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<td>Author(s)</td>
<td>Matsushita, Yuki; Yanamoto, Souichi; Yamada, Shin-ichi; Mori, Hitomi; Adachi, Masaki; Takahashi, Hidenori; Naruse, Tomofumi; Ikeda, Hisazumi; Shiraishi, Takeshi; Minamikawa, Tsutomu; Shibuya, Yasuyuki; Komori, Takahide; Asahina, Izumi; Umeda, Masahiro</td>
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</table>
Original research

Correlation between degree of bone invasion and prognosis in carcinoma of the mandibular gingiva: soft tissue classification based on UICC classification

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Footnote:
Authors declare no conflict of interest.

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Abstract

Objective: The criteria for T4 staging of carcinoma of the mandibular gingiva are controversial. Oral cancer staged as T4 implies “invasion to an adjacent organ,” such as the skin, extrinsic muscles of the tongue, masticator space, or mandibular bone. In this study, we compared different T classifications and retrospectively investigated the correlation between each classification and the prognosis of patients with carcinoma of the mandibular gingiva.

Methods: We investigated 81 patients with squamous cell carcinoma of the mandibular gingiva treated at two institutions.

Results: There was a significant correlation between soft tissue classification and local recurrence ($P < 0.05$) and that the correlation with prognosis is borderline significant ($P = 0.05$).

Conclusions: Soft tissue classification, which does not consider bone invasion, was the most useful for diagnosis, selecting the appropriate surgical procedure, and assessing the correlation to prognosis. We recommended using this classification to define T4. Because this classification is not new but is based on International Union Against Cancer classification, it could be easily adopted. However, the current study is a retrospective analysis of a small number of patients. A multi-institutional, prospective study is necessary to determine the appropriate criteria for the TNM staging of carcinoma of the mandibular gingiva.

Key words: Carcinoma of mandibular gingiva; Oral cancer; UICC classification; T classification; Bone invasion
1. Introduction

The T4 criteria for carcinoma of the mandibular gingiva are challenging and controversial. Oral cancer staged as T4 implies “invasion to an adjacent organ” such as the skin, extrinsic muscles of the tongue, masticator space, or mandibular bone [1]. Carcinoma of the mandibular gingiva originates from the gingiva, which is located just above the mandibular bone. Unlike other oral cancers, carcinoma of the mandibular gingiva can easily invade to the mandibular bone. Because the mandibular bone is adjacent to the mandibular gingiva, a small carcinoma of the mandibular gingiva (such as T1 or T2) could unexpectedly be potentially classified as T4. This phenomenon is inadequate for the concept of T classification because such tumors are not suitable for the classical T classification system. Consequently, various T4 criteria and T classifications have been reported for bone invasion in carcinoma of the mandibular gingiva. The International Union Against Cancer (UICC) has defined T4 cancer with bone invasion as invasion to the cortical bone [1]. The Japan Society for Oral Tumors (JSOT) has defined T4 cancer with bone invasion as invasion to the mandibular canal [2-6]. This T4 criterion is based on a multicenter retrospective study of 1187 cases from 24 institutions of the Department of Oral Surgery. In Japan, many oral surgeons have applied this T4 criterion [5,6]. In recent years, Ebrahimi et al. [7] recommended revising the T staging system such that tumors are classified as T1–T3 based on size and are then upgraded by one T stage in the presence of medullary bone invasion. In addition, some reports have suggested that tumor size is well correlated with adverse prognosis, and that bone invasion is not an independent predictor of survival [8-10]. As seen above, there are still no universally accepted criteria to define T4 for cancer of the mandibular gingiva.

In this study, we reconsidered the T4 criteria for carcinoma of the mandibular gingiva. Therefore, we investigated the correlation between each T4 criterion and the prognosis of patients with carcinoma of the mandibular gingiva.
2. Patients and Methods
2-1. Patients

A total of 81 patients with carcinoma of the mandibular gingiva who had undergone primary surgical excision with curative intent were retrospectively assessed. Of these, 53 patients visited the Department of Oral and Maxillofacial Surgery, Nagasaki University Hospital (Nagasaki, Japan), between 2001 and 2013, and 28 patients attended the Department of Oral and Maxillofacial Surgery, Kobe University Hospital (Kobe, Japan), between 2007 and 2012. The study cohort included patients with histologically confirmed diagnoses of squamous cell carcinoma and a minimum follow-up of 12 months. Inoperable cases which patients have distant metastasis and hesitated to consent to surgical intervention were excluded.

