<table>
<thead>
<tr>
<th>Title</th>
<th>Spindle Cell Carcinoma of the Oral Cavity: the Impact of Chemotherapy on Pulmonary Metastatic Tumor Doubling Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author(s)</td>
<td>Shigeta, Takashi / Minamikawa, Tsutomu / Matsui, Taiki / Kakei, Yasumasa / Akashi, Masaya / Hasegawa, Takumi / Sakakibara, Akiko / Shibuya, Yasuyuki / Komori, Takahide</td>
</tr>
<tr>
<td>Citation</td>
<td>The Kobe journal of the medical sciences, 61(3):64-70</td>
</tr>
<tr>
<td>Issue date</td>
<td>2015</td>
</tr>
<tr>
<td>Resource Type</td>
<td>Departmental Bulletin Paper / 紀要論文</td>
</tr>
<tr>
<td>Resource Version</td>
<td>publisher</td>
</tr>
<tr>
<td>DOI</td>
<td>10.24546/81009158</td>
</tr>
<tr>
<td>URL</td>
<td><a href="http://www.lib.kobe-u.ac.jp/handle_kernel/81009158">http://www.lib.kobe-u.ac.jp/handle_kernel/81009158</a></td>
</tr>
</tbody>
</table>

PDF issue: 2018-11-22
Spindle Cell Carcinoma of the Oral Cavity: the Impact of Chemotherapy on Pulmonary Metastatic Tumor Doubling Time

TAKASHI SHIGETA*, TSUTOMU MINAMIKAWA, TAIKI MATSUI, YASUMASA KAKEI, MASAYA AKASHI, TAKUMI HASEGAWA, AKIKO SAKAKIBARA, YASUYUKI SHIBUYA, and TAKAHIDE KOMORI

Department of Oral and Maxillofacial Surgery, Kobe University Graduate School of Medicine

Received 11 May 2015/ Accepted 11 September 2015

Keywords: spindle cell carcinoma, oral cavity, tumor doubling time, pulmonary metastasis, chemotherapy

Spindle cell carcinoma (SpCC) an aggressive squamous cell carcinoma, variant, frequently metastasizes to regional lymph nodes and distant organs. Unfortunately, an effective treatment method for oral SpCC distant metastasis has not yet been established. Here we present 2 of oral SpCC cases that showed distant metastases after initial treatment, and 2 that showed distant metastases following during surgery. We calculated the tumor doubling time (TDT) and onset of the pulmonary metastatic and examined the TDT of the pulmonary metastatic tumor in patients with or without chemotherapy to determine the effect of anticancer drugs on oral SpCC. Tumor growth curves revealed that pulmonary metastasis likely grew to 1mm, 122 days before the initial examination, indicating that most oral SpCC patients should be treated for metastases. Three patients underwent chemotherapy for pulmonary metastatic tumor, complete response (CR) in one patient and no change (NC) in two. Thus, SpCC patients may have pulmonary micro-metastases even at the initial examination. We recommend wide resection for oral SpCC patients, followed by chemotherapy to prevent metastases.

INTRODUCTION

Spindle cell carcinoma (SpCC), a subtype of squamous cell carcinoma (SCC), recurs and metastasizes more frequently, and is associated with a worse prognosis than SCC.1, 3 Although, SpCC in the head and neck sometimes occurs in the laryngeal region,1, 2 rarely occurs in the oral cavity. Here we present 4 cases of oral SpCC. The purpose of this study was; to describe the clinical features, the treatment and prognosis of this extremely rare malignancy in the oral cavity. In addition, we also examined the tumor doubling time (TDT) of the pulmonary metastatic tumor in patients with or without chemotherapy to determine the effect of anticancer drugs on oral SpCC.

MATERIALS AND METHODS

Four patients with SpCC in the oral cavity visited the Department of Oral and Maxillofacial Surgery, Kobe University Graduate School of Medicine, between 2005 and 2011 (Table I). The patients consisted of 3 men and 1 woman, ages 36 to 88 years old. The tumor was located in the tongue in 2 patients, in the lower gingiva in 1 patient, and in the upper gingiva in the other patient. All of these patients developed pulmonary metastases, with 2 patients showing metastases at the initial treatment and 2 patients showing metastases following surgery. Three patients underwent chemotherapy for the metastatic tumor. Clinical features, treatment method and prognosis were investigated in each patient. In addition, TDT and the onset of the pulmonary metastatic tumors were calculated using computed tomography images and the method described by Collin4 and Umeda5 (Fig. 1).

