Future ONCOLOGY

EXPERT CONSENSUS

Comprehensive treatment of squamous cell cancer of head and neck: Chinese expert consensus 2013

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ABSTRACT: Head and neck cancer is the sixth most common malignant tumor worldwide, and squamous cell cancer of the head and neck accounts for more than 90% of head and neck cancers. In China, the incidence of oral cavity and pharyngolaryngeal cancer is 3.28 per 100,000 with a mortality of 1.37 per 100,000, and the incidence of nasopharyngeal cancer is 3.61 per 100,000 with a mortality was 1.99 per 100,000. In 2013, an expert consensus conference was held in China with the aim of establishing the optimum multimodality treatments that are applied in Chinese patients with squamous cell cancer of the head and neck. The experts, who met to review the literature and discuss and modify treatment strategies used in clinical practice in China, reached a consensus on the optimum therapy approaches, which, in general, combine surgery, radiotherapy, chemotherapy and targeted therapy. The experts strongly recommended that healthcare providers should integrate proper medical resources into a collaborative group involving specialists in several disciplines to agree upon and provide the most effective therapy for individual patients.

KEYWORDS
- expert consensus
- head and neck cancer
- multidisciplinary treatment
- nasopharyngeal cancer
- squamous cell cancer

Head and neck cancer is the sixth most common malignant tumor worldwide [1], with more than 500,000 newly diagnosed cases each year [2,3]. It is also the eighth most common cause of tumor-related death [4]. Squamous cell cancer of the head and neck (SCCHN) accounts for more than 90% of head and neck cancers. An epidemiological study from 72 tumor registries in China found that the incidence of oral cavity and pharyngolaryngeal cancer was 3.28 per 100,000 with a mortality of 1.37 per 100,000, and that the incidence of nasopharyngeal cancer (NPC) was 3.61 per 100,000 with a mortality was 1.99 per 100,000 [5]. In 2013, an expert consensus conference was held in China with the aim of establishing the optimum multimodality treatments that are applied in Chinese patients.

Smoking and alcohol abuse are common risk factors for SCCHN, and there is evidence of a causal association between human papillomavirus (HPV) infection and oropharyngeal cancer [6]. In the USA and several western countries, approximately 60–80% of oropharyngeal cancers are related to HPV infection [7–9], but in the Chinese population, the HPV infection rate is relatively low. The high-risk HPV-16 subtype was found in at least 90% of HPV-positive oropharyngeal cancer patients in a US study [6].

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Although NPC can be anatomically categorized as SCCHN, it has unique biological behavior, epidemiological characteristics and treatment strategies. The incidence and mortality of NPC varies greatly among different races and regions. The incidence is less than 1 per 100,000 in Europe [1], North America and Oceania, but by contrast, it is much higher in China and southeastern Asian countries, especially in Guangdong province in China. The standardized incidence of NPC in that area is 20–30 per 100,000 [10].

To date, the precise tumorigenic mechanism of NPC is not completely understood, but numerous studies have shown a close relationship between the disease and Epstein–Barr virus (EBV) infection [11]. Nonkeratinizing NPC patients tend to show an increased EBV titer, more undifferentiated cases and higher frequencies of locally advanced stage lesions and distant metastasis [12].

In this Chinese consensus, the seventh American Joint Committee on Cancer cancer staging system is used for clinical staging [13]. Patients with early-stage SCCHN other than NPC can be effectively managed by surgery alone or radical radiotherapy (RT). Locally advanced disease is generally treated by traditional surgery combined with RT and concurrent chemotherapy (CT). However, following recent in-depth studies of the EGFR, RT combined with molecular targeted therapy (e.g., the EGFR monoclonal antibody cetuximab) might be a potential treatment option for patients with locally advanced disease. This has already been proven in a trial by Bonner *et al.* which showed that RT combined with cetuximab yielded a better outcome than RT alone in patients with locoregionally advanced head and neck cancer [14].

