The necessity of IIb dissection in T1–T2N0M0 oral squamous cell carcinoma: protocol for a randomized controlled trial

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Abstract

Background: There is growing discussion of the relationship between health-related quality of life (HRQoL) and patient survival, which has been going on for the last few decades. Clinicians’ greatest wish is to extend the latter while improving the former. After neck dissection of early-stage oral carcinoma, “shoulder syndrome” appears due to traction of the accessory nerve during removal of level IIb, which greatly affects patient quality of life. Since occult metastasis in level IIb of early-stage oral carcinoma is extremely low, some surgeons suggest that level IIb can be exempt from dissection to improve HRQoL. However, other surgeons take the opposite view, and thus there is no consensus on the necessity of IIb dissection in T1–2N0M0 oral squamous-cell carcinoma (OSCC).

Methods: We designed a parallel-group, randomized, non-inferiority trial that is supported by Shanghai Ninth People’s Hospital, Shanghai Jiao Tong University, School of Medicine, Shanghai, China. We will enroll 522 patients of early oral carcinoma who match the inclusion criteria, and compare differences in 3-year overall survival, progression-free survival (PFS) and in HRQoL under different interventions (retention or dissection of level IIb) between two groups. The primary end points will be tested by means of two-sided log-rank tests. Analysis of overall and progression-free survival will be performed in subgroups that were defined according to stratification factors with the use of univariate Cox analysis. In addition, we will use post hoc subgroup analyses on the basis of histological factors that were known to have effects on survival, such as death of invasion of the primary tumor. To evaluate HRQoL, we will choose the Constant–Murley scale to measure shoulder function.

Discussion: Currently, there are no RCTs with large sample sizes on the necessity of IIb dissection in T1–T2N0M0 OSCC. We designed this reasonable non-inferiority RCT that combines survival rate and HRQoL to assess the feasibility of IIb neck dissection. The result of this trial may guide clinical practice and change the criteria...
of how early-stage oral cancer is managed. The balance between survival and HRQoL in this trial is based on early-stage breast cancer treatment and may provide new ideas for other malignancies.

**Background**

Surgical treatment of early-stage oral squamous cell carcinoma (OSCC) has presented a dilemma for decades. In 2015, Anil K·D’Cruz published a randomized trial on the relationship between overall survival (OS) and the quality of life in patients who underwent two types of surgery in early-stage OSCC. The study demonstrated that the 3-year OS was greatly improved when patients underwent neck dissection and primary resection at the same time, compared with those who underwent primary resection but not neck dissection.\(^1\) However, if we desperately pursue a higher survival rate, most patients will be regarded as "overtreated". At present, the technique of detecting occult metastatic lymph nodes in the neck is still immature; we can detect susceptible nodes only by physical examination, B-ultrasonography, and enhanced computed tomography (CT)/magnetic resonance imaging (MRI), but diagnoses obtained by these methods are far from precise.\(^2,3\) Studies have shown that the rate of occult metastasis in early-stage of oral cancer is about 30%,\(^1,4,5\) meaning that nearly 70% of patients with negative nodes underwent neck dissection during our routine treatment.

At present, we aim to extend survival and at the same time improve health-related quality of life (HRQoL).\(^6,7\) After neck dissection, shoulder weaknesses such as dyskinesia, trapezius atrophy, loss of shoulder abduction and shoulder and neck pain will occur; collectively, these are called “shoulder syndrome".\(^8-10\) The physiological mechanism of this symptom is still unclear, but it can be explained anatomically: The accessory nerve innervates the sternocleidomastoid and trapezius muscles\(^11\); once the nerve is pulled
during surgery, the function of both muscles is affected, and symptoms occur correspondingly. In addition, direct traction during surgery of the sternocleidomastoid muscle and other muscles associated with shoulder movement can damage the muscle bundle. Therefore, shoulder syndrome can greatly affect post-surgical HRQoL. If the accessory nerve can be protected or the pulling of it avoided during surgery, shoulder syndrome will be greatly controlled.

The accessory nerve divides level II in the neck into two sublevels, level IIa in the front and level IIb in the back. In IIb dissection, the accessory nerve must be pulled, which causes injury to the nerve. It has been reported that the rate of IIb metastasis in early-stage oral cancer is extremely low, no more than 6%. Some clinicians therefore suggest that level IIb be exempted from neck dissection in early OSCC in order to improve HRQoL. However, others disagree, and so there is no consensus about the necessity of IIb dissection in T1–2N0M0 OSCC.

