Retrograde superselective intra-arterial chemotherapy and daily concurrent radiotherapy for T2-4N0 tongue cancer: control of occult neck metastasis

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Objective. To evaluate the therapeutic results and control of occult neck metastasis in patients with T2-4N0 oral tongue squamous cell carcinoma treated with retrograde superselective intra-arterial chemotherapy and daily concurrent radiotherapy.

Study Design. Forty-two patients with T2-4N0 tongue cancer (17 with late T2; 13 with T3; and 12 with T4a disease, M0) were treated with intra-arterial chemoradiotherapy. Treatment consisted of retrograde superselective intra-arterial chemotherapy (docetaxel 50-70 mg/m², cisplatin 125-175 mg/m²) and daily concurrent radiotherapy (50-70 Gy) for 5-7 weeks.

Results. The median follow-up for all patients was 46.5 months (range, 8-105 months). Primary-site complete response was achieved in 42 of 42 cases (100%). Three-year overall survival, progression-free survival, and local control rates were 85.0%, 77.8%, and 91.7%, respectively. Delayed neck metastasis was detected in 5 of 42 cases (11.9%). Grade 3 or 4 toxic changes included oral mucositis in 92.9%, neutropenia in 21.4%, and thrombocytopenia in 4.8%. Grade 3 toxicities included anemia in 16.7%, radiation dermatitis in 9.5%, nausea in 4.8%, and fever in 2.4%.

Conclusions. Retrograde superselective intra-arterial chemotherapy for T2-4N0 tongue cancer provided good overall survival and local control rates and was effective for occult neck metastasis. (Oral Surg Oral Med Oral Pathol Oral Radiol 2017;124:16-23)

Statement of Clinical Relevance
Retrograde superselective intra-arterial chemoradiotherapy for T2-4N0 tongue cancer provided good therapeutic effect for both the primary lesion and occult neck metastasis from administration to sentinel lymph nodes via lymphatic canals and perfusion to the neck from intra-arterial infusion.
range, 34-87 years) with late T2 (>3 cm), T3, or T4a N0M0 underwent intra-arterial CRT (Table I). All patients were primary cases and had not received previous chemotherapy, radiotherapy, or surgery. The primary lesion and cervical lymph nodes were assessed by enhanced computed tomography (CT), magnetic resonance imaging, positron-emission tomography-CT (PET-CT), and ultrasound examination before treatment. The N0 criteria for enhanced CT were minimum axial diameter of node <10 mm and no rim enhancement. The N0 criterion for PET-CT was standardized uptake value <2.5. The N0 criterion for ultrasound was the presence of hilar echoes. TNM staging was classified according to the 2009 Union for International Cancer Control staging system.9 The local institutional research board approved this study (No. B141101002), and informed consent was obtained from each participant. The study was conducted according to the Declaration of Helsinki.

Catheterization via superficial temporal and occipital arteries
Preoperative 3-dimensional computed tomography angiography of the carotid artery was performed to identify the tumor-feeding arteries and determine their morphologies originating from the external carotid artery.4 If the tongue tumor extended to the floor of the mouth and extrinsic muscles of the tongue, 2 catheters were superselectively inserted into the lingual artery (LA) and facial artery (FA); if the tumor extended to the contralateral side across the median line, another catheter was inserted into the contralateral LA and/or FA.4,5 Catheterization into the LA or FA was performed via the superficial temporal artery according to the method described by Tohnai et al.10 and Fuwa et al.11 Catheterization via the occipital artery was performed according to the method described by Iwai et al.12

Perfusion of primary lesion and neck levels
After catheterization, digital subtraction angiography and angio-CT were performed to check perfusion in all cases. Angio-CT was performed from each inserted catheter using 6 mL diluted contrast medium (3 mL iopamidol and 3 mL normal saline) for 5 seconds to confirm perfusion of the primary and neck levels. Neck level was classified according to Som et al.13

Radiotherapy
Patients received external irradiation at a planned total dose of 50-70 Gy/25-35 fractions. The radiotherapy was delivered daily, 5 days per week, using 4 or 6 MV X-rays and a shrinking field technique. The irradiation field for the neck was changed according to primary tumor status (T classification). In cases of T2 disease, the fields contained the primary tumor and levels I-III of the ipsilateral cervical lymph node area. In cases of T3 and T4a disease, the fields contained the primary tumor and levels I-III of bilateral cervical lymph node areas. After a total dose of 40 Gy/20 fractions had been delivered to the primary tumor and neck, the portal was reduced to only the primary tumor, to spare the spinal cord. Therefore, the median total doses for primary tumor and neck were 60 Gy (50–70 Gy) and 40 Gy, respectively. The total dose to the spinal cord was restricted to 40-45 Gy.