Figure 1A. TDT is defined as the time required for the tumor to double in size.

Tumor volume doubling time(TDT) = \[ T \times \frac{\log_2}{\log_{10} (d_2 / d_1)} \]

*T: Time from d2 to d1

d1: Tumor diameter in initial point

d2: Tumor diameter in T days after initial point

Keywords: spindle cell carcinoma, oral cavity, tumor doubling time, pulmonary metastasis, chemotherapy
SPINDLE CELL CARCINOMA OF THE ORAL CAVITY

Table 1. Patients with spindle cell carcinoma in the oral cavity

<table>
<thead>
<tr>
<th>No.</th>
<th>Primary site</th>
<th>Age</th>
<th>Gender</th>
<th>TNM classification</th>
<th>Primary site metastasis</th>
<th>Distant metastasis</th>
<th>TDT average (days)</th>
<th>Outcome (survival time)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Tongue</td>
<td>88</td>
<td>F</td>
<td>T2N0M0</td>
<td>S</td>
<td>Lung</td>
<td>11.4 days</td>
<td>DOD (80 days)</td>
</tr>
<tr>
<td>2.</td>
<td>Upper gingival</td>
<td>74</td>
<td>M</td>
<td>T2N0M1</td>
<td>RT</td>
<td>Lung, Adrenal grand</td>
<td>25.0 days</td>
<td>DOD (70 days)</td>
</tr>
<tr>
<td>3.</td>
<td>Tongue</td>
<td>41</td>
<td>M</td>
<td>T2N0M0</td>
<td>S</td>
<td>Lung</td>
<td>-</td>
<td>NED (64 months)</td>
</tr>
<tr>
<td>4.</td>
<td>Lower gingival</td>
<td>36</td>
<td>M</td>
<td>T4aN2cM0</td>
<td>S</td>
<td>Lung, Colon, Skin</td>
<td>128.0 days</td>
<td>DOD (12 months)</td>
</tr>
</tbody>
</table>


RESULTS

1) Case presentation
Case 1: An 88-year-old woman was referred to our hospital with a chief complaint of a tumor located on the right edge of the tongue (Fig. 2). The tumor was 60 \times 45 \text{ mm} in size and had a rough and irregular surface associated with pain and slight bleeding. Clinical and CT examinations revealed no cervical lymphadenopathy or lung metastasis. Histological diagnosis of the biopsy specimen was SpCC, and the patient underwent partial glossectomy (Fig. 3). However, local recurrence, neck metastasis, and multiple lung metastases occurred 1 month later. No chemotherapy was performed for the recurrent and metastatic tumor, and the patient died of respiratory dysfunction 3 months after surgery (Fig. 4).

Figure 1B.
The onset time (10 \mu m in diameter) and the time when tumor grew to 1mm in diameter are calculated on the same graph paper.

Figure 2. Intraoral findings of Patient 1 at the first visit

Figure 3. Histopathological findings of Patient 1
Photomicrograph showing spindle cell carcinoma primarily consisting of spindle cells.
Case 2: A 74-year-old man was referred to our hospital complaining of an eating disorder due to a tumor of the maxilla. The tumor had a rough and irregular surface and was $26 \times 24$ mm in size (Fig. 5). Multiple distant metastases were present in the lung, adrenal glands, and mediastinal lymph nodes at the initial examination. Histological diagnosis of the biopsy specimen was SpCC. The patient underwent chemo-radiotherapy composed of 60 Gy of irradiation, 5-fluorouracil (2500mg/body), docetaxel (80mg/body), cisplatin (75 mg/body), and pinorbin (20 mg/body). A complete response (CR) was achieved for the primary tumor, and the patient was able to eat food by mouth. However, the pulmonary metastatic tumors showed progression during the chemo-radiotherapy (Fig. 6), and the patient died 70 days after his initial visit.
Case 3: A 41-year-old man visited to our hospital with a chief complaint of a $35 \times 15$ mm tumor with ulceration on the left side of the tongue. Histological diagnosis of the biopsy specimen was SpCC. Enlarged neck lymph nodes were not detected by preoperative imaging. The patient underwent partial glossectomy, ipsilateral elective neck dissection, and reconstructive surgery using a free forearm flap. Adjuvant chemotherapy with CDDP ($20 \text{ mg/m}^2 \times 5 \text{ days}$) and 5FU ($500 \text{ mg/m}^2 \times 5 \text{ days}$) was performed 20 days after surgery. Histological examination revealed no positive lymph nodes, and no recurrent tumors in the tongue and neck were found. However, lung metastasis occurred 13 months later. The patient then underwent chemotherapy with docetaxel ($70 \text{ mg/m}^2 \times 10 \text{ courses}$) and obtained a CR for the lung metastasis. The patient is well 47 months after the last course of chemotherapy (Fig. 7).

