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Japanese clinical practice guidelines for oral cancer, 2023☆

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Abstract. The Japanese Society of Oral Oncology and Japanese Society of Oral and Maxillofacial Surgeons have jointly developed clinical practice guidelines for oral cancer (oral squamous cell carcinoma) to improve and standardize the quality of oral cancer treatment in Japan. The first, second, and third editions were published in 2009, 2013, and 2019, respectively, and the 2023 edition was recently developed. In the development of the 2023 edition, 60 clinical questions (CQs) were listed. Systematic reviews following the GRADE approach were performed for 11 of these CQs. This article outlines the 2023 edition and describes the most relevant guidelines and CQs for the diagnosis, treatment, follow-up, and supportive care of oral cancer patients in Japan.

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The Japanese Society of Oral Oncology and Japanese Society of Oral and Maxillofacial Surgeons have jointly developed clinical practice guidelines for oral cancer, to improve and standardize the quality of oral cancer treatment. The first, second, and third editions were published in 2009[1], 2013[2], and 2019[3], respectively. The 2023 edition was recently developed and is outlined here. According to these guidelines, squamous cell carcinoma arising from the oral mucosa is referred to as 'oral cancer.' The clinical questions (CQs) used in the development of the guidelines are summarized in Supplementary Material Table S1.

Epidemiology

The estimated number of oral cancer cases in Japan was 2100 in 1975 and 6900 in 2005, and was predicted to reach 7800 in 2015[4]. According to data in the Oral Cancer Registry in 2020, the incidence of oral cancer by site was 47.1% for the tongue, 18.4% for the mandibular gingiva, 11.9% for the maxillary gingiva, 8.6% for the buccal mucosa, 6.6% for the floor of the mouth, 2.6% for the hard palate, 1.7% for the intraosseous region, and 0.8% for the lower lip. In terms of the clinical stage (Union for International Cancer Control (UICC), *TNM Classification of Malignant Tumours*, eighth edition), 6% had intraepithelial cancer, 53% had early-stage cancer (stages I and II), and 38% had advanced-stage cancer (stages III and IV). The frequency of cervical lymph node metastases at the time of initial diagnosis was 25%, and that of distant metastases was approximately 1%. The frequency of simultaneous multiple primary cancers at initial diagnosis was 0.5%. Approximately 60–70% of multiple primary cancers are found in the upper gastrointestinal tract or lungs (CQ1)[5].

Prevention

The oral cavity is exposed to chemical stimuli such as smoking, alcohol, and food, as well as mechanical stimuli from the teeth and defective dental prostheses. This anatomical region is characterized by a unique environment that is subject to multiple risk factors for carcinogenesis (CQ2)[5]. Smoking and alcohol consumption are risk factors for oral cancer (CQ3, CQ4)[5]. However, the clinical significance of human papillomavirus (HPV) infection in oral cancer has not yet been established[6].

Early detection of oral cancer is another important preventive measure. The detection rate of oral cancer and

precancerous lesions in oral cancer screening is 0.99%[7], and the prevalence of precancerous lesions in the Japanese population is 2.5%[8]. To date, there have been no studies on the effect of oral cancer screening on the prognosis of oral cancer.

Oral potentially malignant disorders

The malignant transformation rate of erythroplakia is as high as 14–50%[9]. The incidence of leukoplakia varies as a result of the lack of a clear definition for this disorder, as well as factors such as race, lifestyle habits (e.g. smoking), treatment, and the duration of observation (duration of symptoms). The reported rate of malignant transformation is 3.1–16.3% in Japan (CQ5)[5] and 0.13–17.5% in studies performed in other countries[10,11].

The treatment of precancerous lesions includes observation and resection. It is generally accepted that oral leukoplakia with pathological evidence of epithelial dysplasia is likely to transform into cancer and should be surgically resected before it becomes malignant. An excisional biopsy is often performed for small lesions that are suspected to be malignant. However, for oral leukoplakia without histopathological evidence of epithelial dysplasia and large lesions that are difficult to resect, close follow-up is preferred (CQ6)[12].

Examination and diagnosis

The UICC TNM classification and staging manual[13] and the *General Rules for Clinical and Pathological Studies on Oral Cancer*[14] are commonly used for diagnosis. In Japan, classification based on the level of the mandibular canal is also used as a diagnostic criterion for the T classification of mandibular gingival cancer[15,16].

Primary tumors

The site of origin, macroscopic classification, tumor thickness or depth of invasion (DOI), and degree of extension into the surrounding tissues are associated with primary tumor recurrence, cervical lymph node metastasis, and distant metastasis (CQ7–9)[5]. The preferred imaging modality for soft tissues is magnetic resonance imaging (MRI), or computed tomography (CT) if MRI is not available (CQ10)[5]. Intraoral ultrasonography (US) is considered the most accurate method for measuring DOI, followed by MRI (CQ11)[5]. Panoramic radiography, CT, MRI, positron emission tomography (PET)–CT, cone beam CT, and bone scintigraphy are used to determine bone invasion (CQ12)[5]. MRI is useful for assessing the extent of bone marrow involvement and CT is useful for assessing cortical bone involvement and periosteal invasion. Bone invasion is classified as smooth, worm-eaten, or intermediate. Many reports have suggested that patients with the worm-eaten type of bone invasion have a poor prognosis (CQ13)[5].

Regional lymph nodes

All imaging modalities (MRI, CT, US, and PET–CT) are effective in diagnosing cervical lymph node metastases; however, there is no consensus on their superiority or inferiority in terms of diagnostic accuracy (CQ14)[5]. Fluorodeoxyglucose (FDG)-PET is a sensitive method for both regional and distant metastases and is commonly employed.

Distant metastasis and others

PET–CT is appropriate for the evaluation of distant metastases; if PET–CT is not performed, a chest CT should be performed to evaluate the presence of lung metastases. The evaluation of the upper gastrointestinal tract and lungs is necessary before and after treatment (CQ15)[5]. Dental assessment is important for the treatment of oral cancer, and panoramic radiography is essential.

Pathological diagnosis

Regarding cytological examinations, the 'liquid-based cytology' method is recommended over the conventional 'direct smear' method because it causes less drying and loss of cells and can be used in combination with immunostaining[17]. Biopsy, particularly incisional biopsy, is commonly performed. However, incisional biopsy of cancer can cause seeding of cancer cells into the circulation[18], and total excisional biopsy of small lesions is advisable to minimize this risk.

Although it has been suggested that prolonging the time between biopsy/pathological diagnosis and the start of surgical treatment may affect survival, there is no quantitative definition of what constitutes a prolonged time and no consensus has been reached (CQ16)[5]. The mode of invasion at the deep invasive cancer front is one of the histopathological findings useful in determining the prognosis (CQ17)[5,19].

