 82.1% versus 90.0% versus 92.3% versus 100.0%) and grade 2 (56.4% versus 53.3% versus 30.0% versus 30.8% versus 28.6% and 33.3% versus 17.9% versus 10.0% versus 7.7% versus 0.0%), respectively. Grade 3 trismus was 12.8% versus 6.7% versus 0.0% versus 0.0% versus 0.0%, and there was no grade 3 xerostomia (Figure 3A and B).

### Discussion

IMRT has recently become a popular technique for postoperative OCC, and encouraging results for 2- and 3-year LRC rates ranging from 53% to 91% have reported<sup>1–3,17–20</sup> (Table 4). In head and neck cancer, ECE+, PNI, Lysi, pT3–4, and two positive nodes were categorized as important prognostic factors. The proportions of our patients with pT3–4 (47%), PNI (77%), and Lysi (57%) were higher than those in other IMRT reports. In the current study, the actuarial 3-year and 4-year LRC rates were 72.1% and 66.1%, respectively. Our data were compatible with previous reports.

The percentage of buccal cancer (34%) in the current study was higher than in others (0%–23%), except for the report by Chen et al.<sup>1</sup> Local control of OCC is worse than that for head and neck cancer.<sup>21,22</sup> In addition, local recurrence at 3 years after primary treatment for the gingiva–alveolar–buccal complex, lip, and hard palate was as high as 54%, and regional failure was 11%.<sup>23</sup> Lin et al<sup>24</sup> reported that 5-year LRC rates for SCC of the buccal mucosa were poor (36%). T3/4 and node-positive cancer predicted a poorer survival rate, as noted in their report. Additionally, stage IV and node involvement in SCC of the buccal mucosa were also predictors for poor OS.<sup>25</sup> In the current study, buccal mucosa cancer had a poor LRC rate (Figure 1C). For buccal cancer,



**Figure 2 (A–D)** Failure patterns in helical tomotherapy (HT) patients. **(A)** For patient 10, a case of left side buccal mucosa cancer with operative margin close, perineural invasion (PNI<sup>(+)</sup>), lymphovascular space involvement (LVSI<sup>(+)</sup>), and T4N2, treated with HT, out-of-field failure occurred in ipsilateral retromaxillary fat pad and masticator space (circled red area and solid red arrow show location of recurrence). **(B)** original plan with no coverage of these areas was noted (red dotted arrow shows the area of missing targeting). **(C)** For patient 11, a case of right-side oral tongue cancer with operative margin close, extracapsular extension (+), PNI<sup>(+)</sup>, LVSI<sup>(+)</sup>, and T2N2b treated with HT, ipsilateral out-field failure occurred in level Vb (circled red area and solid red arrow show area of recurrence). **(D)** The original plan was selectively targeted without level Vb coverage (red dotted arrow shows areas of inadequate targeting).  
**Abbreviation:** LPH, left, posterior, head.

we found a higher percentage than other reports (34%), with more than 30% of T3/4 and around 60% of lymph nodes positive, and 40% at stage IV.

The character of locoregional failure in OCC is quick, shorter than 1 year. We noted the median time for those with locoregional failure was 7 months, which was similar to Daly et al (8.1 months).<sup>19</sup> Bachar et al found 19 of 70 (27%) patients experienced local failure and six 70 (9%) patients had regional recurrence.<sup>26</sup> Diaz et al reported an overall recurrence rate of 45% and a local recurrence rate of 32%.<sup>25</sup> Ghoshal et al documented a 2% regional recurrence rate (two of 100 patients).<sup>27</sup> Most locoregional failures here were infield (nine, 17.0%). The 4-year infield locoregional control rate was lower than the out-of-field locoregional control rate (Figure 1F and G).

