Facial nerve paralysis after super-selective intra-arterial chemotherapy for oral cancer

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Abstract. Facial nerve paralysis (FNP) after super-selective intra-arterial chemotherapy (SSIAC) is a relatively rare local side effect of SSIAC to the maxillary artery (MA) or the middle meningeal artery (MMA). The incidence and prognosis of FNP after SSIAC in 381 patients with oral cancer (133 with catheterization of the MA, 248 without) was investigated retrospectively. Only three patients (two male and one female) had FNP, for an incidence of 0.8%. All patients with FNP had undergone catheterization of the MA, and the incidence of FNP in this group was 2.3% (3/133). One of the three patients with FNP had paralysis of the third branch of the trigeminal nerve. FNP occurred a mean of 8.7 days (range 5–11 days) after initial SSIAC, and the mean total dose of cisplatin was 55.8 mg (range 42.5–67.2 mg) and of docetaxel was 25.4 mg (range 17.0–33.6 mg). FNP resolved completely a mean of 12.7 months (range 6–19 months) after onset. Because the administration of anticancer agents via the MA or MMA carries a risk of FNP, this information will be useful when obtaining informed consent from patients before treatment.

Intra-arterial chemotherapy (IAC) has been used to treat head and neck cancer since the 1950s; however, the efficacy of early IAC was unproven. Recently, progress in vascular radiological techniques has led to the development of super-selective IAC (SSIAC), which has the advantage of delivering a higher concentration of anticancer agents to the tumour bed than IAC; SSIAC has been applied to head and neck cancers, including oral cancers. However, the infusion of tumour-feeding arteries with highly concentrated anticancer agents may induce local side effects in vital tissues or organs that receive a blood supply from those arteries. Cranial nerve damage, in particular facial nerve paralysis (FNP), is a relatively rare local side effect of IAC or SSIAC to the maxillary artery (MA) or middle meningeal artery (MMA). The purpose of this study was to investigate the incidence and prognosis of FNP after SSIAC.

Materials and methods
This study included 381 patients with oral cancer who underwent retrograde SSIAC and daily concurrent radiotherapy at the authors’ institution between June 2006 and May 2016. Of the 381 patients, 133 underwent catheterization of the MA and 248 underwent catheterization of arteries other than the MA. The incidence of FNP after SSIAC with respect to sex, age, primary tumour site, catheter tip position, anticancer agent, and additional cranial
nerve paralysis, as well as the onset and recovery of FNP after SSIAC, was investigated retrospectively.

**Retrograde super-selective intra-arterial chemoradiotherapy**

Catheterization via the superficial temporal artery was performed according to the method described by Tohnai et al. \(^6\) and catheterization via the occipital artery was performed according to the method of Iwai et al. \(^9\) (Fig. 1). A hook-shaped catheter (Medikit Co., Ltd, Tokyo, Japan) was super-selectively inserted into the target artery and fixed to the skin. When catheterization using a hook-shaped catheter was not stable, the guide wire exchange method was used to replace it with an Anthron P-U catheter (Toray Medical Co., Ltd, Tokyo, Japan). Heparinized saline (100 units/ml) with 10 mg prednisolone was administered continuously into the catheter via an infusion pump (Baxter Infusor, 7-day type; Baxter, Chicago, IL, USA). The anticancer agents were injected for 1 h in a bolus through the intra-arterial catheter when radiotherapy was performed. The dose of cisplatin was 5 mg/m\(^2\)/day and of docetaxel was 10 mg/m\(^2\)/week, and SSIAC was performed for 4–7 weeks. Sodium thiosulphate (1 g/m\(^2\)) was administered intravenously to provide effective neutralization after cisplatin administration. Conventional radiotherapy was performed at 4 or 6 MV and the total dose delivered to the primary tumour was 40–70 Gy (2 Gy/fraction/day).

