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Impact of combined modality treatment with radiotherapy and S-1 on T2N0 laryngeal cancer: Possible improvement in survival through the prevention of second primary cancer and distant metastasis

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ABSTRACT

Background: In patients with head and neck cancer, the management of second primary cancer (SPC) is particularly important for improving survival because of its high incidence and associated mortality. We evaluated the impact of combination chemotherapy on survival and SPC.
Method: We retrospectively analyzed data from 49 patients treated with definitive radiation therapy (RT) for T2N0M0 laryngeal squamous cell carcinoma between 2003 and 2011. Among them, 22 patients received combined modality treatment with radiotherapy and S-1 (RT + CT group).
Results: The median follow-up period was 71 months (32–111 months). A significant difference in overall survival (OS, $P < 0.01$) was observed between the RT + CT group (n = 22) and the RT alone group (n = 27) though no significant differences were observed in local control and disease specific survival. Univariate analyses showed that an older age ($P < 0.05$) and a higher grade ($P < 0.05$) were associated with OS. Multivariate analysis identified chemotherapy as the most significant predictor of survival (OR, 0.056; 95% CI, 0.008–0.353, $P < 0.01$). A significantly lower incidence of distant metastasis (DM) + SPC (5-year incidence: 5% vs. 19%, $P < 0.05$) and fewer deaths from these causes (1 vs. 8: $P < 0.05$) were observed in the RT + CT group. Multivariate analysis showed that chemotherapy was the most significant factor for the incidence of DM + SPC (OR, 0.074; 95% CI, 0.0065–0.84; $P < 0.05$).
Conclusion: The findings of this study suggest the possibility that combined modality treatment with radiotherapy and S-1 improve survival by preventing distant metastasis and second primary cancer.

Introduction

In patients with head and neck squamous cell carcinoma (HNSCC), locoregional control is important for improved survival outcomes. Even if locoregional control is achieved, however, many deaths occur from second primary cancer (SPC) or distant metastasis. Approximately one-third of HNSCC deaths are attributable to SPC, which is triple the number of deaths that arise from distant metastasis [1–3]. In addition, the majority of patients with HNSCC are smokers, and the risk of SPC is approximately two-fold higher in such patients [2,4,5]. Therefore, the management of SPC is thought to be important for improving survival outcomes.

The effectiveness of combination chemotherapy for advanced HNSCC has been reported in a meta-analysis of randomized controlled trials, but its effectiveness for early-stage HNSCC has not yet been confirmed [6]. Therefore, the standard treatment for early-stage HNSCC is surgery or radiation therapy (RT) alone. However, some retrospective studies have indicated that CRT improves the local control and larynx preservation rates in patients with early glottic cancer [7–10].

At our center, early laryngeal cancer is mainly treated using RT in the hope of achieving better functional preservation. In addition, we administer combination chemotherapy mainly to improve the local control (LC) rate in T2 patients with bulky tumors, which are thought to be risk factors for local recurrence [11–13]. In this retrospective single-center experience, we attempted to assess

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the effectiveness of combination chemotherapy with RT in terms of LC, OS, and SPC.

Materials and methods

Patients

Data from a total of 49 previously untreated patients with T2N0M0 laryngeal squamous cell carcinoma who underwent definitive radiotherapy at the Kanagawa Cancer Center between 2003 and 2011 were retrospectively analyzed. Patients who were unable to receive radical treatment because of complications or double cancers were excluded. In this study, the stage of the tumor was determined based on clinical findings and was classified according to the UICC sixth edition. The tumor status was determined routinely using computed tomography (CT), magnetic resonance imaging (MRI), and direct laryngoscopy performed under general anesthesia. In addition, an upper esophagogastroduodenoscopy thoracic-abdominal CT, and abdominal echo were routinely conducted to check for distant metastasis and double cancers before the start of treatment.

Treatments

In this study, each patient received 70 Gy in 35 fractions over 7 weeks or 66 Gy in 33 fractions over 6.5 weeks. In all patients, the radiotherapy was administered using ^{60}Co γ-rays or high-energy photons of 4MV X-rays from a linear accelerator. Parallel-opposed fields were used, irrespective of the radiation device that was employed. For planning radiotherapy, 2 dimensional conventional technique or 3-dimentional conformal technique was used. In 2-dimentional conventional technique, we use a 6 × 6-cm field with the superior border at the top of the hyoid bone, the inferior border at the lower edge of cricoid cartilage, a 1-cm skin flash anteriorly, and a 2-cm margin posteriorly (or the anterior edge of the vertebral body). For T2 larynx tumors, there are typically no CT abnormalities. So even in 3-dimentional technique, we set the field same as 2-dimentional technique.

