1. Principles of diagnosis and treatment of head and neck cancer

During the diagnosis and treatment of head and neck cancer, a multidisciplinary team (MDT) is desired. This is especially important for patients with locally advanced head and neck squamous cell carcinoma. The principle of MDT should be applied throughout the treatment process. During the implementation of MDT, experts from multiple disciplines can evaluate the clinical presentation, images, pathology, and molecular biology data from the patients; and comprehensively assess the performance status, diagnosis, cancer stages/metastasis, development, and prognosis. Based on current national and international treatment standards and guidelines, as well as evidence-based medicine combined with existing treatment options, a treatment strategy tailored to an individual patient can be developed. During the treatment course, the MDT team should adjust the treatment strategy according to changes in the patient’s condition and tumor response, to maximize the survival of the patient, increase the cure rate, and improve the quality of life.

2. Diagnosis principles of head and neck cancer

2.1 Image diagnosis

Head and neck cancer is one of the most common malignant tumors. Its incidence rate ranks sixth in males and the mortality rate ranks seventh in China (2). The most common pathological type is squamous cell carcinoma. With the exception of nasopharyngeal carcinoma, which is mainly caused by Epstein-Barr virus, most other head and neck squamous cell carcinomas are due to cigarette smoking and alcohol abuse (3). In recent years, the incidence of oropharyngeal cancer has significantly increased in Europe and the United States, mainly due to human papillomavirus (HPV) infection, but its exact infection rate is still unclear in China (4).

Enhanced computed tomography (CT) or magnetic resonance imaging (MRI) scans of the primary lesion are common methods for diagnosing head and neck cancer, both of which have advantages and disadvantages. CT has the advantages of simplicity, rapidity, and wide availability. On the other hand, it has the disadvantage of radiation exposure, which is not appropriate for patients with iodine
Allergy or severe renal insufficiency. MRI can show soft tissue with higher resolution than CT and provides a variety of imaging measurements. It is especially useful for tumors originating from the oral cavity, oropharynx, and nasopharynx, and has excellent resolution for the skull base and nerves. While, the disadvantage of MRI is that it is time-consuming and relatively expensive, and is not suitable for patients with metal implants or with claustrophobia. In addition, for the laryngeal and hypopharyngeal organs, it is easy to cause artifacts due to involuntary swallowing during MRI examination. The neck is the most common area for lymph node metastasis from head and neck cancer. Neck-enhanced CT is a standard staging method, especially during the characterization of typical features of lymph node necrosis. The lung is the most common site for distant metastasis from head and neck cancer. Chest CT is the standard staging method that also helps assess other pulmonary diseases such as chronic bronchitis.

Positron emission tomography (PET)/CT mainly uses $^{18}$F-FDG as the tracer, and has been extensively investigated for the management of head and neck cancer in recent years (5). For primary lesions, because PET/CT is commonly performed with low-dose plain CT, its resolution is not as good as that in enhanced CT and can result in false positive or false negative results. For cervical lymph node and distant metastases, some meta-analyses have shown that PET/CT had certain advantages (6,7). A prospective study showed that the combination of PET/CT with conventional staging methods changed the treatment strategy in 13.7% of patients (8). Currently, the National Comprehensive Cancer Network (NCCN) recommends PET/CT for pre-treatment examination in patients with stage III/IV cancer (9).

The diagnosis of primary head and neck cancer mainly depends on oral or endoscopic mass biopsy, whereas lymph node puncture or biopsy is helpful in cancer staging. Other countries usually advocate upper gastrointestinal endoscopy (panendoscopy) under general anesthesia for biopsies on suspicious lesions, which helps to increase the accuracy of diagnosis and the possibility of identifying a second primary cancer.

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Table 1 Image diagnosis

| Content                        | Level I expert recommendation                          | Level II expert recommendation                   |
|--------------------------------|-------------------------------------------------------|--------------------------------------------------|
| Diagnosis                      | Primary lesion enhanced CT                            | PET/CT                                           |
|                                | Primary lesion enhanced MRI                           |                                                  |
|                                | Neck enhanced CT                                      |                                                  |
| Image staging (1)              | Primary lesion enhanced CT                            | PET/CT                                           |
|                                | Primary lesion enhanced MRI                           |                                                  |
|                                | Neck enhanced CT                                      |                                                  |
|                                | Chest enhanced or plain CT                            |                                                  |
| Technique to obtain tissue or  | Oral or endoscopic mass biopsy                        | Endoscopic examination and biopsy under general   |
| cytology analysis              | Cervical lymph node puncture or biopsy                 | anesthesia                                       |

CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.
2.2 Pathological diagnosis