**Results**

Among 381 patients with oral cancer who underwent SSIAC, only three (two male and one female) had FNP (Table 1), for an incidence of 0.8%. All patients with FNP had undergone catheterization of the MA, and the incidence of FNP in this group was 2.3% (3/133). There were no patients with FNP among the 248 with catheterization of arteries other than the MA. One of the three patients with FNP had paralysis of the third branch of the trigeminal nerve. FNP occurred a mean of 8.7 days (range 5–11 days) after initial SSIAC, and the mean total dose of cisplatin was 55.8 mg (range 42.5–67.2 mg) and of docetaxel was 25.4 mg (range 17.0–33.6 mg). All patients with FNP were treated immediately with an intravenous administration of steroid, and the FNP had resolved completely at a mean of 12.7 months (range 6–19 months) after onset.

**Discussion**

Although FNP after IAC for head and neck cancer is relatively rare,\(^2,3,7,10\) the blood supply of the facial nerve (FN) is

![Fig. 1. Super-selective intra-arterial catheterization via the superficial temporal artery and occipital artery.](image)

**Table 1.** Reported cases of facial nerve paralysis after (super-selective) intra-arterial chemotherapy.

<table>
<thead>
<tr>
<th>Case No. (Ref.)</th>
<th>Sex/age</th>
<th>Primary tumour site</th>
<th>Catheter tip position</th>
<th>Anticancer agent (total dose)</th>
<th>Onset after initial infusion</th>
<th>Additional paralysis</th>
<th>Recovery (month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (10)</td>
<td>NA/NA</td>
<td>NA</td>
<td>ECA</td>
<td>CDDP (100 mg/m(^2) × 1)</td>
<td>3 days</td>
<td>None</td>
<td>CR (0.5)</td>
</tr>
<tr>
<td>2 (2)</td>
<td>70/F</td>
<td>Nasopharynx</td>
<td>ECA</td>
<td>CDDP (20 mg/day × 8)(^a)</td>
<td>10 days</td>
<td>None</td>
<td>(NA)</td>
</tr>
<tr>
<td>3 (8)</td>
<td>63/F</td>
<td>Parotid gland</td>
<td>PAA</td>
<td>CDDP (100 mg/m(^2)/week × 6)</td>
<td>NA</td>
<td>None</td>
<td>None (60)</td>
</tr>
<tr>
<td>4 (3)</td>
<td>60/M</td>
<td>Maxillary sinus</td>
<td>MMA</td>
<td>CDDP (100 mg/m(^2) × 1)</td>
<td>3 days</td>
<td>V2</td>
<td>None (12)</td>
</tr>
<tr>
<td>5 (3)</td>
<td>71/M</td>
<td>Maxillary sinus</td>
<td>MMA</td>
<td>CDDP (100 mg/m(^2) × 1)</td>
<td>5 days</td>
<td>None</td>
<td>CR (6)</td>
</tr>
<tr>
<td>6 (7)</td>
<td>NA/NA</td>
<td>Maxillary sinus</td>
<td>MA</td>
<td>CDDP (5 mg/m(^2)/day × 5)</td>
<td>2 weeks</td>
<td>None</td>
<td>CR (30)</td>
</tr>
<tr>
<td>7 (Present study)</td>
<td>62/M</td>
<td>Upper gingiva</td>
<td>MA</td>
<td>DOC (10 mg/m(^2)/week × 1)</td>
<td>5 days</td>
<td>V3</td>
<td>CR (6)</td>
</tr>
<tr>
<td>8 (Present study)</td>
<td>78/F</td>
<td>Upper gingiva</td>
<td>MA</td>
<td>CDDP (5 mg/m(^2)/day × 9)</td>
<td>11 days</td>
<td>None</td>
<td>CR (13)</td>
</tr>
<tr>
<td>9 (Present study)</td>
<td>82/M</td>
<td>Buccal mucosa</td>
<td>MA</td>
<td>DOC (10 mg/m(^2)/week × 2)</td>
<td>10 days</td>
<td>None</td>
<td>CR (19)</td>
</tr>
</tbody>
</table>