Treatment

The treatment algorithm for the early stages of oral cancer (stage I, II) is shown in Fig. 1, while the treatment algorithm for resectable advanced oral cancer (stage III, IV) is shown in Fig. 2 and the treatment algorithm for unresectable cancer and patients with advanced oral cancer (stage III, IV) who refuse or are contraindicated for surgery is shown in Fig. 3. The treatment algorithm for distant metastatic oral cancer (M1) at initial diagnosis is shown in Fig. 4 and the treatment algorithm for recurrent or residual cancer is shown in Fig. 5.

Follow-up observation

Studies have suggested that at least 5 years of postoperative follow-up is necessary[20]. The recommended intervals for follow-up after treatment are at least once a month (twice a month if possible) for the first year, once a month for the second year, once every 2 months for the third year, once every 3 months for the fourth year, once every 4 months for the fifth year, and once every 6 months thereafter, depending on the individual case (CQ52)[5].

US, contrast-enhanced CT, and MRI are the effective modalities recommended for follow-up. Chest CT effectively detects distant metastases. If recurrence or metastasis is suspected, additional PET is recommended (CQ53)[5]. There is no strong evidence to support the use of tumor markers in the follow-up of oral cancer (CQ54)[5].

Surgical therapy

Surgical resection of the primary tumor

Regarding the appropriate safety margin for oral cancer resection, ≥10 mm is recommended; however, there is no clear significant evidence (CQ19)[5]. Removal of the surrounding epithelial dysplasia (especially severe epithelial dysplasia) is recommended; however, the relationship between the degree of epithelial dysplasia and the recurrence rate is unclear (CQ20)[5]. The identification of epithelial dysplasia and malignancy using vital staining is useful

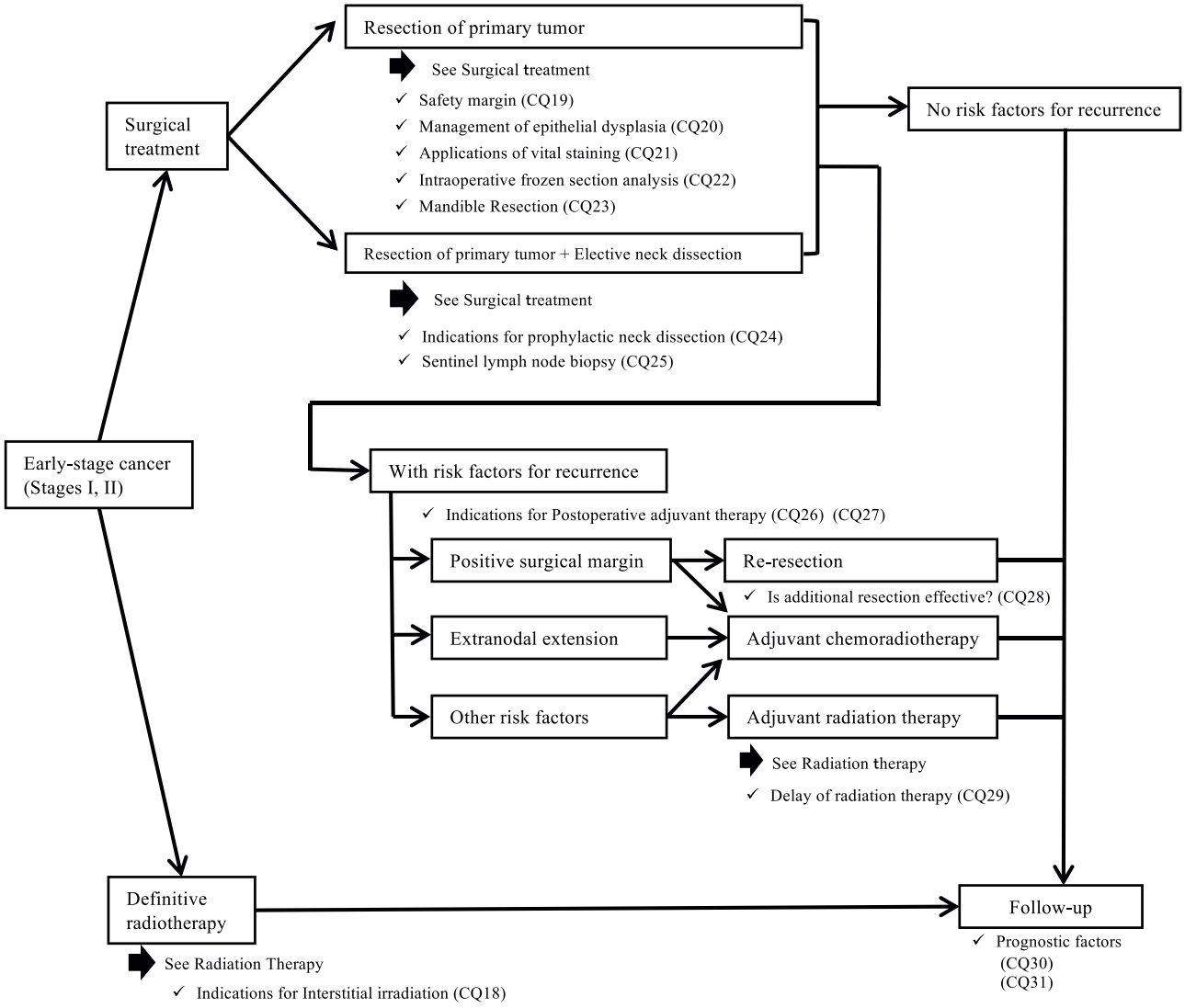


Fig. 1. Treatment algorithm for the early stages of oral cancer (stage I, II).

(CQ21)[5]. Pathological diagnosis during surgery is useful for reliable surgical management (CQ22)[5]. If margins are positive, additional resection or post-operative chemoradiotherapy may be considered, but no trials have compared these options, hence treatment in the case of positive surgical margins needs to be tailored to the circumstances of the case and facility (CQ28)[5].

Tongue cancer

Shallow-depth (DOI < 5 mm) T1N0, T2N0, and T3N0 tongue cancers are treated with partial glossectomy. In the case of T2N0, T3N0, and T4N0 with a deep DOI (DOI ≥ 5 mm), a hemi-glossectomy or subtotal glossectomy is performed. When performing an elective neck dissection, the tongue may be removed as a single unit, along with the neck dissection tissue, using a pull-through procedure (CQ24) [21]. If neck metastases are present, the primary tumor is removed as one unit, along with the neck dissection tissue, using pull-through surgery. In the case of T4 tongue cancer, resection of the primary tumor and neck dissection are performed concurrently, including hemiglossectomy or subtotal glossectomy depending on the extent of cancer invasion, as well as combined resection of the surrounding tissues, such as the mandible.