The pathology of head and neck cancer is critical for identifying stages and deciding treatment strategies (1). For both biopsy and punctured specimens, it is essential to distinguish the benign lesion from the malignant tumor, and determine its histological type. If necessary, immunohistochemical staining should be applied. For surgical specimens obtained from radical resection of head and neck squamous cell carcinoma, information including tumor size, differentiation, margin, vascular invasion, peripheral nerve infiltration, bone or cartilage infiltration, site, number of lymph node metastases, and extracapsular invasion is required. For oral cancer, it is necessary to clarify the depth of tumor invasion, which is helpful in guiding the follow-up treatment strategy (2). For oropharyngeal cancer, immunohistochemical examination of p16 can be performed if possible, to determine whether it is associated with HPV infection, although current guidelines do not recommend that individualized treatment strategy be based on this test result (2).

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2.3 Staging

Current guidelines apply the Union for International Cancer Control/American Joint Committee on Cancer (AJCC) Tumor-Node-Metastasis staging system (7th edition), due to its popularity. The 8th edition was published on January 1, 2018, but we did not use it here, as it recommends an HPV test in patients with oropharynx cancer and requires the detection of the depth of invasion in patients with oral cancer, which are not routine tests performed in China.

3. Treatment principles of early and locally advanced head and neck squamous cell carcinoma

3.1 Treatment of oral cancer

3.1.1 Treatment of early oral cancer (Table 2)

The main radical treatment method for early oral cancer should be surgery. Local radiation therapy is only considered for patients who do not meet the criteria for surgery. During surgery, a safe resection margin of at least 5 mm should be ensured; otherwise, treatment outcomes may be affected (2). Early oral cancer also carries a certain risk of cervical lymph node metastasis. Although a phase III randomized trial confirmed the survival benefit of preventive cervical lymph node selective clearance (zones I–III), it is still inconclusive if all patients with early oral cancer should receive cervical lymph node clearance (3). In recent years, several studies have shown that the depth of tumor invasion correlates with cervical lymph node metastasis and prognosis, which also contributes to the 8th edition of the AJCC staging system to include the depth of invasion in the T staging criteria for oral cancer (4-6). The NCCN guideline recommends ipsilateral or bilateral cervical lymph node clearance in zones I–III for patients with tumor invasion depth >4 mm (when the tumor is located at or close to the midline). For patients with invasive depths between 2 mm and 4 mm, whether to perform lymph node clearance based on the actual clinical situation is recommended by NCCN guidelines (7). Sentinel lymph node biopsy is a method to replace cervical lymph node clearance, but it has to be performed in an experienced center (8). Postoperative radiation therapy or chemoradiation therapy should be performed in patients with high risk factors suggested by postoperative pathological or histological examinations. For a small number of patients with early stage oral cancer who do not meet the criteria for surgery due to their physical conditions, radiation therapy, especially brachytherapy, is

| Staging | Patient classification | Level I expert recommendation | Level II expert recommendation |
|---------|------------------------|-------------------------------|------------------------------|
| T1–2N0  | Patients who meet criteria for surgery | Surgery (1) (class 2A evidence) | — |
|         | Patients who do not meet criteria for surgery | Radiation therapy alone (1) (class 2A evidence) | — |
another option, but it needs to be performed in an experienced center and according to guidelines from relevant authorities (9,10).

### 3.1.2 Treatment of locally advanced oral cancer (Table 3)

For patients with advanced oral cancer, surgery is still a main radical treatment method. The surgical methods are the oral or mandibular lingual release and mandibular incision approaches, and include the necessary repair and reconstruction of the defects from the surgery. Cervical surgery should be performed with selective or radical clearance of the lymph nodes. For N2c or primary lesions located at or close to the midline, contralateral cervical lymph node clearance should be considered. Postoperative adjuvant radiation therapy should be performed within 6 weeks after surgery. It is recommended that patients with high risk factors (e.g., T3–4, lymph node metastasis, vascular invasion, peripheral nerve infiltration) receive postoperative radiotherapy alone. Patients with positive/ incomplete resection margins or exnodal extension should receive concurrent chemoradiation therapy. Studies have shown that patients with exnodal extension and/or resection margin <1 mm under microscopic examination had a better survival outcome if they received postoperative concurrent chemoradiation therapy compared with radiation therapy alone (18). For patients with advanced oral cancer who do not meet the criteria for surgery, radiation therapy combined with cisplatin is a common treatment option. For patients who are not suitable for cisplatin or for elderly patients (>70 years old), radiation therapy alone can be given. For patients with a large unresectable tumor mass, sequential therapy with induction chemotherapy combined with radiation therapy may also be considered. The commonly used induction chemotherapy regimen is 5-fluorouracil (TPF), but randomized studies have not demonstrated superior survival outcomes compared with concurrent chemoradiation therapy (14-16).

