General Rules for Clinical and Pathological Studies on Oral Cancer: A Synopsis


*For reprints and all correspondence: Tadaaki Kirita, Department of Oral and Maxillofacial Surgery, Nara Medical University, 840 Schijo-cho, Nara-Kashihara 634-8521, Japan. E-mail: tkirita@naramed-u.ac.jp

Received April 10, 2012; accepted August 6, 2012

For the doctors and other medical staff treating oral cancers, it is necessary to standardize basic concepts and rules on oral cancers to progress in the treatment, research and diagnosis. Oral cancers are integrated in head and neck cancers and are applied to the general rules on head and neck cancer, but it is considered that more detailed rules based on the characteristics of oral cancers are essential. The objectives of this ‘General Rules for Clinical and Pathological Studies on Oral Cancer’ are to contribute to the development of the diagnosis, treatment and research of oral cancers based on the correct and useful medical information of clinical, surgical, pathological and image findings accumulated from individual patients at various institutions.

Key words: oral cancer – general rules – clinical and pathological studies

INTRODUCTION

The oral cavity, an organ important for humans to live rich lives, has a complicated structure including the teeth. If cancer arises in the oral cavity, it markedly impairs the quality of life. Oral cancers are integrated in head and neck cancers and are applied to the general rules on head and neck cancer, but it is considered that more detailed rules based on the characteristics of oral cancers are essential. This is why we authored the ‘General Rules for Clinical and Pathological Studies on Oral Cancer’. These rules were formulated on the basis of the UICC and WHO classifications, in principle, but they were partially revised when revision was considered necessary and were proposed as a draft by the Japan Society for Oral Tumors.

We already published the Japanese edition (1) originally in 2010 and it consisted of three parts, i.e. the overview, rules and explanations, totaling 102 pages. In this paper, the English edition of the ‘Rules’ section is primarily presented because of space limitation.

OBJECTIVES

For people handling oral cancers in various positions to be able to conduct diagnosis, treatment and research with a common perception, the standardization of basic concepts and specific methods for their handling is necessary. The objectives of these rules are to collect clinical, surgical and pathological findings including image information by employing common standards, clarify detailed pathological features, accumulate useful medical information from individual patients at various facilities and contribute to the development of the diagnosis, treatment and research of oral cancers.
TARGET DISEASES

In the present rules, oral cancers mean carcinomas originating in the covering mucosa at six sites in the oral cavity according to the UICC classification. They are targeted to: (1) tongue cancer, (2) upper gingival cancer, (3) lower gingival cancer, (4) buccal mucosal cancer, (5) oral floor cancer and (6) hard palate cancer in the order of incidence, and secondary cancers are excluded. Cancer of the salivary gland is dealt with as a separate item.

RULES

I. CLINICAL FINDINGS

1. PRIMARY LESION

1) Anatomical sites and subsites (Fig. 1)
   - Tongue (TON-0,1,2), Upper gingiva and alveolus (UG), Lower gingiva and alveolus (LG), Buccal mucosa (BM-0,1,2,3,4), Floor of mouth (FOM), and Hard palate (HP)

2) Locations of the lesion
   - Tongue (TON-0,1,2)
     - dorsal surface (0)/lateral borders (1)/ventral surface (2)
   - Upper gingiva and alveolus (UG)
     - dentulous jaw (teeth: 8/7/6/5/4/3/2/1/1/2/3/4/5/6/7/8), edentulous jaw (Molar/Premolar/Canine/Incisor/I/C/P/M)
   - Lower gingiva and alveolus (LG)
     - dentulous jaw (teeth: 8/7/6/5/4/3/2/1/1/2/3/4/5/6/7/8), edentulous jaw (Molar/Premolar/Canine/Incisor/I/C/P/M)

3) Size
   - (long diameter)/C2 (short diameter)/C2 (thickness) cm or (mesio-distal diameter)/C2 (bucco-lingual diameter)/C2 (thickness) cm

4) Clinical types
   - Superficial type: Those primarily showing superficial growth
   - Exophytic type: Those primarily showing exophytic growth
   - Endophytic type: Those primarily showing endophytic growth
   - Unclassified type: Those not belonging to any of the above types

   Note (1) Iodine vital staining is performed
   Note (2) The clinical type before treatment is recorded
   Note (3) If pretreatment has been conducted, this fact is recorded with the disease type

   Ex.) Type C-1, Type CR-0

5) Depth
   - Depth: Tissue name of the deepest part of cancer invasion (See the tissue names below according to the subsites.)
   - Deepness: Distance from the surface of the imaginary normal mucosa to the deepest part of cancer invasion

   In the present rules, original evaluation criteria were prepared for the invasion of adjacent tissues (T4a) by attaching importance to evaluation of the depth.

   1) Tongue (TON): mucosa (M)/submucosa (SM)/shallow part of the proper muscle layer of the tongue (MP1)/deep part of the proper muscle layer of the tongue (MP2)/extrinsic muscles of the tongue (HG)

   2) Upper gingival and alveolus (UG): mucosa (M)/submucosa (SM)/periosteum (PER)/cortical bone (CB)/bone marrow (CAN)/maxillary sinus (MS) • nasal cavity (NC)

   3) Lower gingiva and alveolus (LG): mucosa (M)/submucosa (SM)/periosteum (PER)/cortical bone (CB)/upper part of the mandibular canal in bone marrow (CAN1)/lower part of the mandibular canal in bone marrow (CAN2).