Overall survival (OS) and disease-specific survival (DSS) were calculated from the time of initial examination to the time of death or the time of last follow-up. Local control (LC) was calculated from the time of initial examination to the time of local disease recurrence or the last follow-up.

This study is approved by the ethics committees of the Nagasaki University Hospital.

2-2. Surgical procedure

TNM classification was defined using inspection, palpation, and some imaging findings like Panorama X-ray, computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonic echo. The oral surgeons made a final clinical TNM diagnosis by reference to radiologist’s findings. Surgical procedure was depends on TNM classification. The extent of resection was decided considering from above the clinical elements. In all cases, ≥15mm safety margin far from tumor was fundamentally set both the bone and soft tissue. Thereby, marginal or segmental resections were consequently chose. All patients underwent surgery with curative intent. Elective neck dissection was not performed routinely in our institutions.

2-3. T4 criteria
UICC defines that T4a is moderately advanced local disease prescribed as tumor invades adjacent structures (e.g., through cortical bone, into extrinsic muscle of tongue like genioglossus, hyoglossus, palatoglossus, and styloglossus, and skin of face). And T4b is very advanced local disease prescribed as tumor invades masticator space, pterygoid plates, or skull base, and/or encases internal carotid artery.

The T4 criteria described by UICC, JSOT, Ebrahimi et al., and soft tissue classification were evaluated [1-7]. The T4 criteria required by each classification system are listed in Table 1. Each classification system is fundamentally based on the UICC TNM classification [1], with differences mainly regarding the degree of bone invasion. JSOT defined T4 as invasion to the mandibular canal [2-6]; Ebrahimi et al. [7] classified it as T1–T3 according to UICC classification, followed by an upgrade of one T stage in the presence of medullary bone invasion. The soft tissue T4 criteria do not consider the contribution of bone invasion. These T4 criteria were re-classified from the aspect of bone invasion. Two oral surgeons and a radiologist decided the grade of bone invasion using panoramic X-ray pictures and CT images.

2-4. Statistical analysis

Statistical analyses were performed using StatMate IV (ATMS Co., Tokyo, Japan). The significance of categorical data was assessed using \( \chi^2 \) tests or Fisher’s exact tests, as appropriate. DSS and LC were calculated using the Kaplan–Meier method, and significance was evaluated using the log-rank test. \( P < 0.05 \) was considered significant.
3. Results

3-1. Patient characteristics

Demographics of the patient cohort are summarized in Table 2. The male-to-female ratio was 0.88, with 38 male subjects. The mean age at diagnosis was 69.4 years (range, 36–92 years). Marginal resection was performed in 40 (49.4%) cases and segmental resection in 41 (50.6%). Local recurrence occurred in 18 (22.2%) patients during the follow-up period. Five-year OS was 74.2%, and 5-year DSS was 83.1%. The mean follow-up period was 40.8 months for the entire patient series (range, 1–119 months).

Sixty-five patients were classified as UICC T4 (80.2%), whereas 29 (35.8%) patients were classified as JSOT T4. According to the criteria described by Ebrahimi et al., 29 (35.8%) patients had T4 cancer, while according to soft tissue classification, 17 (21.0%) had T4 cancer.

3-2. Correlation between T4 criteria and type of surgical resection

When T4 cases were compared with T1–T3 cases, segmental resection was significantly more common in T4 cases (regardless of classification). However, segmental resection was performed in only 60.0% of UICC T4 cases compared with >85% of T4 cases according to the other three classifications (Table 3).

3-3. Correlation between T4 criteria and pathological nodal status

In our cases, total 31 patients had pathological nodal metastasis. Lymph node metastasis cases had a significant relationship with OS and DSS ($P < 0.05$). Considering the relationship between each T classification and lymph node metastasis, the rates of lymph node metastasis of each T4 were from 35.3% to 44.8% (Table 4). There were no significant relations each T4 criteria and lymph node metastasis. These results indicated that it was able to compare the relationship between each T4 criteria and prognosis.

