Retrospective study of treatment outcomes after postoperative chemoradiotherapy in Japanese oral squamous cell carcinoma patients with risk factors of recurrence

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Background. The purpose of this study was to investigate the feasibility of postoperative concomitant chemoradiotherapy (CRT) with cisplatin (CDDP), and compare the prognosis in 3 groups—without postoperative therapy (S-only), with radiotherapy (RT) alone (S+RT), and with CRT (S+CRT)—in oral squamous cell carcinoma (OSCC) patients at high risk of recurrence.

Methods. Clinicopathologic data and treatment modality were investigated. Endpoints evaluated were locoregional control (LRC), relapse-free survival, overall survival (OS), and type of recurrence.

Results. The S+CRT group was associated with a better LRC rate than the S-only ($P < .001$) and S+RT groups ($P = .044$). However, there was no significant difference in OS rates between the S+RT and S+CRT groups.

Conclusion. The addition of concomitant CDDP to postoperative RT improved LRC. However, there may be no benefit from the addition of concomitant CDDP to postoperative RT for improvement of distant metastasis and OS rates in OSCC patients.
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Treatment of oral squamous cell carcinoma (OSCC) with surgery and/or adjuvant chemoradiation has improved the locoregional control rate of this disease.[1,2] However, the control rate of distant metastasis and overall survival (OS) rates remain low.[3,4] Initial surgical treatment for resectable advanced OSCC is the most common approach.[5-7] Postoperative radiotherapy (RT) was also widely used to treat patients with a high risk of recurrence.

Recently, 2 randomized trials conducted by the European Organization for Research and Treatment of Cancer (EORTG) and the Radiation Therapy Oncology Group (RTOG), demonstrated the utility of concomitant chemoradiotherapy (CCRT) in postoperative head and neck squamous cell carcinoma (HNSCC) patients with a high risk of recurrence and metastasis.[3,4] In these 2 trials (EORTG 22931 and RTOG 9501), postoperative CCRT with high doses of thrice-weekly cisplatin was compared with postoperative RT alone in HNSCC patients with a high risk of recurrence.[3,4] The definitions of high-risk factors of recurrence were different between the 2 trials. Therefore, the 2 trials carried out a collaborative comparative analysis. The results demonstrated that microscopically involved section margins (incomplete resection [ICR]) and extracapsular extension (ECE) of neck nodes were the most significant prognostic factors of poor outcome.[8] They also indicated that the addition of concomitant cisplatin (CDDP) to postoperative RT improved outcome (locoregional control, LRC), disease-free survival (DFS), and OS in HNSCC patients with one or both of these 2 prognostic factors.

Therefore, CCRT with high-dose CDDP has recently been recognized as the standard treatment for resectable advanced HNSCCs in patients with a high risk of recurrence. However, only about a quarter of all HNSCC patients in the 2 trials were OSCC patients. Also, according to the long-term follow-up of the RTOG 9501 trial, there were no long-term benefits from the addition of concomitant CDDP to postoperative RT in OS of 10 years.[9] Therefore, it is not clear whether the results of these studies can translate to the OSCC population. In this study, the feasibility of postoperative CCRT with high doses of thrice-weekly CDDP was investigated, and the prognoses in 3 groups (without postoperative therapy, with postoperative RT alone, and with postoperative chemoradiotherapy [CRT]) were retrospectively compared in Japanese OSCC patients at high risk of recurrence.

MATERIALS AND METHODS

This was a nonrandomized multicenter retrospective cohort study. The Institutional Review Board of Kobe

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University Graduate School of Medicine approved this study. This validation study included pooled individual patient data from 3 institutions. Between January 2002 and January 2013, 152 cases were investigated at the following institutions: Department of Oral and Maxillofacial Surgery, Kobe University Graduate School of Medicine; Department of Oral and Maxillofacial Surgery, Division of Surgery, Tokai University School of Medicine; and Department of Clinical Oral Oncology, Nagasaki University Graduate School of Biomedical Sciences. A total of 99 male and 53 female patients who were at pathologically high risk of recurrence (ICR and/or ECE) were investigated. Mean patient age was 65.3 ± 13.2 years (range 33-92 years). Among the 152 patients at initial visit, there were 7 patients (4.6%) with stage I disease, 23 (15.1%) with stage II disease, 23 (15.1%) with stage III disease, and 99 (66.2%) with stage IV A/B disease. Among patients who were at pathologically high risk of recurrence (ICR and/or ECE), 57 (37.5%) were treated without postoperative therapy (the surgery-only [S-only] group), 41 (27.0%) with postoperative RT alone (the S+RT group), and 54 (35.5%) with postoperative CRT (the S+CRT group) (Table I).