CDDP, cisplatin; CR, complete recovery; DOC, docetaxel; ECA, external carotid artery; F, female; M, male; MA, maxillary artery; MMA, middle meningeal artery; NA, not available; PAA, posterior auricular; V2, second branch of the trigeminal nerve; V3, third branch of the trigeminal nerve. \(^a\) Continuous infusion.
important in considering the mechanism of FNP after IAC. The intratemporal segments of the FN are supplied by several sources: the internal auditory artery, stylomastoid artery, petrosal artery, and a branch of the internal carotid artery. In the auditory canal, the FN is supplied by branches from the internal auditory artery. In the facial canal, the FN is supplied by the petrosal artery, which is a branch of the MMA, and the stylomastoid artery, which is a branch of the posterior auricular artery or the occipital artery (Fig. 2). The MMA gives off a short stem vessel that divides laterally into the petrosal artery and medially into a branch to the trigeminal ganglion. The petrosal artery is sometimes double, with the second vessel arising from the common trunk or the accessory meningeal artery. The accessory meningeal artery originates from the MMA in 47–75% of individuals, from the MA in 25–47%, and from both in 0–6%. Among the three patients with FNP in the present study, the accessory meningeal artery originated from the MMA in two patients (67%) and from the MA in one patient (33%).

The incidence of FNP has been reported previously in the English-language literature as being 1.6–10% (Table 2). Although conventional IAC—which places the catheter tip in the external carotid artery—provides a lower dose of anticancer agents to the feeding artery of the FN compared with SSIAC, FNP has still been reported in such cases. Because low-dose anticancer agents are administered daily in the present authors’ method of SSIAC, the dose of anticancer agents to target arteries may be similar to high-dose IAC. The incidence of FNP in the present study (0.8% in 381 patients) is lower than that in other reports, and no FNP was observed in patients without catheterization of the MA; however, the incidence of FNP in patients with catheterization of the MA was 2.3% (3/133). Takanami et al. analyzed the relationship between the position of the catheter tip and the incidence of FNP after high-dose SSIAC. Of 20 patients with head and neck cancer, three underwent catheterization of the MA and five underwent catheterization of the MMA. Although there was no FNP in patients with catheterization of the MA, two patients with catheterization of the MMA had FNP, for an incidence of

Table 2. Incidence of facial nerve paralysis after (super-selective) intra-arterial chemotherapy.

<table>
<thead>
<tr>
<th>Author (Ref.)</th>
<th>Incidence of FNP</th>
<th>Primary tumour site</th>
<th>Catheter tip position</th>
<th>Anticancer agent (dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frustaci et al.</td>
<td>1.6% (1/63)</td>
<td>Head and neck cancer</td>
<td>ECA</td>
<td>CDDP (20 mg/day)</td>
</tr>
<tr>
<td>Mortimer et al.</td>
<td>4% (1/25)</td>
<td>Head and neck cancer</td>
<td>ECA</td>
<td>CDDP (100 mg/m²)</td>
</tr>
<tr>
<td>Claudio et al.</td>
<td>5% (2/40)</td>
<td>Head and neck cancer</td>
<td>ECA</td>
<td>Vincristine (1.5 mg/week), bleomycin (45 mg/week), MTX (20 mg/week)</td>
</tr>
<tr>
<td>Cruz et al.</td>
<td>9.1% (4/44)</td>
<td>Head and neck cancer</td>
<td>ECA</td>
<td>5-FU (15 mg/kg/day), MTX (5 mg/day), vinblastine (0.02 mg/kg/day)</td>
</tr>
<tr>
<td>Damascelli et al.</td>
<td>10% (6/60)</td>
<td>Head and neck cancer</td>
<td>ECA, its branches</td>
<td>Paclitaxel (150–230 mg/m²)</td>
</tr>
<tr>
<td>Takanami et al.</td>
<td>10% (2/20)</td>
<td>Head and neck cancer</td>
<td>MMA, MA, ECA, others</td>
<td>CDDP (100 mg/m²)</td>
</tr>
<tr>
<td>Kaneko et al.</td>
<td>2.8% (1/36)</td>
<td>Maxillary sinus</td>
<td>MA, ECA</td>
<td>CDDP (20–50 mg/m²)</td>
</tr>
<tr>
<td>Present study</td>
<td>0.8% (3/381)</td>
<td>Oral cancer</td>
<td>MA, FA, LA, ECA, others</td>
<td>CDDP (5 mg/m²/day), DOC (10 mg/m²/week)</td>
</tr>
<tr>
<td></td>
<td>2.3% (3/133)</td>
<td>Gingiva, hard palate, buccal mucosa</td>
<td>MA</td>
<td></td>
</tr>
</tbody>
</table>