Oral floor

For T1N0 and superficial (DOI < 5 mm) T2N0 and T3N0, a partial resection is performed. For T2N0 with invasive disease (DOI ≥ 5 mm), T3, and T4, a pull-through procedure is performed to remove the primary tumor and neck dissection tissue as one unit. A combined resection is performed if the tumor involves the tongue or mandible. Additionally, it is important to note that neck metastases often occur bilaterally.

Buccal mucosa

In T1 and T2 cases, a partial buccal mucosa resection is performed. Advanced cases may be treated with partial resection of the buccal mucosa or combined excision of the mandible, maxilla, and skin, or an extended excision above or behind the posterior molar triangle.

Mandibular gingiva

The algorithm for the surgical treatment of mandibular gingival cancer is

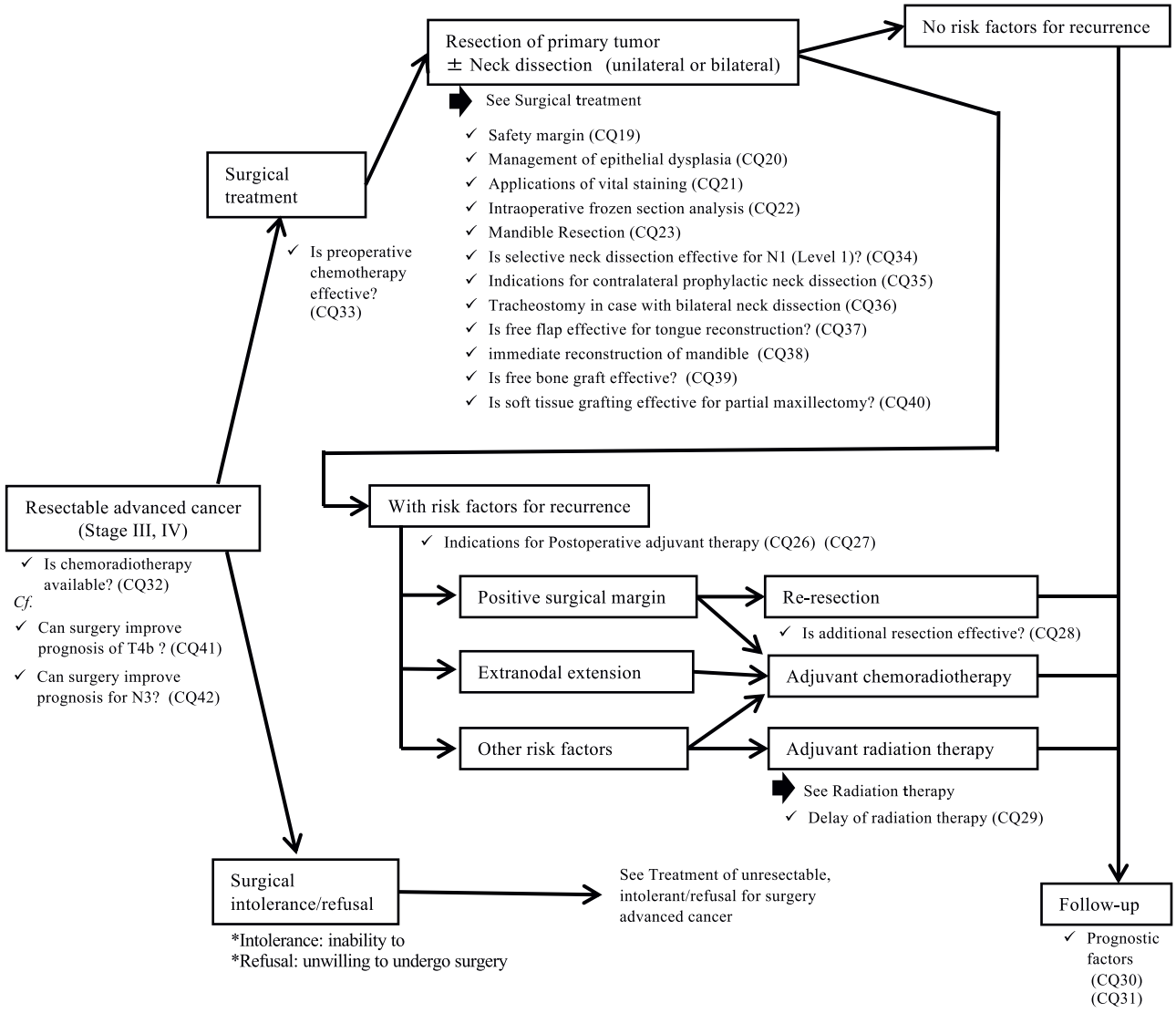


Fig. 2. Treatment algorithm for resectable advanced oral cancer (stage III, IV).

shown in Fig. 6[22]. In cases of bone invasion confined to the alveolar region, the choice of marginal or segmental resection of the mandible is based on selection criteria, in particular taking into consideration the relationship between the depth and the type of bone invasion (CQ23)[5,23,24]. There are many reports that recurrence of the primary tumor after resection occurs from the soft tissue margin rather than the bone margin[25–27]; marginal resection alone may be inadequate to achieve soft tissue resection, especially in cases involving the mylohyoid muscle or the pharyngeal side. Tumors that reach the mandibular canal progress along the inferior alveolar neurovascular bundle[28,29], and a segmental resection that includes the mental foramen and mandibular canal is required.

Maxillary gingiva and hard palate

A gingivectomy including the periosteum may be performed for exophytic early-stage cancers; however, most patients undergo a partial or subtotal maxillectomy. In cases of significant progression to the maxillary sinus, a total or extended maxillectomy is indicated, as in maxillary sinus cancer.

Tracheostomy

Generally, tracheostomy is used when a primary tumor of the tongue is extensively resected (more than hemi-glossectomy), when more than half of the mandible is removed, or when a bilateral neck dissection is performed concurrently, or if there is a possibility of airway obstruction due to the volume of the skin flap reconstruction (CQ36)[5,30].

Reconstructive surgery

It is difficult to standardize the indications for reconstructive procedures and their evaluation methods, and to obtain evidence. The method and timing of reconstruction are determined according to the condition of the defect and evaluation after oral cancer resection, considering the patient's age, general condition, and social life.