Superselective intra-arterial chemoradiotherapy
Radiotherapy was performed while the anticancer drugs were injected in a bolus infusion for 1 hour via the intra-arterial catheter. Cisplatin (CDDP) was infused at 5 mg/m²/day, and the total dose was 125-175 mg/m² (median 150 mg/m²). Docetaxel was infused at 10 mg/m²/week, and the total dose was 50-70 mg/m² (median 60 mg/m²) (Figure 1). Sodium thiosulfate 1 g/m² was administered intravenously to provide effective neutralization after infusion of CDDP.4,5

Assessment and follow-up after treatment
To evaluate treatment, PET-CT, magnetic resonance imaging, enhanced CT, and ultrasound examinations were performed 4 weeks after completion of intra-arterial CRT. If residual primary tumor was present after treatment, the policy was to perform a salvage operation 6-8 weeks after the end of intra-arterial CRT. If neck and/or primary recurrence was detected, radical surgery was performed as soon as possible.

Adverse event assessment
Adverse events during treatment were evaluated according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events, version 4.0.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N or median</th>
<th>(% or range)</th>
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</thead>
<tbody>
<tr>
<td>Age (y)</td>
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<td>(34-87)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29</td>
<td>(69)</td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
<td>(31)</td>
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<tr>
<td>T classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2 (late T2)</td>
<td>17</td>
<td>(40)</td>
</tr>
<tr>
<td>T3</td>
<td>13</td>
<td>(31)</td>
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<tr>
<td>T4a</td>
<td>12</td>
<td>(29)</td>
</tr>
<tr>
<td>Stage classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>17</td>
<td>(40)</td>
</tr>
<tr>
<td>III</td>
<td>13</td>
<td>(31)</td>
</tr>
<tr>
<td>IV</td>
<td>12</td>
<td>(29)</td>
</tr>
</tbody>
</table>
Statistical analysis
The differences between T classifications in overall survival (OS), progression-free survival (PFS), and local control (LC) rates were analyzed by log-rank test. Statistical significance was defined as $P < .05$. All analyses were performed using SPSS version 20 (IBM, Chicago, IL, USA).

RESULTS
Treatment results
The median follow-up period was 46.5 months (range, 8-105 months). After retrograde superselective intra-arterial CRT, primary tumor CR was achieved in 42 cases (100%). Three of 42 cases (7.1%) showed local recurrence during follow-up. Delayed neck metastasis was detected in 5 cases (11.9%): 2 T2, 1 T3, and 2 T4a (Table II). In 4 of 5 cases, delayed neck metastasis was observed in the neck area that had no perfusion of anticancer drugs. In the other case, both the primary lesion and neck showed recurrences, and neck metastasis occurred in the perfusion area of the anticancer drugs. Eight patients (19.0%) died: 6 of distant metastasis, 1 of uncontrollable cervical lymph node metastasis, and 1 of non-cancer-related causes.

The Kaplan-Meier method was used to estimate the 3-year OS, PFS, and LC rates, which were 85.0% (95% confidence interval [CI]: 73.8—96.2%), 77.8% (95% CI: 64.9—90.7%), and 91.7% (95% CI: 82.5—100%), respectively (Figure 2).

Adverse events
Among the early adverse events, grade 3 or 4 toxic changes included oral mucositis in 39 cases (92.9%), neutropenia in 9 cases (21.4%), and thrombocytopenia in 2 cases (4.8%). Grade 3 toxicities included anemia in 7 cases (16.7%), radiation dermatitis in 4 cases (9.5%), nausea in 2 cases (4.8%), and fever in 1 case (2.4%). Grade 3 dysphagia with severe oral mucositis occurred in 35 cases (83.3%). Dysphagia has a tendency to improve within 3 months in most cases. Grade 3 or greater acute kidney injury was not observed. Among late adverse events, grade 3 osteonecrosis of the jaw was observed in 2 cases (4.8%). No patients died due to adverse events (Table III).