Induction CT (ICT) has been shown to have a role in improving the larynx preservation rate. However, the TREMPLIN randomized Phase II study showed that there was no significant difference in larynx preservation at 3 months (95 and 93%, respectively), larynx function preservation at 18 months (87 and 82%, respectively) and overall survival at 18 months (92 and 89%, respectively) between patients assigned to ICT followed by chemoradiotherapy (CRT; arm A) or to ICT followed by Erbitux® (Merck KGaA, Darmstadt, Germany; cetuximab) plus RT (ERT; arm B) [15]. CRT or ERT was difficult to deliver after paclitaxel plus cisplatin plus 5-fluorouracil (5-FU; TPF)-based ICT because of limiting acute toxicity, but compliance was higher with ERT. Although there were fewer local failures in the CRT arm, successful salvage surgery was achieved in the ERT arm only [15]. As for the neoadjuvant CT regimens, TPF has been proven to be superior to cisplatin plus 5-FU (PF) [16].

For patients with unresectable or recurrent/metastatic SCCHN, cisplatin with 5-FU or cetuximab has been established as the standard first-line treatment. The Phase III EXTREME study demonstrated that combining cetuximab with platinum/5-FU significantly improved overall survival in the first-line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck compared with platinum/5-FU alone [17].

RT is the mainstay of treatment for NPC. Concurrent radiochemotherapy combined with targeted therapy can improve the survival rate of patients with advanced NPC. The Chinese ENCORE study showed that intensity-modulated radiation therapy (IMRT) with cetuximab and concurrent cisplatin CT was well tolerated and achieved a favorable 2-year primary tumor control rate and overall survival rate in patients with locally advanced NPC [18].

In general, multidisciplinary comprehensive therapy combining surgery, RT, CT and targeted therapy is forms the mainstream in the treatment of SCCHN. It is strongly recommended that healthcare providers should integrate proper medical resources into a collaborative group with experts from all related areas, including ear, nose and throat, oral and maxillofacial surgery, head and neck surgery, RT, oncology, radiology and pathology, and adjunctive groups from nursing, physical and rehabilitation therapy, psychological therapy, and nutritional support to perform comprehensive evaluations for each patient, provide optimized treatment and reduce adverse events, complications and functional disorders.

Treatment of early-stage & locally advanced squamous cell carcinoma of head & neck

SCCHN is a group of heterogeneous diseases. Owing to the specificity of its anatomic location (mostly vital organs), its complexity and the variety of types, SCCHN not only greatly damages and impacts on the physical appearance, basic physiological function (e.g., mastication, deglutition and respiration/chewing), sensory function (gustation, olfaction, auditory sense/taste, smell and hearing) and speech of patients, but also significantly compromises their

quality of life (QoL). While the assessment of QoL differs from the health status and functional assessment of patients, there connections among these three concepts. Assessment of the health status is undertaken to describe the physical, emotional and social ability of an individual; functional assessment is used to evaluate the ability to perform an important role, undertake a task or participate in a particular activity; while QoL relates to patients' self-evaluation of their health condition, which mainly depends on their own feelings.

Surgery, RT and CT are the traditional treatment modalities of SCCHN, but these treatments also cause damage to patients' head and neck organs and their functions, and simultaneously reduce QoL. With the development of surgical techniques such as function-preserving surgery and minimally invasive surgery, the post-treatment QoL of patients with head and neck squamous cell carcinoma has been considerably improved. The development of molecular biology in recent years, targeted therapy, RT and CT approaches that conserve organ function have made some progress in improving patients' QoL. To achieve maximum preservation of physiological features and QoL while achieving the goal of tumor control, a comprehensive evaluation that includes patients' general status, tumor location, TNM stage and pathological type, and a weighing of the advantages and disadvantages of all treatment modalities is needed before an appropriate treatment strategy can be decided upon. In making this decision, the patients' personal wishes, compliance and the timing and costs of treatment also need to be considered [19].

• Early-stage disease (Tis, T1N0 & some T2N0 disease)

The principle of treating early-stage SCCHN is as follows: surgery can be recommended initially if it will have little impact on function and cosmetic appearance (for carcinoma *in situ*, surgery should be considered as the first choice); otherwise, RT is preferred. Carcinoma *in situ* of the larynx can be resected via an endoscope or by laser. For early stage disease, retrospective studies have shown that similar locoregional control can be achieved by function-preserving surgery or radical RT (external RT or brachytherapy); however, there is still a lack of prospective, randomized studies to prove this [20]. The requirements and willingness of patients should also be taken into consideration before a treatment modality is finalized.

