Influence of pathologic complete response to neoadjuvant chemotherapy on long-term survival of patients with advanced head and neck squamous cell carcinoma

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Objective. The aim of this study was to analyze whether pathologic complete response (PCR) to neoadjuvant chemotherapy (NAC) affected long-term survival in advanced head and neck squamous cell carcinoma (HNSCC) patients.
Materials. All patients with advanced HNSCC were previously untreated and underwent NAC followed by surgery. The 5-year overall survival, disease-free survival, local control rate, and reasons for treatment failure were analyzed.
Results. A total of 101 cases were included, and the response rate to NAC was 67.3%, including 17 patients (16.8%) who achieved PCR. The 5-year overall survival (OS) of the PCR group (82.4%; histologically complete response group [HCG]) was higher than that of the pathologic incomplete responder group (45.4%; histologically incomplete response group [HICG]) ($P = 0.045$). No statistically significant difference was noted between the two groups in terms of local recurrence and nodal recurrence, but the local control rate in HCG (88.2%) was higher than that in HICG (62.7%) ($P = 0.034$).
Conclusions. Achieving PCR could improve locoregional control and long-term survival in patients with advanced HNSCC.
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Neoadjuvant chemotherapy (NAC) refers to the application of systemic chemotherapy before a malignant tumor is treated with local surgery or radiation therapy. After the platinum-based regimens were identified as a common and effective treatment modality,[1] cisplatin-(or diamminedichloroplatinum)-based NAC was widely used in the treatment of advanced head and neck squamous cell carcinoma (HNSCC). Studies by the Department of Veteran Affairs Laryngeal Study Group[2] and the European Organization[3] for Research and Treatment of Cancer demonstrated that NAC with cisplatin and 5-fluorouracil (PF) followed by radiation therapy in responders with advanced laryngeal and hypopharyngeal cancer, respectively, resulted in two thirds of the patients retaining their larynx without a survival disadvantage compared with nonresponders who received surgery and postoperative radiation therapy. In the randomized phase III trial reported by Zorat et al.[4] and another randomized study by Licitra et al.,[5] there was no significant difference in overall survival (OS) rates between a NAC with PF regimen before locoregional therapy and locoregional therapy alone. However, a meta-analysis suggested a 5% survival rate increase for trials specifically using NAC with the combination of cisplatin and 5-fluorouracil.[6,7]

The potential benefits of NAC in locally advanced HNSCC included reducing the tumor burden to improve the outcome of local therapy, selecting patients for radiation therapy depending on response, and eradicating subclinical metastatic disease.[8] Reports from institutions described clinical response rates ranging from 54% to 80.8%, whereas complete clinical responses ranged from 6.6% to 24% in patients treated with a cisplatin-based regimen.[7,9-11] Patients with clinical responses to chemotherapy almost invariably had a better prognosis than those who did not respond.[9,11] However, in the absence of high-quality evidence from randomized clinical trials directly comparing pathologic complete responders (PCR) with pathologic in-

Statement of Clinical Relevance

The aim of this study was to analyze whether the absence of tumor cells in the specimen affected survival in patients with advanced head and neck squamous cell carcinoma and to derive value for future work.

Competing interests.
The authors state no competing interest.
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complete responders, the influence of PCR to NAC on long-term survival was unclear. This study evaluates those patients who had a clinical response after NAC followed by surgery and analyzes whether PCR in the target specimen affected long-term survival in patients with advanced HNSCC.

MATERIAL AND METHODS

Our retrospective study and chart reviews were exempt or not applicable in accordance with the institutional review board standards of individual institutions. In this study, we read the Helsinki Declaration and followed the guidelines in this investigation.

PATIENTS

The patient eligibility criteria in this study were as follows: previously untreated, histologically confirmed HNSCC, in resectable stage ($T_{1-4a}N_{0-3}M_0$; International Union against Cancer, 2002), and each patient received an initial three cycles of NAC with surgery following at the Cancer Center, Sun Yat-Sen University, between June 1996 and December 2005.

Pretreatment evaluation included a complete history, physical examination, performance status, serum chemistry profile, complete blood cell count, chest radiography, bilateral cervical and supraclavicular ultrasonography, abdominal ultrasonography, and computed tomography magnetic resonance imaging. Patients' characteristics including age, sex, primary site, clinical stage, initial clinical response to chemotherapy, subsequent local modalities, date of disease progression, and final status on the last follow-up examination were recorded.

TREATMENT

All patients were evaluated by surgeons, radiation oncologists, and medical oncologists before receiving an initial three cycles of NAC, and the responses to treatment were evaluated by appropriate radiological studies. Patients' clinical responses were categorized in accordance with Response Evaluation Criteria in Solid Tumors.[12] Pathologic responses to NAC were evaluated on the basis of the final surgical pathology review. Toxic effects associated with NAC were categorized and graded according to the Common Toxicity Criteria scale (version 2.0).[13]

Responsive patients exhibiting either clinical complete or partial remission received local treatment (i.e., surgery). Sometimes, despite a clinical complete response, surgery was chosen for tumors infiltrating into bone or cartilage. Surgery was performed 3 weeks after the end of NAC and the recovery of the white blood cell count. Moreover, the extent of eventual surgical resection was not altered by subsequent response to NAC. Regular follow-up, postsurgical examinations were usually followed by postoperative radiotherapy with doses depending on surgical specimen histopathologic examination (e.g., positive margins, number of positive neck nodes, or extracapsular spread).

STATISTICAL ANALYSES

The survival time was calculated from the month of hospitalization until the date of death or the date of last contact, and survival rate was represented as the percentage of survivals at the end of the observed interval (in months). Locoregional control was calculated from the time of initiation of NAC until locoregional progression. We used Kaplan–Meier curves and log-rank tests for survival analysis. Each factor was studied according to the univariate analysis. Comparisons were also performed using a log-rank test. Statistical significance was assumed when the P value was less than 0.05. We conducted these analyses using SPSS (version 16.0).

RESULTS

Patient's characteristics and chemotherapy regimen

A total of 101 patients received NAC followed by surgery. The response rate to preoperative chemotherapy was 67.3% (68 of 101 patients), including 17 patients (16.8%) who achieved a PCR. These patients' characteristics are summarized in Table I and the TN stage is shown in Table II. All patients were treated with PF. The NAC with PF regimen included intravenous cisplatin, 20 mg/m^2 per day on days 1 to 5, and 5-fluorouracil, 1000 mg/m^2 per day, in continuous intravenous infusion on days 1 to 5, every 21 days during three cycles.

Response to chemotherapy

Among the 68 responsive patients, 17 patients had no histologic evidence of residual disease in the surgically resected specimen. These 17 patients (25.0%) with PCR were assigned to the histologically complete response group (HCG), and the remaining 51 patients (75.0%) were assigned to the histologically incomplete response group (HICG).

For the 17 patients in the HCG, the oncological panel considered that there was a partial response after NAC in 6 patients, whereas in the remaining 11 patients, surgery was chosen despite obtaining a complete clinical response. Nine of these 11 patients had tumors demonstrating osseous or cartilaginous invasion, whereas 2 other patients had tumors demonstrating invasion of the surrounding tissue. In all cases, the pathologists made an exhaustive examination of the primary tumor region and the local regional lymph nodes affected by the