   <Images of mandibular resorption> In the evaluation of the depth of lower gingival cancer, additional comments concerning the following findings on X-ray studies are attached.

   a) Type of images examined ( )
   b) Degree of mandibular resorption: none/alveolar process of bone marrow/upper mandibular canal of bone marrow/lower mandibular canal of bone marrow
c) Deepest part of mandibular bone resorption: dentulous jaw (Retromolar/7/6/5/4/3/2/1/2/3/4/5/6/7/8/R), edentulous jaw (Retromolar/Molar/Premolar/Canine/Incisor/IC/P/M/R)
d) Mandibular resorption type: pressure type/mixed type/moth-eaten type

(4) Buccal mucosa (BM): mucosa (M)/submucosa (SM)/buccinator muscle (oral orbicular muscle) (BM, OOM)/buccal sulcus (BS)/buccal fat (BF)/muscles of facial expression•SMAS (FM)/subcutaneous fat (SCF)
   anterior type: buccal space—mucous membrane of facial expression • SMAS (FM)/subcutaneous fat (SCF)
   posterior type: buccal space—masticator muscle space (MS)

(5) Floor of mouth (FOM): mucosa (M)/submucosa (SM)/sublingual space (SLS)/mylohyoid muscle (MH)/submandibular space (SMS)
   median type: sublingual space—genioglossus muscle (GG)/geniohyoid muscle (GH)/mylohyoid muscle (MH)/submandibular space (SMS)
   lateral type: sublingual space—mylohyoid muscle (MH)/submandibular space (SMS)

(6) Hard palate (HP): mucosa (M)/submucosa (SM)/peristomeum (PER)/cortical bone (CB)/bone marrow (CAN)/maxillary sinus (MS)/nasal cavity (NC)

6) Invasion to adjacent structures
(1) Tongue (TON): none/floor of mouth/sublingual space/mylohyoid muscle/extrinsic muscles of the tongue/root of the tongue/gingiva/mandibular cortex/mandibular bone marrow
(2) Upper gingiva and alveolus (UG): none/maxillary sinus/nasal cavity/buccinator muscles/buccal space/muscles of facial expression/masticator space/pterygoid plate/skull base/internal carotid artery/subcutaneous fat/skin
(3) Lower gingiva and alveolus (LG): none/floor of mouth/sublingual space/tongue/buccal mucosa/buccinator muscles/buccal space/masticator space/muscles of facial expression/subcutaneous fat/skin
(4) Buccal mucosa (BM): none/masticator space/lower gingiva/mandibular cortex/mandibular bone marrow/floor of mouth/upper gingiva/maxillary cortex/mandibular bone marrow/oropharynx/lips/subcutaneous fat/skin
(5) Floor of mouth (FOM): none/mylohyoid muscle/tongue/extrinsic muscles of the tongue/gingiva/mandibular cortex/mandibular bone marrow/submandibular space/masticator space/oropharynx
(6) Hard palate (HP): none/maxillary sinus/nasal cavity/gingiva/soft palate/masticator space/pterygoid plate/skull base/internal carotid artery

7) T factor (cT)
TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
Tis: Carcinoma in situ (squamous intraepithelial neoplasia)

T1: Maximum diameter ≤2 cm
T2: Maximum diameter >2 and ≤4 cm
T3: Maximum diameter >4 cm
T4: Invasion to adjacent structures

(1) Tongue (TON-0,1,2):
   T4a: Invasion into the mandibular bone marrow, invasion into the submandibular space, invasion into the extrinsic muscles of the tongue
   T4b: Invasion into the masticator space, invasion into the pterygoid plate, invasion into the skull base, invasion circumferentially surrounding the internal carotid artery

(2) Upper gingiva and alveolus (UG):
   T4a: Invasion into the maxillary sinus and nasal cavity, invasion into the buccal space or subcutaneous fat
   T4b: Invasion into the masticator space, invasion into the pterygoid plate, invasion into the skull base, invasion circumferentially surrounding the internal carotid artery

Note (1) If the tumor is confined in the alveolar bone, the tumor is classified as T1-3 according to the tumor size.
Note (2) Tumors invading the maxillary sinus are judged to be T4a regardless of the size.

(3) Lower gingiva and alveolus (LG):
   T4a: Invasion reaching the mandibular canal, invasion into the buccal space or subcutaneous fat, invasion into the submandibular space, invasion into the extrinsic muscles of the tongue
   T4b: Invasion into the masticator space, invasion into the pterygoid plate, invasion into the skull base, invasion circumferentially surrounding the internal carotid artery

Note (1) If the tumor is confined in the upper part of the mandibular canal in bone marrow, the tumor is classified as T1-3 according to the tumor size.
Note (2) Tumors invading the mandibular canal are judged to be T4a regardless of the size.

