Thermochemoradiation Therapy Using Superselective Intra-arterial Infusion via Superficial Temporal and Occipital Arteries for Oral Cancer With N3 Cervical Lymph Node Metastases

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Summary
Patients with head-and-neck squamous cell carcinoma with N3 metastases have a poor prognosis (3-year survival rates of 17.9% in patients undergoing surgery and 7.1% in those treated with radiation therapy alone). Our strategy for treating patients with N3 is to use thermochemoradiation therapy with retrograde superselective intra-arterial infusion. Five-year survival and locoregional control rates were 51% and 86%, respectively. It is expected

Purpose:
To evaluate the therapeutic results and histopathological effects of treatment with thermochemoradiation therapy using superselective intra-arterial infusion via the superficial temporal and occipital arteries for N3 cervical lymph node metastases of advanced oral cancer.

Methods and Materials:
Between April 2005 and September 2010, 9 patients with N3 cervical lymph node metastases of oral squamous cell carcinoma underwent thermochemoradiation therapy using superselective intra-arterial infusion with docetaxel (DOC) and cisplatin (CDDP). Treatment consisted of hyperthermia (2-8 sessions), superselective intra-arterial infusions (DOC, total 40-60 mg/m²; CDDP, total 100-150 mg/m²) and daily concurrent radiation therapy (total, 40-60 Gy) for 4-6 weeks.

Results:
Six of 9 patients underwent neck dissection 5-8 weeks after treatment. In four of these 6 patients, all metastatic lymph nodes, including those at N3, were grade 3 (non-viable tumor cells present) or grade 4 (no tumor cells present) tumors, as classified by the system by Shimosato et al (Shimosato et al Jpn J Clin Oncol 1971;1:19-35). In 2 of these 6 patients, the metastatic lymph nodes were grade 2b (destruction of tumor structures with a small amount of residual viable tumor cells). The other 3 patients did not undergo neck dissection due to distant metastasis after completion of thermochemoradiation therapy (n = 2) and refusal (n = 1). The patient who refused neck dissection underwent biopsy of the N3 lymph node and primary sites and showed grade 3 cancer. During follow-up, 5 patients were alive without disease, and 4 patients died due to pulmonary metastasis (n = 3) and noncancer-related causes (n = 1). Five-year survival and locoregional control rates were 51% and 88%, respectively.

Conflicts of interest: none.

Acknowledgment—The authors thank Dr Masaharu Hata and Dr Suomi Kurihara, Department of Radiology, for performing the radiation therapy and hyperthermia treatments.
that this method will become the new treatment for oral cancer patients with N3 cancer.

Conclusions: Thermochemoradiation therapy using intra-arterial infusion provided good histopathologic effects and locoregional control rates in patients with N3 metastatic lymph nodes. However, patients with N3 metastatic lymph nodes experienced a high rate of distant metastases. © 2012 Elsevier Inc.

Introduction

Patients with head-and-neck squamous cell carcinoma with advanced cervical metastases present a treatment dilemma because their prognosis is generally considered poor. When cervical lymph node metastases exceed 6 cm in the largest diameter (N3), treatment of these metastases is extremely difficult and often results in poor prognoses (1). The use of hyperthermia (HT) has generally been confined to treatment of cervical lymph node metastases, accessible with a radiofrequency system using external application, and in combination with synergistic chemoradiation therapy (CRT). HT is appealing because it is a physical treatment with fewer side effects than chemotherapy or radiation therapy. Repeated HT treatments should be feasible without concern for cumulative toxic side effects. Preoperative thermochemoradiation therapy has been shown to reduce N3 cervical lymph node metastases to surgically treatable sizes and to result in high clinical and pathological responses and improved survival rates (2).