Perfusion of primary lesion and neck levels
Figure 3 shows flow check digital subtraction angiography, angio-CT, and tumor staining after catheterization. The LA was catheterized on 54 sides: 38 on the affected side and 16 on the unaffected side. Levels IA, ipsilateral IB, and contralateral IB were perfused in 28 (51.9%), 40 (74.1%), and 12 (22.2%), respectively.

Table II. Cases of delayed neck metastasis

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (y)/Sex</th>
<th>T classification</th>
<th>Site</th>
<th>Period (mo)</th>
<th>Perfusion</th>
<th>Local recurrence</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>68/F</td>
<td>T4a</td>
<td>Ipsilateral IIA</td>
<td>4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>67/M</td>
<td>T2 (late T2)</td>
<td>Ipsilateral VB</td>
<td>8</td>
<td>-</td>
<td>-</td>
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<tr>
<td>10</td>
<td>74/F</td>
<td>T3</td>
<td>Ipsilateral IB</td>
<td>34</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>16</td>
<td>68/M</td>
<td>T2 (late T2)</td>
<td>Ipsilateral IIA, IIB</td>
<td>7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>18</td>
<td>69/M</td>
<td>T4a</td>
<td>Ipsilateral III</td>
<td>4</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

Period (mo): the period (months) until delayed neck metastasis occurred; Perfusion: perfusion of anticancer drug at neck level with delayed neck metastasis.
The FA was catheterized on 33 sides: 30 on the affected side and 3 on the unaffected side. Levels IA, ipsilateral IB, IIA, and contralateral IB were perfused in 22 (66.7%), 32 (97.0%), 5 (15.2%), and 6 (18.2%), respectively (Table IV).

**DISCUSSION**

Superselective intra-arterial infusion for head and neck cancer has the advantage of delivering a high concentration of anticancer drugs to the tumor. Lee et al.\textsuperscript{14,15} reported superselective intra-arterial chemotherapy via the femoral artery by the Seldinger method. Robbins et al.\textsuperscript{16,17} reported the effectiveness of rapid intra-arterial administration of high-dose CDDP combined with radiotherapy and sodium thiosulfate neutralization. We developed a regimen of retrograde superselective intra-arterial infusion via the superficial temporal artery that can be used to provide daily concurrent chemoradiotherapy for patients with advanced oral cancer. We evaluated the therapeutic results and the rate of organ preservation in patients with stage III or IV oral cancer treated with intra-arterial CRT and reported excellent outcomes (5-year OS rate 71.3%, LC rate 79.3%).\textsuperscript{5}

Neck recurrence is associated with a poor prognosis in oral cancer.\textsuperscript{18,19} In particular, tongue cancer is associated with higher rates of occult neck metastases than other oral cancers\textsuperscript{20,21}; the frequency is reported to be 25% to 58% in T2-4 tongue cancer.\textsuperscript{6-8} In the present study, delayed neck metastasis was detected in 5 of 42 patients (11.9%). Three reasons might explain the lower rate of delayed neck metastasis after superselective CRT. First, irradiation to the neck of at least 40 Gy, according to primary tumor status, was performed. Second, perfusion of anticancer drugs to the neck through intra-arterial infusion was administered. Previously, some authors reported on the treatment effect on cervical lymph node metastasis treated with superselective intra-arterial chemotherapy combined with radiotherapy, which obtained good histopathologic effects on metastatic lymph nodes.\textsuperscript{22,23} Shah et al.\textsuperscript{24} reported on the prevalence and distribution of neck node metastases in 192 patients with N0 oral cavity SCC after elective radical neck dissection. Occult neck metastasis was present in 65

![Fig. 2](image-url)
of the 192 patients (34%). The overall prevalence of nodal metastasis at neck levels I, II, III, IV, and V was 20%, 17%, 9%, 3%, and 0.5%, respectively. In the present study, neck levels perfused with retrograde superselective intra-arterial infusion from the LA and FA were IA, ipsilateral IB, IIA, and contralateral IB. In addition, a number of cervical lymph nodes at levels I-IIA were perfused from the intra-arterial catheter placed in LA/FA (Figure 4). These results suggest that intra-arterial CRT can increase levels of anticancer drugs in levels I-IIA and has a therapeutic effect on occult neck metastases in the perfused neck area. The third reason for the lower rate of delayed neck metastasis was that intra-arterially injected anticancer drugs passed into sentinel lymph nodes (SLNs) via lymphatic canals. Yokoyama et al.25