(4) Buccal mucosa (BM-0,1,2,3,4):
   T4a: Invasion into the subcutaneous fat, invasion into the maxillary and mandibular bone marrow, invasion into the maxillary sinus
   T4b: Invasion into the masticator space, invasion into the pterygoid plate, invasion into the skull base, invasion circumferentially surrounding the internal carotid artery

(5) Floor of mouth (FOM)
   T4a: Invasion into the mandibular bone marrow, invasion into the submandibular space, invasion into the extrinsic muscles of the tongue
   T4b: Invasion into the masticator space, invasion into the pterygoid plate, invasion into the skull base, invasion circumferentially surrounding the internal carotid artery

(6) Hard palate (HP)
   T4a: Invasion into the maxillary sinus and nasal cavity
   T4b: Invasion into the masticatory muscle space, invasion into the pterygoid process, invasion into the base
of the skull, invasion circumferentially surrounding the internal carotid artery

2. **REGIONAL LYMPH NODE METASTASIS**

The classification and range of cervical lymph nodes are the same as described in the Rules Regarding Lymph Nodes by the Japan Society of Clinical Oncology (JSCO), and lymph node metastasis was evaluated according to the UICC classification. Internationally, the level classification system by ACHNSO based on the area of neck dissection is widely used, and the AAO-HNS classification, a fragmented version of the ACHNSO classification, has also been proposed.

1) Site
   - Regional lymph node groups (JSCO), Level classification (AAO-HNS)
2) Number of metastasis
   - Number of metastatic lymph nodes
3) Size (<3 cm) or size (>3 cm)
4) Adhesiveness (+/-) Extranodal invasion (+/-)
5) N factor cN
   - NX: Regional lymph nodes cannot be assessed
   - N0: No regional lymph node metastasis
   - N1: Metastasis in a single ipsilateral lymph node, <3 cm in greatest dimension
   - N2a: Metastasis in a single ipsilateral lymph node, >3 cm but ≤6 cm in greatest dimension
   - N2b: Metastasis in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension
   - N2c: Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension
   - N3: Metastasis in a lymph node, >6 cm in greatest dimension

<Level classification> (Fig. 2)
- Level IA: Submental lymph nodes
- Level IB: Submandibular lymph nodes
- Level IIA: Superior deep cervical lymph nodes (Jugulodigastric nodes) (anterior)
- Level IIB: Superior deep cervical lymph nodes (Jugulodigastric nodes) (posterior)
- Level III: Middle deep cervical lymph nodes (Jugulo-omohyoid nodes)
- Level IV: Inferior deep cervical lymph nodes
- Level VA: Spinal accessory lymph nodes
- Level VB: Supraclavicular lymph nodes

3. **METASTASIS TO DISTANT ORGANS cM**

Distant metastases are evaluated according to the UICC classification.

- M: Distant metastasis
  - MX: Presence of distant metastasis cannot be assessed
  - M0: No distant metastasis
  - M1: Distant metastasis

The category M1 may be further specified according to the following notation: pulmonary (PUL), hepatic (HEP), osseous (OSS), lymph nodes (LYM), adrenal gland (ADR), brain (BRA), skin (SKI) and others (OTH)

4. **STAGING (cStage) (Table 1)**

The clinical stage (cStage) is determined according to the UICC classification. The T, N, M factors and stage are recorded.

<Stages> Stages 0, I, II, III, IVA, IVB and IVC.

5. **MULTIPLE, DOUBLE AND MULTIPLE PRIMARY CANCERS**

1) Multiple oral cancers: The occurrence of two or more primary cancers fulfilling the following conditions:
   - (1) Cancers located at different sites according to the UICC classification.
   - (2) Cancers located at the same but contralateral sites.
   - (3) Cancers located at ipsilateral sites but not continuous and clinically separated by 1.5 cm or more.
   - (4) Each lesion is histopathologically confirmed to be a carcinoma.

2) Double cancer: The concurrence of primary oral cancer with primary malignant tumors of other organs. If both multiple and double cancers are observed, they are expressed as multiple–double cancers.

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3) Multiple primary cancers: The term multiple primary cancers is used to comprehensively express multiple and double cancers.

4) Synchronous and heterochronous cancers
   (1) Cancers diagnosed within a period of less than 1 year are defined as synchronous cancers.
   (2) Cancers diagnosed at an interval of 1 year or longer are defined as heterochronous cancers.
   (3) If there are both synchronous and heterochronous cancers, they are called synchronous/heterochronous cancers.
   Note (1) The organs affected by double cancers are indicated.
   Note (2) Whether the cancers are synchronous or heterochronous is indicated.
   Ex.) Double cancers: Stomach (synchronous)

6. ORAL PRECANCEROUS LESIONS
Since oral cancers are often accompanied by oral precancerous lesions such as leukoplakia and erythroplakia, their sites, sizes, surface properties, number, whether they are synchronous or heterochronous etc. are recorded.