• Locally advanced disease (any T, N1-3,M0 & T3-T4N0,M0 disease)

The optimal treatment for locally advanced oral cavity cancer is surgery. Based on the surgical margin and lymph nodal extracapsular spread, postoperative RT or concurrent CRT (CCRT; single-agent platinum therapy) is recommended. For unresectable disease or for patients in whom tumor resection may cause serious organ or tissue defects, preoperative ICT or RT could be used to improve tumor resectability.

Treatment options for resectable, locally advanced carcinoma of the larynx, oropharynx and hypopharynx are: surgery plus RT (patients with laryngocarcinoma and those in whom laryngeal function can be preserved or reconstructed after resection of the primary tumor would be the most suitable candidates for this modality); cisplatin CCRT (category I evidence) plus salvage surgery (which can be reserved for patients with residual disease); and ICT plus RT or CCRT plus surgery.

The principles of adjuvant therapy are as follows: for patients with lymph node extracapsular extension (ECE) or positive surgical margins, CCRT is recommended (single-agent platinum therapy); otherwise RT alone (category I evidence) is the preferred option.

Patients with unresectable locally advanced cancers should undergo RT with concurrent CT (category I evidence), or ICT plus RT with or without concurrent CT. For patients who are considered to be poor candidates for the above treatments, cetuximab plus RT remains the best alternative treatment option (category I evidence). It should be noted that the term 'unresectable' refers to the anatomical location of the tumor such that all of it cannot be removed or local control is not likely to be achieved after an operation, even with the addition of RT/CRT. Typically, unresectable tumors are those that densely invade the cervical vertebrae, brachial plexus, deep muscles of the neck or carotid artery [4].

In a meta-analysis of 50 trials of concomitant CT in the treatment of locally advanced SCCHN (LASCCHN) published in 2009, CCRT was found to increase overall survival with an absolute survival benefit of 6.5% at 5 years ($p < 0.0001$), improve locoregional control by 9.3%, and reduce distant metastases by 2.5% in comparison with RT alone [21]. With RT, accelerated

hyperfractionation and accelerated fractionation did not show any extra benefit compared with conventional fractionation. For the CT regimens, there was no significant survival difference when various combination regimens or single-agent regimens were compared. As cisplatin appeared to be the best agent when single-agent regimens were compared, single-agent cisplatin therapy is currently preferred for CCRT. It should be noted that CCRT causes more acute and late toxicities, and the treatment-related mortality rate has been reported to be 10–15% [22–24]; moreover, nearly 50% of patients cannot complete this treatment due to toxicity [25]. Thus, attempts to identify other drug combinations with RT to better enable CCRT are ongoing.

EGFR expression, which is found in more than 95% of SCCHN [26], is recognized as an adverse prognostic factor as it is correlated with an increased risk of tumor invasiveness, metastasis and resistance to RT/CT. A recent study indicated that the EGFR monoclonal antibody cetuximab combined with RT can significantly improve the sensitivity of RT [14]. Long-term follow-up results also showed that cetuximab combined with RT increased the 5-year overall survival by 9% in comparison with RT alone ($p = 0.018$), and the median survival time was prolonged by almost 20 months [14]. Apart from acne-like rash and a few instances of allergic reactions, no other severe toxicities occurred.

At the 2013 meeting of the American Society of Clinical Oncology, a Phase II/III clinical study that compared CRT versus cetuximab/RT (CET/RT) with or without induction TPF therapy in patients with LASCCHN was reported [27]. A total of 421 patients with stage III–IV unresectable LASCCHN were enrolled, and patients were randomized to treatment in a 2 × 2 factorial design. The median follow-up was 32.9 months. The results showed that the CET/RT group (n = 160) and CRT group (n = 261) had similar complete response and partial response rates (39 vs 36% and 88 vs 83%, respectively), and no significant differences were observed in median progression-free survival (PFS) and OS between the CRT and CET/RT groups (21.6 vs 20.7 months, and 44.7 vs 44.7 months, respectively). Data from a 3-year follow-up of this study have yet to be reported. Thus, for patients with unresectable, locally advanced or organ-preserved LASCCHN, CRT plus salvage surgery or alternatively CET/RT may be considered.

