Ten-year Clinical Trends among 575 Consecutive Oral Cancer Patients at Tokyo Dental College Oral Cancer Center

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Abstract

The facilities comprising Tokyo Dental College (TDC) —the college itself and its medical institutions at Suidobashi, Ichikawa, and Chiba— have been officially recognized as a center for treating oral cancer. The TDC Oral Cancer Center (OCC) was established on April 1, 2006. It provides comprehensive medical care, including that aimed at recovery of postoperative function, such as restoration of stomatognathic function, dysphagia therapy, and placement of maxillary prostheses. The purpose of this study was to investigate patient trends at TDC-OCC over the 10 years following its establishment in order to determine how the safe and high-quality cancer care already provided might be even further improved. Oral cancer patients attending TDC-OCC between April 2007 and March 2017 were investigated. Clinical information was obtained from medical records and analyzed, including that on patient numbers, age, sex, primary site of tumor, clinical stage, and surgery provided. There were 758 new cases, and the number of new cases showed an annual increase. Among the total number of new patients, 575 (75.9%) represented primary cases. The number of operations also showed an increase, which correlated with the increase in the number of patients. The incidence in oral cancer has increased in several countries, including Japan. Oral cancer can be observed macroscopically and touched. In contrast to with cancers at many other sites, and despite various diagnostic devices for early detection having been developed, however, cases are often advanced when first encountered. Many advanced cases were treated at TDC-OCC, and the number of reconstructive operations following progressive cancer also increased over time.

Key words: Oral cancer — Patient survey — Prognosis — Hospital — Oral Cancer Center
Introduction

Oral cancer is the most common malignancy of the head and neck\textsuperscript{10}, and is the 10th most common cancer worldwide\textsuperscript{10}. Lip and oral cancers account for approximately 355,000 new cases and approximately 177,000 deaths each year globally\textsuperscript{3}. The rates of incidence of oral cancer incidence have increased in several countries, including Japan\textsuperscript{5}. Overall and 5-year survival rates in oral cancer are approximately 60%, but vary from 10% to 82% depending on clinical stage, age, race, comorbidity, and primary site\textsuperscript{3}. Treatment for oral cancer has steadily progressed with advances in surgical techniques, such as reconstructive surgery, and improvements in examination and diagnosis. Oral cancer can be observed macroscopically and touched. In contrast to with cancers at many other sites, and despite the availability of diagnostic methods for early detection, however, cases are often already advanced when first encountered. Such cases have a poor prognosis because surgery may be impossible or local recurrence and nodal and/or distant metastasis is common, even if surgery was carried out. In these cases, chemotherapy and radiotherapy must be performed together, and surgery is often required as well.

The facilities comprising Tokyo Dental College (TDC)—the college itself and its medical institutions at Suidobashi, Ichikawa, and Chiba—have been officially recognized as a center for treating oral cancer. Established in April 2006 at the Ichikawa General Hospital of TDC, the Oral Cancer Center (OCC) is the first specialized institution for oral cancer in Japan. The Ambulatory Center for maxillary prosthesis cases was subsequently established in October 2011. The TDC-OCC provides comprehensive medical care, including that aimed at recovery of postoperative function, such as restoration of stomatognathic function, therapy for dysphagia, and placement of maxillary prostheses.

The purpose of the present study was to investigate patient trends at TDC-OCC over the 10 years following its establishment with the aim of ascertaining how the safe and high-quality cancer care already provided might be even further improved.

Patients and Methods

The medical records of patients with oral cancer attending TDC-OCC between April 2007 and March 2017 were reviewed. Clinical information was obtained on primary cases, including data on patient numbers, age, sex, primary site of tumor, clinical stage, and type of surgical procedure undergone. The cumulative 5-year survival rate was estimated and nodal and distant metastases evaluated among all surgical cases. The TNM Classification of Malignant Tumors published by the Union for International Cancer Control (7th edition) was used to determine clinical stage.

