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**MAIN ARTICLE**

# Submandibular gland invasion and feasibility of gland-sparing neck dissection in oral cavity carcinoma

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## Abstract

*Objective*: This study investigated the incidence and routes of submandibular gland involvement in oral cavity carcinoma to determine the feasibility of submandibular gland sparing neck dissection.

*Methods*: The records of 155 patients diagnosed with oral cavity squamous cell carcinoma, with a total of 183 neck specimens, including those involving level I, were reviewed retrospectively.

*Results*: Submandibular gland involvement, via direct invasion from the anatomical proximity of $T_{4a}$ tumours, was evident in two patients. The floor of mouth location, either primarily or as an extension of the primary tumour, was the only risk factor for submandibular gland involvement in oral cavity carcinoma ($p = 0.042$). Tumour location, clinical and pathological tumour (T) and nodal (N) stages, and radiological suspicion of mandible invasion, were not found to be statistically relevant ($p > 0.05$).

*Conclusion*: The results suggest the feasibility of preserving the submandibular gland in early stage oral cavity carcinoma unless the tumour is located in, or extends to, the floor of mouth.

**Key words:** Oral Neoplasms; Submandibular Gland; Organ Preservation; Neck Dissection; Squamous Cell Cancer

## Introduction

Oral cavity cancers are the most frequent tumours of the head and neck region, and squamous cell carcinoma (SCC) constitutes the vast majority of cases.[1] The standard treatment for oral cavity SCC is surgery, and adjuvant radiotherapy or chemoradiotherapy if indicated.[1] Neck dissection is an integral part of treatment, in addition to primary tumour surgery for tumour control even in clinically negative necks.[2,3] Lesions of the oral cavity usually metastasise to levels I, II and III, while levels IV and V are rarely involved.[4,5]

Routine excision of the submandibular gland during level I dissection causes a significant decrease in unstimulated saliva production, leading to xerostomia.[6] Another cause of xerostomia is adjuvant radiotherapy, and it may not be possible to spare the submandibular glands from radiotherapy fields in advanced stage diseases.[7] However, as the submandibular gland does not contain intraglandular lymph nodes, removal of an uninvolved submandibular gland may not always be necessary, particularly in cases of early stage oral cavity SCC, with the potential benefit of reducing post-operative xerostomia.[1] On the other hand, the oncological safety of preserving the submandibular gland remains an open question.

Therefore, we aimed to investigate the incidence and relevant factors associated with submandibular gland involvement in oral cavity SCC, and to discuss the possibility of preserving the submandibular gland in cases of early stage oral cavity SCC from a pathological point of view.

## Materials and methods

After obtaining the approval of the Dokuz Eylul University Institutional Review Board (protocol number: 2382 GAO, resolution number: 2017/06-26), we reviewed the medical charts of 155 consecutive patients with oral cavity SCC who underwent primary tumour surgery and concomitant neck dissection, including level I dissection, between January 1987 and December 2015 in our department.

Exclusion criteria were: patients with the diagnosis of non-squamous cell cancer, paediatric patients (aged under 18 years), the presence of synchronous malignancy, stage $T_{4b}$ tumours, patients with distant

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metastatic disease, and a previous history of head and neck cancer.

Clinical and pathological tumour–node (T and N) staging of the patients was performed according to American Joint Committee on Cancer staging;[8] all records collected prior to the 2010 edition of the *AJCC Cancer Staging Manual* were converted to this particular version. Tumour location, clinical and pathological T and N stages, clinical and radiological suspicion of mandible invasion, and extension of a tumour to the floor of mouth, were investigated for their relevance to level I metastasis and submandibular gland involvement.

Statistical analysis was performed using the SPSS software package for Windows, version 20.0 (SPSS, Armonk, New York, USA). Fisher's exact test and Pearson chi-square test were carried out to identify potential risk factors associated with level I metastasis and submandibular gland involvement. A $p$-value of less than 0.05 was accepted as statistically significant.