To assess whether IIb neck dissection should be performed in T1–T2N0 OSCC, and its effects on OS and HRQoL, we designed this parallel-group, randomized, non-inferiority trial according to the SPIRIT 2013 Checklist (Additional file 1).

Methods

Study aims and design

Before designing this protocol, we searched the PubMed database for randomized controlled trials (RCTs) of IIb neck dissection in early-stage oral cancer on May 30, 2018, but we found no results. We repeated the search on November 26, 2018, using the keywords “IIb” and “neck” and searching only in English. We found only one RCT with a small sample size, from 2018; and six prospective analyses of IIb after neck dissection, from 2004 to 2018. In addition, we found two retrospective systematic reviews and meta-
analyses. All of the above indicated that the rate of IIb metastasis in early-stage oral cancer is extremely low, no more than 6%. However, there is still no strong evidence to prove the necessity of IIb dissection in T1-T2N0M0 OSCC.

We are conducting a parallel-group, non-inferiority randomized trial to assess whether IIb neck dissection should be performed in T1-T2N0 OSCC and its impacts on OS and HRQoL. Our study plan is summarized in Figure 1.

**Eligibility criteria**

In this prospective, randomized, non-inferiority trial, only patients who are in the clinical stages of T1-2N0M0 according to the American Joint Committee on Cancer (AJCC) Cancer staging Manual, 8th ed., will be enrolled. Based on the NCCN guideline, the treatment of T1-T2N0 oral cancer is primary resection with or without ipsilateral or bilateral cervical lymph node dissection or sentinel lymph node biopsy, and radiotherapy or chemotherapy is decided upon according to the specific circumstances. Patients with T2+ stage oral cancer are often recommended postoperative radiotherapy and a broader range of neck dissection. Radiation may affect the sensory and motor function of the shoulder, and it has been shown that >90% of breast cancer patients have shoulder pain and motor dysfunction after radiotherapy. If clinical T stage >2, the probability of neck occult lymph node metastasis is greatly improved. Therefore, we will enroll patients in stage T1 or T2. There may be discrepancies between post-operative pathological T (pT) stage and clinical (cT) stage, as some tumors can be pre-surgically staged as T1 or T2 but stage T3 is confirmed after surgery because of its deep infiltration depth. We have decided to enroll these patients. The treatment principle for tumors located in an oral-cavity site such as the soft palate, tonsil or root of the tongue is different from that for oral cancer. Although it is reported that level IIb of the neck can be preserved in T1-T2N0
oropharyngeal cancer,\textsuperscript{21,22} such patients should not be enrolled. We will eliminate all patients in stage cN+ because the possibility of the occult metastasis in IIb increases.\textsuperscript{17}

Neck status is usually evaluated by bilateral cervical B-ultrasound and enhanced CT/MRI. Patients who have no suspicious lymph nodes will be enrolled after all such examinations have been conducted. In addition, patients with distant metastases should not be enrolled. Inclusion and exclusion criteria are summarized in Table 1.

\textbf{Interventions}

After randomization, the two groups will be allocated to different interventions (See Table 2 for details). Primary resection will be 1.5–2 cm away from the tumor, and the negative margin must be attained. During neck dissection, if suspicious nodes in level III are found and metastasis is confirmed according to the examination of frozen biopsies, we will expand neck dissection to level IV or V. For the IIb retention group, if a suspicious positive lymph node is found in level IIa during surgery and metastasis is confirmed by frozen examination, both level IIa and IIb must be dissected.\textsuperscript{5,13}

All our surgical treatments will be based on the National Comprehensive Cancer Network (NCCN) baseline.

\textbf{Outcomes}

\textit{Primary outcome:} overall survival (OS)

We will use the 3-year OS after surgery as the primary outcome, and follow-up at 3 months, 6 months, 1 year, 1.5 years, 2 years, 2.5 years and 3 years after surgery (Figure 2).

\textit{Secondary outcomes:}

1. Health-related quality of life (HRQoL). We will use the Constant–Murley scale to evaluate patients' shoulder function, with follow-up at 7 days, 21 days, 3 months, 6
months, 1 year, 2 years and 3 years after surgery.

2. Progression–free survival (PFS). There are many reasons for setting OS as the primary outcome. First, it is widely used as a reliable indicator for evaluating the prognosis of tumors. It is reported that the 3-year OS rate in an IIb dissection group is about 80%, which includes disease-free survival and living with disease. Metastasis in level IIb is extremely low, and even if it happens it is nonlethal and can be instantaneously controlled by surgery or radiotherapy. Theoretically, 3-year OS in the IIb retention group will resemble that in the dissection group. A summary of 38 randomized controlled trials (RCTs) reports no significant association between PFS duration and HRQoL. In addition, as PFS is not as reliable as OS and can also increase difficulties in follow-up, we did not use PFS as the primary outcome.