5-FU, fluorouracil; CDDP, cisplatin; DOC, docetaxel; ECA, external carotid artery; FA, facial artery; FNP, facial nerve paralysis; LA, lingual artery; MA, maxillary artery; MMA, middle meningeal artery; MTX, methotrexate.

* Continuous infusion.

** Paclitaxel-charged human albumin nanoparticles.
40% (2/5). Considering the blood supply of the FN, the risk of FNP after SSIAC may increase when the position of the catheter tip is closer to the feeding artery.1 Through a search of the English-language literature, six well-described cases of FNP after IAC or SSIAC were identified. These reported cases of FNP, along with the three cases in the present study, were reviewed with regard to sex, age, primary tumor, catheter tip position, anticancer agent, additional cranial nerve paralysis, and onset and recovery of FNP (Table 1). The catheter tip was placed in the MMA, MA, posterior auricular artery, or external carotid artery, all of which supply blood to the FN from branches including the petrosal artery or stylomas- toid artery. Although cisplatin was administered in all well-described cases of FNP after IAC or SSIAC (Table 1), FNP after IAC or SSIAC may also be caused by the administration of other anticancer agents such as fluouracil, methotrexate, bleomycin, vinblastine, vincristine, doce- taxel, and paclitaxel-charged human albu- min nanoparticles (Table 2). Because FNP has been shown to occur after IAC as well as after SSIAC, and with the administration of various doses of anticancer agents to the tumour-feeding artery, the type or dose of anticancer agent administered is unlikely to be associated with the incidence of FNP. On the other hand, the catheter tip position appears to be important in determining the occurrence of FNP, considering the blood supply of the FN. The onset of FNP after the initial infusion of anticancer agents ranged from 3 days to 2 weeks. Two of nine patients (22.2%) had trigeminal nerve paralysis. The FNP had resolved completely at 2 weeks to 30 months after onset in most patients, but some patients did not recover. FNP after IAC or SSIAC occurs by direct or indirect neural impairment. Direct neural impairment includes local neurotoxicity, which is influenced in a dose-dependent manner by anticancer agents such as cisplatin; in this case, FNP develops slowly and complete recovery is difficult. The review showed that chemotherapy in two of three patients with persistent FNP was administered super selectively via the posterior auricular artery or MMA, which provides a blood supply to the FN. This suggests that a high concentration of anticancer drug may induce direct neurotoxicity. Indirect neural impairment includes haematogenous dis orders of the FN that may be caused by blood vessel embolism or inflammation of the feeding artery. According to de Vries et al., FNP after embolization of the MMA, MA, occipital artery, and their branches—including the stylomastoid artery or petrosal artery, which is the feeding artery of the FN—is not commonly reversible.15 In some patients, FNP is accompanied by trigeminal nerve paralysis caused by an obstruction in the accessory meningeal artery, which supplies a portion of the trigeminal nerve and ganglion.19 In contrast, previous studies have suggested that FNP caused by blood vessel inflammation after IAC or SSIAC is usually mild and reversible, taking several days to resolve. Because of the vascular anatomy of the FN tract, the horizontal segment of the intratemporal FN is considered to be the most vulnerable to damage by oedema, as the FN occupies almost the entire intracranial space and could become ischemic if intracranial pressure increases. Blood flow to this portion is supplied by the petrosal artery, the terminal branch of the MMA. When SSIAC is performed for head and neck cancer, including oral cancer, the administration of anticancer agents via the MA or MMA carries a risk of FNP. The information presented herein regarding this risk will be useful when obtaining informed consent from patients before treatment.

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Competing interests
No conflict of interest.

Ethical approval
Ethical approval was not required because this study was a retrospective investigation.

Patient consent
Written patient consent was obtained.

References


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