All treatment provided at TDC-OCC is in compliance with the National Comprehensive Cancer Network guidelines\textsuperscript{14}, and is similar in standard to that offered at other facilities. Computed tomography (CT) with contrast-enhanced and/or magnetic resonance imaging was performed to evaluate primary disease and cervical lymph nodes, and positron emission tomography CT (PET-CT) to determine distant metastases prior to commencement of treatment. Oral cytology using the direct smear method\textsuperscript{21} and biopsy were also performed. If possible, upper and lower gastrointestinal endoscopy were also carried out to determine whether multiple primary cancers were present. If dysphagia was anticipated postoperatively, speech and swallowing evaluation were conducted. Radical surgery was selected under standard practice at this institution. Although definitive radiation therapy (RT) is effective, it is not routinely used, as osteoradionecrosis occurs frequently; therefore, chemoradiotherapy is used as adjuvant postoperative treatment\textsuperscript{5}. Postoperative adjuvant chemoradiotherapy (3-weekly cisplatin [CDDP] + RT) was performed in cases requiring radical surgery when any of the following adverse risk features were found: involvement of ≥2 nodes,
microscopic positive margins, and extra-nodal extension. Depending on the patient’s performance status, single-agent systemic therapy or palliative RT was considered. Figure 1 shows the treatment algorithm adopted at the TDC-OCC.

Patients being treated at Chiba Dental Center or Suidobashi Hospital who required chemoradiotherapy were transferred to the TDC-OCC because the Chiba Dental Center and Suidobashi Hospital do not have the facilities to provide it.

The protocol of this study was approved by the Research Ethics Committee of Tokyo Dental College (Approval no: I16-07).

Statistical analysis

All the statistical analyses were performed using EZR ver. 1.36 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics. All the p-values given are two-sided, and a p-value of ≤0.05 was considered to be statistically significant. Spearman’s rank correlation coefficient was used to test annual trends among younger patients; they are denoted below by “rs”.

Results

1. Patient trends and characteristics

A total of 758 patients visited the TDC-OCC between April 2007 and March 2017. The number of patients showed an annual increase, approximately doubling in 2017 compared with in 2007. A total of 575 patients presented with primary disease (75.9% of all cases). Of these, 526 patients (91.5% of primary cases) were treated at the TDC-OCC, with 441 of them (76.7% of primary cases) undergoing radical surgery. Seventy-seven patients (13.4% of primary cases) underwent radiation therapy alone or chemoradiation therapy, and 57 (9.9% of primary cases) received best supportive care or hospital transfer. A total of 137 patients presented with secondary disease (17.5% of all cases). Additionally, the numbers of patients treated with postoperative adjuvant chemoradiotherapy...
for recurrent/metastatic high-risk cancer, maxillary prostheses, and those who visited TDC-OCC for a second opinion increased over time (Table 1).

Among the 575 patients with primary disease, the age ranged from 23 to 95 years, with an average age of 67 years. Male-to-female ratio was 1.4:1. Although there was a male preponderance, the number of females aged ≥80 years was also large (Fig. 2). Furthermore, the number of patients aged ≤45 years showed a significant increase during the 10-year period covered by the study (Fig. 3, Spearman’s rank correlation coefficient, p = 0.0394, rs = 0.673).

2. Primary site

Among the total number of primary cases (n = 575), the tongue was the most frequent site (n = 249, 43.3%), followed by the mandibular gingiva (n = 138, 24.0%), maxillary gingiva (n = 77, 13.4%), buccal mucosa (n = 43, 7.5%), oral floor (n = 40, 7.0%), hard