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### Table 3 Treatment of locally advanced oral cancer

| Staging                                      | Patient classification 1                                      | Patient classification 2                                      | Level I expert recommendation                                                                 | Level II expert recommendation                                                                 |
|----------------------------------------------|----------------------------------------------------------------|----------------------------------------------------------------|-----------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| T1−2N + T3−4 with different N                | Patients who meet criteria for surgery                       | --                                                              | Surgery (1) (class 2A evidence)                                                                 | --                                                                                           |
|                                              | Appropriate for cisplatin treatment                           | Radiation therapy + cisplatin (11-13) (class 1A evidence)       | Induction chemotherapy → radiation therapy alone (14-16) (class 1B evidence)                     |                                                                                              |
|                                              | Not appropriate for cisplatin treatment                       | Radiation therapy alone (1) (class 2A evidence)                 |                                                                                               |                                                                                              |

Patients not suitable for surgery: poor physical condition, reject operation for various reasons, or heavy tumor burden. Patients not appropriate for cisplatin treatment: age >70 years, performance status (PS) >2, loss of hearing, renal dysfunction (creatinine clearance <50 mL/min), or > level 1 neuropathy (17).
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3.2 Oropharyngeal cancer

3.2.1 Treatment of early oropharyngeal cancer (Table 4)

Early oropharyngeal cancer should be treated with either surgery or radiation therapy alone. Retrospective analyses have shown that the overall efficacy of these two methods is similar (2,3). The selection of management should be based on the tumor size and location, possible postoperative dysfunction, and the skills and experience of the surgeon or radiologist. It is strongly recommended that the MDT perform a comprehensive assessment of quality of life and treatment outcomes (e.g., efficacy, function maintenance, and complications) and select the most appropriate management. The surgery can be performed by an open or oral approach to remove the primary lesion. An oral approach can provide a better functional outcome. Laser microsurgery or robotic surgery through the oral approach can be selected for appropriate patients. Early oropharyngeal cancer can have occult cervical lymph node metastasis. Thus, ipsilateral selective cervical lymph node clearance is required in addition to primary lesion resection. Lymph node clearance should include the ipsilateral II–IV zones, which may have to include zone I when the cancer shows signs of forward invasions (4). If the primary lesion is located at or close to the midline, such as the soft palate, the base of the tongue, or the posterior pharyngeal wall, the contralateral clearance should be considered for obtaining accurate staging of the contralateral cervical lymph nodes. A retrospective analysis found that there was no need to perform cervical clearance in the IIb zone, when there was no invasion in the neck IIa zone before surgery. Patients with high risk factors suggested by postoperative pathological or histological examinations will require postoperative radiation therapy or chemoradiation therapy. The oral cavity, diet, and speech of patients should be assessed before radical radiation therapy. Delineation of the target volumes for radiation therapy should be based on enhanced CT, and MRI scan can be used for further reference. The target volumes for the radiation therapy commonly include the primary cancer and cervical lymph nodes at zones II–IV, as well as the Ib zone when the tumor invades forward and/or involves the anterior tonsil pillars. Prophylactic radiation of the ipsilateral cervical lymph nodes is recommended if the primary lesion is unilateral (such as tonsil). If the primary lesion is located at or close to the midline, such as the soft palate, tongue root, or posterior pharyngeal wall (midline structure invasion >1 cm), bilateral prophylactic radiation

| Table 4 Treatment of early oropharyngeal cancer |
|-----------------------------------------------|
| **Staging** | **Patient classification** | **Level I expert recommendation** | **Level II expert recommendation** |
| T1–2N0 | Patients who meet criteria for surgery | Surgery (1) (class 2A evidence) | — |
| | Patients who do not meet criteria for surgery | Radiation therapy alone (1) (class 2A evidence) | — |

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therapy should be performed. At least the three-dimensional conformal radiation therapy is used for radiotherapy, and the intensity-modulated radiation therapy (IMRT) is recommended.