Fig. 3. Perfusion check in squamous cell carcinoma of the right tongue (T3N0M0). Two catheters were superselectively inserted into (A) the right lingual artery via the occipital artery (OA-LA) and (B) the right facial artery via the superficial temporal artery (STA-FA). (A) The tumor stain of the right tongue is seen on digital subtraction angiography (OA-LA; arrow). (C) Perfusion of the right tongue from the right LA (arrowhead) and (D) the right floor of the mouth from the right FA (arrowhead) can be seen with the use of contrast medium. (E) Staining by injection of indigotindisulfonate sodium in the right LA is visible to the right of the tongue; however, staining is not visible on the floor of the mouth (arrowhead). (F) Staining of the floor of the mouth and lower gingiva is seen from the right FA (arrowhead).
reported on a translymphatic chemotherapy procedure targeting SLNs, using intra-arterial chemotherapy of 50 mg/m² CDDP administered either once or twice weekly for patients with tongue cancer who underwent surgical treatment including partial tongue resection and neck dissection. The mean CDDP concentrations

Table IV. Perfusion of neck levels from catheters

<table>
<thead>
<tr>
<th></th>
<th>IA</th>
<th>IB</th>
<th>IIA</th>
<th>IIB-V</th>
<th>IB</th>
<th>IIA</th>
<th>IIB-V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lingual Artery (N = 54)</td>
<td>28 (51.9%)</td>
<td>40 (74.1%)</td>
<td>0</td>
<td>0</td>
<td>12 (22.2%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Facial Artery (N = 33)</td>
<td>22 (66.7%)</td>
<td>32 (97.0%)</td>
<td>5 (15.2%)</td>
<td>0</td>
<td>6 (18.2%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Fig. 4. Perfusion of cervical lymph nodes from catheters inserted into the lingual (LA) and facial (FA) arteries. Case 1: Left tongue cancer (T3N0). (A) Small lymph node is observed in neck level IA before treatment (arrowhead). (B) Perfusion from the left LA is observed in neck level IA and ipsilateral level IB, and level IA lymph node is enhanced (arrowhead). Case 2: Right tongue cancer (Late T2N0). (C) Small lymph nodes are observed in bilateral neck level IB before treatment (arrowheads). (D) Perfusion from the right LA is observed in neck level IA and bilateral level IB, and bilateral level IB lymph nodes are enhanced (arrowheads). Case 3: Right tongue cancer (Late T2N0). (E) Lymph node is observed in right neck level IIA before treatment (arrowhead). (F) Perfusion from the right FA is observed in neck level IA, ipsilateral level IB and IIA, and the ipsilateral level IIA lymph node is enhanced (arrowhead).
in SLNs and non-SLNs were 1.2 μg/g and 0.35 μg/g, respectively. Sakashita et al.26 also reported on platinum concentrations of SLNs after preoperative intra-arterial CDDP chemotherapy. Patients with T1-2N0 tongue cancer were treated with preoperative intra-arterial chemotherapy (cisplatin, 100 mg/m²) to the LA, targeting the primary cancer only, and partial glossectomy with SLN biopsy and elective neck dissection was performed 2 weeks after chemotherapy. The platinum concentration was higher in SLNs (0.682 ± 0.246 μg/g) than in non-SLNs (0.506 ± 0.274 μg/g) (P = .049). These results indicate that CDDP administered to primary tongue cancer moves selectively to SLNs via lymphatic canals. Thus, intra-arterial chemotherapy is effective for occult neck metastases both administration to SLNs via lymphatic canals and perfusion to the neck from the LA/FA.

Three-year LC rates of late T2, T3, and T4aN0 tongue cancer patients were 100%, 90.0%, and 83.3%, respectively, and there were no significant differences among T classifications. These results indicate that retrograde superselective intra-arterial CRT provided good local control even in locally advanced tongue cancer. On the other hand, OS and PFS of T3N0 retrograde superselective intra-arterial CRT provided among T classiﬁcations respectively, and there were no signiﬁcant differences among T classiﬁcations.

In conclusion, intra-arterial chemotherapy is a method of lymphatic chemotherapy for the treatment of occult neck metastasis. Retrograde superselective intra-arterial CRT has a therapeutic effect not only for the primary lesion, but also for occult neck metastasis.

REFERENCES


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