Reconstruction of soft tissue

An important aspect of soft tissue defect repair is the selection of a method that allows the maintenance of residual tissue function. For small tissue defects, simple sutures are often the most useful method to improve postoperative function[31–33]. In cases where there is difficulty closing the tissue defect by

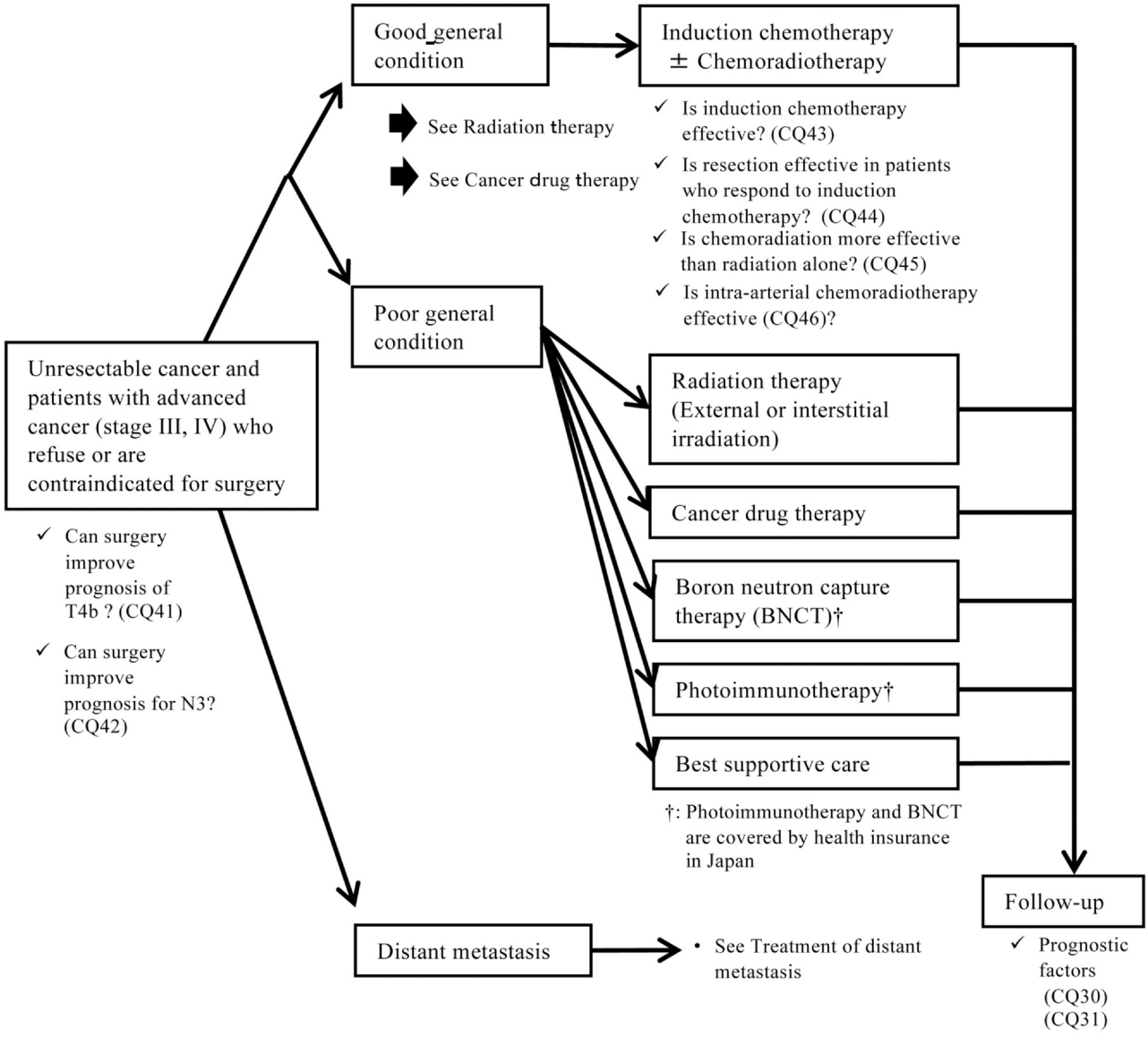


Fig. 3. Treatment algorithm for unresectable cancer and patients with advanced cancer (stage III, IV) who refuse or are contraindicated for surgery.

simple suturing and it is considered that the use of tissue grafting will contribute to improved postoperative function, reconstruction is the method of choice. The choice of reconstructive tissue is determined based on the size and morphology of the tissue defect (CQ37)[5]. In the case of unilateral resection of the movable part of the tongue, it is considered advantageous for postoperative function to avoid impairing the movement of the remaining tongue, and a relatively thin skin flap, forearm flap, or anterolateral thigh skin flap is used[33,34]. In unilateral or total tongue resection, it is important to facilitate contact between the reconstructed tongue and the palate and pharynx to restore articulation and swallowing function; therefore, a rectus abdominis myocutaneous flap is most useful because of its capacity and long-term morphological maintenance[35,36]. Anterior resection of the tongue can cause severe functional impairment even with reconstruction. In cases of bilateral suprahyoid muscle and sublingual nerve resection, severe dysphagia may persist, especially in older patients.

Reconstruction of hard tissue (jawbone)

After mandibulectomy, continuity of the mandible is lost, resulting in mastication disorders and facial deformities caused by mandibular deviation (CQ38)[5]. Currently, vascularized free bone grafts are widely used for primary mandibular reconstruction; however, a combination of a reconstruction plate and soft tissue (skin or myocutaneous flap) or soft tissue alone may also be used (CQ39)[5,37–41]. For autologous bone grafts, a block of iliac bone or particulate cancellous bone and marrow (PCBM) is used. A titanium mesh or poly L-lactic acid mesh is used to hold the PCBM[42,43]. Autogenous or vascularized bone grafts are mainly used for secondary reconstruction[44]. In mandibular reconstruction, alveolar ridge augmentation with secondary bone grafts and distraction osteogenesis may be performed for the final