### 3.2.2 Treatment of locally advanced oropharyngeal cancer (Table 5)

For patients with stage T1–2N1–2 oropharyngeal cancer, the outcome of surgery (usually combined with postoperative radiation therapy or chemoradiation therapy) is similar to that of chemoradiation therapy, but the latter provides functional protection. When the size of the primary tumor is too large or surgery may cause significant loss of function, concurrent chemoradiation therapy should be considered. Surgery can be performed through an oral approach or via open resection of the primary lesion, although an oral approach can provide better functional protection. Oral laser microsurgery or robotic surgery can be selected for appropriate patients. Cervical surgery should be performed with selective or radical lymph node clearance. If the N2c or primary lesion is located at or near the midline, such as the soft palate, tongue root, or posterior pharyngeal wall, the lymph node clearance at the contralateral side should be considered. Postoperative radiation therapy is required after surgery. For patients with stage T3–4 cancer, only a small number of patients with T3 may undergo surgery, and most of them should choose concurrent chemoradiation therapy to preserve functions. Postoperative adjuvant radiation therapy should be performed within 6 weeks after surgery. It is recommended that patients with high risk factors (e.g., T3–4, lymph node metastasis, vascular invasion, peripheral nerve infiltration) receive postoperative radiation therapy alone. It is also recommended that patients with positive/incomplete resection margins or exnodal extension receive concurrent chemoradiation therapy. Studies have shown that patients with exnodal extension and/or resection margin <1 mm under microscopic examination have a better survival advantage if they receive postoperative concurrent chemoradiation therapy compared with those who receive radiation therapy alone (12). For advanced oropharyngeal cancer, radiation therapy combined with cisplatin is the standard treatment method (5). For patients in whom cisplatin is not appropriate, radiation therapy combined with cetuximab can be given (6,7). Patients with advanced stage cancer who are not candidates for concurrent chemotherapy, especially elderly patients (>70 years old) who have unclear survival benefits during the same period, can receive radiation therapy alone (13). For patients with stage T4 or N2c–N3 cancer, induction chemotherapy may be considered to reduce tumor mass and also reduce the risk of distant metastasis, although randomized studies have not demonstrated its superiority to concurrent chemoradiation therapy (8-10). A

| Staging | Patient classification 1 | Patient classification 2 | Level I expert recommendation | Level II expert recommendation |
|---------|--------------------------|--------------------------|-------------------------------|-------------------------------|
| T1–2N1–2 | Patients who meet criteria for surgery | Appropriate for cisplatin treatment | Surgery (1) (class 2A evidence) Radiation therapy + cisplatin (5) (class 1A evidence) | Radiation therapy + cetuximab (6,7) (class 1B evidence) |
| | Patients who do not meet criteria for surgery | Not appropriate for cisplatin treatment | Surgery (1) (class 2A evidence) | Radiation therapy + cetuximab (6,7) (class 1B evidence) |
| T3–4N0–3/T1–2N3 | Patients who do not meet criteria for surgery | Appropriate for cisplatin treatment | Radiation therapy + cisplatin (6) (class 1A evidence) Radiation therapy alone (1) (class 2A evidence) | Radiation therapy + cetuximab (6,7) (class 1B evidence) |
| | — | Not appropriate for cisplatin treatment | Radiation therapy alone (1) (class 2A evidence) | Radiation therapy + cetuximab (6,7) (class 1B evidence) |

Patients not suitable for surgery: poor physical condition, reject operation for various reasons, or heavy tumor burden. Patients not appropriate for cisplatin treatment: age >70 years, performance status (PS) >2, loss of hearing, renal dysfunction (creatinine clearance <50 mL/min), or > level 1 neuropathy (11).
commonly used induction chemotherapy regimen is TPF (10). For patients with N2–3 cancer and undergoing radical radiation therapy, if the PET/CT shows complete remission 3 months after radiation therapy, cervical lymph node clearance is not required (14). For patients with residual or local recurrence after radiation therapy/concurrent chemoradiation therapy, it is recommended that eligible patients receive salvage surgery (15).

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3.3 Treatment of laryngeal cancer

3.3.1 Treatment of early laryngeal cancer (Table 6)

Early-stage laryngeal cancer should be treated with a single method of either surgery or radiation therapy alone. A systematic review showed that the overall efficacy of the two methods was similar (2). The selection of a treatment method should be based on the tumor volume, location (for example, tumors with anterior commissure involvement usually are treated with radiation therapy), possible postoperative dysfunction, and the skills and experience of the surgeon or radiologist. It is strongly recommended that the MDT perform a comprehensive assessment of the pronunciation function, quality of life, and treatment outcomes (e.g., effectiveness of treatment, function preservation, and complications) before selecting the most appropriate method. The surgery can be performed by an open or trans-oral approach to remove the primary lesion. Trans-oral surgery can provide better function preservation. Trans-oral laser microsurgery or robotic surgery can be selected if possible. Early-stage glottic laryngeal carcinoma rarely causes cervical lymph node