3-4. Correlation between T4 criteria and prognosis

We next evaluated OS, DSS, and LC among the different T4 classifications. In patients
with T4 cancer according to UICC classification, OS was 73.9% compared with 78.8% in patients with T1–T3 cancer. According to JSOT classification, OS was 70.3% in patients with T4 cancer compared with 75.4% in patients with T1–T3 cancer. Using classification described by Ebrahimi et al., OS was 77.4% in patients with T4 cancer compared with 73.1% in patients with T1–T3 cancer. Finally, OS was 67.6% in T4 cases and 76.7% in T1–T3 cases according to soft tissue classification (Figure 1).

Using UICC classification, DSS was 82.8% in patients with T4 cancer compared with 84.0% in patients with T1–T3 cancer. According to JSOT classification, DSS was 82.1% in T4 cases and 83.3% in T1–T3 cases. According the classification system described by Ebrahimi et al., DSS was 80.4% and 84.6% in T4 and T1–T3 cases, respectively. Finally, according to the soft tissue classification system, DSS was 67.6% in patients with T4 cancer compared with 87.2% in those with T1–T3 cancer (Figure 2). There was no significant difference between OS and DSS in patients with T4 cancer compared with those with T1–T3 cancer using any classification system. However, DSS in soft tissue T4 cases, which did not consider bone invasion, had a trend toward unfavorable prognosis ($P = 0.05$).

LC in UICC cases T4 was 75.8% compared with 72.2% in T1–T3 cases. LC in JSOT T4 cases was 68.7% compared with 78.3% in T1–T3 cases. Using classification described by Ebrahimi et al., LC was 62.8% in T4 cases and 78.3% in T1–T3 cases. Soft tissue T4 cases exhibited a LC of 57.9% compared with that of 79.8% in T1–T3 cases (Figure 3). There was no significant difference in LC between T4 and T1–T3 using the UICC and JSOT classifications. In contrast, tumors classified as T4 by classification described by Ebrahimi et al. and soft tissue classification recurred significantly more frequently. Moreover, considering the detail of the soft tissue classification, invasion to the skin of face was not associated with bad prognosis. In fact, when cases in which invasion to the exterior skin was observed were excluded from the soft tissue classification, 5-year DSS of the soft tissue classification was
significantly worse in T4 (62.6%) cases than in T1–T3 (77.2%) cases \((P = 0.02)\). Therefore, soft tissue T4 tumors that invade to the interior or posterior organs had worse prognosis.

3.5. Recurrence and prognosis

We compared OS and DSS between cases with and without local recurrence. Data revealed that prognosis was significantly worse in patients who experienced recurrence \((P = 0.05)\).
4. Discussion

Several institutions of the Department of Oral Surgery in Japan adopt the JSOT T4 criteria [3,6] because the UICC T4 criteria seem inadequate. Carcinoma of the mandibular gingiva originates from the gingiva, which is located just above the mandibular bone. Therefore, it can more easily invade to the bone marrow compared with other head and neck cancers. In our patient cohort, >80% of cases were classified as T4 when the UICC criteria were applied. Hence, the UICC classification system is inadequate because of an imbalance in the T distribution.

Muvke et al. [11] identified bone invasion by postoperative histopathological analysis in 15.5% of patients in whom bone invasion could not be diagnosed preoperatively. Furthermore, Mohammad et al. [12] compared the diagnostic accuracy of cone-beam computed tomography (CT) and panoramic radiography for assessing mandibular invasion by lower gingival carcinoma using postoperative histopathological findings. The mean sensitivity for cone-beam CT was 89% compared with that of 73% for panoramic radiography. Taken together, these studies suggest that carcinoma of the mandibular gingiva with bone invasion is more common than expected; therefore, the preoperative diagnosis of bone invasion using UICC classification is difficult.

Some studies reported that cancer cells extended along the inferior alveolar nerve when carcinoma infiltrated the mandibular canal [13]. Therefore, segmental mandibulectomy or hemimandibulectomy was performed such patients [14]. However, many other reports suggested that oral squamous cell carcinoma rarely extended along the nerve [15-20]. Histopathologically, carcinoma of the mandibular gingiva is divided into the following two types: expansive and infiltrative [20-22]. The mechanism underlying this carcinoma has not been well elucidated. Nevertheless, it is possible that a specific cell-adhesion factor exists that adheres to nerves more readily. Although further studies are needed to analyze this, there is
little current evidence to support the implementation of the JSOT T4 criteria for bone invasion.