A method of superselective intra-arterial infusion via a superficial temporal artery (STA) was developed (3, 4). This treatment can be used to provide daily concurrent radiation therapy and chemotherapy for patients with advanced head-and-neck cancer. This method has been used in the clinical setting since 1996 for organ preservation and improvement of treatment of patients with advanced head and neck cancer (3, 5); however, this method showed insufficient effects on cervical lymph node metastases, especially N2 and N3 disease. There have been a few clinical trials of patients with head-and-neck squamous cell carcinoma with N3 cervical lymph node metastases who were treated with thermochemistry plus systemic chemotherapy, but no trials using thermochemistry plus superselective intra-arterial chemotherapy have been reported. The present study evaluated the therapeutic results and histopathological effects of thermochemoradiation therapy using superselective intra-arterial infusion via STA and an occipital artery (OA) in patients with N3 cervical lymph node metastases of advanced oral cancer.

Methods and Materials

Patients

Between April 2005 and September 2010, 9 patients with stage T2-T4 N3 squamous cell carcinoma of the oral cavity and no evidence of distant metastasis when initially evaluated underwent intra-arterial CRT combined with HT at the Department of Oral and Maxillofacial Surgery of the Nagoya Graduate School of Medicine, Nagoya, and the Yokohama City Graduate School of Medicine, Yokohama, Japan (Table 1). Patients were required to have an Eastern Cooperative Oncology Group performance status (http://ecog.dfci.harvard.edu/general/perf_stat.html) of 0 or 1, a white blood cell count of at least 3500 cells/mm³, a platelet count of at least 100,000/mm³, and a hemoglobin level of at least 9 g/dL. Patients with cerebral infarction and severe liver, kidney, heart, or lung dysfunction were also excluded. Staging was performed according to the 2002 International Union Against Cancer staging system (6).

Superselective intra-arterial catheter replacement via STA and OA

STA catheterization was performed according to the method of Tohnai et al (3) and Fuwa et al (4). After the patient was given local anesthesia, the hook-shaped catheter (Medikit Corp., Tokyo, Japan) was superselectively inserted into the target artery under fluoroscopic guidance. After the catheter was inserted into the target artery, the guide wire exchange method was used to replace it with a P-U catheter (Toray Medical Co., Ltd, Tokyo, Japan) (4). This was because the temperature of the hook-shaped catheter increased when radiofrequency HT was applied. Catheterization from the OA was performed according to the method of Iwai et al (7).

Radiation therapy

Three-dimensional computed tomography (3D-CT)-based radiation therapy treatment planning was performed for all patients. Patients were treated with 3D conformal radiation therapy after appropriate immobilization using a thermoplastic mask. Conventional radiation therapy was performed with 4 or 6 MV at 2 Gy/fraction/day. Radiation therapy was delivered using bilateral opposed fields and an anterior single field to cover the primary and lymph node metastases. Gross tumor volume (GTV) was defined as any visible evidence of disease on physical examination and any imaging modality, including CT, (MRT), and/or positron emission tomography (PET)-CT. Clinical target volume (CTV) was defined as the GTV plus a margin of 15-20 mm to cover microscopic disease, and the planning target volume was defined as the CTV plus a margin of 5-7 mm, depending on the proximity of critical structures, in order to compensate for set-up errors.

When thermochemoradiation therapy was followed by radical surgery for the primary lesion and neck disease, the total dose delivered to primary tumor and levels I to V of the neck bilaterally was 40-50 Gy/20-25 fractions (Table 1, cases 1, 4, 5, and 6). In the case of organ preservation of the primary lesion, the total dose delivered to the primary tumor was 60 Gy/30 fractions, and the total dose delivered to levels I to V of the neck bilaterally was 50-60 Gy/25-30 fractions (Table 1, cases 2, 3, 7, 8, and 9).

Superselective intra-arterial chemotherapy

The anticancer agent was injected in a bolus through the intra-arterial catheter when radiation therapy was performed. The total dose of docetaxel was 40-60 mg/m² (10 mg/m²/week), and that of...
cisplatin (CDDP) was 100-150 mg/m² (5 mg/m²/day). Sodium thiosulfate (1 g/m²) was administered intravenously to provide effective CDDP neutralization after the anticancer agent was given.