Table 6 Treatment of early laryngeal cancer

| Staging | Patient classification       | Level I expert recommendation | Level II expert recommendation |
|---------|------------------------------|-------------------------------|-------------------------------|
| T1–2N0  | Patients suitable for surgery| Surgery (1) (class 2A evidence)| –                            |
|         | Patients not suitable for surgery| Radiation therapy alone (1) (class 2A evidence) | – |

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metastasis; thus, it is not necessary to perform cervical lymph node dissection. For supraglottic laryngeal cancer, selective cervical lymph node dissection should be performed in the bilateral cervical zones II–IV. Patients with high risk factors suggested by postoperative pathological or histological examinations require postoperative radiation therapy or chemoradiation therapy. Patients should be assessed for diet, speech, and oral cavity before the radical radiation therapy. Delineation of the target area for the radiation therapy should be based on the enhanced CT or MRI scan, which usually provide good reference. For early-stage glottic laryngeal carcinoma, the target area for the radiation therapy generally only includes the primary tumor, and it is not necessary to perform prophylactic radiation therapy to the cervical lymph node drainage area. For supraglottic laryngeal cancer, the target area for the radiation therapy includes the primary tumor and bilateral lymph nodes in the cervical zones II–IV. Radiation therapy should be performed at least with three-dimensional dosimetry and IMRT is recommended.

### 3.3.2 Treatment of locally advanced laryngeal cancer

(Table 7)

For patients with locally advanced laryngeal cancer, most of them, except T1–2 and some T3 lesions (please refer to the previous section for the surgical treatment), require surgical treatment including total laryngectomy, which usually should be combined with postoperative radiation therapy or chemoradiation therapy. Surgery on the neck should choose either selective or radical bilateral cervical lymph node dissection according to the sites of cervical lymph node metastasis and should include at least zones II–IV, and zone V if necessary (such as T4). Postoperative adjuvant radiation therapy should be performed within 6 weeks after the surgery. It is recommended that patients with gernal high risk factors (T3–4, lymph node metastasis, vascular invasion, peripheral nerve infiltration) receive

| Staging          | Patient classification 1 | Patient classification 2 | Level I expert recommendation | Level II expert recommendation |
|------------------|--------------------------|--------------------------|-------------------------------|-------------------------------|
| **T1–2N1–3/ T3 any N** | Patients suitable for surgery | Patients suitable for cisplatin treatment | Surgery (1) (class 2A evidence) Radiation therapy + cisplatin (3,4) (class 1A evidence) Induction chemotherapy → radiation therapy alone (5,6) (class 1A evidence) | Radiation therapy + cetuximab (7,8) (class 1B evidence) Induction chemotherapy → radiation therapy + cetuximab (9) (class 2A evidence) |
|                  | Patients not suitable for cisplatin treatment | | Surgery (1) (class 2A evidence) | Radiation therapy + cetuximab (7,8) (class 1B evidence) Radiation therapy alone (1) (class 2A evidence) |
|                  | Patients suitable for cisplatin treatment | Patients not suitable for surgery | Radiation therapy + cisplatin (3,4) (class 1A evidence) Induction chemotherapy → radiation therapy alone (10-12) (class 1B evidence) | Radiation therapy + cetuximab (7,8) (class 1B evidence) |
|                  | Patients not suitable for cisplatin treatment | | Radiation therapy alone (1) (class 2A evidence) | Radiation therapy + cetuximab (7,8) (class 1B evidence) |
| **T4 with different N** | Patients suitable for surgery | | Surgery (1) (class 2A evidence) | |
|                  | Patients not suitable for surgery | Patients suitable for cisplatin treatment | Radiation therapy + cisplatin (13-15) (class 1A evidence) Induction chemotherapy → radiation therapy alone (10-12) (class 1B evidence) | Radiation therapy + cetuximab (7,8) (class 1B evidence) |
|                  | Patients not suitable for cisplatin treatment | | Radiation therapy alone (1) (class 2A evidence) | Radiation therapy + cetuximab (7,8) (class 1B evidence) |