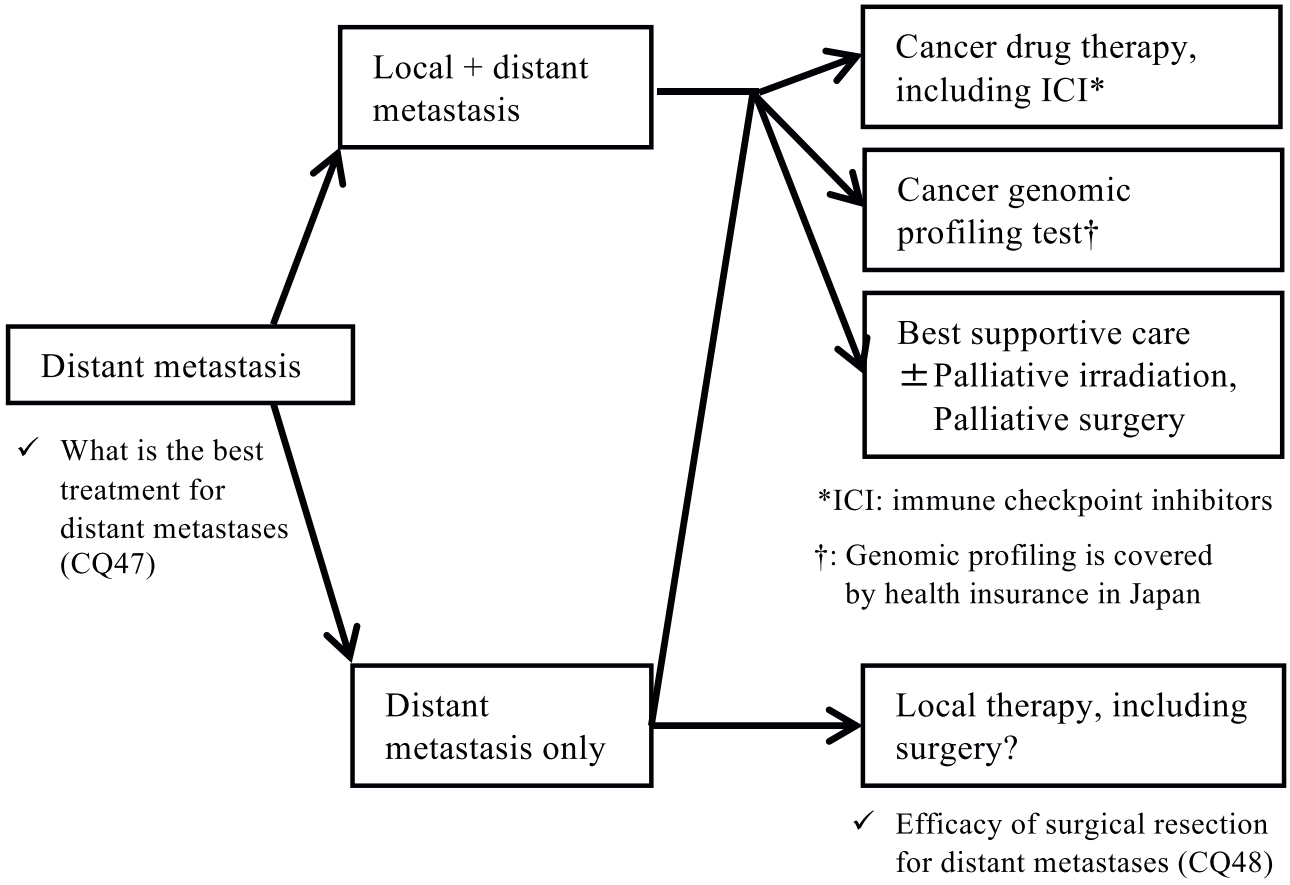


Fig. 4. Treatment algorithm for distant metastatic oral cancer (M1) at initial diagnosis.

occlusal reconstruction with dental implants or prostheses.

In the case of maxillary reconstruction, a free osteocutaneous flap is introduced[45–47]. In the case of partial maxillectomy, if there is less than a unilateral loss of the hard palate, alveolar region, and residual teeth, a maxillary prosthesis is considered more effective than closure with a skin valve[45,48,49]; however, reconstruction with soft tissue grafts (such as buccal fat and local skin flaps) has also been performed. No conclusion has been reached regarding which method is more appropriate; this will depend on the patient's wishes and other factors (CQ40)[50].

Neck dissection

In the case of T1N0 and T2N0 tongue cancer, close follow-up is conducted. Elective neck dissection is performed for T1 and T2 cases with a strong suspicion of potential metastasis, or for T2 or higher cases with invasive disease (DOI > 5 mm)[51]. In general, sentinel lymph node (SLN) biopsy or DOI is thought to be the best predictor of occult metastatic disease and should be used to guide decision-making. The guidelines suggest the use of elective neck dissection when primary tumor resection is performed in patients with T1–2N0 tongue, floor of the mouth, or buccal mucosal cancer (CQ24)[21]. However, this proposal does not include consideration of DOI. In addition, SLN biopsy is not yet widely used in Japan. Under these circumstances, the guidelines also state the opinion that elective neck dissection should not be proposed. A prospective observational study of elective neck dissection for clinically node-negative oral tongue squamous cell carcinoma (END-TC study; UMIN-CTR Clinical Trial, ID UMIN000027875) is currently underway.

Elective neck dissection is also performed in cases where the primary tumor extends to the floor of the mouth or where reconstructive surgery is required. The usefulness of SLN has been reported (CQ25)[5].

With regard to the elective neck dissection technique, many argue that a supraomohyoid neck dissection (SOHND) should be used because it causes less postoperative functional impairment. Metastasis to level IV due to stepping stone metastasis is observed in approximately 16% of cases, hence there is an opinion that an extended SOHND, including level IV, should be applied[52,53].

Conventional radical neck dissection/modified radical neck dissection (MRND) is the basic approach for therapeutic neck dissection in N1–3 cases; however, MRND should be performed considering the metastatic status, such as the absence of adhesions (extranodal extension) to organs to be spared. SOHND may be selected for level I N1 cases, but evidence for this has not been established (CQ34)[54].

In cases of oral cancer crossing the midline, if the tumor is T3 or higher and metastasis is suspected in the ipsilateral cervical lymph nodes, a contralateral elective dissection should be considered because of the high likelihood of contralateral cervical metastasis (CQ35)[5]. Moreover, bilateral cervical metastases are more likely to occur in cases involving the root of the tongue or cancer of the palate.