• Induction & subsequent adjuvant CT

Most randomized clinical trials published in the 1980s and 1990s showed that the ICT regimen of PF produces a high response rate, but no survival benefit has been reported [21]. Response rates for patients treated with the ICT TPF regimen or ICT followed by radical RT were both significantly enhanced in comparison with the PF regimen (68 vs 54%; $p = 0.006$; and 72 vs 59%; $p = 0.006$, respectively) [28]. After a 5-year follow-up, both the PFS and OS rates of patients in the TPF arm were superior to those of patients in the PF arm (22.9 vs 13.5% and 27.5 vs 18.6%, respectively) [29]. A study by Pointreau *et al.* also showed that patients receiving TPF had a significantly higher 3-year larynx preservation rate than those receiving the PF regimen (70.3 vs 57.5%; $p = 0.03$) [30]. Moreover, a series of studies published in recent years have demonstrated that when docetaxel (T) was added to PF for induction CT (TPF), long-term OS and larynx preservation rates were both improved [28–32]. For instance, in the Phase III TAX 323 study in which patients with unresectable LASCCHN were assigned to either TPF (n = 177) or PF (n = 181) ICT followed by RT, the TPF regimen improved PFS from 8.2 to 11.0 months ($p = 0.007$) and OS from 14.5 to 18.8 months ($p = 0.02$) in comparison with the PF regimen. However, despite these data, the role of ICT in SCCHN still requires more clinical evidence.

In a French randomized Phase II study that enrolled 116 patients with stage III–IV laryngeal/hypopharyngeal squamous cell carcinoma, the patients were randomly assigned to conventional RT with concurrent cisplatin or concurrent cetuximab after three cycles of ICT (docetaxel, cisplatin and 5-FU) [15]. The results showed that that after TPF ICT, treatment with either concurrent CCRT or RT concomitantly with cetuximab was difficult to complete. While laryngeal function preservation and locoregional control rates were equal in the two arms, renal toxicity was more common in the cisplatin group. This result indicates that after TPF ICT, patients who receive RT concurrently with cetuximab have less unmanageable toxicity (renal toxicity) than patients treated with RT concurrently with cisplatin.

Despite the superior efficacy of the TPF regimen, its adverse effects, notably grade III/IV neutropenia and febrile neutropenia, are significantly greater than those of the PF regimen, and that fact that approximately 20%

of patients are not able to complete the subsequent CCRT [28–32] indicates that we should pay more attention to adverse effects in clinical practice. On the other hand, due to the higher tumor response rates after ICT, this treatment provides a favorable option for organ/function preservation. Patients who have a good response to ICT (complete or partial remission) are recommended to receive CCRT (platinum) or RT concurrently with cetuximab to achieve the best opportunity for organ preservation. In those with a poor response to ICT, surgery followed by postoperative RT or CRT may be considered.

• Postoperative treatment of high-risk patients

ECE of the lymph node and/or microscopically involved surgical margins are adverse prognostic factors for SCCHN, and patients with these adverse prognostic factors should receive postoperative CCRT. Other patients with locally advanced disease can receive postoperative RT alone. This recommendation is based on the results of the RTOG 95-01 trial [22,33] and the EORTC 22931 study [22]. In the RTOG 95-01 trial, a total of 231 patients who had high-risk resected head and neck cancers (oral or oropharyngeal cancer and laryngeal or hypopharyngeal cancer) were randomized to receive radiation therapy alone or RT plus concurrent CT. The definition of high risk was more than two positive nodes, microscopically involved surgical margins or ECE. After a median follow-up of 45.9 months, the CCRT group had a significantly decreased locoregional failure rate (hazard ratio [HR]: 0.61; p = 0.01) and an improved disease-free survival (death risk ratio: 0.78; p = 0.04), but did not show an OS benefit. In addition, the randomized controlled EORTC 22931 study also found that CCRT significantly decreased the 5-year locoregional failure rate in comparison with radiation alone (18 vs 31%, respectively; p = 0.007), increased the 5-year PFS (47 vs 36%, respectively; p = 0.04), and also improved OS (death risk ratio: 0.70; p = 0.04) [22]. Although these two large studies provided category I evidence for selecting postoperative treatment for high-risk SCCHN patients, no overall survival benefit was found in the 10-year follow-up results of the RTOG 95-01study reported in 2012 [34].