**Participant timeline**

1. **Period −t: recruitment**

At the clinic, patients will be preliminary screened. The number of all eligible patients will be represented as n. After eligibility screening, we will record the number of cases that do not meet inclusion criteria as m, and the number of patients to be enrolled will be represented as n₁ = n − m. The number of patients who are not willing to sign the informed consent form as m₁, and they will be excluded. All patients (n₂ = n₁ − m₁) who will accept to participate will be randomized according to a repeatable randomized-number table produced by statisticians.

2. **Period 0: randomization**

This is the starting point of our trial, indicating when patients officially enter it. Patients will be enrolled in the IIb retention or IIb dissection group according to the repeatable randomized number table.
3. Period $t_1$: intervention

The number of patients who must be removed from our trial for any reason during intervention (surgery) will be represented as $m_2$, and the number of patients during follow-up will be represented as $n_3 = n_2 - m_2$.

4. Period $t_2$: follow-up

Follow-up timepoints include immediately, 7 days, 1 month, 6 months, 1 year, 1.5 years, 2 years, 2.5 years and 3 years after surgery. Follow-up will include physical examination, enhanced CT/MRI, bilateral neck B-ultrasonography, Constant-Murley score and the safety observation. There will be different evaluations at different timepoints, but overall evaluation will be the same between the two groups. The number of patients who quit our trial for any reason during follow-up will be represented as $m_3$, and the number of patients who will be included in our analysis will be represented as $n_4$ (See Figure 3 for details).

**Sample size**

In calculating sample size, we assumed the 3-year OS rate in the IIb retention group will be about 78%, $\alpha = 0.05$ (1-sided), power of 80% ($\beta = 20$) and that in the IIb dissection group will be 80%. The non-inferiority margin will be 12%, so the sample size as generated by PASS Sample Size Software 15.0 (NCSS LLC, Kaysville, Utah, USA) will be 261 for IIb retention and 260 for IIb dissection. In order to attain a reasonable sample size and make sure the trial is instructive for clinical work, we combined the common opinions of oral and maxillofacial experts, and the statistician defined the non-inferiority margin as 12%. Although the value seems to be large, its role is to control the large sample size that would otherwise be unapproachable.

**Assignment of interventions**
A statistician will write randomized code to generate a repeatable randomized number table. To reduce the predictability during enrollment, the statistician will determine block length, and a team that is not involved in our trial will keep all the blind codes safely. This team will create opaque sealed envelopes according to the randomized-number table, and we will distribute patients according to this table.

**Stratification**

OS can be affected by many factors, such as T stage (T1, T2), primary subsite (tongue, buccal mucosa, mouth floor, gingiva, posterior molar region or hard palate), depth of invasion. To balance the number of patients between groups and minimize the bias of the trial, we will use T stage and primary subsite as stratification.

**Blinding**

Since the intervention in this clinical trial is a surgical procedure and the surgical records can be queried, surgeons and patients know the specific grouping information. After trial we will send data to statisticians and blind to this evaluator.

**Data collection methods**

**Primary outcome**

Patients will be followed up by phone on their survival status at each timepoint during period $t_2$, as shown in Figure 2. After 3-year follow-up of the last patient is complete, we will calculate the 3-year OS rate of both groups.

**Secondary outcomes**

1. Health-related quality of life (HRQoL). We will use the Constant-Murley scale to evaluate shoulder function at each follow-up timepoint. In order to improve the reliability of shoulder function evaluation, two clinicians will be systematically trained on use of the scale.
2. Progression-free survival (PFS). Observation will start at time of randomization and end when events (see below) occurred. In the period of time from stage 0 (Figure 3) to primary recurrence, local metastasis, distant metastasis, and other life-threatening events or death will be defined as PFS.

If a patient has not returned to the clinic for more than two months after the follow-up timepoint, a telephone inquiry will be conducted.

**Data management**

All paper versions of the original materials will be photographed and saved in an encrypted public database. All electronic data will be stored in the electronic medical records of the Shanghai Ninth People's Hospital. All procedures for evaluating shoulder function will be filmed and saved.

**Statistical methods**

1. Overall survival

This trial will be terminated when the last patient has been followed up on for 3 years. After the trial ends, the primary end points will be tested by means of two-sided log-rank tests.