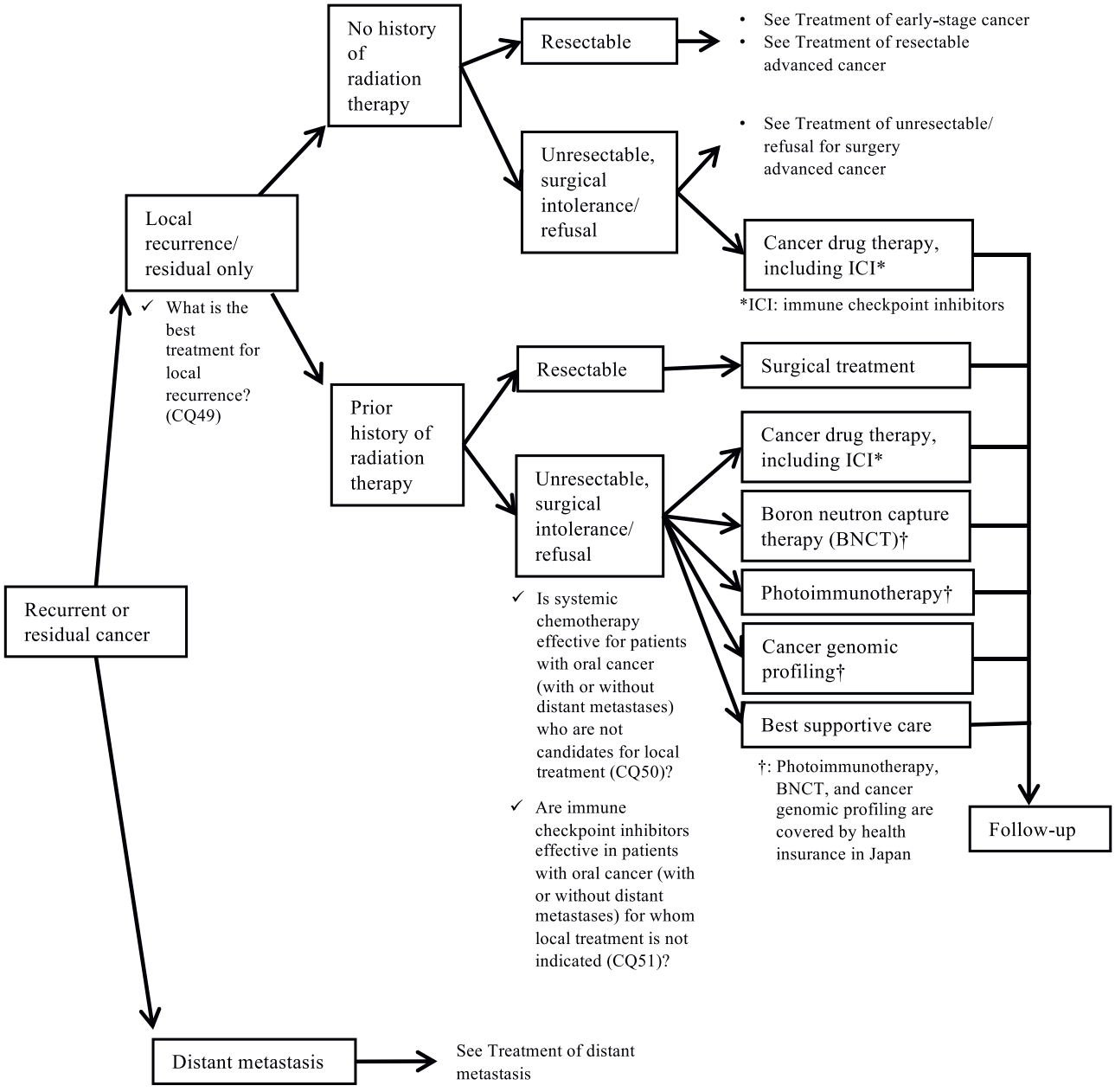


Fig. 5. Treatment algorithm for recurrent or residual cancer.

Radiation therapy

Brachytherapy

Brachytherapy has become established as a treatment that preserves function and morphology. Soft tissues such as the tongue are irradiated using interstitial irradiation. In Japan, however, the number of facilities where brachytherapy can be performed is limited.

Low-dose-rate interstitial brachytherapy

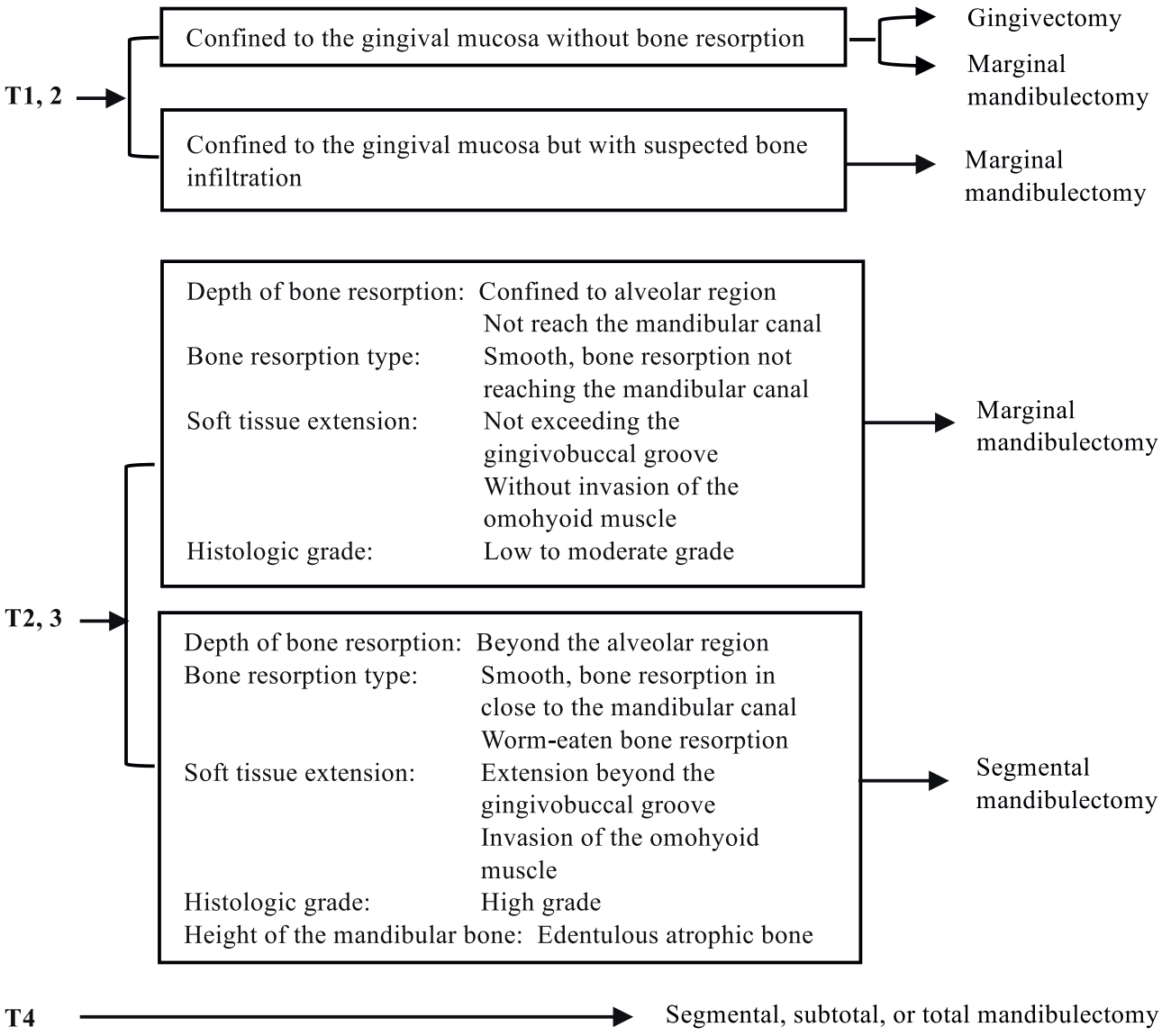
Low-dose-rate brachytherapy with ^{192}Ir pins is commonly applied. Normally, single-plane insertion is used for tumors < 10 mm thick[55] and 70 Gy is irradiated over 5–7 days[56]. ^{198}Au grains are an alternative radiation source when the application of ^{192}Ir pins is difficult; these are permanent implants. For small superficial tumors, a maintained and uniform dose distribution is required[57].

