Clinical outcomes of radiation-based locoregional therapy in locally advanced head and neck squamous cell carcinoma patients not responding to induction chemotherapy

Yoojoo Lim, MD,[a] Bhumsuk Keam, MD,[a,b] Youngil Koh, MD,[a] Tae Min Kim, MD, PhD,[a,b] Se-Hoon Lee, MD, PhD,[a,b] J. Hun Hah, MD, PhD,[b,c] Tack-Kyun Kwon, MD, PhD,[c] Dong-Wan Kim, MD, PhD,[a,b] Hong-Gyun Wu, MD, PhD,[d] Myung-Whun Sung, MD, PhD,[b,c] Dae Seog Heo, MD, PhD,[a,b] and Kwang Hyun Kim, MD, PhD[c]

Seoul National University Hospital; and Seoul National University College of Medicine

Objective. The purpose of this study was to evaluate the efficacy of radiation-based locoregional therapy for locally advanced head and neck squamous cell carcinoma (LA-HNSCC) patients who did not respond to induction chemotherapy (IC).

Study Design. Outcomes after radiation-based locoregional therapy were retrospectively analyzed.

Results. Among a total of 208 patients treated with IC, 46 (22.1%) did not respond. After IC, patients were treated with radiotherapy (RT), concurrent chemoradiotherapy (CCRT), or surgery with or without postoperative RT. Among the 46 nonresponders, 17 (37.8%) patients underwent surgery and 28 (62.2%) were treated with RT or CCRT. Responses to subsequent RT or CCRT for 26 evaluable patients were as follows: complete response = 7 (26.9%), partial response = 9 (34.6%), stable disease = 4 (15.4%), and progressive disease = 6 (23.1%).

Conclusion. A significant proportion of LA-HNSCC patients who did not respond to IC can benefit from subsequent RT or CCRT. (Oral Surg Oral Med Oral Pathol Oral Radiol 2013;116:55-60)

Head and neck cancer is the sixth most common cancer worldwide and accounts for >55,000 of new cancer cases annually.[1] Although head and neck cancers are curable at early stage, treatment outcomes of patients with advanced disease remain unsatisfactory. Most patients with head and neck squamous cell carcinoma present with locally advanced disease. The treatment goal for patients with locally advanced head and neck squamous cell carcinoma (LA-HNSCC) is cure, and a multimodality treatment strategy is required, considering the potential for functional and esthetic consequences.

For treatment of LA-HNSCC, both locoregional and systemic controls are important and concurrent chemoradiotherapy (CCRT) is generally recommended.[2] Induction chemotherapy (IC) followed by definitive local therapy is one accepted approach used for LA-HNSCC, although the benefits of this approach still remain controversial.[3,4] Advantages of IC include the potential to reduce tumor bulk in responders allowing for a better chance of organ preservation and a decrease in the risk of distant failure. Additionally, response to IC appears to predict responsiveness to subsequent chemoradiotherapy, providing more information for choosing a tailored definitive treatment modality.[5,6] For those patients who do not respond to IC, the general consensus for subsequent therapy is surgical resection, and earlier studies evaluating IC in LA-HNSCC have been designed based on this approach.[7-10]

However, surgery is not always a feasible option as a subsequent therapy in these nonresponding patients as the tumor might be even less resectable than at the time of diagnosis or the patients' performance status (PS) may have worsened. Practically in some cases, chemoradiotherapy is the only option although not generally preferred. However, how these patients will actually

Statement of Clinical Relevance

The general recommendation for the LA-HNSCC patients who do not respond to IC has been surgical resection, as poor response to RT was expected. Our findings suggest that a significant proportion of these patients can benefit from subsequent radiation-based locoregional therapy.

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[a]Department of Internal Medicine, Seoul National University Hospital.

[b]Cancer Research Institute, Seoul National University College of Medicine.

[c]Department of Otorhinolaryngology, Seoul National University Hospital.

[d]Department of Radiation Oncology, Seoul National University Hospital.

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respond to subsequent chemoradiotherapy has not been clearly reported. The purpose of this study was to analyze the outcome of subsequent chemoradiotherapy in patients with LA-HNSCC who did not respond to IC and were not eligible for surgery as a subsequent therapy.