Patients not suitable for surgery: poor physical condition, reject operation for various reasons, or heavy tumor burden. Patients not appropriate for cisplatin treatment: age >70 years, performance status (PS) >2, loss of hearing, renal dysfunction (creatinine clearance <50 mL/min), or > level 1 neuropathy (16).
postoperative radiation therapy alone. It is also recommended that patients with positive/incomplete resection margins or lymph node capsular invasion receive concurrent chemoradiation therapy. Studies have shown that patients with lymph node capsular invasion and/or resection margin <1 mm under microscopic examination have clear survival advantage if they receive postoperative concurrent chemoradiation therapy compared with those receiving radiation therapy alone (17). For patients with primary tumor staging of T4, surgical treatment is strongly recommended for patients who have potential for surgical resection, as radiation therapy has poor throat function preservation and efficacy in these patients. In addition, the recently published American Society of Clinical Oncology guideline recommends that total laryngectomy might provide better survival chances and quality of life in patients with extensive T3, T4 cancers or patients with severely impaired laryngeal function before the treatment (18). For other patients who desire to preserve the throat function, radiation therapy combined with cisplatin is a common treatment choice (3,4). For patients who are not candidates for cisplatin treatment, radiotherapy combined with cetuximab can be given (7,8). For patients with locally advanced cancer who are not suitable for concurrent chemotherapy, especially for elderly patients (>70 years old) who have unclear survival benefits with concurrent treatment, radiation therapy alone may be used (14). For patients with N2−3 undergoing radical radiation therapy, if the PET/CT shows complete remission 3 months after the radiation therapy, cervical lymph node dissection is not required (19). For patients with residual or local recurrence after the radiation therapy/concurrent chemoradiation therapy, it is recommended that eligible patients receive salvage surgery, usually with total laryngectomy (20).

Induction chemotherapy is another treatment strategy for preserving laryngeal functions. If patients reach complete or partial remission after chemotherapy, they could receive follow-up radiation therapy with or without concurrent cetuximab; otherwise they should receive total laryngectomy (5,6,9). The standard induction chemotherapy regimen is TPF. In addition, patients with a unresectable large tumor volume or stage T4 or N2c–N3 cancer may also consider sequential therapy with induction chemotherapy combined with follow-up radiation therapy. This approach may reduce the risk of distant metastasis while reducing tumor mass. The commonly used chemotherapy regimen is again TPF, but randomized studies have not demonstrated that survival results are superior to concurrent chemoradiation therapy (10-12).

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Treatment of early hypopharyngeal cancer

3.4.1 Treatment of early hypopharyngeal cancer (Table 8)

Early-stage hypopharyngeal cancer should be treated with a single treatment method of either surgery or radiation therapy alone. Retrospective analysis has shown that the overall efficacy of these two methods is similar (2,3). The selection of a treatment method should be based on the tumor volume and location, possible postoperative dysfunction, and the skills and experience of the surgeon or radiologist. It is strongly recommended that the MDT perform a comprehensive assessment of quality of life and treatment outcomes (e.g., efficacy, function preservation, and complications) before selecting the most appropriate method. The surgery can be performed by an open or trans-oral approach to remove the primary lesion. The trans-oral approach can provide better function preservation. Trans-oral laser microsurgery or robotic surgery can be selected if possible. Early-stage hypopharyngeal cancer can have occult cervical lymph node metastasis. Thus, ipsilateral selective cervical lymph node dissection in zones II–IV is required in addition to primary lesion resection. If the primary lesion is located at or close to the midline, such as the posterior pharyngeal wall, posterior sulcus, or the inner wall of the piriform fossa, contralateral lymph nodes dissection should be considered to obtain the accurate staging of the contralateral cervical lymph nodes. Patients with high risk factors suggested by the postoperative pathological or histological examinations require postoperative radiation therapy or chemoradiation therapy. Patients should be assessed for diet, speech and oral cavity before the radical radiation therapy. Delineation of the target area for radiation therapy should be based on the enhanced CT or MRI scan that can usually provide good References. The target area for radiation therapy commonly includes the primary cancer and the cervical lymph nodes at zones II–IV. Prophylactic radiation of ipsilateral cervical lymph nodes is recommended if the primary lesion is unilateral. If the primary lesion is located at or close to the midline, such as the posterior pharyngeal wall, the posterior sulcus, or the inner wall of the piriform fossa, bilateral prophylactic radiation therapy should be performed. The radiation therapy should be performed with at least three-dimensional dosimetry and IMRT is recommended.

3.4.2 Treatment of locally advanced hypopharyngeal cancer (Table 9)

Surgical resection for most patients with locally advanced hypopharyngeal cancer should include total laryngectomy, except those with T1 or some T2 lesions (please refer to the previous section for the surgical treatment), which usually should combine with postoperative RT or concurrent chemoradiation. Selective or radical neck dissection should be performed. Bilateral neck dissection would be considered for an N2c or primary lesions located at or close to the midline, such as the posterior pharyngeal wall, the posterior sulcus, or the inner wall of the piriform fossa. Postoperative adjuvant radiotherapy should be performed within 6 weeks after surgery. It is recommended

| Staging | Patient classification | Level I expert recommendation | Level II expert recommendation |
|---------|------------------------|-------------------------------|-------------------------------|
| T1−2N0  | Patients suitable for surgery | Surgery (1) (class 2A evidence) | — |
|         | Patients not suitable for surgery | Radiation therapy alone (1) (class 2A evidence) | — |
that patients with adverse features (e.g., T3–4, lymphatic metastasis, vascular embolism, perineural invasion) receive single postoperative radiotherapy, while those with positive margins and/or extranodal extension receive concurrent chemoradiation. For patients with extranodal extension and/or resection margin <1 mm under microscopic examination, studies have shown that those received chemoradiation has a better survival than those received RT alone after surgical resection (16).

