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Transoral robotic surgery-based therapy in patients with stage III-IV oropharyngeal squamous cell carcinoma

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ABSTRACT

Objective: TORS-based therapy including chemotherapy or RTx was administered to patients with stage III-IV OPSCC. We analyzed the oncological and functional outcomes of stage III-IV OPSCC patients who underwent TORS-based therapy.

Materials and methods: Between May 2008 and May 2016, 80 patients participated in this clinical trial.

Results: A negative margin was identified in 66 patients (82.5%) and a positive margin in 14 (17.5%). TNM stages were III in 13 patients (16.3%) and IV in 67 patients (83.8%). Of the patients, 13 received surgery alone, 28 had adjuvant RTx and 39 had adjuvant CCRTx. At last follow-up, 67 patients had no evidence of disease, seven were alive with disease, and six had died. Local recurrence developed in 2 patients and regional recurrence in 10. Five-year overall survival was 88.8%, disease-specific survival was 89.9%, and recurrence-free survival was 78.3%. The 5-year disease-specific survival of OPSCC patients with p16+ disease was 93.2%, which was higher than 89.0% of patients with p16− disease, but the difference was not statically significant. On multivariate analysis, only extranodal extension showed a significant relationship with recurrence-free survival on Cox regression analysis.

Conclusion: TORS-based therapy showed excellent oncological and functional outcomes for treatment of stage III-IV OPSCC. For advanced T stage OPSCC, clear margins were obtained using TORS-based therapy and patients with clear margins showed good local control. Risk stratification of patients based on pathological information obtained after surgery and decision about additional treatment based on the information helped improve OS and DSS of OPSCC patients.

Introduction

The main treatment modalities for stage III-IV oropharyngeal squamous cell carcinoma (OPSCC) are surgery, radiotherapy (RTx), chemotherapy, or combined therapies. Conventional surgical approaches such as mandibulotomy or composite resection show high morbidity rates associated with treatment and postoperatively induce deterioration of the voice and swallowing function [1,2]. Therefore, concurrent chemoradiotherapy (CCRTx) is mainly used in patients with advanced OPSCC as an organ-preserving strategy. Although CCRTx has comparable oncological results to conventional surgical treatments, it increases toxicities from the combination of chemotherapy and RTx and causes chronic mucosal damage and tissue fibrosis, resulting in loss of function. Several studies report 9–38% gastrostomy dependence after CCRTx [3–5].

Smoking and drinking have been the main causes of OPSCC, but in recent years, OPSCC associated with human papillomavirus (HPV) has been increasing. HPV-associated OPSCC has a favorable response to all treatment modalities and the average age of patients is low [6]. Therefore, in these patients, reducing morbidity from treatment is important for improving quality of life after treatment [7,8]. Transoral robotic surgery (TORS) has the advantages of an operation performed through the oral cavity with a low accompanying morbidity rate and quick patient recovery after operation. We have used TORS for treatment of OPSCC since 2008 and have reported the usefulness of the procedure and initial oncological results [9,10]. With additional

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experience with TORS, we broadened the indications to treatment for OPSCC. TORS-based therapy combined with chemotherapy or RTx was administered to patients with stage III-IV OPSCC. In this study, we analyzed the oncological and functional outcomes of patients with stage III-IV OPSCC who underwent TORS-based therapy.

Materials and methods

Patients

Of stage III-IV OPSCC patients who visited the Yonsei Head and Neck Cancer Center between May 2008 and May 2016, 80 received TORS-based therapy for treatment of their disease. This study was approved by the Institutional Review Board of Yonsei University and all patients provided written informed consent. Prior to treatment, patients were well informed about the advantages and disadvantages of treatment methods including definitive CCRTx, conventional surgery with adjuvant RT or CRT, and TORS-based therapy. Inclusion criteria were: (1) stage III-IV OPSCC diagnosed histologically as squamous cell carcinoma; and (2) no previous surgery, chemotherapy, or radiation therapy. Patients were excluded for: (1) a lesion that could not be surgically resected via TORS, (2) unresectable nodal disease, (3) distant metastasis. All patients underwent p16 immunochemical detection for HPV status. TNM stage was classified based on the 7th edition of the American Joint Committee on Cancer guidelines (AJCC).

Procedure for primary lesions

TORS was performed as follows. First, an incision was made on the buccal mucosa and the pterygomandibular raphe where the buccinator muscle and superior constrictor muscle meet was resected (Fig. 1). Dissection was performed on the submuscular plane of the superior constrictor, anterior tonsillar pillar and posterior tonsillar pillar. During resection, the medial pterygoid muscle was identified and parapharyngeal fat pad was confirmed. After resection of the soft palate area, the posterior pharyngeal wall was excised while confirming the prevertebral fascia. For tongue base cancer, a margin of 1 cm was created around the tumor and a resection margin was designed. No additional reconstruction was performed on defect sites after resection of primary lesions.