7. CONDITIONS OF THE ORAL CAVITY
State of oral hygiene: good/poor
Teeth and prosthetics related to the primary lesion: absent/present
(1) State of fit: good/poor
(2) Sharp edges: absent/present
(3) Lingual inclination or displacement: absent/present
(4) Edging into the mucosa: absent/present
(5) Type of dental prosthesis ( )
(6) Periodontal disease: absent/present (severe/moderate/mild)
(7) Impacted/half-impacted teeth: absent/present
Surgical procedures at the lesion site such as tooth extraction and incision: absent/present (contents of treatment)
Motor/sensory/gustatory disorders
(1) Trismus: absent/present (distance of mouth opening mm)
(2) Motor disorders: absent/present (site)
(3) Sensory disorders: absent/present (site)
(4) Gustatory disorders: absent/present

8. LIFESTYLE
Individual lifestyle is very significant as a risk factor of oral cancer. Particularly, smoking and drinking are major risk factors of cancer. Therefore, the lifestyle history is recorded in consideration of the risk of recurrence and double cancers.

Regarding smoking, whether the patient is a smoker or non-smoker is indicated. The amount of smoking is expressed as the product of the mean number of cigarettes smoked per day and the number of years of smoking (Brinkman index). The amount of drinking is also expressed as the product of the mean daily amount of drinking (in ml of sake or ounces of alcohol) and the number of years or drinking (Sake index etc.).

- Brinkman index = mean number of cigarettes smoked per day × number of smoking years
- Sake index = mean amount of drinking per day (in ml of sake) × number of drinking years

<Scales for conversion into ml of sake>
180 ml of sake = a large bottle of beer (633 ml) = 2 single glasses of whisky (70 ml) = 90 ml of shochu (distilled spirit) = 2 glasses of wine (220 ml)

9. BIPSY
In performing biopsy with the expectation of treatment, cancer tissue together with adjacent non-cancerous mucosa is generally sampled by wedge resection. The objective of biopsy is not only to make a definitive diagnosis of cancer, but also to obtain detailed information concerning the degree of histological malignancy, invasion pattern, vascular infiltration and probability of lymph node metastasis. It is desirable to collect a tissue block 5 mm or larger in long diameter containing the margin of invasion by biopsy. If a wide non-stained area is observed around the cancer by iodine vital staining, information useful for the determination of the resection margin can be obtained by further collecting tissue samples containing both stained and non-stained areas.

If the lesion is an early and small cancer (early T2 or less advanced) on careful examination of its depth by palpation and imaging, mucosal resection of an area containing the entire iodine non-stained area is also recommended.

II. RECORDING OF INTRAOPERATIVE FINDINGS AND THOSE ON GROSS EXAMINATION OF THE RESECTED SPECIMENS

1. SURGICAL PROCEDURE
The matters entered into the operation record should be illustrated in detail. Whether reconstruction was performed and the construction procedure, intraoperative complications, radicality of the procedure and postoperative course should also be recorded.

1) Primary lesion
   (1) Tongue cancer
      a) partial tongue resection, b) unilateral resection of the movable part of the tongue, c) (sub)total resection of the movable part of the tongue, d) unilateral resection of the tongue and e) (sub)total tongue resection
   (2) Upper gingival and alveolus cancer/hard palate cancer
      a) local resection, b) partial maxillectomy, c) sub-total maxillectomy, d) total maxillectomy, e)
extended total maxillectomy and f) skull base dissection

(3) Lower gingival and alveolus cancer
a) gingival resection, b) marginal mandibulectomy,
c) segmental mandibulectomy, d) hemimandibu-
lectomy, e) subtotal mandibulectomy and f) total
mandibulectomy

(4) Buccal mucosal cancer
a) partial (buccal mucosal) resection, b) full-
thickness buccal resection (through and through
operation) and c) combined resection
Note) If combined resection is performed, the
resected parts, extent of resection, depth of re-
section etc. must be recorded.

(5) Floor of mouth cancer
a) partial resection (of the floor of the mouth), b)
combined resection
Note) If combined resection is performed, the
resected parts, extent of resection, depth of re-
section etc. should be recorded.

2) Cervical lymph nodes

(1) Radical neck dissection (RND)
(2) Modified radical neck dissection (MRND)
(3) Selective neck dissection
a) Supraomohyoid neck dissection (SOHND)
b) Extended supraomohyoid neck dissection
(extended SOHND)
c) Others
a) Suprahyoid neck dissection (SHND)
b) Submandibular neck dissection (SMND)

2. GROSS FINDINGS IN RESECTED SPECIMENS

1) Primary lesions
(1) Anatomical sites and subsites same as I-1-1)
(2) Locations of the lesion same as I-1-2)
(3) Size same as I-1-3)
(4) Clinical type same as I-1-4)
(5) Depth same as I-1-5)
(6) Invasion to adjacent structures same as I-1-6)
(7) T factor (sT) same as I-1-7)
(8) Evaluation of the resection margin (sRM)
   Horizontal (mucosal) margin (HM), distance from
   the resection margin ( ) cm
   sHMX: Impossible to determine the resection
   margin
   sHM0: Resection margin (−)
sHM1: Resection margin (+)
   Vertical (deep) margin (VM), distance to the
   resection margin ( ) cm
   sVMX: Impossible to evaluate the resection
   margin
   sVM0: Resection margin (−)
sVM1: Resection margin (+)
Note) In osteotomy patients, the results of evaluation of
the bone resection margin must be recorded. In patients
who underwent mandibular or mandibular canal resec-
tion, the result of evaluation of the resection margin of
the inferior alveolar nerve should be recorded.