• Surgical margins

As tumor recurrences are associated with surgical margins, it is widely believed that a sufficient surgical margin should be ensured. According to the National Comprehensive Cancer Network guidelines [4], adequate excision is defined as a resection margin with at least 2-cm clearance from the gross tumor or a clear frozen section margin. A clear margin is defined as a distance of 5 mm or more from the invading tumor edge to the resected margin, while a close margin is defined as a distance of less than 5 mm from the invading tumor edge. However, these standards are not absolute because of the specific anatomic location of the tumors and the characteristics of the head and neck, and it is difficult to achieve the above 'sufficient margins' in clinical practice. Studies to determine the appropriate scope of the surgical margin should be based on the tumor classification, its anatomic location and organ function. For instance, in radical surgery for cancer of the tongue, the lingual septum, mandibular lingual periosteum and hyoid can be considered a natural barrier, and following the principle of 'compartmentectomy' in the operation will improve the resection thoroughness of primary tumors.

A consensus on the surgical margin for a minimal security boundary has yet to be reached. The range of resection margins for a downstaging after ICT should not be less than the scope of the primary lesion, and the resected margin should be at least 2–3 mm clear of the primary tumor [35–37].

• RT technology & principles

The selection of radiation technology should be based on the characteristics of the patient, tumor location, the RT techniques utilized and the physician's proficiency and experience in using the technology. IMRT has been routinely used to treat tumors in areas with little mobility such as nasal sinus cancers and oropharyngeal and nasopharyngeal carcinomas. It is widely recognized that IMRT plays an important role for increasing the treatment dose and for protecting normal organs around the target area. For other sites such as the larynx, the base of the tongue and for hypopharyngeal carcinoma where there are target identification and organ motion difficulties, the use of IMRT requires physician experience and strict quality control.

The commonly used dose fractionation for SCCHN RT is conventional fractionation given five times a week and continued for 7 weeks (for simultaneous modulated accelerated radiation therapy the duration may be slightly shorter). Unconventional fraction RT includes accelerated

fractionation and hyperfractionation RT. Accelerated fractionation shortens the total treatment time, reduces tumor proliferation and may improve local control rates. Hyperfractionation RT (given two to three times a day) can reduce the late toxicity. In 2012, the RTOG reported the final analysis of a Phase III clinical trial comparing hyperfractionation and two types of accelerated fractionation with standard fractionation (RTOG 90-03 study) [38]. In this study, 1113 patients with LASCCHN were randomized to four treatment arms: arm A (standard fractionation 70 Gy/7 weeks); arm B (hyperfractionation 81.6 Gy/7 weeks); arm C (split-course accelerated hyperfractionation 67.2 Gy/6 weeks); and arm D (late-course accelerated hyperfractionation 72 Gy/6 weeks). The 5-year follow-up data show that although unconventional fractionation RT did not improve overall survival, it significantly improved the locoregional control rate. Except for split-course accelerated hyperfractionation, the locoregional control rate with both hyperfractionation and late-course accelerated hyperfractionation was 51%, whereas it was 45% with conventional fractionation. This study also demonstrated that unconventional fractionation RT did not increase late toxicity. Another RTOG study of SCCHN (RTOG 01-29) that compared postoperative accelerated hyperfractionation given concurrently with cisplatin with conventional fractionation given concurrently with cisplatin concluded that accelerated hyperfractionation did not produce a survival benefit, but increased toxicity [39].

Treatment of recurrent &/or metastatic SCCHN

For patients with resectable recurrent SCCHN, radical surgery should be performed. However, in those unresectable recurrent lesions, radical RT should be performed in RT-naive patients. For younger patients (<70 years of age) and those with good performance status (PS score 0 or 1), RT with concurrent platinum therapy or a targeted agent (cetuximab) might be considered.

For patients with recurrent or metastatic SCCHN who are not suitable for local treatment (surgery or RT), palliative CT with or without targeted therapy are the major treatment options for prolonging survival and maintaining QoL.