## Results

The mean age of the 155 included patients was 56.9 years (range, 19–83 years). There were 63 women and 92 men. Of the 155 patients, 127 underwent unilateral neck dissection and 28 underwent bilateral neck dissection, constituting a total of 183 neck dissections.

The submandibular gland was excised routinely in all 183 neck dissections. Histopathologically, there were no intraglandular metastatic lymph nodes in any of the 183 neck dissection specimens. Submandibular gland invasion was observed in only two cases (1.3 per cent). Both of these patients (described below) had involvement of the submandibular gland directly as a result of the anatomical proximity of $T_{4a}$ tumours, without metastatic lymph nodes at level I.

Case one was a 70-year-old female who presented with a clinically staged $T_{4a}N_{2c}$ oral tongue cancer, with floor of mouth extension. The pathological tumour–node–metastasis (TNM) staging was $T_{4a}N_{2c}M_0$. There were bilateral pathologically metastatic level II lymphadenopathies, while level I was uninvolved. Direct invasion of submandibular gland through the ipsilateral tumour was correctly identified in the pre-operative contrast-enhanced cervical magnetic resonance imaging (MRI) scan, as shown in Figure 1. A histological view of the SCC invading the submandibular gland of case one is presented in Figure 2.

Case two was a 59-year-old female who presented with a clinically staged $T_{4a}N_0$ cancer of the floor of mouth, with a clinical suspicion of mandibular invasion according to pre-operative contrast-enhanced cervical computed tomography (CT) scan. The pathological examination confirmed mandibular invasion, and pathological staging was $T_{4a}N_0M_0$. When re-evaluating the CT scan during the preparation of this article, the authors noted a suspicious invasion of the ipsilateral submandibular gland (not noticed pre-operatively), as shown in Figure 3. A histological view of the SCC invading the submandibular gland of case two is presented in Figure 4.

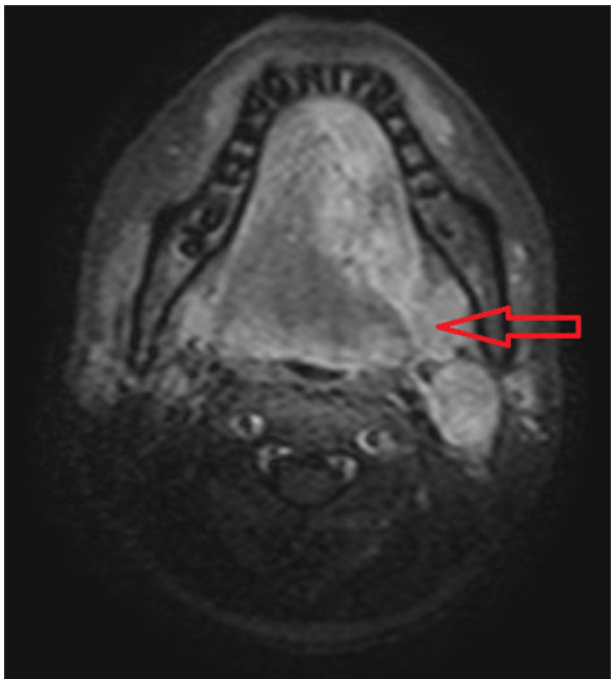

FIG. 1
Axial T1-weighted contrast-enhanced magnetic resonance image of case one, showing submandibular gland invasion with anatomical proximity (red arrow indicates submandibular gland).

The most frequent tumour location subsite was the oral tongue, compromising 85 cases. Other tumour location sites were, in order of decreasing frequency: the floor of mouth, buccal mucosa, retromolar trigone, alveolar ridge and hard palate. The distribution of primary tumour subsites within the oral cavity are summarised in Figure 5.