2) Metastases to regional lymph nodes
   In patients who undergo neck dissection, the following
   items must be examined postoperatively concerning the
   resected lymph nodes according to the lymph node
   groups or level classification
   (1) Sites
      Lymph node groups (JSCO), Level classification
      (AAO-HNS)
   (2) Number of metastatic lymph nodes
      Number of metastatic lymph nodes/number of
      resected lymph nodes
   (3) Size (<3<6<) cm
   (4) Extranodular invasion (−/+)
   (5) Invasion to adjacent vessels (−/+)
   (6) N factor (sN): NX, N0, N1, N2-N2a, N2b, N2c, N3

3) Staging (sStage) same as I-4

4) Degree of residual cancer (sR)
   RX: Presence of residual tumor cannot be assessed
   R0: No residual cancer
   R1: Microscopic residual tumor
   R2: Macroscopic residual tumor
Note) The evaluation of residual cancer is made concern-
ing all primary and metastatic lesions.

III. HANDLING OF SURGICAL SPECIMENS

1. SECTIONING METHOD
   It is a principle of surgical pathological studies of mucosal
cancer to prepare cross-sections perpendicular to the
mucosal surface.

   1) Sampling of soft tissues of the tongue, buccal mucosa
and floor of the mouth
   In cancers of the tongue, buccal mucosa and floor of the
mouth, examination of coronal sections is preferably
recommended.
   Sections are obtained at intervals of ~5–7 mm by step
sectioning, and tumoral and ulcerative lesions in each
section are photographed as magnified images.
   Large samples containing the skin, muscle or bone tissue
are sectioned at intervals of ~1–2 cm and photographed
after checking the spread of the tumor on the mucosal
surface and depth. Subsequently, a tissue block of ~4–
5 mm thick is sectioned from a representative cross-section
to prepare specimens.

   2) Sampling of maxillary or mandibular gingival cancer
   (1) Surgical sample consisting of soft tissues alone
   After checking the extent of the lesion (particularly, the
anteroposterior dimension, lateral margins, gingival margin
at the dental neck adjacent to the next tooth), the sample is
sectioned coronally or sagittally by referring to image
information such as computed tomography and magnetic resonance imaging. In sectioning, the resection margin is first sectioned, the center of the primary lesion is sectioned next and serial sections are obtained at intervals of \( \approx 4-5 \) mm.

(2) Surgical samples containing hard tissues

(a) Method to examine the sample without separating hard and soft tissues

The basic method to section samples of upper or lower gingival cancer containing tooth or bone tissue is to section them perpendicularly to the dental arch centering around the deepest part of the primary tumor. If the tumor is located in the incisor region, the dental arch is markedly curved, so the sample should be sectioned radially.

As the lateral and molar regions are also arched gently, sections should be made by checking the direction of the teeth. Sections containing hard tissue are cut out at intervals of 7–8 mm using a diamond cutter and decalcified after photographing the cross-sections.

(b) Method to examine the sample by separating soft tissue and bone

Since the stainability of soft tissue is expected to be reduced by the decalcification of bone, specimens may also be prepared after separating hard and soft tissues. By employing this method, accurate diagnosis is impossible unless the spatial relationship between bone and soft tissue is clear. Their locations must be determined using photographs etc., and the spatial relationships of invasion sites and the resection margin should be clarified, before the separation. In mandibular gingival cancer, since tumor cells are present more often in the margin of soft tissue rather than bone, judgment using high-quality specimens is meaningful. Particularly, in patients who have undergone preoperative treatments such as chemotherapy, the judgment of the therapeutic effect is often difficult using decalcified soft tissue specimens.

2. Decalcification Methods

Tissue sections 7–8 mm thick containing hard tissue are placed in a decalcification solution after washing under running water or without washing or after defatting in a mixture of equal volumes of methanol and chloroform for \( \approx 1 \) day as a pretreatment. Usually, Plank-Rychlo’s rapid decalcification solution is used. The stainability after decalcification is preserved by performing low-temperature decalcification in a refrigerator (low-temperature decalcification). A sufficient amount of decalcification solution for the sample (several tens of times) should be prepared and changed during the decalcification process when considered appropriate. Also, decalcification is accelerated by shaking the decalcification solution. EDTA decalcification solution must be used if a process such as immunostaining is anticipated.

IV. Recording of Pathological Findings

1) Primary lesion

   (1) Anatomical sites and subsites same as I-1-1)
   (2) Location of the lesion same as I-1-2)
   (3) Size same as I-1-3)
   (4) Clinical type same as I-1-4)
   (5) Depth same as I-1-5)
   (6) Invasion to adjacent structures same as I-1-6)
   (7) T factor (pT) same as I-1-7)

2) Resection margin (pRM)

   Horizontal margin (HM), distance from margin ( ) mm
   pHMX: Impossible to evaluate the resection margin
   pHM0: Margin (−)
   pHM1: Margin (+)
   Note) Also record presence or absence of OED at the mucosal stump.

   Vertical margin (VM), distance from margin ( ) mm.
   pVMX: Impossible to evaluate the resection margin
   pVM0: Margin (−)
   pVM1: Margin (+).
   Note) Also record the results of evaluation of the bone stump in patients after osteotomy and stump of the inferior alveolar nerve in patients after mandibular/mandibular canal resection.