To further explore local recurrence, we evaluated the specific regions of recurrence. The rate of local recurrence was higher in tumors that invaded adjacent soft tissues compared with those without local invasion. Most instances of recurrence were from the soft tissues of organs adjacent to the mandible, particularly interior and posterior organs such as the masticator space. Nomura et al. [16] reported that tumors recurred from the mucosa around the resection margin after both marginal and segmental resection, and they suggested that sufficient resection of soft tissue is important for preventing recurrence. Many other studies reported that invasion of the mandibular bone was not related to outcomes among patients with carcinoma of the mandibular gingiva [11, 23-26]. In general, superficial extent of carcinoma in soft tissue is broader than that in bone from CT or MRI images. Then, when the surgical margin was decided considering soft tissue, it is more likely to be able to remove the tumor in mandibular bone consequently. Moreover, it is easy to decide surgical margin in bone because of form of mandible. Mucke et al. [11] reported that cancer recurrence was associated with OS, which is consistent with the current study. It is important to control local recurrence from the adjacent soft tissue rather than the bone.

Summarizing the four different classifications, the UICC and JSOT T4 criteria are strongly related to bone invasion because tumors are classified as T4 when they invade to the bone marrow or the mandibular canal. Ebrahimi et al.’s classification is moderately related to bone invasion because the tumor upgrade of one T stage in the presence of medullary bone invasion. In contrast, soft tissue T4 classification is unrelated to bone invasion. In the present study, UICC- and JSOT T4-related bone invasion had no effect on OS, DSS, and LC. In contrast, the Ebrahimi et al. T4, which diminished the influence of bone invasion, had no effect on OS or DSS but lead to significant decreases in LC. Soft tissue T4, which does not
consider bone invasion, had an almost significant relationship with DSS and lead to
significant decreases in LC. Therefore, it is more important to consider the surgical margin in
soft tissue than in bone though we must not ignore the factor of bone invasion.

The UICC defines T4 as invasion to an adjacent organ. It is possible to adopt the bone
invasion criterion to the T4 criteria for other oral cancers such as cancers of the tongue, oral
floor, and buccal mucosa. However, carcinoma of the mandibular gingiva differs from other
oral cancers because it can easily invade to the bone marrow because of the thin gingiva.
Specifically, it is inadequate to regard the mandibular gingiva and the mandibular bone as
different organs; although they are histologically different tissues, they are anatomically the
same organ. As such, soft tissue classification evaluated in the present study is not a new
classification but is based on the UICC classification. Various reports including the current
study have demonstrated the importance of considering controlling recurrence in soft tissue. It
is unnecessary to develop a new classification; instead, the current, well-defined UICC
classification should be expanded; it has distinct advantages and disadvantages.

TNM staging directly affects treatment strategy and the prediction of prognosis. T4 is
strongly correlated with segmental resection compared with T1–T3. However, when only
UICC T4 cases were evaluated in the current study, segmental resection was performed in
only 60.0%. UICC T classification is inadequate when deciding treatment strategy. For
predicting prognosis, each classification was unrelated to OS and DSS. However, soft tissue
classification was almost significantly related to DSS and significantly related to local
recurrence. The soft tissue T4 criterion, which is UICC T4 without bone invasion, was the
most effective for defining T4.
5. Conclusions

The present study suggests that there is no relationship between bone invasion and prognosis, and that T classification should be reconsidered. Because of long-term use of UICC classification, we recommend modifying UICC classification to the soft tissue classification for carcinoma of the mandibular gingiva. However, the current study is a retrospective analysis of a small number of patients. As such, a multi-institutional, prospective study is necessary to determine the appropriate criteria for the TNM staging of carcinoma of the mandibular gingiva.
References


**Figure legends**

Figure 1.
Comparison of Kaplan–Meier curves for 5-year overall survival of T4 and T1–T3 tumors. A, UICC classification; B, JSOT classification; C, Ebrahimi’s classification; D, soft tissue classification.

Figure 2.

Comparison of Kaplan–Meier curves for 5-year disease-free survival of T4 and T1–T3 tumors. A, UICC classification; B, JSOT classification; C, Ebrahimi’s classification; D, soft tissue classification.

Figure 3.