Tumour location was not statistically significantly associated with level I metastasis (Pearson chi-square test, $p = 0.119$) or submandibular gland involvement

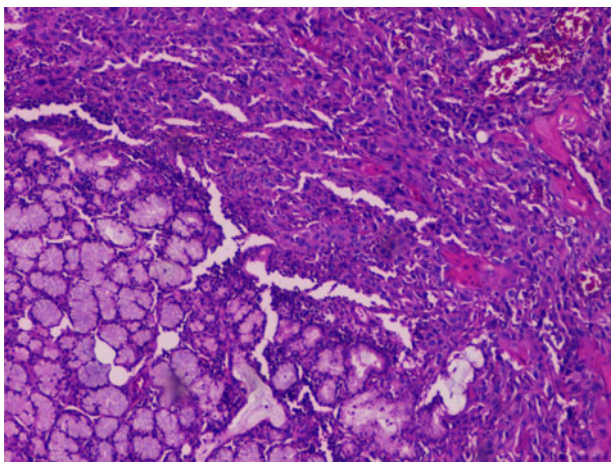

FIG. 2
Squamous cell carcinoma invading submandibular gland in case one. (H&E; ×200)

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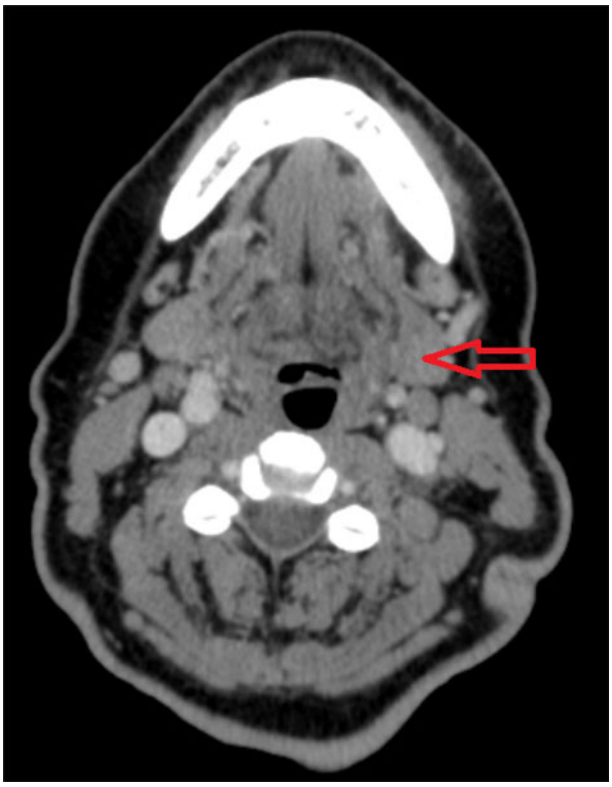

FIG. 3
Axial contrast-enhanced computed tomography section of case two, showing suspicious submandibular gland invasion (red arrow indicates submandibular gland).

(Pearson chi-square test, $p = 0.845$). Evaluation did not reveal statistically significant relationships between level I metastasis and: anatomical proximity of the tumour (tumours with primary location in or extension to the floor of mouth) (Fisher's exact test, $p = 0.101$), tumours with a pre-operative suspicion of mandibular invasion (Fisher's exact test, $p = 0.359$) or histopathologically verified mandibular invasion (Fisher's exact test, $p = 1.000$). Tumours located primarily in or

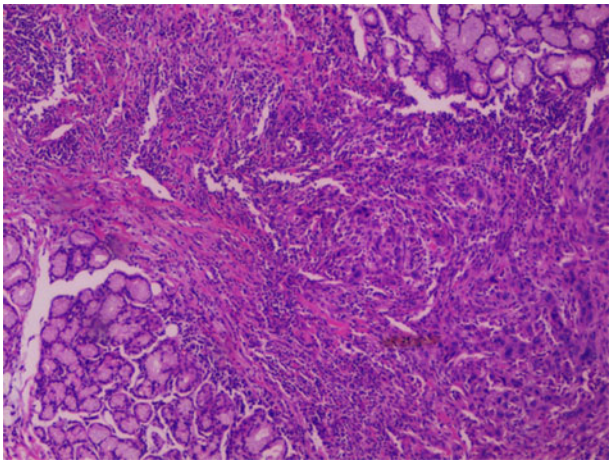

FIG. 4
Squamous cell carcinoma invading submandibular gland in case two. (H&E; ×100)