3) Invasion to lymphatic vessels, veins, and nerves

   (1) Lymphatic vessel invasion
      ly0: No lymphatic vessel invasion
      ly1: Mild lymphatic vessel invasion
      ly2: Marked lymphatic vessel invasion.
      Note) If immunostaining has been used for the evaluation of lymphatic vessel invasion, it must be recorded. Ex.: ly1 (D2-40).

   (2) Venous invasion
      v0: No venous invasion
      v1: Mild venous invasion
      v2: Marked venous invasion.
      Note) If elastic fiber staining has been used for the evaluation of venous invasion, it must be recorded. Ex.: v1 (EVG).

4) Neural invasion

   neu0: No neural invasion
   neu1: Mild neural invasion
   neu2: Marked neural invasion
   Note) If immunostaining has been used for the evaluation of neural invasion, it must be recorded. Ex.: neu1 (S-100)

5) Histological classification
(1) Tis cancer: Oral intraepithelial neoplasia (OIN)/carcinoma in situ (CIS)

Oral type Tis cancer has been known as a cancer that develops into squamous cell carcinoma other than CIS based on the WHO diagnostic criteria. This is squamous intraepithelial neoplasia, a tumor that retains the maturation and differentiation characteristics of the stratified squamous epithelium. In the present rules, the term OIN is used to avoid confusion with the conventional (WHO) diagnostic criteria for CIS and to indicate that the tumor is characteristically an oral lesion.

(1) Basaloid type: This tumor corresponds to CIS by the WHO classification and shows a histological profile in which basal cell-like cells are observed in all or nearly all layers.

(2) Differentiated type: This is an oral type intraepithelial neoplasia showing no clear atypia in the superficial stratum corneum or stratum spinosum but markedly atypical cells on the stratum basal side. Note) Oral epithelial dysplasia (OED)

A borderline lesion suspected to be an intraepithelial neoplasia but difficult to differentiate from a reactive atypical lesion. Long-term follow-up of 5 years or longer is necessary. Most of the tumors of this type are mildly atypical intraepithelial neoplasias corresponding to low-grade dysplasia according to the 4th version of the General Rules for Clinical and Pathological Studies of Head and Neck Cancer, but reactive atypical lesions are included.

1) Squamous cell carcinoma

(1) Grade (WHO)
   Grade 1: Well-differentiated type
   Grade 2: Moderately differentiated type
   Grade 3: Poorly differentiated type

(2) Mode of invasion
   Classification of the invasion pattern at the tumor-host interface of oral squamous cell carcinoma. Corresponds to INF of digestive tract cancer.
   YK-1: Well defined borderline
   YK-2: Cords, less marked borderline
   YK-3: Groups of cells, no distinct borderline
   YK-4C: Diffuse invasion, cord-like type invasion
   YK-4D: Diffuse invasion, diffuse type invasion

(3) Mandibular invasion (mandibular gingival cancer)
   (a) Degrees of mandibular invasion: none/bone marrow alveolar process/bone marrow upper mandibular canal/bone marrow lower mandibular canal
   (b) Deepest part of mandibular invasion: denutulous jaw (teeth: 8/7/6/5/4/3/2/1/1/2/3/4/5/6/7/8); edentulous jaw (Molar/Premolar/Canine/Incisor/I/C/P/M)
   (c) Mode of mandibular invasion: expansive type/invasive type
   (d) Route of intramandibular development: development through the periodontal membrane (+/-), development in the mandibular canal (+/-)

2) Special types
   (1) Verrucous carcinoma
   (2) Basaloid squamous cell carcinoma
   (3) Adenoid squamous cell carcinoma
   (4) Spindle cell carcinoma
   (5) Adenosquamous carcinoma
   (6) Papillary squamous cell carcinoma
   Note) Primary intraosseous carcinoma

3) Regional lymph node metastasis
   (1) Site
   Lymph node groups
   (2) Number of metastasis
   Number of metastatic lymph nodes/number of resected lymph nodes
   (3) Size (<3<6<) cm
   (4) Extracapsular invasion (-/+)
   (5) Adjacent vascular invasion (-/+)
   (6) N factor (pN): NX, N0, N1, N2-N2a, N2b, N2c, N3
      Note (1) Lymph nodes of the median region are ipsilateral lymph nodes.
      Note (2) Direct invasion of the primary tumor to lymph nodes is classified as lymph node metastasis.
      Note (3) Tumors of 3 mm or larger at sites corresponding to lymph nodes are classified as regional lymph node metastases even without a histological lymph node remnant.
      Note (4) If the size is within the evaluation criteria of the pN classification, the size of the metastatic focus rather than the entire lymph node is measured.

4) Stage (pStage) same as I-4
5) Degree of remnant (pR) same as III-2-4)
6) Multiple, double, multiple primary cancers same as I-5
7) Histological evaluation of therapeutic effect

If radiation therapy or chemotherapy has been conducted against oral cancer, conditions of treatment including the dose of radiation, irradiation method, kinds, doses and administration methods of the drugs used, and time from the last treatment to resection of the lesion should be recorded.

In examining patients after preoperative treatment, specimens of the grossly estimated lesion must be prepared as much as possible, and the state of the remaining tumor must be evaluated histologically.