**HT**

Radiofrequency capacitive heating equipment (8 MHz, radiofrequency output range of 60-1500 W; Thermotron RF-8; Yamamoto Vinyter Co Ltd, Osaka, Japan) was used for HT. Two opposing 10-cm electrodes were generally used for heating the cervical lymph node metastases. Both electrodes were covered with a water pad, and one was placed along the N3 metastatic node, while the other was used for the contralateral site (see Fig. 2a). HT was applied once or twice per week and was administered for 50 min within 30 min after each session of radiation therapy. Thermometry of the central skin surface of the neck tumor was performed using thermocouples.

**Surgery**

The primary lesion and N3 cervical lymph node metastases were assessed by magnetic resonance imaging (MRI), CT, ultrasonographic examination, and/or PET-CT at 4 weeks after completion of all treatments. Patients were scheduled to undergo radical surgery 5-8 weeks after the end of thermochemoradiation therapy, unless distant metastases were found.

**Toxicity assessment**

Toxicities encountered during therapy were evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf). Evaluation categories were neutropenia, anemia, thrombocytopenia, oral mucositis, dermatitis, fever, and burns.

**Pathological response**

Pathologic effects on the primary lesion and lymph nodes were defined by the grading system of Shimosato et al (8).

**Results**

**HT treatment**

The median number of HT treatments was 4 (range, 2-8 sessions), the median maximum temperature in the central surface of the N3 disease was 43.4°C (range, 43.1°C-44.0°C), and the median minimum temperature was 42.2°C (range, 39.6°C-43.0°C) (Table 1).

**Treatment results and pathological responses**

Pathological responses and outcomes are shown in Table 2. For all patients, the median follow-up was 37 months (range, 7-70 months). Therapy as described above was completed in all patients. No major complications, such as cerebral infarctions or other neurological complications, occurred in any patients.

A total of 6 of the 9 patients (Patients, cases 1, 4, 5, 6, 7, and 9) underwent radical surgery. Both a primary lesion and neck disease were present in 4 patients (Table 2, cases 1, 4, 5, and 6), and only neck disease was present in 2 patients due to pathological CR at the primary lesion (Table 2, cases 7 and 9). In 4 of these 6 patients, all metastatic lymph nodes, including N3, were grade III or grade IV. In 2 of the 6 patients, N3 disease showed grade III; however, a metastatic contralateral lymph node showed grade IIb (destruction of tumor structures with a small amount of residual viable tumor cells) in 1 patient (Table 2, case 4), and N3 disease showed grade IIb in 1 patient (Table 2, case 9). One patient refused radical surgery (Table 2, case 2). Biopsy of the primary lesion and N3 disease showed grade IV after treatment, and the patient was free of disease for 70 months. Two patients (Table 2,
cases 3 and 8) achieved clinical CR in both the primary lesion and N3 disease, but distant metastases were found after completion of thermochemoradiation therapy. In 1 of these 2 patients (Table 2, case 8), recurrent N3 neck disease was detected 14 months after treatment. No recurrence of the primary lesion occurred in any patients. During follow-up, 5 patients were alive without diseases, and 4 patients had died due to pulmonary metastasis (n = 3) and noncancer-related causes (n = 1).

Kaplan-Meier method estimates of the 1-year, 3-year, and 5-year overall survival (OS) rates were 89%, 64%, and 51%, respectively, and the 1-year, 3-year, and 5-year locoregional control (LRC) rates were 100%, 88%, and 88%, respectively (Fig. 1).

**Toxicities**

Grade 3 or 4 toxicities included mucositis in all patients (100%) and dermatitis in 5 patients (54%) (Table 3). Grade 3 anemia occurred in 2 patients (22%), and neutropenia occurred in 1 patient (11%). All other toxicities were grade 2 or less. All patients completed the planned treatment regimen. No patients died as a result of treatment toxicity.