High-dose-rate interstitial brachytherapy

In high-dose-rate interstitial brachytherapy, high-dose ^{192}Ir is used as the radiation source. Although the segmentation method, total dose, and procedure have not yet been established, good results have been reported with twice-daily irradiation at 6 Gy per dose and a total dose of 60 Gy[58].

External irradiation

Conventional external irradiation using X-rays or gamma rays alone cannot be expected to radically control oral cancer. In recent years, highly accurate intensity-modulated radiation therapy (IMRT) has become popular[59], and along with particle therapy[60] is



1. Gingivectomy is limited to T1 and T2, and histopathological confirmation of localization to the gingival mucosa is required.
2. The depth of bone resorption at T4 is defined as the bone resorption caused by the tumor reaching to the mandibular canal according to the mandibular canal classification.
3. The intermediate type of bone resorption is considered as an intermediate condition between the smooth and the worm-eaten type.
4. Immediate or secondary reconstruction of the jawbone should be considered after resection, if necessary.
5. The indication for a hemisection or a subtotal mandibulectomy is determined by the progression of the cancer.

Fig. 6. Algorithm for surgical treatment of mandibular gingival cancer.

expected to be useful in the treatment of advanced cancer.

Indications for radiation therapy

Definitive radiotherapy

If the primary lesion is < 10 mm thick and T1N0 or T2N0, flat penetrating interstitial irradiation can offer a control rate of approximately 90%, which is equivalent to that of surgical therapy. However, for primary lesions > 10 mm thick, surgical therapy is recommended over interstitial irradiation (CQ18)[5].

There is no evidence that chemoradiotherapy or radiotherapy clearly improves primary tumor/neck control or survival compared with surgery for resectable advanced oral cancer (CQ32)[5], making it a treatment option for unresectable tumors, patients refusing surgery (those preferring non-surgical treatment), or patients for whom surgery is contraindicated (cases where surgical procedures would be difficult to perform). The combination of radiotherapy with chemotherapy (chemoradiotherapy) may be used rather than radiation alone (CQ45)[61]. The standard regimen is concurrent cisplatin (CDDP) or carboplatin (CBDCA) + 5-fluorouracil (5-FU)[62] and radiation therapy of 60–70 Gy in 35 fractions (radical radiotherapy: 66–70 Gy, 1.8–2.0 Gy/fraction; accelerated multifractionated radiation: 60–70 Gy, 1.2–1.5 Gy/fraction twice a day). In cases where CDDP is difficult to administer, bioradiotherapy with cetuximab is recommended[63].

Postoperative radiotherapy

Postoperative (chemo)radiotherapy has been shown to improve the primary site, neck control, and survival in patients at high risk of recurrence after surgical treatment for oral cancer[64–66]. Positive microscopic resection margins and extranodal extension are considered high risk factors for recurrence, and postoperative chemoradiation with CDDP is recommended. However, because there is no clear benefit of concomitant chemoradiotherapy in patients with other risk factors such as close margins, pT3, pT4, multiple cervical lymph nodes, distal cervical node metastases (levels IV and V), perineural invasion, venous invasion, or lymphovascular invasion[67], postoperative radiation therapy alone is recommended (CQ26, CQ27)[5]. The interval between surgery and postoperative radiotherapy should be < 6 weeks, and it has been suggested that a prolonged total treatment time between surgery and the completion of adjuvant therapy may influence the overall survival rate (CQ29)[5]. Irradiation doses are 60–66 Gy for patients at high risk of postoperative recurrence, such as those with positive margins; 44–50 Gy (2.0 Gy/fraction) for low-to-intermediate-risk patients (when there is a suspicion of residual tumor) for three-dimensional primary body radiation therapy or continuously planned IMRT; and 54–63 Gy (1.6–1.8 Gy/fraction) for IMRT using the dose painting method.

Palliative radiotherapy

Palliative radiation therapy is used to maintain and improve the quality of life of patients by relieving pain and various symptoms caused by cancer. As there is no consensus on the treatment regimen for head and neck cancer, decisions should be made on an individual basis to achieve the required goals and benefits while considering radiation-related adverse events; serious radiation-related adverse events should be avoided. Representative regimens are as follows[68–71]: (1) 50 Gy in 20 fractions; (2) 7.5 Gy in 15 fractions (if tolerated, add five more fractions for a total of 50 Gy); (3) 30 Gy in 10 fractions; (4) irradiation with 30 Gy five times (twice a week, with at least 3 days between irradiations); (5) irradiation with 44.4 Gy for 12 fractions in three cycles (two irradiations every 6 h for two consecutive days for one cycle, avoiding the spinal cord after two cycles).

Cancer drug therapy

Radical control of oral cancer is rarely achieved using drug therapy alone. Currently, cancer drug therapy is utilized as (1) concurrent chemoradiotherapy for patients at risk of recurrence after surgery (postoperative chemoradiotherapy); (2) induction chemotherapy and chemoradiotherapy for unresectable tumors, patients refusing surgery, and patients for whom surgery is contraindicated; (3) systemic therapy for distant metastases; and (4) therapy for unresectable or recurrent advanced cancers that are not amenable to radiation therapy.

Evidence for the benefits of preoperative chemotherapy for resectable oral cancer is very weak, and the Joint Working Group suggest that preoperative chemotherapy should not be used (CQ33)[72]. In Japan, some centers have reported good outcomes with intra-arterial chemoradiotherapy for patients with locally advanced oral cancer, but clear evidence has not yet been obtained (CQ46)[73].

Postoperative chemoradiotherapy

CDDP (80 or 100 mg/m^2, every 3 weeks, three courses) has been used in cases where chemoradiotherapy has been applied as adjuvant therapy[64–66,74]. A recent randomized phase II/III trial (JCOG1008) demonstrated the non-inferiority of weekly CDDP (cisplatin 40 mg/m^2) plus radiation therapy (total dose 66 Gy) over postoperative chemoradiotherapy with CDDP (cisplatin 100 mg/m^2) administered every 3 weeks[75].

Induction chemotherapy and chemoradiotherapy for unresectable cancer and patients with advanced cancer who refuse or are contraindicated for surgery

The Joint Working Group propose the use of chemoradiotherapy rather than radiation alone when radiation therapy is administered to patients with unresectable locally advanced oral cancer (CQ45)[61]. In head and neck cancer, TPF (docetaxel/cisplatin/5-FU) has been used as induction chemotherapy, and its effect on laryngeal preservation has been reported. However, no benefits have been demonstrated in patients with unresectable locally advanced oral cancer, and it is suggested that induction chemotherapy should not be administered before chemoradiation (CQ43)[12]. In chemoradiation therapy for unresectable cancer and patients with advanced cancer who refuse or are contraindicated for surgery, high-dose CDDP (100 mg/m^2)[76], weekly doses of CDDP (40 mg/m^2)[77–79], and cetuximab[80] have been used.