Case 4: A 36-year-old man was referred to our hospital because of a $30 \times 15$ mm tumor in the median lower gingiva. Histological diagnosis of the biopsy specimen was SpCC. Bilateral neck lymph nodes were enlarged. Preoperative colon fiber examinations revealed a tumor in the transverse colon, with histological findings similar to those of the intraoral tumor. The patient was diagnosed with SpCC of the mandible with metastases to the bilateral regional lymph nodes and the colon. He underwent marginal mandibulectomy accompanied by bilateral neck dissection, followed by 2 courses of DCF therapy (cplatin: $70 \text{ mg/m}^2$, docetaxel: $60 \text{ mg/m}^2$, fluorouracil: $750 \text{ mg/m}^2 \times 5 \text{ days}$), and 3 courses of FP therapy (cplatin: $80 \text{ mg/m}^2$, fluorouracil: $800 \text{ mg/m}^2 \times 5 \text{ days}$). Despite these therapies, pulmonary metastasis occurred 5 months after the initial visit. The patient died 9 months after the last course of chemotherapy.
2) TDT and onset of pulmonary metastasis

TDT of the pulmonary metastasis was calculated in each patient, except Patient 3 who achieved a CR for the metastatic tumor by chemotherapy. TDT in Patient 1, 2, and 4 was 11.4, 25.0, and 128 days, respectively. TDT in Patient 1, who did not undergo chemotherapy, was much shorter than that of Patient 2 or 4, who did undergo chemotherapy.

Patients 2 and 4 had distant metastases clinically at the initial treatment. Although Patient 1 was diagnosed initially not to have lymph node- and distant metastases, lung metastasis likely grew to 1 mm in diameter 122 days before the initial examination based on the tumor growth curves (Table II).

Table II. Incubation period back-calculated with TDT in Patient 1

<table>
<thead>
<tr>
<th>Tumor size</th>
<th>Tumor volume (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>59 days: Φ 15.3 × Φ 13.0 mm</td>
<td></td>
</tr>
<tr>
<td>14 days: Φ 5.5 × Φ 5.5 mm</td>
<td></td>
</tr>
</tbody>
</table>

DISCUSSION

SpCC is a rare variant of SCC in the head and neck region, composed of squamous cells and a malignant spindle cell component.1-3,6-8, 9-13, 15-18. The most frequent site of SpCC occurrence in the head and neck region is the larynx, whereas in the oral cavity, SpCC often occurs in the lip and tongue, but rarely in the gingiva.3, 7-9 The primary sites of occurrence in our cases were the tongue and the gingiva (2 cases each).

The prognosis of SpCC is extremely poor in contrast to that of SCC. In many SpCC cases, metastasis occurs in the cervical lymph node, lung, and heart. Of 59 cases of oral SpCC examined, recurrence and metastasis occurred in 12 cases, 16 cases, respectively. Seven of these cases involved cervical lymph node metastasis alone, while 9 cases involved distant metastasis. The reported survival rate for SpCC for this group of patients was 36%.7 Similarly, Su et al. reported a metastasis rate of 33.3% and a 3-year survival rate of 27.5%.3 Another study of 34 patients with laryngeal and hypopharyngeal SpCC, showed that recurrence occurred in 10 patients, with a 3-year survival rate of 56.8%.19

In our study, 3 of the 4 patients died within 1 year of local recurrence and distant metastasis. The cause of this extremely low survival rate seems to be the aggressive, biological characteristics of SpCC.