Chan et al reported that 12 of 38 (32%) patients had marginal or out-of-field locoregional recurrences following postoperative IMRT for OCC.<sup>28</sup> The rate of marginal or

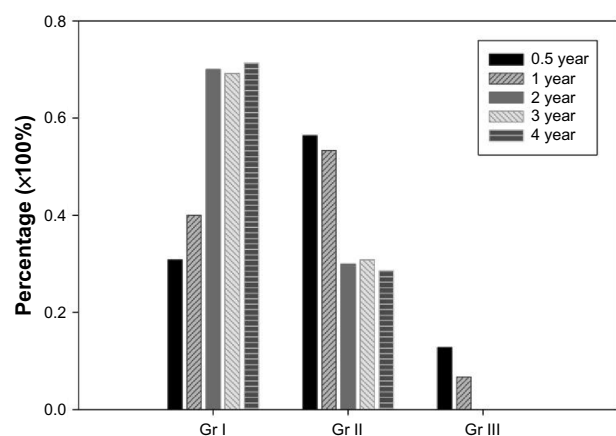
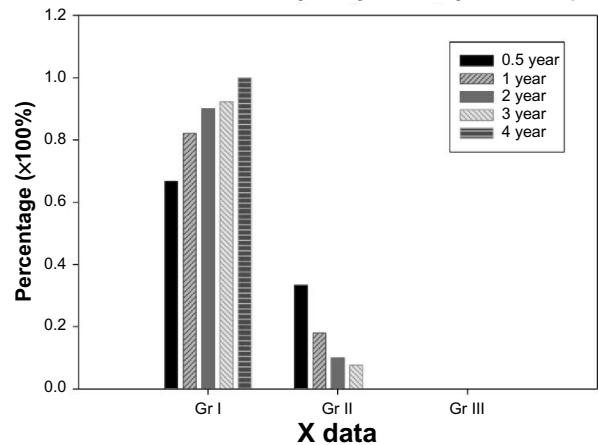
out-of-field failure for head and neck patients treated with IMRT was 10.8%–15.1%.<sup>4,19</sup> In the current study, no marginal failure and only 4% out-of-field failure were noted. The data showed the benefits of image-guided modality with daily check using 3 mm as PTV margin could decrease marginal or out-of-field failure potential.

Murthy et al noted that the 3-year local recurrence rate of gingiva–alveolar–buccal complex, lip, and hard palate cancer after primary treatment was as high as 54%.<sup>23</sup> Malignant epithelia contain cancer stem or clonogenic cells with regenerative abilities under cytotoxic stress that tend to repopulate tumors with very short stem cell-cycle times during the course of RT, and may become a major cause of RT failure.<sup>29,30</sup> Furthermore, the cancer stem cell markers, integrin- $\beta$ 1 and Oct4, linked with resistance to RT for squamous cell head and neck cancers with poor prognostic outcome, have been noted recently.<sup>31</sup> Additionally, tumor

**Table 3** Acute toxicities for oral cavity cancer patients treated with helical tomotherapy

Variable	Helical tomotherapy (n=53)
<b>*Xerostomia (acute)</b>	
†Gr 1	34 (64.2%)
Gr 2	19 (35.8%)
Gr 3	0
Gr 4	0
Gr 5	0
<b>Mucositis</b>	
Gr 1	5 (9.4%)
Gr 2	30 (56.5%)
Gr 3	18 (33.9%)
Gr 4	0
Gr 5	0
<b>Dermatitis</b>	
Gr 1	25 (47.2%)
Gr 2	22 (41.5%)
Gr 3	6 (11.3%)
Gr 4	0
Gr 5	0
<b>Body-weight loss</b>	
Gr 1	42 (79.2%)
Gr 2	11 (20.8%)
Gr 3	0
Gr 4	0
Gr 5	0
<b>Dysphagia</b>	
Gr 1	40 (75.5%)
Gr 2	6 (11.3%)
Gr 3	7 (13.2%)
Gr 4	0
Gr 5	0
<b>Fistula formation</b>	
No	51 (94.7%)
Yes	2 (5.3%)
<b>Anemia</b>	
Gr 1	45 (84.9%)
Gr 2	7 (13.2%)
Gr 3	1 (1.9%)
Gr 4	0
Gr 5	0
<b>Leucopenia</b>	
Gr 1	38 (71.7%)
Gr 2	9 (17.0%)
Gr 3	5 (9.4%)
Gr 4	1 (1.9%)
Gr 5	0
<b>Thrombocytopenia</b>	
Gr 1	51 (96.2%)
Gr 2	2 (3.8%)
Gr 3	0
Gr 4	0
Gr 5	0

**Notes:** \*Acute toxicity defined as occurring <90 days after beginning radiation therapy; †grade of toxicity as per Common Terminology Criteria for Adverse Events version 3.0.