Postoperative therapy was performed after initial therapy during primary tumor resection and neck dissection (n = 110; 72.4%) or secondary neck dissection with/without local recurrence (n = 42; 27.6%). Postoperative RT alone was performed using a total of 50-70 Gy. Concomitant RT was administered at 2 Gy/d for 5 d/wk. A large volume encompassing the primary site and area of lymph nodes at risk received up to 60 Gy in 30 fractions. Regions at high risk for malignant dissemination or ICR margins received a 6 Gy boost. Chemotherapy consisted of 100 mg cisplatin per square meter of body surface area given on days 1, 22, and 43 during a course of RT. The entry criteria and treatment methods were according to previous reports.[10,11] Major exclusion criteria were older age, past history of renal failure and hepatitis, and poor performance status (PS). Patients were evaluated every month and examined using computed tomography and ultrasonography every 3 months for the first 12 months to check their postoperative status. Clinicopathologic data, including sex, age, subsite, clinical T classification, clinical N classification, clinical stage, treatment modality (S only, S+RT, or S+CRT), pathologic nodal status (presence and number of lymph node metastasis), histologic grade (high, moderate, or low), surgical margin, and ECE were investigated. In the S+CRT group, toxicities were graded using the Common Terminology Criteria for Adverse Effects (NCI-CTCAE version 4.0). Adverse events were classified as acute (occurring within 90 days of initiation of CRT) and late (continuing or occurring after 90 days) (Tables II and III). Endpoints evaluated were LRC, relapse-free survival (RFS) rate, OS rate, and type of recurrence.

Statistical analysis

Data collection and statistical analyses were carried out with SPSS 15.0 (SPSS, Chicago, IL, USA) and StatView J-4.5 software (Abacus Concepts, Berkeley, CA, USA). The association of each variable was tested by using the Mann-Whitney U nonparametric test for ordinal variables and Fishers exact test or Chi-squared test for categorical variables. Cumulative LRC, DFS, and OS were calculated using the Kaplan-Meier product-limit method. The significant levels among the curves were determined using the log-rank test. A value of $P < .05$ was considered statistically significant.

RESULTS

Clinical and pathologic patient characteristics and treatment modalities are summarized in Table I. There were more men than women. The most common tumor subsite was oral tongue, followed by gingiva. The presence of ECE, ICR, and multiple lymph node metastases (MLM) was 116 (76.3%), 56 (36.8%), and 102 (67.1%), respectively. The PS of the S-only group was higher than that of the other groups. The most common histologic differentiation was well differentiated (n = 78, 51.3%). The cumulative radiation dose in the S+RT group was less than that in the S+CRT group.

In the S+CRT group, 53 patients (98.1%) completed radiation therapy of more than 60 Gy. A total of 21 patients (38.9%) received 3 cycles of cisplatin at a dose of 300 mg/m^2. There were 45 patients (83.3%) in the S+RT group and 36 (66.7%) in the S+CRT group who were administered a cumulative cisplatin dose of more than 200 and 240 mg/m^2, respectively. A summary of acute adverse events is listed in Table II. The most common grade 3/4 acute adverse event was leucopenia (46.3%), followed by neutropenia (27.8%), anorexia (22.2%), and anemia (20.4%). A summary of the late adverse events is listed in Table III. The most common grade 3/4 late adverse event was anemia (5.6%), followed by leucopenia (1.9%) and neutropenia (1.9%). Osteonecrosis of the jaw occurred as a grade 1 or 2 late adverse event in 4 patients.

A total of 12 (21.1%), 19 (46.2%), and 28 (51.9%) patients survived in the S-only, S+RT, and S+CRT groups, respectively. A total of 27 (47.4%), 13 (31.7%), and 8 (14.8%) patients died of locoregional failure in the S-only, S+RT, and S+CRT groups, respectively. A total of 5 (8.8%), 4 (9.8%), and 12 (22.2%) patients died of distant metastasis in the S-only, S+RT, and S+CRT groups, respectively (Table I). The major failure pattern in the S+CRT group was death from