Some reports have shown that analysis of tumor growth rate, expressed as TDT, is an accurate method for comparison of the biologic aggressiveness of malignant tumors in different patients. In general, a tumor of 10 μm in diameter grows to 1 mm after 20 doublings, 1 cm after 30 doublings, and 10 cm after 40 doublings. Umeda et al. reported that the average TDT in other malignant neoplasms varied from 14 to 393 days. In our study, the TDT for 1, who did not undergo chemotherapy, was 11.4 days. This findings suggests that the TDT for SpCC is much shorter than most other malignant neoplasms and almost equal to that of Ewing sarcoma (Fig. 8). Moreover, the TDT for Patients 2 and 4, who did undergo chemotherapy, were longer than that of Patient 1 (25.0 and 128 days, respectively), suggesting that chemotherapy delayed the speed of metastatic SpCC growth.

Using the TDT graph curves, we were able to calculate the probable timing of pulmonary metastatic tumor growth. Two of the 4 patients in the present study already showed distant metastases at the initial treatment and the rest showed distant metastases following during surgery. We selected the pulmonary metastatic tumor as a distant metastatic site of calculating TDT because distant metastatic site in our case were commonly lung (4 cases) and the pulmonary metastatic tumors were convenient to calculate using computed tomography. Based on the TDT growth curve in 1 of these patients, the pulmonary metastasis likely grew to 1 mm in diameter 122 days before the initial examination. These results strongly suggest that SpCC in the oral cavity is more aggressive and...
SPINDLE CELL CARCINOMA OF THE ORAL CAVITY

has a poorer prognosis than SCC because SpCC patients may have pulmonary micro-metastases even at the initial examination.

Although the prognosis of SpCC is poor, the most effective treatment has not yet been established. In general, SpCC is treated with surgery alone or in combination with radiotherapy similar to SCC, since the results of radiation therapy alone have not been satisfactory. Ellis et al. reported that wide surgical excision, alone or with radical neck dissection, was the most successful therapeutic modality. Most authors agree that although radiotherapy is not very effective, it is acceptable for inoperable cases and cases with, surgically positive margins, or positive nodal metastasis at the time of diagnosis. Conversely, Ampil et al. suggested that radiotherapy for SpCC may be equivalent to its use for SCC of the larynx and hypopharynx. In the current study, radiotherapy was performed as a treatment against the primary site in Case 2, and a CR was achieved. The finding suggests that radiotherapy is sometimes effective for control of the local tumor, but the effect on overall survival is still unknown.

The role of chemotherapy for oral SpCC, as well as that of radiotherapy, is not yet clear, and development of more effective adjuvant therapies for metastatic SpCC is expected. However, Colozza et al. reported that a patient with SpCC of an unknown primary site, metastatic to the neck and lung, treated with chemotherapy, had a CR and was disease-free 12 months after diagnosis. In our study, chemotherapy was performed in 3 of 4 patients (Cases 2, 3, and 4) for distant metastasis after surgery or radiation. Patient 3 achieved a CR of the metastatic tumor. The other patients did not show a response to chemotherapy; however, their TDTs were longer than that of Patient 1, who did not undergo chemotherapy, suggesting that chemotherapy delayed the speed of metastatic tumor growth. These findings support the use of chemotherapy in the treatment of oral SpCC. On the other hand, TDT of patient 2 was longer than that of patient 1, but the survival time of patient 2 was shorter than that of patient 1. This discrepancy suggests that TDT was useful for evaluating the speed of tumor growth and response to chemotherapy, but not for predicting the survival period. It is necessary to collect more cases to identify the relationship TDT and survival time.

Although no definitive conclusion can be made due to the limited number of patients, our findings suggest that most patients with oral SpCC should be treated for distant metastases, given its aggressive behavior, frequent recurrence and metastases, and poor prognosis compared to oral SCC. Thus, we recommend wide resection for oral SpCC patients, immediately followed by chemotherapy or chemo-radiotherapy. Radiation therapy can be used as an optional therapy for primary and nodal control after initial or salvage surgery, and to extend the patient’s life in inoperable cases, whereas chemotherapy may play an important role in preventing distant metastasis. As more cases are collected, biological features and appropriate therapies for oral SpCC will become more definitive.

![Figure 8. TDT of various malignant tumors (Quotation figure from a paper by Umeda et al.)](image-url)
ACKNOWLEDGEMENTS
The authors are deeply grateful to Masahiro Umeda and Hideki Komatsubara for supporting this work.

REFERENCES