Neoadjuvant chemotherapy was performed preoperatively in patients with T3-4 tumor or bulky nodal disease. It was used to decrease the tumor volume, lower clinical stage, increase lesional resectability, and in turns broaden the indications for TORS. Chemotherapy regimen consisted of cisplatin (70 mg/m^2) by intravenous infusion on day 1, TS-1 (combination of gimeracil 5.8 mg/m^2, oteracil 19.6 mg/m^2, tegafur 20 mg every 21 days). If myelosuppression appeared, chemotherapy was delayed for one week until leukocyte and platelet counts recovered. After two cycles of neoadjuvant chemotherapy, response was evaluated by imaging studies and endoscopy based on Response Evaluation Criteria in Solid Tumors. The largest diameter of tumor and neck masses was measured to verify response.

A representative treatment example was shown in Fig. 2. The case was diagnosed as T3N1M0 tonsillar cancer. A tumor of 4 cm in size was observed in the tonsil fossa and a single metastatic node was observed in the right neck level II. After 3 cycles of neoadjuvant chemotherapy, tumor size was significantly decreased and transoral robotic lateral oropharyngectomy was performed based on the initial extent of the disease including residual tumor. The pathologic specimen was analyzed and negative margin was confirmed. Other adverse pathologic features were not observed. Therefore, adjuvant treatment was not performed.

Adjuvant therapy

Adjuvant therapy was started 4–6 weeks after operation. Adjuvant RTx was given to patients with perineural invasion, lymphovascular invasion, or multiple metastatic lymph nodes. Adjuvant CCRTx was given to patients with positive margin or extranodal extension.

Statistical analysis

Data were collected and analyzed for patient personal information, tumor location and stage, operation record, admission notes, feeding tube dependence, and survival. Overall survival (OS), recurrence-free survival (RFS) and disease-specific survival (DSS) were analyzed using the Kaplan-Meier method. Cox regression analysis was performed for multivariate analysis. The functional outcome swallowing scale (FOSS) was measured to evaluate swallowing function at 12 months after the completion of treatment. FOSS evaluates the swallowing function in six stages with a score system designed by Salassa et al. [11]. Stages 0–2 indicate normal function or compensated abnormal function. Stages

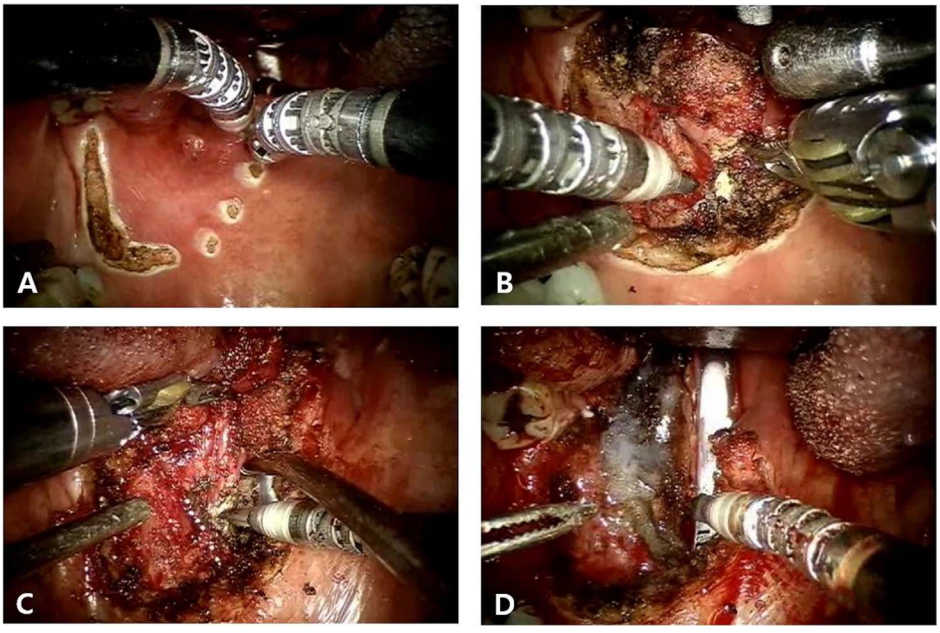

Fig. 1. Transoral robotic lateral oropharyngectomy. First, an incision was made on the buccal mucosa and the pterygomandibular raphe where the buccinator muscle and superior constrictor muscle meet, was resected (A). Dissection was performed on the submuscular plane of the superior constrictor, anterior tonsillar pillar and posterior tonsillar pillar. During resection, the medial pterygoid muscle was identified and parapharyngeal fat pad was confirmed (B). After resection of the soft palate area, the posterior pharyngeal wall was excised while confirming the prevertebral fascia. Then, the tongue base area was dissected (C). No additional reconstruction was performed on defect sites after resection of primary lesions (D).