Grade 0: Ineffective
   No therapeutic effect is noted in cancer tissue or cancer cells.

Grade 1: Slightly effective
   Some degenerative change is noted in cancer tissue/cells, but cancer cells considered to be capable of proliferation (those showing the eosinophilic cytoplasm with vacuolation and enlargement of the nucleus are also included) occupy 1/3 or more of the cancer in a tissue section.
Grade 1a: Very slightly effective
Cancer cells considered ‘capable of proliferation’ occupy 2/3 or more of the cancer.
Grade 1b: Mildly effective
Cancer cells considered ‘capable of proliferation’ occupy 1/3 or more but less than 2/3 of the cancer.
Grade 2: Moderately effective
Cancer cells considered ‘capable of proliferation’ occupy less than 1/3 of the cancer, and those showing a tendency toward nuclear disintegration are dominant.
Grade 3: Markedly effective
No cancer cell considered ‘capable of proliferation’ is observed, and all cancer cells show a tendency toward nuclear disintegration, or only a trace of cancer is noted.

Note) If a part clearly judged to be a focus of reproliferation is noted in a treated cancer focus, the entry ‘evidence of reproliferation (+)’ should be made after the judgment.

V. OTHER TREATMENTS AND CLINICAL EVALUATION OF THE THERAPEUTIC EFFECT

1. RADIATION THERAPY

Desirable entry items
- Gross tumor volume (GTV)
- Initial clinical target volume (CTV)
- Planning target volume (PTV)
- Irradiation strategy: radical, palliative, preoperative, preventive, control of recurrent metastatic foci etc.
- Presence or absence of concomitant treatments: irradiation alone, concomitant treatments performed (surgery, chemotherapy etc.)
- Degree of completion of radiation therapy: completed (no interruption), completed (with interruption), not completed as planned
- Irradiation method

1) External irradiation methods
   (1) Radiation type, instrument and energy
       X-ray (Linac, Microtron, MV), cobalt γ-ray, electron beam (MeV), proton beam, heavy particle beam, fast neutron beam etc.
   (2) Irradiation sites
       primary lesion, cervical lymph nodes, distant metastases (sites)
   (3) Objective of irradiation
       radical, palliative, preoperative, postoperative, preventive etc.
   (4) Irradiation methods
       one field irradiation (anterior, posterior, others), two-field irradiation (left—right, anterior—posterior, diagonal, others), multiple field irradiation, special irradiation (three-dimensional conformal radiotherapy, intensity-modulated radiation, stereotactic radiation therapy, others)

If two or three sites are treated, treatment for each site is recorded separately.
If the irradiation method has been changed, the objective of the change (reduction in the irradiation field, change in the junction line, protection of the spinal cord, others) and the dose at the change are recorded.

(5) Planning of radiation therapy
   Using and not using a radiation therapy planning device (MU calculation alone, preparation of the dose distribution chart)
(6) Whether compensatory instruments, bolus or fixation instruments are used
   Use of a wedge, use of shell fixation, bite block, others.
(7) Radiation dose
   Dose per fraction (cGy), total dose (cGy, Gy), number of fractions, number of irradiations per day, irradiation intervals, irradiation period, completed or not completed. If two or three sites are treated, treatment for each site is recorded separately.
   Ex.) 60 Gy/30 fr/43 days (2009.7.6—8.17)

(8) Dose on risk organs
   Brain, eye (lens), spinal cord, salivary gland, others.

2) Brachytherapy
   (1) Types, high- or low-dose rate and shape of radiation source
   (2) Irradiation dose
       Target dose, number of irradiations, time of irradiation (time at the beginning, time at the end), dose rate (dose/h), source strength during use (MBq).
   (3) Relationships of reference points or planes for dose evaluation with tumor and radiation source.
   (4) Dose calculation method
       A radiation therapy planning device used or not used (manual calculation)
   (5) Doses on risk organs

3) Treatment assessment
   (1) Effects of irradiation
       The therapeutic effects shortly after, 1 month after and 3 months after irradiation are recorded.
   (2) Acute adverse events
       The severest organ or tissue damage, signs and symptoms, and the period of their observation are recorded according to CTCAE v.3.0, a Japanese translation of the JCOG/JSCO edition.
   (3) Late adverse events
       Adverse events that occur more than 91 days after the beginning of irradiation and are
considered to be related to irradiation are recorded.

2. CHEMOTHERAPY

Concerning the drugs that have been administered, their names (generic) are recorded with the following items:

1) Entries at treatment: entries in the treatment plan
   (1) Drugs used and their administration methods and routes
      Data of each patient necessary for the determination of the dose (body weight, body surface area, renal function etc.), regimen name, drugs used, dose per administration, days of administration and administration period, administration method, dose (/body surface area or /body), administration route (i.v., p.o., intra-arterial, ultra-selective intra-arterial, local, i.m. etc.) and scheduled courses of administration should be indicated, and the total dose of each drug should be recorded.

   (2) Concomitant treatments and therapeutic attitude
      If chemotherapy is performed with surgery or radiation therapy, the periods of treatment, their timing (synchronous, heterochronous) and objectives (radical, preoperative, palliative) should be recorded.