**A** Incidences of trismus grading according to time sequence**B** Incidences of xerostomia grading according to time sequence

**Figure 3** Incidence of late toxicities for (A) trismus and (B) xerostomia, according to the time sequence for oral cavity cancer patients receiving adjuvant helical tomotherapy.

hypoxia has been shown to be an important predictor of response to therapy and outcome.<sup>32,33</sup> In the current study, even using image-guided modality, the infield failure rate in the primary and regional lymph-node area was 11% and 6%, respectively. Furthermore, the median time of failure was 7 months. Possible reasons may be cancer stem cells or tumor hypoxia. Targeting cancer stem cell molecules with monoclonal antibodies or pharmaceutical agents, or using hypoxia imaging to address hypoxic subvolumes through dose painting delivering higher doses to potentially more radioresistant parts of a tumor, may provide chances to overcome infield failure of OCC in future.<sup>31,34</sup>

A patient with ipsilateral masticator space recurrence (Figure 2A and B) and another with unexpected recurrence in level V were noted (Figure 2C and D). Retrograde perineural tracking toward the masseter<sup>3,19</sup> or lymphatics might become altered and unpredictable after surgery,<sup>35</sup> which could have placed these regions at risk for failure. Five-year actuarial LRC rates were significantly worse in

**Table 4** Four-year estimated overall survival (OS), disease-free survival (DFS), locoregional progress-free survival (LRPF), and distant metastasis-free (DMF) rate of postoperative helical tomotherapy (HT) with or without chemotherapy (CT) for high-risk oral cavity cancer at the Far Eastern Memorial Hospital (FEMH) compared with selected published series treated by intensity-modulated radiation therapy (IMRT)

Selected published series	Postoperative patients, n	CT	T3–4	LN involvement $\geq 2$ positive	Stage III, IV	Resection margin positive or close	ECE
Studer et al <sup>17</sup>	28	78%	32%	57%	68%	–	–
Yao et al <sup>3</sup>	55	11%	56%	33%	91%	–	–
Gomez et al <sup>2</sup>	35	29%	–	–	80%	–	–
Chen et al <sup>1</sup>	22	9%	–	32%	100%	5%	32%
Sher et al <sup>20</sup>	31	77%	26%	30%	64%	17%	20%
Daly et al <sup>19</sup>	30	66%	44%	7%	76%	63%	35%
Geretschläger et al <sup>4</sup>	53	47%	38%	–	70%	72%	32%
Moon et al <sup>18</sup>	23	9%	39%	52%	87%	–	–
Hsieh et al <sup>8</sup>	19	84%	68%	58%	95%	53%	42%
FEMH	53	87%	47%	47%	74%	36%	26%

OCC patients with PNI.<sup>36</sup> There were 64% who were PNI<sup>+</sup> or LVSI<sup>+</sup>. Moreover, 55% were PNI<sup>+</sup> concurrent with LVSI<sup>+</sup> in our study. Our observations also reflected previous suggestions, even using HT. Nerves at risk in the tumor bed or tumor adjacent to pterygoid muscle should be covered in a retrograde fashion within the RT field, and the selective approach should be very cautious, especially in the setting of lymphatics that might become altered after surgery or PNI<sup>+</sup> and LVSI<sup>+</sup> disease.

Mucosa is part of the CTV for OCC, and it is mucosal reactions that dominate acute reactions; therefore, grade 3 mucositis was as high as 34%, even with the highly conformal techniques provided by HT (Table 3). Nevertheless, for acute toxicities, no grade 3 xerostomia or body-weight loss was noted. Grade 3 dermatitis and dysphagia occurred with postoperative IMRT concurrent with chemotherapy at a rate of 7%–10% and 24%–83%, respectively.<sup>18–20</sup> However, the rates of grade 3 dermatitis and dysphagia for patients treated with adjuvant HT were 11% and 13%, respectively.