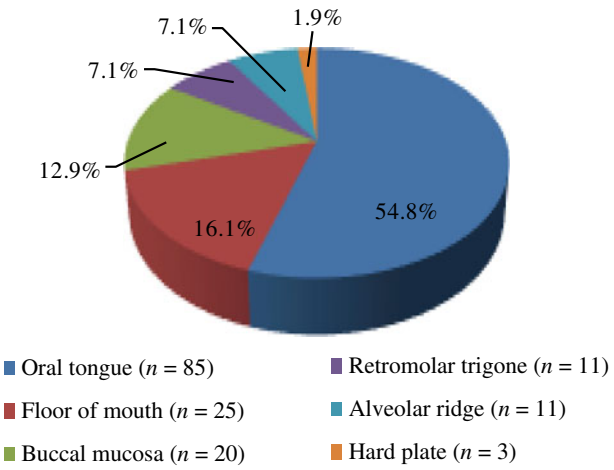


FIG. 5
Distribution of tumour location sites ($n = 155$ patients).

extending to the floor of mouth were statistically significantly more prone to invade the submandibular gland (Fisher's exact test, $p = 0.042$). However, there was no statistically significant association between submandibular gland involvement and pre-operative suspicion of mandibular invasion (Fisher's exact test, $p = 0.101$) or pathologically confirmed mandibular invasion (Fisher's exact test, $p = 0.149$).

According to the final histopathology report, 45 patients had pathologically staged $T_1$ tumours, 54 patients had pathologically staged $T_2$ tumours, 18 patients had pathologically staged $T_3$ tumours, and 38 patients had pathologically staged $T_{4a}$ tumours. Table I shows the tumour location and pathological T classification for the patients.

There was no significant association between pathological T stage and level I metastasis (Pearson chi-square test, $p = 0.111$). In addition, there was no statistically significant association between clinical T stage (based on the findings of pre-operative physical examination and radiological assessment) and level I metastasis (Pearson chi-square test, $p = 0.220$). Furthermore, clinical T stage (Pearson chi-square test,

TABLE I
TUMOUR LOCATION AND PATHOLOGICAL TUMOUR (T) CLASSIFICATION

| Tumour location | $T_1$ | $T_2$ | $T_3$ | $T_{4a}$ |
|---|---|---|---|---|
| Oral tongue ($n = 85$) | 36 (42) | 34 (40) | 10 (12) | 5 (6) |
| Floor of mouth ($n = 25$) | 2 (8) | 9 (36) | 2 (8) | 12 (48) |
| Buccal mucosa ($n = 20$) | 5 (25) | 6 (30) | 4 (20) | 5 (25) |
| Alveolar ridge ($n = 11$) | 1 (9) | 3 (27) | – | 7 (64) |
| Retromolar trigone ($n = 11$) | 1 (9) | 1 (9) | 1 (9) | 8 (73) |
| Hard palate ($n = 3$) | – | 1 (33) | 1 (33) | 1 (33) |
| Total ($n = 155$) | 45 (29) | 54 (34.8) | 18 (11.6) | 38 (24.5) |

Data represent numbers (percentages) of patients.