Table 1  Patient trends

<table>
<thead>
<tr>
<th>Fiscal year</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>All cases (Surgical cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>47</td>
<td>49</td>
<td>42</td>
<td>76</td>
<td>62</td>
<td>75</td>
<td>97</td>
<td>83</td>
<td>115</td>
<td>112</td>
<td>758</td>
</tr>
<tr>
<td>Primary cases</td>
<td>39</td>
<td>40</td>
<td>39</td>
<td>59</td>
<td>54</td>
<td>56</td>
<td>72</td>
<td>49</td>
<td>84</td>
<td>83</td>
<td>575</td>
</tr>
<tr>
<td>Treated at OCC</td>
<td>38</td>
<td>39</td>
<td>39</td>
<td>52</td>
<td>49</td>
<td>50</td>
<td>65</td>
<td>42</td>
<td>77</td>
<td>75</td>
<td>526 (441)</td>
</tr>
<tr>
<td>Transferred to another hospital</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>8</td>
<td>49</td>
</tr>
<tr>
<td>Secondary cases</td>
<td>8</td>
<td>9</td>
<td>2</td>
<td>13</td>
<td>7</td>
<td>14</td>
<td>16</td>
<td>25</td>
<td>24</td>
<td>19</td>
<td>137</td>
</tr>
<tr>
<td>Recurrent/Metastasis (Treated at OCC)</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>8</td>
<td>8</td>
<td>13</td>
<td>12</td>
<td>62 (48)</td>
</tr>
<tr>
<td>Adjuvant chemoradiotherapy request</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>7</td>
<td>4</td>
<td>21</td>
</tr>
<tr>
<td>Follow-up request</td>
<td>2</td>
<td>8</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>14</td>
<td>2</td>
<td>3</td>
<td>41</td>
</tr>
<tr>
<td>Transferred to another hospital</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Other cases*</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>5</td>
<td>9</td>
<td>7</td>
<td>10</td>
<td>46</td>
</tr>
</tbody>
</table>

*Other cases include patients seen for a second opinion or maxillary prosthesis.

Fig. 2  Tendencies in patient age and sex

Total of 575 patients presenting with primary disease. Age ranged from 23 to 95 years, with an average age of 67 years. Male-to-female ratio was 1.4:1.

Fig. 3  Tendency among young oral cancer patients

Number of younger patients (<45 years) showed a significant increase (Spearman’s rank correlation coefficient, p = 0.0394, rs = 0.673).
palate (n = 14, 2.4%), and lip (n = 6, 1.0%) (Fig. 4).

3. Clinical cancer stage

Among the total number of primary cases (n = 575), 82 (14.3%) were stage I, 185 (32.2%) were stage II, 64 (11.1%) were stage III, and 244 (42.4%) were stage IV. The primary site at each cancer stage is shown in Fig. 5. The tongue cancer ratio exhibited a decrease with increase in cancer stage. However, the mandibular gingiva cancer ratio showed an increase with increase in cancer stage.

4. Operations

The total number of operations, including those for primary and recurrent cases, was 656 between 2009 and 2016. The number of operations performed showed an annual increase, with ≥100 operations performed after 2014. Among the total number of patients with primary disease, 444 had local disease, and 208 of these patients underwent neck dissection including elective neck dissection at the same time. One hundred and thirty-five patients underwent reconstructive surgery, and this number showed an annual increase (Fig. 6). Free flap reconstructive surgery was carried out in cooperation with a plastic surgeon. Details of the reconstructive surgery provided are shown in Table 2.

5. Late nodal and distant metastases

Late nodal metastases were found in 49 cases (19.8%) among the 247 patients that did not undergo elective neck dissection at first surgery. Nodal metastases occurred frequently with tongue and maxillary gingiva cancers (Fig. 7).

Distant metastases were found in 43 cases (9.8%) among the 441 patients that underwent radical surgery. Distant metastases increased with progression of clinical stage, and were most frequent among stage IV patients (Fig. 7).

6. Prognosis

The 5-year overall survival rate among the 441 primary patients who underwent radical surgery is shown in Fig. 8. Overall survival among the total number of patients was 86.9%. That for stage I, II, III, and IV was 97.4%, 91.3%, 89.9%, and 75.9%, respectively. The number of patients with stage I, II, III, and IV disease was 75 (17.0%), 162 (36.7%), 51 (11.6%), and 153 (34.7%), respectively. Overall survival showed a significant decrease in stage IV compared with in the other stages (log-rank test, p<0.01).

Discussion

Although oral cancer can often be detected macroscopically and by touch, cases are often at the advanced stage before they are actually encountered. The reasons for this include that fact that many early-stage cancers are asymptomatic; that recognition of oral cancer is low; and that differentiation from other oral mucosal diseases, such as oral lichen planus or oral leukoplakia, is difficult. Treatment of advanced cases may require chemotherapy and radiotherapy in addition to surgical resection. Therefore, the number of institutions that can provide such
treatment is limited, and the prognosis is often poor in patients with advanced disease.