**Discussion**

Superselective intra-arterial chemotherapy for head and neck cancer has the advantage of delivering a high concentration of chemotherapeutic agents to the tumor bed, and it is divided into 2 types: one type is selective arterial infusion through the femoral artery by Seldinger’s method (9, 10); and the other type is retrograde selective infusion via STA and OA (3-5, 7). Of note, retrograde superselective intra-arterial infusion has become feasible for daily concurrent radiation therapy and chemotherapy for advanced head and neck cancer, and it has high clinical efficacy (5). That method was originally designed to target the primary lesion, not metastatic lymph nodes. However, the artery feeding into the metastatic lymph node varies: jugulodigastric lymph nodes are fed by the occipital, superior thyroid, and facial arteries; mid-jugular lymph nodes are fed by the superior and inferior thyroid arteries; and low jugular lymph nodes are fed by the ascending cervical artery (11). In the present method, catheters can be inserted into the branches of external carotid arteries. It is therefore presumed that chemotherapeutic agents can be delivered solely through the feeding arteries of the primary lesion and to the jugulodigastric metastatic lymph nodes but not to those of mid-to-low jugular metastatic lymph nodes. Thus, in the present study, the strategy in cases of advanced oral cancer with N3 nodal or mid-to-low jugular lymph node metastases was to use CRT using superselective intra-arterial infusion in combination with HT. After catheterization, it is necessary to assess the flow to the primary tumor and neck disease by using flow check DSA and angio-CT. In one patient in the present study (Table 2, case 4), tumor staining of the left N3 neck disease from the left facial artery was seen with the use of contrast medium on DSA and angio-CT (Fig. 2, b-e); the histopathological efficacy of N3 disease evaluated after neck dissection was grade 3. However, a metastatic lymph node on the right side was grade 2b. This was thought to be because the HT treatment was applied for only the N3 disease, and so was not applied to the contralateral neck metastasis.

**Table 2** Pathological response to N3 disease and outcome after thermochemoradiation therapy

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>N3 pathological response</td>
<td>3</td>
<td>3</td>
<td>—</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>—</td>
<td>2b</td>
</tr>
<tr>
<td>N3 LN control</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Dead</td>
<td>Good</td>
<td>Metastasis</td>
<td>Metastasis</td>
<td>Metastasis</td>
<td>Metastasis</td>
<td>Metastasis</td>
<td>Metastasis</td>
<td>Metastasis</td>
</tr>
<tr>
<td>Cause of death</td>
<td>Heart failure</td>
<td>Alive</td>
<td>Dead</td>
<td>Alive</td>
<td>Alive</td>
<td>Alive</td>
<td>Dead</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>37</td>
<td>70</td>
<td>22</td>
<td>7</td>
<td>46</td>
<td>46</td>
<td>43</td>
<td>16</td>
<td>14</td>
</tr>
</tbody>
</table>

Abbreviation: LN = lymph node.

| | Evaluation from biopsy specimen. |
| | No pathological evaluation. |
| | Contralateral metastatic lymph node showed grade IIb cancer. |

**Table 3** Toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>No. of patients with toxicity grade shown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>2 4 1</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 3 2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>Mucositis</td>
<td>8 1</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>1 3 3 2</td>
</tr>
<tr>
<td>Fever</td>
<td>3 1</td>
</tr>
<tr>
<td>Burn</td>
<td>6 3</td>
</tr>
</tbody>
</table>
HT treatment itself has anti-cancer effects. When cells are exposed to elevated temperatures over 40°C, lethal damage is inflicted, predominantly to proteins (12). In addition, HT is the most potent cellular radiosensitizer. Heat interacts with radiation and potentiates the cellular action of radiation by interfering with the cells’ capability to deal with radiation-induced DNA damage (13). It is well known that hypoxic tumor cells are less responsive to both chemotherapeutic agents and radiation. Radiosensitive cells such as hypoxic cells, low-pH cells, and cells in late S phase are thermosensitive (14). Moreover, radiation therapy and numerous chemotherapeutic agents display complementary effects with HT that are synergistic. These effects of HT are temperature dependent. Large-volume lymph node metastases usually display poor perfusion that results in central hypoxic conditions, anaerobic glycolysis, and low pH. Therefore, combination CRT using superselective intra-arterial infusion with HT should improve the clinical outcomes of large lymph node metastases, and superficial metastatic neck nodes seem to be suitable for HT. Plataniotis et al reported tumor control probabilities (TCPs) calculated for hypothetical combined trimodality (RT plus CT plus HT) treatment, and reported that trimodality treatment could give considerably higher tumor control probabilities for low to intermediately radiosensitive tumors; however, combined trimodality treatment was not expected to improve prognosis in radioresistant tumors (15). The great difference in chemotherapy between the present method and their method was the use of intra-arterial instead of systemic chemotherapy. The present method of intra-arterial chemotherapy combined with thermoradiation therapy provided good locoregional control rates. Randomized clinical trials of the effects of the present method need to be considered.