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TABLE II
ASSOCIATION OF PARAMETERS WITH LEVEL I METASTASIS AND SUBMANDIBULAR GLAND INVOLVEMENT

| Parameter | Level I metastasis | Submandibular gland involvement |
|---|---|---|
| Primary tumour location | 0.119 | 0.845 |
| Clinical tumour stage | 0.220 | 0.091 |
| Clinical neck stage | 0.000* | 1.000 |
| Clinical suspicion of mandibular invasion | 0.359 | 0.101 |
| Primary tumours in or extended to floor of mouth | 0.101 | 0.042* |
| Pathological tumour stage | 0.111 | 0.129 |
| Pathological neck stage | 0.000* | 1.000 |
| Histopathologically confirmed mandibular invasion | 1.000 | 0.149 |

Data represent $p$-values. *$p < 0.05$.

$p = 0.091$) and subgroup analysis of early and advanced clinical T stages (Fisher's exact test, $p = 0.129$) were not risk factors for submandibular gland involvement.

Of the 183 neck dissection specimens, 58 were clinically node-positive and 71 were pathologically node-positive. Level I metastasis rates were 34.5 per cent (20 out of 58) in clinically node-positive necks and 30.9 per cent (22 out of 71) in pathologically node-positive necks. Level I metastasis was more prevalent in clinically node-positive and pathologically node-positive necks (Fisher's exact test, $p < 0.001$ for both). However, there was no statistically significant association between submandibular gland involvement and clinically node-positive or pathologically node-positive necks (Fisher's exact test, $p = 1.000$ for both).

Table II presents the risk parameters associated with level I metastasis and submandibular gland involvement.

## Discussion

Removal of the submandibular gland has been introduced as a standard component of radical, modified radical and selective neck dissections while performing level I dissection.[1] Although metastasis to the submandibular gland is uncommon, excision of the gland is frequently practised because of its proximity to the primary lesion and adjacent lymph nodes.[9] Three possible routes of submandibular gland tumoural involvement may be classified: an anatomical neighbourhood, lymphatic spread and haematogenous metastasis.[10] Haematogenous metastases usually originate from tumours located outside the head and neck, particularly the lung and breast.[11] Haematogenous metastasis of the submandibular gland from oral cavity squamous cell cancer has been previously reported as non-existent.[1,5,10,12–15]

Submandibular gland involvement through a metastatic peri-glandular lymph node in level I is also a rare entity. Its incidence in oral cavity SCC was reported as between 0.3 and 1.7 per cent.[16] The level I lymph nodes compromise six subgroups of nodes known as the pre-glandular, pre-vascular, retrovascular, retroglandular, intra-capsular and deep submandibular groups.[17] The pre-vascular and retrovascular groups were suggested to be the most and the least commonly involved level I nodes respectively.[17,18] On the contrary, the intraglandular and deep submandibular group nodes are rarely detectable, and the intraglandular nodes are frequently absent.[19] Junquera *et al*. evaluated submandibular gland involvement in patients with primary cancer of the floor of mouth, and documented the peri-glandular (pre-glandular and retroglandular) metastasis rate as 31.7 per cent, while no submandibular gland involvement was detected.[20] Lim *et al*. analysed the tumours emerging from the tongue and floor of mouth, and concluded that the overall incidence of perivascular (pre-vascular and retrovascular) lymph node involvement and recurrences in this area after dissection was very low.[18]

- **Although shown in only two cases, primary placement in or extension to floor of mouth was the only risk factor for submandibular gland metastasis**
- **Tumour location, clinical and pathological tumour and nodal stages, and radiological suspicion of mandible invasion were not associated with submandibular gland metastasis**
- **Contrast-enhanced magnetic resonance imaging is superior to computed tomography in detecting submandibular gland metastasis**
- **Preserving the submandibular gland in oral cavity squamous cell carcinoma can be safe and feasible**
- **However, this is not an option if the tumour is in or extends to floor of mouth, or there is no radiological or clinical suspicion of submandibular gland invasion pre-operatively**