For T4 primary lesions, surgical resection is strongly recommended, since radiation therapy does poor in larynx-preserving and treatment efficiency. For others desiring to preserve throat function, RT combined with cisplatin is a common choice (4–6). Cetuximab is an alternative for cisplatin in patients intolerable with cisplatin (9,10). Single radiotherapy may be used in patients with locally advanced cancer unfit for concomitant chemotherapy, especially in the elderly (>70 years old) who may not benefit from concomitant chemotherapy (5). Neck dissection is not required for N2–3 patients showing complete remission (CR) by PET/CT 3 months after radical RT (17). For patients with locoregional recurrence after the radiation therapy/concurrent chemoradiation therapy, salvage surgery is recommended if resectable (18).

Induction chemotherapy is another strategy for larynx-preserving patients. Patients reaching complete or partial remission after induction chemotherapy will receive RT with or without concurrent cetuximab; otherwise, they will receive total laryngectomy (7,8,11). TPF is the standard induction chemotherapy. In addition, patients with unresectable big tumor burden or staging T4 or N2c–N3, sequential therapy may be considered with induction chemotherapy followed by radiation therapy. This approach may reduce tumor mass and the risk of distant metastasis. The commonly used chemotherapy regimen is still TPF, although randomized studies have not demonstrated a prolonged survival compared with concurrent chemoradiation therapy (12-14).

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**Table 9** Treatment of locally advanced hypopharyngeal cancer

| Staging | Patient classification 1 | Patient classification 2 | Level I expert recommendation | Level II expert recommendation |
|---------|--------------------------|--------------------------|-------------------------------|-------------------------------|
| T1–2N1–3/ T3 any N | Patients suitable for surgery | Patients suitable cisplatin treatment | Surgery (1) (class 2A evidence) Radiation therapy + cisplatin (4–6) (class 1A evidence) Induction chemotherapy → radiation therapy alone (7,8) (class 1A evidence) | Radiation therapy + cetuximab (9,10) (class 1B evidence) Induction chemotherapy → radiation therapy + cetuximab (11) (class 2A evidence) |
| | Patients not suitable for cisplatin treatment | | Surgery (1) (class 2A evidence) | Radiation therapy alone (1) (class 2A evidence) |
| | Patients not suitable for cisplatin treatment | | Radiation therapy + cisplatin (4–6) (class 1A evidence) Induction chemotherapy → radiation therapy alone (12-14) (class 1B evidence) | Radiation therapy + cetuximab (9,10) (class 1B evidence) |
| | Patients not suitable for cisplatin treatment | | Radiation therapy alone (1) (class 2A evidence) | Radiation therapy + cetuximab (9,10) (class 1B evidence) |
| T4 with different N | Surgery candidates | — | Surgery (1) (category 2A) | — |
| | Patients unfit for surgery | — | Radiation therapy alone (1) (category 2A) | Radiation therapy + cetuximab (9,10) (category 1B) |
| | Patients not suitable for cisplatin treatment | — | Radiation therapy + cisplatin (4–6) (category 1A) Induction chemotherapy → RT (12-14) (category 1B) | Radiation therapy + cetuximab (9,10) (category 1B) |
| | Not appropriate for cisplatin treatment | — | Radiation therapy alone (1) (category 2A) | Radiation therapy + cetuximab (9,10) (category 1B) |

Patients not suitable for surgery: poor physical condition, reject operation for various reasons, or heavy tumor burden. Patients not appropriate for cisplatin treatment: age >70 years, performance status (PS) >2, loss of hearing, renal dysfunction (creatinine clearance <50 mL/min), or > level 1 neuropathy (15).
Treatment of recurrent or metastatic squamous cell carcinoma of head and neck (Table 10)

Patients with recurrent squamous cell carcinoma of the head and neck (SCCHN) may receive locoregional treatment for a small part, such as surgery or re-irradiation.