Distant metastasis and unresectable advanced or recurrent cancer not amenable to radiation therapy

Pembrolizumab/cisplatin or carboplatin/5-FU or pembrolizumab alone (first choice if the patient is PD-L1-positive with a combined positive score

(CPS) ≥ 20) is appropriate as a first-line treatment for recurrent or metastatic squamous cell carcinoma of the head and neck[81]. Nivolumab[82,83], pembrolizumab[84–86], and paclitaxel/cetuximab[87,88] have been used in cases of CDDP refractory disease or patients with a contraindication to its use (CQ50, CQ51)[5].

Other therapies include cetuximab/cisplatin or carboplatin/5-FU[89], cisplatin, carboplatin, nedaplatin, paclitaxel, docetaxel, 5-FU, TS-1 (tegafur/gimeracil/oteracil), and methotrexate. Cisplatin, carboplatin, nedaplatin, paclitaxel, docetaxel, 5-FU, TS-1, and methotrexate are administered either alone or in combination. Genetic profiling tests are covered by health insurance in Japan and are expected to be widely used in the future.

Supportive care (including rehabilitation)

Nutrition

Poor pre-treatment nutritional status is associated with worse outcomes (CQ55)[5]. If the preoperative evaluation indicates that the patient is undernourished or at high risk of being undernourished, aggressive nutritional therapy is administered. Perioperative management with immunonutrient-enriched enteral nutrition is recommended for adult patients with advanced oral cancer who are scheduled for surgery (CQ56)[5].

Oral intake is the preferred route of nutrition; however, tube feeding (nasogastric tube or gastrostomy) should be chosen if the patient is unable to consume the required amount orally. Gastrostomy is also used in patients with long-term oral intake difficulties after oral cancer treatment. However, the effectiveness of gastrostomy nutritional management during radiation therapy or chemoradiotherapy is uncertain (CQ57) (Suzuki et al. accepted for publication; *J Oral Maxillofac Surg Med Pathol*, 2024).

Rehabilitation (feeding and swallowing, cervical and upper extremity, and donor site)

Providing explanations and guidance only after the patient is experiencing problems is inefficient. Therefore, it is important to introduce training before surgery.

Eating and swallowing rehabilitation

The recovery of oral function is difficult in patients who have undergone resection of more than half of the tongue, an extensive resection of the floor of the mouth, resection of more than half of the mandible, including the suprahyoid muscles, and in those who have extensive palatal defects extending to the soft palate. In terms of masticatory function, the number and condition of the remaining teeth are key to postoperative functional recovery.

Expectoration and drainage training are essential in eating and swallowing rehabilitation. Indirect training, such as range of motion expansion training, muscle strengthening training, skill acquisition training, and swallowing reflex induction training should be selected and implemented depending on the case. Direct training using food and drinks is incorporated while evaluating the effectiveness of the training, degree of aspiration, ability to expel aspirated material, and presence or absence of the cough reflex. In direct training, compensatory methods such as a swallowing control diet, postural adjustment methods, and swallowing function improvement devices, including palatal augmentation prostheses (PAP), are applied according to the case (CQ58)[5,90].

Disability after neck dissection

In cases of shoulder rotation dysfunction and difficulty raising the upper extremity, which occur after neck dissection, rehabilitation by a physical therapist should be performed if the patient's prevention and recovery training is insufficient.

Dental and oral management

During surgery, radiation, and drug therapy in patients with oral cancer, dental and oral functional management before, during, and after treatment can reduce the incidence of acute and late adverse events and complications related to the treatment (CQ59)[5].

Comprehensive oral care

Comprehensive oral healthcare includes cleaning, rinsing, moisturizing, removing mechanical stimuli, and providing lifestyle guidance.

Measures to prevent oral dryness

For xerostomia caused by salivary gland disorders, the avoidance of caffeine-containing foods, use of artificial saliva[91], use of choline receptor agonists (pilocarpine and cevimeline)[92], and use of alcohol-free mouthwashes are recommended. In addition to dietary advice, oral hygiene should be maintained with an interdental brush and dental floss, rinsing with an alcohol-free mouthwash twice daily, topical application of 1.1% sodium fluoride, and regular dental checkups[93].

Control of mucositis/stomatitis

Comprehensive oral care is essential to relieve oral mucositis. The use of spacers is recommended to minimize the adverse effects of radiotherapy. In addition, because metal prostheses in the oral cavity can lead to artifacts and more severe mucositis due to scattered radiation, demetallization before treatment has been proposed[94]. In addition, a hydrogel wound and dressing protectant (Episil oral liquid; Meiji Seika Pharma Co., Ltd, Tokyo, Japan) has been applied for pain due to mucositis and reported to be effective[95].

Prevention of osteoradionecrosis

It is widely known that the extraction of teeth within the irradiated field can result in osteonecrosis of the jaw. If a tooth has a poor long-term prognosis, elective extraction should be performed before radiation therapy. However, there are no reports of randomized controlled clinical trials or systematic reviews on tooth extraction within the irradiation field during and after radiation therapy regarding the development of radiation-induced osteonecrosis of the jaw. The evidence for the safety of tooth extraction during and after radiation therapy in an irradiated field is unclear (CQ60)[5].

Management of other functions

Occasionally, oral cancer surgery or irradiation results in a postoperative mouth-opening disorder. Prophylactic mouth-opening training is effective in preventing or treating this condition. No effective perioperative management has been found for taste disorders; however, zinc sulfate has been used to treat taste disorders during radiotherapy.

Palliative medicine (palliative care)

It is necessary to have a system in which palliative medicine can be applied from the time of the initial diagnosis. The quality of life of cancer patients and their families can be improved by actively providing medical treatment and care to alleviate physical, mental, and social distress from the early stages of cancer diagnosis.

Methodology

The Clinical Practice Guidelines for Oral Cancer 2023 were developed using the GRADE approach[96] and the Medical Information Network Distribution Service (Minds) Manual for Guideline Development 2020[97]. CQs were collected from committee members, and a list of 60 CQs was obtained. Preliminary screening of the CQs was conducted by a systematic review team consisting of one committee member and two systematic review members, based on the systematic review protocol. Based on the preliminary screening, it was decided to conduct a systematic review for 11 CQs. The excluded CQs were used for a narrative review and to write the guidelines. The systematic reviews were conducted following the GRADE approach.

Ethical approval

Not required.

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Competing Interests

None.

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Competing interests

None.

Patient consent

Not required.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ijom.2024.11.012.

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