OS and LRC rates after definitive treatment for patients with N3 diseases reported in previous studies are listed in Table 4.
Ahmed et al (16) used concomitant CRT with intra-arterial high-dose CDDP infusion and surgical salvage for N3 nodal disease. Three-year OS and LRC rates were 41% and 67%, respectively. No neck recurrences were reported, as targeted CRT followed by surgical salvage is a highly effective approach for regional control in patients with N3 nodal disease. Preoperative thermochemoradiation therapy for oral cancer patients with N3 nodal disease has been reported to yield good clinical and pathological response rates. Three-year OS and LRC rates were 70% and 86%, respectively (2). Carvalho et al (17) reported a 3-year OS rate of 18% for patients who underwent surgery and 7% for radiation therapy alone, which suggested that large-volume lymph node metastasis was unlikely to be cured by radiation therapy or by CRT alone. Ballonoff et al (18) evaluated 32 patients with locally advanced head and neck squamous cell carcinoma and N3 neck disease treated with concurrent CRT. Three-year OS and LRC rates were 42% and 57%, respectively. Igidbashian et al (19) divided their patients into two groups: a clinical CR (cCR) group that achieved cCR after concomitant CRT and a clinical PR-ND (cPR-ND) group that underwent neck dissection after achieving cCR at the primary site and clinical PR in the neck. Their 2-year OS rates for the cCR and cPR-ND groups were 63% and 80%, respectively. Patients with N3 disease who achieved regional PR and primary clinical CR who underwent neck dissection seemed to have better outcomes than patients who achieved global CR without neck dissection. Planned neck dissection regardless of response for advanced head-and-neck squamous cell carcinoma, especially in patients with N3 disease, is recommended (19). The LRC rate in the present study was higher than in those of other reports, suggesting that CRT using superselective infusion combined with HT results in high clinical and pathological responses in both primary and neck lesions.

Outcomes for patients with nodal metastases of >6 cm (N3) treated with definitive CRT are poorly defined. This is because patients with N3 disease are generally considered unresectable due to adhesions between metastatic nodes and surrounding tissue, and patients with N3 disease treated with CRT experience a very high rate of distant failure (16-18). Merino et al (20) analyzed the incidence of distant metastases in patients with squamous cell carcinoma of the upper respiratory and digestive tracts. The incidence of distant metastases with N3 disease was 27.1%. The high rate of distant metastases indicates that patients with N3 neck disease are at an even higher risk of having clinically occult micrometastatic disease on presentation. These patients may benefit most from additional systemic therapy. Future studies investigating the role of additional systemic therapy in these patients are warranted.

### Conclusions

In conclusion, the present study has demonstrated that thermochemoradiation therapy using intra-arterial infusion provided good histopathologic effects and LRC rates for patients with advanced oral cancer with N3 cervical lymph node metastases. However, patients with N3 metastatic lymph nodes had a high rate of distant failure. Adjuvant chemotherapy after definitive treatment is recommended to reduce the risk of distant metastases for all patients with N3 disease.

### References