Comparison of Kaplan–Meier curves for 5-year local control of T4 and T1–T3 tumors. A, UICC classification; B, JSOT classification; C, Ebrahimi’s classification; D, soft tissue classification.
Fig. 2

A

UICC DSS

Log-Rank P=0.78

--- T1 to T3

--- T4

B

JSOT DSS

Log-Rank P=0.67

--- T1 to T3

--- T4

C

Ebrahimi’s DSS

Log-Rank P=0.60

--- T1 to T3

--- T4

D

Soft tissue DSS

Log-Rank P=0.05

--- T1 to T3

--- T4
Fig. 3

(A) UICC LC

Log-Rank P = 0.74

--- T1 to T3
--- T4

(B) JSOT LC

Log-Rank P = 0.17

--- T1 to T3
--- T4

(C) Ebrahimi’s LC

Log-Rank P < 0.05

--- T1 to T3
--- T4

(D) Soft tissue LC

Log-Rank P < 0.05

--- T1 to T3
--- T4
Table 1. Classification of each classifications

<table>
<thead>
<tr>
<th>Classification</th>
<th>Feature</th>
</tr>
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<tr>
<td>UICC</td>
<td>T4 of oral cancer means ‘invasion to the adjacent organ’, such as the skin, extrinsic muscles of the tongue, masticator space, or mandibular bone.</td>
</tr>
<tr>
<td>JSOT</td>
<td>Modified UICC classification: T4 about mandibular bone invasion means invasion to the mandibular canal</td>
</tr>
<tr>
<td>Ebrahimi et al.'s</td>
<td>Modified UICC classification: 1 T stage upstaged in the presence of medullary bone invasion.</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>Another aspect of UICC classification: T4 means invasion to the adjacent organ except bone invasion</td>
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Table 2. Demographic characteristics of patients.

<table>
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<th>No. of cases(%)</th>
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<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>38 (46.9)</td>
</tr>
<tr>
<td>Female</td>
<td>43 (53.1)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>≥71</td>
<td>41 (50.6)</td>
</tr>
<tr>
<td>≤70</td>
<td>40 (49.4)</td>
</tr>
<tr>
<td><strong>T4 criteria</strong></td>
<td></td>
</tr>
<tr>
<td>UICC</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>65 (80.2)</td>
</tr>
<tr>
<td>T1 to T3</td>
<td>16 (19.8)</td>
</tr>
<tr>
<td>JOST</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>29 (35.8)</td>
</tr>
<tr>
<td>T1 to T3</td>
<td>52 (64.2)</td>
</tr>
<tr>
<td>Ebrahimi et al's</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>29 (35.8)</td>
</tr>
<tr>
<td>T1 to T3</td>
<td>52 (64.2)</td>
</tr>
<tr>
<td><strong>Soft tissue</strong></td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>17 (21.0)</td>
</tr>
<tr>
<td>T1 to T3</td>
<td>64 (79.0)</td>
</tr>
<tr>
<td><strong>Resection type</strong></td>
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<td>Marginal</td>
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<tr>
<td>Segmental</td>
<td>41 (50.6)</td>
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<td><strong>Local recurrence</strong></td>
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<td>No</td>
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<tr>
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<td>18 (22.2)</td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>66 (81.5)</td>
</tr>
<tr>
<td>Dead</td>
<td>15 (18.5)</td>
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<tr>
<td><strong>Disease specific survival</strong></td>
<td></td>
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<tr>
<td>Alive</td>
<td>70 (86.4)</td>
</tr>
<tr>
<td>Dead</td>
<td>11 (13.6)</td>
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Table 3. Correlation between T4 criteria and surgical resection types.

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<th>Segmental resection</th>
<th>P value</th>
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</tr>
<tr>
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<td>26</td>
<td>39</td>
<td>0.002</td>
</tr>
<tr>
<td>T1-T3</td>
<td>14</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>JSOT classification</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>2</td>
<td>27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T1-T3</td>
<td>38</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td><strong>Ebrahimi et al.’s classification</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>4</td>
<td>25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T1-T3</td>
<td>36</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td><strong>Soft tissue classification</strong></td>
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</tr>
<tr>
<td>T4</td>
<td>2</td>
<td>15</td>
<td>0.001</td>
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<td>T1-T3</td>
<td>38</td>
<td>26</td>
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Table 4.
Rate of pathological nodal status among each T4.

<table>
<thead>
<tr>
<th></th>
<th>pN+</th>
<th>pN−</th>
<th>Total</th>
<th>Rate of pN+ (%)</th>
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<td>16</td>
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<tr>
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<td>6</td>
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<td>17</td>
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