It is widely accepted that the submandibular gland does not contain a rich network of lymphovascular structures and intraglandular lymph nodes, reducing the probability of lymphatic spread to the submandibular gland, which is an important distinction from the parotid gland.[1,10] In our study, although level I metastasis was observed to be statistically more prevalent in clinically node-positive and pathologically node-positive necks, there was no statistically significant association between submandibular gland involvement and clinically node-positive or pathologically node-positive necks. In the literature, rare incidences of metastatic intraglandular lymph nodes in oral cavity SCC have been reported, in 0.3–0.7 per cent of cases, mostly

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with advanced stage tumours located on the tongue and buccal mucosa.[21]

Direct invasion, on the other hand, has been reported more frequently, with rates between 0.3 and 2.8 per cent.[1] In our series, there were only 2 patients with submandibular gland involvement out of 155 patients in 183 neck dissections. Both instances of submandibular gland involvement were the result of direct invasion of a primary tumour through the floor of mouth, and in one patient there was an additional mandibular invasion, while there was no submandibular gland involvement via haematogenous or lymphatic spread.

In most series, tumour invasion of submandibular gland was found to be associated with tumours primarily located in or extending to the floor of mouth or mandible, or with an advanced T stage.[1,10,13,14,21–23] In our study, only primary tumours in or extended to the floor of mouth were statistically significantly associated with submandibular gland invasion. Of the tumours invading the submandibular gland, one was located in the floor of mouth while the other was a tongue tumour extending to the floor of mouth. Although there were only two cases with submandibular gland invasion, statistical analysis showed that primary floor of mouth placement or extension to the floor of mouth was a statistically significant risk factor for submandibular gland invasion (Fisher's exact test, $p = 0.042$). We acknowledge that the number of cases with submandibular gland invasion was low in our series; however, we present the findings as a promising contribution to the literature. Further research focusing on floor of mouth tumours will surely provide more information. Despite the lack of statistical significance, both of the tumours were $T_{4a}$ and negative for level I metastasis.

Although on a case basis, we observed the potential superiority of MRI for detecting submandibular gland involvement. Invasion of the submandibular gland was correctly identified in one patient pre-operatively by MRI; in another patient, contrast-enhanced CT scan was not as effective as MRI in revealing submandibular gland invasion. In our opinion, the superiority of MRI was a result of its higher specificity and sensitivity in evaluating soft tissues. Likewise, Fives *et al.* pointed out the false negativity and false positivity of contrast-enhanced CT in a case with bilateral metastatic submandibular glands and in another case wherein the submandibular gland was pathologically confirmed not to be involved.[23]

Owing to its principal effect on unstimulated salivation, removal of the submandibular gland or adjuvant radiotherapy to level I including the submandibular gland results in saliva reduction and xerostomia.[6,24] Different studies have investigated techniques for reducing xerostomia sequela, focusing on primary radiotherapy that spares salivary glands from the radiotherapy field whenever primary tumour location permits, or that involves surgical transposition of the submandibular gland out of the radiotherapy field.[25,26] Although it is not possible to spare level I and associated submandibular gland tissue from the adjuvant radiotherapy field to prevent xerostomia in advanced stage oral cavity SCC, it may be worth preserving the submandibular gland during neck dissection in early stage $N_0$ tumours to avoid xerostomia. Currently, there is no evidence of an uninvolved submandibular gland causing local recurrence or decreased survival when preserved during neck dissection. Our results and the current literature suggest that primary submandibular gland invasion is the most common form of involvement, especially for floor of mouth tumours. As the likelihood of submandibular gland metastasis or invasion is very low in early stage oral cavity SCC, attempts to preserve the gland in this group of patients may improve their quality of life by reducing xerostomia.

Our results support the feasibility of preserving the submandibular gland in early stage oral cavity SCC from a pathological point of view. However, the shortcoming of our study is the retrospective cross-sectional nature and absence of patients with submandibular gland sparing neck dissections. Further investigations with long-term follow up of oral cavity carcinoma patients who are undergoing submandibular gland sparing dissections are needed to prove the oncological safety of this approach on a clinical basis.

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