PATIENTS AND METHOD

Patient population

We retrospectively analyzed a consecutive database of LA-HNSCC patients who were treated with IC at Seoul National University Hospital between January 2005 and December 2011. Patient medical records were reviewed, and clinical parameters were analyzed. Eligibility criteria were (1) pathologically proven LA-HNSCC, (2) receipt of IC, (3) presence of an objectively measurable lesion, (4) age $\geq$18 years, and (5) no distant metastasis at the time of diagnosis, confirmed by whole-body scan with positron emission tomography (PET). Patients with initial stage of T2 were included if they had bulky N2 disease that led to the decision that these patients would benefit more with IC than initial definitive treatment with surgical resection or chemoradiotherapy. Patients who were previously diagnosed and treated for other cancers were included if they were cured and were without evidence of recurrence for >5 years.

IC regimens

Chemotherapeutic regimens used for IC were 5-fluorouracil (FU) 1200 mg/m^2 given on days 1-4 with cisplatin 60 mg/m^2 on day 1 (PF), docetaxel 70 mg/m^2 on day 1 with 5-FU 1200 mg/m^2 on days 1-3 and cisplatin 40 mg/m^2 on days 2 and 3 (TPF), or docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 on day 1 (TP) with or without cetuximab 400 mg/m^2 every week.[11] Patients were treated with 2 or 3 cycles of the above regimen.

Subsequent therapy after IC failure

After IC, patients were treated with radiotherapy (RT), CCRT, or surgery either alone or with postoperative RT. CCRT was given with cisplatin 100 mg/m^2 administered every 3 weeks or 30 mg/m^2 every week. The choice of treatment for both IC and subsequent therapy were made by the multidisciplinary team of Seoul National University Hospital, which is consisted of medical oncologists, head and neck surgeons, radiation oncologists, and radiologists, taking into consideration multiple factors including size and site of the tumor, possibility of curative resection, general PS of the patient, and the preference of each patient.

Tumor response evaluation

Staging and tumor evaluation were done at the time of diagnosis, after 2 cycles of IC, and after subsequent therapy (either after surgery or 6 weeks after completion of RT). Evaluation modalities included laryngoscopic examination and computed tomography (CT) or magnetic resonance imaging (MRI) of primary site and/or neck. Patients who showed clinical signs of progression were evaluated at the time of suspected progression, even if it was earlier than the scheduled evaluation. CT and/or PET scans were used in cases where it was necessary to rule out new distant metastasis that occurred after initial diagnosis. Responses were evaluated using the Response Evaluation Criteria In Solid Tumors (RECIST) criteria.[12] The longest diameters of the selected measurable lesions were measured and the sums were compared in accordance with the guidelines of the criteria. The RECIST criteria define response as complete response (CR) if all target lesions have disappeared; partial response (PR) if at least a 30% decrease in the sum of the diameters has occurred; progressive disease (PD) if at least a 20% increase has occurred; and stable disease (SD) if neither sufficient shrinkage nor increase has occurred to qualify for PR or PD. For this study, CR or PR by RECIST criteria was categorized as a response to IC; SD or PD as a lack of response or induction failure.

Outcome measurements

The primary end point of the study was the overall response rate (ORR) to subsequent chemoradiotherapy in patients who showed lack of response to IC. Secondary end points were progression-free survival (PFS) after chemoradiotherapy and overall survival (OS) of those patients. PFS was defined as the time from the date chemoradiotherapy was started to the date progression or relapse was documented. OS was measured from the date of diagnosis to the date of disease-specific death, censored at the date of data collection if alive, or date of last follow-up if follow-up was lost.

Statistical analysis

Survival outcomes were determined using the Kaplan–Meier method and compared with log-rank test. All statistical analyses were done with IBM SPSS 19.0 (IBM Corp., Armonk, NY). The study protocol was approved by the institutional review board (IRB) of Seoul National University Hospital (IRB approval number: H-1201-091-395) and was conducted in accordance with the Principles of the Declaration of Helsinki.

RESULTS

Patient characteristics

Between January 2005 and December 2011, 208 patients newly diagnosed with pathologically confirmed LA-HNSCC received IC. Of these patients, 46 (22.1%) did not respond to IC. One patient refused further