Saarilahti et al<sup>37</sup> found the median basal saliva flow rate was 0.13 mL/minute prior to RT, and 0.04 and 0.07 mL/minute at 6 and 12 months after RT, respectively. Recently, a Phase III trial proved parotid-sparing IMRT caused better recovery of saliva secretion than conventional RT.<sup>10</sup> They found grade 2 or worse xerostomia at 12 months and 24 months was 38% and 29%, respectively. Here, the rates of patients treated with HT experiencing grade 2 late xerostomia at 12 months and 24 months were 18% and 10%, respectively. HT showed a trend of decreasing acute and late toxicities to the salivary gland (Figure 3B).

Trismus is one of the long-term sequelae of RT for head and neck cancer. The prevalence of trismus for head and

neck cancer after treatment could as high as 42%.<sup>38</sup> Wang et al measured the maximal interincisal distance (MID), and demonstrated that MID decreased gradually by 2.4%, 0.2%, and 0.1% after RT at 1–9 months, 12–24 months, and 24–48 months, respectively.<sup>39</sup> For nasopharyngeal carcinoma (NPC) patients treated with IMRT, the average MID before IMRT and at 12 months post-IMRT was 46.2 mm and 45.4 mm.<sup>11</sup> Compared with baseline MID levels for IMRT-treated NPC patients, the differences for normalized MID levels between 6 months to 5 years was only 4%.<sup>12</sup> Here, the incidence of grades 1, 2, and 3 trismus show an inverse trend to the time sequence with post-HT treatment (Figure 3A). Additionally, the ratios of grade 1 and 2 trismus treated by HT were stationary after 24–48 months. Our results provide evidence of decreasing late complications of HT by better normal-tissue sparing and sharper dose gradients.<sup>7–9</sup> In addition, the data support no more significant decreases at time points beyond 1 year after RT.<sup>12,39</sup>

This study has several limitations, most of which are related to its retrospective nature. However, all patients were reviewed by the multidisciplinary tumor board, and all individuals were treated with a consistent treatment philosophy. Additionally, the case numbers of HT were limited. Third, the current study lacks objective data of MID for trismus and saliva flow rate for xerostomia. However, trismus and xerostomia grades based on the CTCAE abstracted from the medical record could have diminished the insufficiency of objective measurement in the current study. Finally, toxicity data were not prospectively collected but rather abstracted from the medical record. Such a process is limited by the underlying inadequacies of medical documentation when used for research purposes.



Table 4 (Continued)

PNI	LVSI or VEs	Postoperative modality	Percentage of		Follow-up	OS	DFS	LRPF	DMF
			Oral tongue	Buccal mucosa					
–	–	IMRT	–	–	2 years	83%	87%	91%	95%
–	–	IMRT	36%	11%	3 years	68%	74%	82%	89%
–	–	IMRT	31%	23%	3 years	74%	64%	77%	85%
–	–	IMRT	9%	82%	3 years	67%	64%	–	–
43%	17%	IMRT	55%	5%	2 years	85%	82%	91%	94%
50%	–	IMRT	57%	0%	3 years	60%	–	53%	81%
–	–	IMRT	41%	–	3 years	73%	–	79%	90%
–	–	IMRT/HT	83%	0%	3 years	61%	61%	82%	66%
74%	68%	HT	47%	32%	2 years	94%	84%	92%	94%
77%	57%	HT	53%	34%	3 years	72%	59%	72%	84%
					4 years	60%	59%	66%	84%

**Abbreviations:** LN, lymph node; ECE, extracapsular extension; PNI, perineural involvement; LVSI, lymphovascular space involvement; VE, vascular embolism.

In conclusion, HT may provide tumor control and a less severe morbidity profile, especially in life quality-impairing xerostomia and trismus, in comparison with historical data for postoperative high- and intermediate-risk OCC patients. More careful and accurate target-volume delineation is essential to the success of treatment, even with image-guided techniques.

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## Disclosure

The authors report no conflicts of interest in this work.

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