Table 10 Treatment of recurrent or metastatic squamous cell carcinoma of head and neck

| Staging          | Treatment selection | Level I expert recommendation | Level II expert recommendation |
|------------------|---------------------|--------------------------------|--------------------------------|
| Recurrence or Metastasis | First-line therapy  | Cisplatin + 5-FU (1) (category 1A) | Cisplatin + 5-FU + cetuximab (4) (category 1A) |
|                   |                     | Carboplatin + 5-FU (1) (category 1A) | Carboplatin + 5-FU + cetuximab (4) (category 1A) |
|                   |                     | Cisplatin + paclitaxel (2) (category 1A) | Cisplatin + docetaxel + cetuximab (3) (category 2A) |
|                   |                     | Cisplatin + docetaxel (3) (category 2A) | Cisplatin + cetuximab (5,6) (category 2A) |
|                   | Salvage therapy     | Methotrexate (8) (category 2A) | Paclitaxel (10) (category 2A) |
|                   |                     | Docetaxel (9) (category 2A) | Cetuximab (11) (category 2A) |
|                   |                     | Paclitaxel (10) (category 2A) | Clinical trials (category 2A) |

5-FU, 5-fluorouracil.
Most of them relied on systemic therapy [performance status (PS) 0–1] or appropriate supportive treatments (PS≥2), similar to the management for metastatic patients. Cisplatin combined with 5-fluorouracil (5-FU) or paclitaxel is a commonly used first-line chemotherapy strategy. Carboplatin will be an alternative option for patients not amenable to cisplatin. The ECOG 1395 study indicated that cisplatin combined with 5-FU or paclitaxel had similar efficacies, with the former having a higher risk for oral mucositis and the latter having a higher incidence of peripheral neurotoxicity (2). Epidermal growth factor receptor (EGFR) is an important prognostic factor and therapeutic target in SCCHN (12). EXTREME, a prospective phase III randomized study, demonstrated that the addition of cetuximab to the combination of a platin and 5-FU had significantly prolonged overall survival and improved patients’ quality of life (4,13). For patients unable to tolerate 5-FU as the first-line treatment, a combination of cisplatin, docetaxel, and cetuximab may be considered (3). Cisplatin plus cetuximab is a reasonable choice for patients unbearable combination chemotherapy (5,6). For patients who cannot tolerate platinum agents (such as patients with advanced age), paclitaxel monotherapy combined with cetuximab is a reasonable option (7).

Thus far, there was no standard treatment regimen in China for patients with recurrent or metastatic SCCHN progressing after first line treatment, while methotrexate is commonly used in other countries (8). For these patients treated without taxane in their first-line therapy, paclitaxel or docetaxel may have certain salvage effects as second-line treatment (9,10). Cetuximab is also appropriate for patients who have not been exposed to this agent or have a poor PS score (11). In recent years, immunological checkpoint inhibitors, such as anti-programmed cell death protein 1 (PD-1) inhibitors, have been developed in advanced SCCHN. In 2016, the US Food and Drug Administration (FDA) consecutively approved pembrolizumab and nivolumab as the salvage treatment for recurrent or metastatic SCCHN. In a prospective phase III randomized controlled trial CheckMate-141, when compared with the control, nivolumab significantly prolonged the median overall survival time and improved the quality of life of patients progressing within 6 months after treatment with platinum (14,15). To date, pemizumab and nivolumab have not gone on the market in China. Thus, clinical trials containing anti-PD-1/programmed death ligand 1 (PD-L1) antibodies may be benefitting as second-line therapy after failure of first-line platinum-based chemotherapy.

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5. Follow-up

Post-treatment follow-up in head and neck cancer is very important for the purpose of evaluating the therapeutic effects, detecting early recurrent lesions, identifying second primary tumor, monitoring and managing treatment-related complications, and promoting functional rehabilitation (1). The recommended follow-up includes physical examination and endoscopy evaluation for the primary lesions. Further reimaging is recommended for areas inaccessible to clinical examination. If there are signs or symptoms indicating tumor recurrence, PET/CT examination should be considered (2). For patients undergoing radical treatment, especially those receiving radiation therapy, tumor assessment should be conducted 3 months after treatment. For those staging with N2–3, PET/CT should be performed 3 months post treatment to determine whether neck dissection is required (3). About 3%–5% patients will develop a second primary tumor on account of the high proportion of patients with smoking/alcohol history. Thus, examination of the entire upper digestive tract was required during follow-up (4).

Chest CT is recommended for patients with smoking history to detect early stage lung cancer (5). For patients undergoing neck radiation therapy, thyroid function should be regularly evaluated to prevent hypothyroidism and regular dental function examinations should be conducted as well. For head and neck cancer, both surgery or radiation therapy may damage the important physiological functions of the head and neck organs. It is recommended that regular functional assessments of pain, language, hearing, swallowing, and nutrition, as well as active participation in the rehabilitation be provided to patients if possible.

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