2. Health-related quality of life (HRQoL)

We will use a repeated analysis of variance (ANOVA) measure to analyze changes in Constant–Murley score between the 2 groups. It is reported\(^{26}\) that about 67% of patients have shoulder syndrome after neck dissection even if the accessory nerve is spared. Currently, two methods might work to deal with the problem of shoulder dysfunction. The first is to restore the damaged nerve with such methods as intraoperative brief electrical stimulation of the spinal accessory nerve (BEST SPIN). However, this technique has little effect,\(^{27}\) and literature on treatment of damaged accessory nerves is rare. The second is
retention of level IIb during surgery in order to preserve the integrity of accessory nerve function and structure. By measuring changes in the action potential of the accessory nerve during surgery, it was found that level IIb dissection can greatly damage the accessory nerve.\textsuperscript{6} We will use the Constant–Murley scale\textsuperscript{28} to assess shoulder function. Although the scale’s reliability in evaluating shoulder function has been questioned,\textsuperscript{29} it has been clinically applied for more than 30 years, and it can reflect both subjective indicators (such as pain or daily activity) and objective standards (such as the muscle mobility and power). Because of the tissue defect caused by primary resection, distant free or adjacent flaps are used to restore it. In order to ensure the flaps alive, movement control after surgery is crucial. Patients with free flaps are clinically permitted to lift the upper body on the 5th day after surgery and can also to sit up in bed. On the 6th day after surgery, mild activities such as walking are permitted. Therefore, the first timepoint for evaluating shoulder function will be the 7th day after surgery, and then there will be follow-up at 1 month, 6 months, 1 year, 2 years and 3 years.

3. Progression-free survival (PFS)
We will use a two-sided log-rank test to check the difference in PFS between the two groups.

4. Others
In addition, we will use post hoc subgroup analyses on the basis of histological factors that were known to have effects on survival, such as death of invasion of the primary tumor.

Harms
Patients will be informed of all surgical risks and adverse effects of intervention before surgery, which will be performed only if the informed consent is signed. The Ethics
Committee of Shanghai Ninth People’s Hospital will be notified of any accidents (such as hemorrhagic shock, myocardial infarction, or death) that occur during surgery.

Primary recurrence or neck/distant metastasis (bone, lung) may occur in both two groups. We will expand tumor resection if primary recurrence happens and perform radiotherapy or neck dissection depending on the tumor size. If IIb metastasis is detected during follow-up in the retention group, we will dissect level IIb and perform radiotherapy if necessary. If level IV or V is affected, we will perform additional ipsilateral or bilateral neck dissection, plus radiotherapy or chemotherapy later if needed.

Discussion

For decades, the treatment of early-stage oral cancer has created an apparent dilemma between survival and HRQoL.\textsuperscript{1,30-33} To guarantee a higher survival rate, HRQoL must often be sacrificed. The neck metastatic rate in early-stage OSCC is about 30\textsuperscript{\%},\textsuperscript{34} and methods of neck treatment include therapeutic dissection and observation. Data from India\textsuperscript{1} show that the 5-year survival rate is about 13\textsuperscript{\%} higher in the therapeutic group than in the control one, but overtreatment still happens in those patients whose neck lymph nodes are actually negative. As far as we know, this is also true in the treatment of breast cancer. Axillary lymph node metastasis often appears in early-stage breast cancer, at a rate of about 15–20\textsuperscript{\%}.\textsuperscript{35} Previously, axillary dissection was the gold standard in treating early-stage breast cancer, as it reduced recurrence and improved OS; but it also brought complications like lymphedema, which greatly affected HRQoL for patients after surgery. Sentinel-lymph node biopsy has since replaced axillary dissection, as it offers better disease control and HRQoL.\textsuperscript{36-38} There are therefore commonalities between oral cancer in their early stages.

Because there is higher occult metastasis in early-stage oral carcinoma than in early-
stage breast cancer, despite post-surgical HRQoL considerations, surgeons prefer to perform therapeutic neck dissection to enhance OS. During neck dissection in oral cancer, traction of the accessory nerve can decrease shoulder function, and damage to the nerve occurs when level IIb is dissected. The occult metastatic rate for IIb is <6%, so if level IIb is retained, the nerve will not be pulled, and HRQoL for patients with early-stage oral cancer can be greatly increased. This trial is designed to assess whether IIb neck dissection should be performed in T1-T2N0 OSCC, and to discuss its effects on survival rates and HRQoL.