In the present study, the number of patients attending the TDC-OCC and undergoing operations showed an increase compared with in the first year after its establishment. This is in agreement with the general tendency toward an increase in the number of such patients throughout Japan. Additionally, the number of young cancer patients attending the TDC-OCC showed an increase. Both these results are in agreement with those reported in other recent studies. Most of the patients in the present study presented with stage IV disease. This may be explained by the fact that many advanced cases are referred to this center from external institutions. Tongue cancer was the most frequent
type of cancer at every clinical stage. It accounted for approximately half the stage I and II cases, and showed a decrease with worsening clinical stage. This suggests that tongue cancer is being detected relatively early. Conversely, the number of patients with lower gingival cancer showed an increase with progression in clinical stage, suggesting that early detection of this type may be more difficult. Concerning patient age, those aged ≤70 years were mainly male, whereas those aged >80 years were female. We believe that these results reflect the long average life span of women in Japan.

The survival rate among patients attending the TDC-OCC was good, which was attributed

<table>
<thead>
<tr>
<th>Type of flaps</th>
<th>No. of cases</th>
<th>Total cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free flaps</td>
<td></td>
<td>99</td>
</tr>
<tr>
<td>Forearm flaps</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Rectus abdominis flaps</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Anterolateral thigh flaps</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Fibular flaps</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Free latissimus dorsi flaps</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Scapular flaps</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Distant pedicled flaps</td>
<td></td>
<td>36</td>
</tr>
<tr>
<td>Pectoralis major flaps</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Deltopectoral flaps</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Pedicled latissimus dorsi flaps</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Local pedicled flaps</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical island flaps</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Submental flaps</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Nasolabial flaps</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 7 Late nodal and distant metastases
Late nodal metastases were found in 49 patients among 247 patients who did not undergo elective neck dissection at first surgery. Distant metastases were found in 43 patients among 441 patients who underwent radical surgery.
to strict postoperative follow-up and early intervention for local recurrence or metastasis. Generally, recurrence and metastasis of oral cancer is most often detected within 1–2 years postoperatively. Early diagnosis of recurrence or metastasis and prompt appropriate treatment was reported to improve the survival rate. Therefore, it is standard practice at the TDC-OCC to perform a monthly follow-up and CT scan for 1 year postoperatively. At 2 years postoperatively, CT is performed once every 3–4 months. A PET-CT is performed if needed, and in advanced cases it is performed at least once every 6 months. If feasible, the lesion is resected after consultation with the respiratory surgery department regarding possible metastasis to the lungs. Furthermore, in recent years, oral cancer treatment has advanced, particularly in the field of chemotherapy. Indications for cetuximab, an anti-epidermal growth factor receptor monoclonal antibody, were expanded to include the head and neck region in 2012 in Japan. Cetuximab has been administered to patients treated at TDC-OCC, and was found to improve treatment outcomes. Furthermore, nivolumab, an immune checkpoint inhibitor, was approved for use in oral cancer in April 2017. Nivolumab is also used in TDC-OCC, and anticipated to become a treatment choice in unresectable locally advanced cases or those of distant metastases. Additionally, superselective arterial injection chemotherapy is a common treatment option. It is carried out in collaboration with a radiologist, and is effective in unresectable cases. However, as these are new treatments, unanticipated adverse events may occur. These concerns are currently being addressed in cooperation with the medical department of our hospital.

The mission of the TDC-OCC is to provide safe, high-quality medical services for patients with oral cancer. Therefore, multidisciplinary teams are assigned to each patient. Pre- and postoperative oral care are provided by a dental hygienist; dysphagia rehabilitation exercise and assessment by a rehabilitation doctor; nutrition management and education by the nutrition support team; and postoperative maxillary prosthesis treatment by a maxillary prosthesis specialist. All these efforts are aimed at further improving the already high-quality treatment provided for patients with oral cancer at this center.

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References

2) Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, Chau I, Ernstoff


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