Chemotherapy was administered to patients with T2 cancer, mainly those with bulky tumors which depicted as a mass in CT or MRI, who were under 80 years old and did not have renal dysfunction. In principle, either CRT or adjuvant chemotherapy was performed. However, for the patient who received CRT, if requested for continuation of chemotherapy, adjuvant chemotherapy was added. We used S-1 for CRT as well as for adjuvant chemotherapy. For CRT, 2 cycles of chemotherapy were given. Adjuvant chemotherapies were continued for until up to 1 year. S-1, a 5-fluorouracil (5-FU) prodrug, is an oral antitumor agent consisting of tegafur, 5-chloro-2, 4-dihydroxypyridine (CDHP), and potassium oxonate in a molar ratio of 1:0.4:1. Tegafur is a prodrug of 5-fluorouracil (5-FU), and CDHP and potassium oxonate prolong the half-life of 5-FU in the blood and reduce 5-FU toxicity, respectively. The chemotherapeutic regimen consisted of one cycle of S-1 given at a dose of 80–120 mg/day (80 mg/day for BSA(m2) < 1.3, 100 mg/day for $1.3 \leqq$ BSA < 1.6, and 120 mg/day for BSA $\geqq$ 1.6) for 2 weeks, followed by 1 week of rest.

Evaluation

The response during the period of radiotherapy was evaluated weekly using a fiberscope. After the completion of treatment, the patients were followed up monthly during the first year, bimonthly during the second year, and every 3–6 months thereafter. The detection of evidence of a tumor at or within 2 months of the completion of radiation therapy was defined as persistent disease; evidence of a tumor detected 2 months or longer after the completion of therapy was defined as a local recurrence. Local control was defined as the freedom from persistent or locally recurrent disease. Salvage treatment for persistent disease or local recurrence usually consisted of transoral laser microsurgery or a total laryngectomy. Adverse feature was evaluated based on CTCAE version 3.0.

Statistical analysis

The means of continuous variables (such as age) were compared between groups using *t* tests with unequal variances. Chi-square tests were used to assess intergroup differences in categorical variables (for example, sex and primary sites). The survival rates were estimated using the Kaplan-Meier product limit method. Comparisons between subgroups divided by patient-, tumor-, and treatment-related variables were performed using the log-rank test. Backward stepwise logistic models were applied for multivariate analysis with exclusion of covariates with univariate p values greater than 0.2.

Results

The median duration of the follow-up period was 71 months (32–111 months). The male-to-female ratio was 49:0, and the median age was 69 years (48–91 years). There were 44 glottic-type, 2 supraglottic-type, and 3 subglottic-type tumors. Of note, the majority of patients were smokers (96%) and drinkers (76%), and 10 patients (20%) had previous cancer history or double cancers at the start of therapy. Among these 10 patients, 5 patients had a history of previous cancer that had been radically cured and had survived for more than 5 years from the radical treatment. Six patients had double cancers, all of which had been treated radically at the same time or after the treatment for laryngeal cancer.

Of the 49 patients in total, 27 patients (55%) were treated with RT alone (RT alone group) and 22 patients (45%) were received combined modality treatment with radiotherapy and S-1 (RT + CT group). In the RT + CT group, 17 patients were treated with CRT, 3 patients were treated with RT + adjuvant chemotherapy, and remaining 2 patients were treated with CRT + adjuvant chemotherapy. Of the total 19 patients who received CRT, 16 patients received two cycles of S-1 and the remaining 3 patients received only one cycle of S-1 because of adverse events (2 patients had grade 2 diarrhea and the one had grade 3 mucositis). Of the total 5 patients who received adjuvant chemotherapy, the median treatment period was 3 months (1–12 months). The reasons of stop the continuation of adjuvant chemotherapy were the requests of the patients (3 patients) and the local recurrence (1 patient).

The acute toxicities more than grade 3 were seen in 3 patients only in RT + CT group, one showed both mucositis grade 3 and dermatitis grade3, one showed both mucositis grade 3 and diarrhea grade 3, and one developed mucositis grade 3. There was no acute toxicity more than grade 3 of stomatitis, dysphagia, laryngitis, myelosuppression and transaminits. The late toxicity more than grade 3 was not seen in both groups.

The patient characteristics of both groups are summarized in Table 1. No statistical differences in follow-up time, age, sex, subsite, grade, total radiation dose, previous cancer history or double cancers at the start of therapy were seen between the two groups.

The 5-year LC rates were 71% in the RT + CT group and 70% in the RT alone group, as shown in Fig. 1 ($P = 0.680$). However, in recurrent cases, there was a significant difference in the average period until recurrence between the RT + CT group and RT alone at 19.2 months (9–37 months) and 6.1 months (2–12 months), respectively ($P < 0.05$). The 5-year disease specific survival (DSS)