Our trial has some limitations. 1. Currently, it is noteworthy that for T1N0 OSCC, many surgeons would actually not undertake a staging neck dissection, which seems in contrast to the study. However, according to the NCCN guidelines, the recommended treatment options for T1 and T2 are the same, all of which is resection of primary (preferred) ± ipsilateral (guided by tumor thickness) or bilateral (guided by location of primary) neck dissection or SLN biopsy. In order to clarify the relationship between depth of invasion and occult metastasis, we will put the depth of invasion into final analysis. 2. At present, there are many auxiliary methods for cervical examination, such as B-ultrasound, enhanced CT/MRI, 18F-fluorodeoxyglucose positron emission computerized tomography and computer tomography (FDG PET/CT), etc. In this trial, we will use B-ultrasound and enhanced CT/MRI to detect occult metastatic lymph nodes. However, the sensitivity of these examinations is relatively not high. It has been reported that PET/CT offers a distinct advantage over other conventional imaging modalities because it provides functional insights into tumor biology and tissue metabolism, so PET/CT has a higher sensitivity and advantages for detecting cervical metastasis. But PET/CT also has some limitations. First of all, the expenditure is relatively high. Besides, the main advantage of
PET/CT applies to clinically node positive OSCC, and PET/CT has a higher false negative rate for detecting nodal involvement in the setting of a cN0 neck. NCCN guidelines currently recommend PET/CT imaging for most stage III and IV OSCC. Therefore, in our trial, PET/CT is not considered to apply for detecting neck status.

In summary, this parallel-group, randomized, non-inferiority RCT aims to assess whether IIb neck dissection should be performed in T1–T2N0 OSCC and to also assess the effects of IIb neck dissection on OS and HRQoL. Although there are some limitations to this study, it is still worth conducting for the advantages it may have for patients.

**Trial status**

Protocol version 2.0, 1 October 2018. Enrollment has not yet started, and is expected to be started by 1 June 2019, and completed by 1 June 2024.

**Abbreviations**

<p.OSCC: oral squamous cell carcinoma; OS: overall survival; CT: computed tomography; MRI: magnetic resonance imaging; HRQoL: health-related quality of life; RCT: randomized controlled trial; AJCC: American Joint Committee on Cancer; NCCN: National Comprehensive Cancer Networks; PFS: progression-free survival; BEST SPIN: brief electrical stimulation of the spinal accessory nerve; FDG PET/CT: 18F-fluorodeoxyglucose positron emission computerized tomography and computer tomography.

**Declarations**

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authorized by the Clinical Trial Center of the Shanghai Ninth People’s Hospital, Shanghai Jiao Tong University, School of Medicine, Shanghai, China.

**Availability of data and materials**

Not applicable.

**Authors’ contributions**

QXJ and GB conceived the study and contributed equally to this trial. WL did the literature research. QXJ, GB, WLI, WLG, SXF, CC, MCC, designed the study. WLI wrote the first draft of the article. QXJ and GB revised the article.

**Ethics approval and consent to participate**

The study was approved by the Ethics Committee of Shanghai Ninth People’s Hospital on 27 September 2017 (SH9H-2018-T43-1). Any protocol modifications will be submitted to the Ethics Committee for review and participants will be informed. Consent obtained from participants was written, so after eligibility screening, we will request signed consent from participants. Participants are also informed that their choice to participate or not participate in the study would not affect their access to health services or treatment, and that there is no penalty for not participating in the study.

**Consent of publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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Tables

Due to technical limitations the tables could not be inserted. They can be found in the supplemental file section as JPEG files.

Figures

Figure 1

Trial profile
| ASSESSMENT                        | Recruitment | Intervention | Follow-up |
|----------------------------------|-------------|--------------|-----------|
| History collection               | ×           |              |           |
| Informed consent                 | ×           |              |           |
| Eligibility screen               | ×           |              |           |
| Patient randomization            |             | ×            |           |
| Biopsy                           | ×           |              |           |
| Constant-Murley scale            | ×           |              |           |
| Enhanced CT/MRI                  | ×           | ×            | ×         | ×         | ×         |
| Bilateral neck                   | ×           |              |           |
| B-ultrasonography                 | ×           |              |           |
| Safety observation               |             |              |           |

Figure 2

SPIRIT figure, trial visits and assessments
Figure 3
Timeline of the trial

Supplementary Files
This is a list of supplementary files associated with the primary manuscript. Click to download.

CONSORT-2010-Checklist.doc
Table 2.jpg
Table 1.jpg