   (3) Identification of lesions to be evaluated
      Since evaluation of the therapeutic effect is made according to the Response Evaluation Criteria in Solid Tumors (RECIST)—Japanese translation JCOG edition, the target and non-target lesions should be identified in advance at the baseline.

   (4) Presence or absence of adverse events and their contents
      Recorded according to the CTCAE v.3.0 Japanese translation JCOG/JSCO edition.

2) Reasons for discontinuation of administration (classified as follows)
   Planned treatments completed, exacerbation of the lesion, treatment discontinued due to adverse events, rejected by the patient (related to adverse events), rejected by the patient (unrelated to adverse events)

3) Evaluation results and judgments concerning therapeutic effects
   At the time of evaluation, the conditions of the target and non-target lesions are described, and the evaluation results and judgments are recorded.

3. OTHER TREATMENTS

Hyperthermia, laser treatment, cryosurgery etc., are recorded to the maximum detail including the instruments used and procedures as surgical, radiation and drug therapies. If alternative therapies have been conducted, they should also be recorded.

4. CLINICAL EVALUATION OF THERAPEUTIC EFFECTS

By respecting the intent of the Evaluation Criteria for Direct Effects of Chemotherapy against Solid Cancers by the Japan Society of Clinical Oncology, and in consideration of the organ specificity of head and neck and oral cancers, the Evaluation Criteria for Therapeutic Effects have been adopted. Internationally, however, the Response Evaluation Criteria in Solid Tumors (RECIST) Guideline was published in 2000 as a revision of the WHO criteria and also adopted by the Japan Society of Clinical Oncology. Therefore, this guideline is also applied to oral cancers, but, as it is not a specific guideline for oral cancer, some consideration is necessary in its evaluation. The evaluation criteria are designed to evaluate the effects of non-surgical treatments including not only preoperative treatments but also chemotherapy, radiation therapy and immunotherapy.

<Outline of the RECIST, JCOG edition>

1) Complete response (CR): disappearance of all target lesions
2) Partial response (PR): a 30% or greater decrease in the sum of long diameters of the target lesions compared with the baseline level
3) Stable disease (SD): a decrease in the tumor size insufficient to be classified as PR and an increase in the tumor size compared with the minimum sum of long diameters after the beginning of treatment insufficient to be classified as PD
4) Progressive disease (PD): a 20% or greater increase in the sum of long diameters of the target lesions compared with the minimum recorded after the beginning of treatment

To judge the response as CR or PR, fulfillment of the criteria for CR or PR should be confirmed on re-evaluation 4 or more weeks after the initial fulfillment of the criteria. In some studies, setting a longer interval by the protocol may be appropriate.

SD is defined by the protocol. The criteria for SD should be met at least once beyond a minimum period after registration of the study (generally 6–8 weeks or longer). The response rate is calculated by counting CR and PR alone as positive responses.

VI. THERAPEUTIC RESULTS

1. POSTOPERATIVE COURSE

1) No recurrence
2) Local recurrence: day of confirmation of recurrence
3) Recurrence in the cervical region Day of confirmation of recurrence
   (1) Recurrence inside the dissected area
   (2) Recurrence outside the dissected area
4) Delayed metastasis to the cervical lymph nodes
5) Distant metastasis
6) Multiple oral cancers: Heterochronous/synchronous Site
7) Cancers of other organs: Heterochronous/synchronous Site
2. **EVALUATION OF POSTOPERATIVE MASTICATION (SWALLOWING, VOCALIZATION) FUNCTION**

1) Evaluation of speech function: clarity of single syllable pronunciation, clarity of speech

2) Evaluation of eating function:
   
   (1) Occlusion/mastication: questionnaire survey using Yamamoto’s bite scale, color gum test, dental prescale test
   
   (2) Swallowing: water swallowing test, videofluorography (VF), nasal endoscopy (VE), cervical auscultation

3. **OUTCOME**

1) Survival state
   
   (1) Survivors: date of confirmation of being alive
   
   (2) Those that have died: date of death
   
   (3) Those lost to follow-up: last date of confirmation of being alive

2) Causes of death

   (1) Treatment-related death (death due to surgical treatments, chemotherapy, radiation therapy etc.)
   
   (2) Death due to oral cancer (death due to primary disease)
   
   (3) Death due to another malignant disease: record the tumor name
   
   (4) Death due to another disease: record the disease name
   
   (5) Death due to an accident: including suicide
   
   (6) Cause of death unclear
   
   (7) Autopsy performed or not performed

4. **METHOD FOR THE CALCULATION OF LONG-TERM FOLLOW-UP RESULTS**

It is desirable to show various survival rates as cumulative survival rates from the day of the beginning of treatment, and this is usually done using the Kaplan–Meier method. Tests to examine the significance of differences in the survival rate include the generalized Wilcoxon test, Mantel–Haenszel test, log-rank test and Cox–Mantel test.

Details concerning the survival rate are handled according to the Japan Society of Clinical Oncology, General Rules about Cancer, in principle.

**Conflict of interest statement**

None declared.

**References**


**Appendix**

Co-authors: Satoru Shintani, Yoichi Tanaka, Eiji Nakayama, Takahumi Hayashi, Akihiro Miyazaki, Hisao Yagishita and Masayuki Yamane.