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Sentinel node biopsy for oral cancer: A prospective multicenter Phase II trial[☆]

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ABSTRACT

Objective: A recent study identified a survival benefit with prophylactic neck dissection (ND) at the time of primary surgery as compared with watchful waiting followed by therapeutic neck dissection for nodal relapse, in patients with cN0 oral squamous cell carcinoma (OSCC). Alternative management of cN0 neck cancer is recommended to minimize the adverse effects of ND, indicating the need for sentinel node biopsy (SNB) and limited neck dissection.

We conducted a multicenter Phase II study to examine the feasibility of SNB for clinically N0 OSCC.

Methods: Previously untreated N0 OSCC patients ($n = 57$) with clinical late-T2 or T3 tumors were enrolled across 10 institutions. SNB navigated with multislice frozen section analysis of sentinel nodes (SNs) and SNB supported sentinel node lymphatic basin dissection (SN basin dissection) were performed in a one-stage procedure. The endpoint was to investigate the rate of false-negative metastases after SN basin dissection and SNB alone.

Results: Most tumors were late-T2 lesions ($n = 50$; 87.7%). SNs were identified in all patients. A total of 196 SNs were detected. Among these SNs, 35 (17.8%) were positive for metastasis (9 in level I, 12 in level II, 12 in level III, 1 in level V and 2 in the contralateral region of the neck). The

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false-negative rate of SNB supported by SN basin dissection and SNB alone was 4.5% and 9.1%, respectively. The concordance of the SN status in intraoperative frozen sections with the permanent histopathology was 97.4% (191/196). The sensitivity and specificity of intraoperative pathological evaluation were 85.7% (30/35) and 100% (30/30), respectively. The 3-year overall survival (OS) and disease-free survival was 89.5% and 82.5%, respectively. The OS of SN-negative patients was significantly longer than that of SN-positive patients ($P = 0.047$).

Conclusion: The current study verified that SN basin dissection was a useful back-up procedure for SNB performed as a one-stage procedure, showing a low false-negative rate. SNB alone is an appropriate staging method for patients with clinical N0 staging, and a reliable procedure to determine the appropriate levels for neck dissection.

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1. Introduction

Currently, prophylactic neck dissection (ND) is the standard treatment for clinically node-negative (cN0) early-stage oral squamous cell carcinoma (OSCC) [1–5], because the rate of occult neck metastasis can be as high as 30% [1]. A recent study also identified a survival benefit with prophylactic ND at the time of primary surgery as compared with watchful waiting followed by therapeutic neck dissection for nodal relapse, in patients with cN0 early-stage OSCC [6]. However, complications, such as paralysis of the mandibular branch of the facial nerve, shoulder disability, and morbidity, are frequent. Therefore, alternative management of cN0 neck cancer is recommended to minimize the adverse effects of ND, indicating the need for sentinel node biopsy (SNB) and limited neck dissection, which was also reported in a recent study [6].

SNB has been suggested to be an efficient nodal staging method for detecting occult neck metastasis [7–11] without increasing morbidity [12,13]. It may also be associated with a survival benefit for patients with OSCC [14,15]. It is therefore a potentially valuable diagnostic approach for head and neck cancer treatment [9,16–20], but several problems need to be addressed regarding its applicability. First, the detection procedure and pathological analysis vary among facilities [20,21]. Second, SNB requires a two-stage procedure for node-positive patients, which could increase the rate of complications and the physical and psychological burdens on the patient compared with a one-stage procedure. Third, the sensitivity of conventional frozen analysis is insufficient to detect small metastases after SNB [22]. Fourth, the frozen section analysis has the possibility to occur as the false negative especially at the facilities with short learning curve. Therefore, a novel strategy in multicenter study is required to overcome these problems.

The lymphatic drainage pattern of OSCC is well known owing to the results of several large-scale studies [23,24]. They showed that occult metastases were usually located in the lymphatic basin region where sentinel nodes (SNs) are present. Regarding OSCC, the lymphatic basin region usually includes levels I, II, or III where occult nodal metastases, as well as SNs, are often observed. Because metastatic lymph nodes missed by SNB are most likely to be present in the same lymphatic basin, SN basin dissection which refers to the dissection of the level where SNs are observed, could help improve the sensitivity of SNB in detecting occult metastasis and reduce the false-negative rate.

In the current study, we performed the prophylactic ND supported with SNB in a one-stage procedure as a personalized surgery for the patient with late-T2 and T3 tumors, followed by sentinel node basin dissection (SN basin dissection) as a reasonable safety net.

Here, we report the results of a Phase II study evaluating the feasibility and usefulness of one-stage SN-navigated ND for OSCC patients.

2. Materials and methods

2.1. Definitions

The American Joint Committee on Cancer neck dissection classification system was used to classify lymph nodes in the neck [25]. According to this system, the SN lymphatic basin was defined as the neck level where the SNs were present. SN basin dissection was defined as the dissection of the SN lymphatic basin, as determined during surgery. For example, if the SN was observed at contralateral level I, SN basin dissection comprised contralateral level I dissection. A false-negative SN basin dissection was defined in such cases as if lymph node metastasis was observed outside of the dissected SN lymphatic basin during the follow-up period.

2.2. Patients

This was a prospective, multicenter, Phase II clinical trial conducted in Japan. Between October 2009 and December 2011, 57 patients from 10 medical facilities were enrolled. The number of patients per institution ranged from 2 to 29, with a median number of 5. Patients were included if they had been diagnosed with cN0 stage, had pathologically confirmed OSCC, and had a clinical tumor stage of “late-T2” (T2 tumor with a diameter ≥ 3 cm or any T2 tumor with a tumor depth of ≥ 5 mm) or T3. Clinical stage was determined by a physical examination and radiological computed tomography (CT). Tumor depth was defined as the distance from the surrounding normal tissue to the bottom of the tumor, and was estimated using CT or magnetic resonance imaging (MRI) in addition to palpation. Clinical positivity was also determined by physical examination, and CT findings according to the following criteria: a diameter of >15 mm for level I and II lymph nodes; a diameter of >10 mm for level III, IV, and V lymph nodes; a retropharyngeal node diameter of >8 mm; central necrosis; a

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