• First-line therapy

Palliative CT is the primary treatment for most recurrent and/or metastatic SCCHN. Multiple CT agents including platinum, 5-FU, taxanes, methotrexate, ifosfamide and bleomycin have all shown antitumor effects, and platinum-based (cisplatin or carboplatin) single-agent or combined CT regimens are frequently adopted as first-line treatments. Compared with single-agent CT, combined CT regimens can increase the tumor response rate, although they do not significantly improve overall survival [40]. Taxanes (paclitaxel or docetaxel) combined with platinum agents have produced a good synergistic effect and shown no significant superimposed toxicity. A Phase III study comparing regimens of cisplatin in combination with either paclitaxel or 5-FU showed similar tumor response and survival rates [41].

Recently, great progress been made with cetuximab-containing regimens in the treatment of recurrent/metastatic SCCHN. The EXTREME Phase III randomized study showed that the addition of cetuximab to a platinum (cisplatin or carboplatin)/5-FU combination regimen increased the tumor response rate from 20 to 36%, PFS from 3.3 to 5.6 months and, more importantly, median OS from 7.4 to 10.1 months [17]. Furthermore, cetuximab-containing regimens do not increase the hematological toxicities induced by cytotoxic agents. At the 2012 American Society of Clinical Oncology conference, preliminary results from the GORTEC 2008-03 Phase II study were reported [42]. The addition of cetuximab to a docetaxel/carboplatin regimen in this study yielded a 54% tumor response rate, a median PFS of 6.7 months and a median OS of 14 months. Another Phase II clinical trial that evaluated the addition of cetuximab to a weekly paclitaxel/carbopaltin regimen showed similar results to the EXTREME study [43]. Therefore, for patients with 5-FU intolerance, such as oral mucositis, taxanes combined with platinum-based agents are a reasonable first-line treatment option, and the addition of cetuximab is likely to further improve the outcome. Another appropriate treatment option is cisplatin combined with cetuximab. A randomized study showed that this combination achieved a significantly higher tumor response rate than cisplatin alone, although the improvement in survival did not reach statistical significance [44].

Cisplatin is an important first-line agent in the treatment of recurrent and/or metastatic SCCHN; however, intolerance is commonly seen in elderly patients and patients with poor

PS or renal insufficiency. For such patients, paclitaxel/cetuximab is a potentially ideal combination owing to its low toxicity. With this regimen, Hitt *et al.* reported a tumor response rate of 54%, a median PFS of 4.2 months and a median OS of 8.1 months [45]. Other single-agent CT regimens such as methotrexate can also be considered.

• Second-line/salvage treatment

For patients with recurrent/metastatic SCCHN who have failed first-line platinum therapy, second-line single-agent CT may be considered if the patient's physical condition allows it. Otherwise, best supportive therapy should be recommended. First-line agents such as a taxane and methotrexate can be given if these treatments have not previously been used. Cetuximab is another candidate with proven effectiveness in certain clinical scenarios and has relatively milder toxicity in comparison with traditional CT agents. An analysis of three Phase II clinical studies showed that the median PFS and median OS with cetuximab treatment with or without platinum-based agents as second-line/salvage treatment were 2–3 months and 5–6 months, respectively [46–48]. For such patients, there is currently no evidence that cetuximab is effective in overcoming platinum resistance. Moreover, cetuximab combined with platinum agents is associated with increased toxicity. Therefore, single-agent cetuximab therapy is recommended in such patients.

Recently, two Phase II studies evaluated single-agent taxane regimens combined with cetuximab [49,50]. In these studies, in which docetaxel/cetuximab or paclitaxel/cetuximab regimens were given and repeated weekly, the median PFS was 3.1 and 3.9 months, respectively, and the median OS was 6.7 and 7.6 months, respectively. Although the advantage of combination therapy has not yet been proven in randomized controlled studies, weekly taxane CT is well tolerated and is likely to show improved effectiveness without compromising patients' QoL when combined with cetuximab. Other single-agent chemotherapies including methotrexate can sometimes be used as alternative options.

Best palliative treatment is the only solution for recurrent/metastatic SCCHN patients with poor performance status (PS scores >2), including possible palliative RT, three-step analgesic treatment and appropriate nutritional support.

• Conclusion: current treatment options for patients with recurrent/metastatic SCCHN

Recommended first-line therapies:

- Platinum/5-FU combined with cetuximab (category 1 evidence);
- Platinum/taxanes combined with cetuximab (5-FU intolerance);
- Taxanes with cetuximab (platinum intolerance);
- Platinum combined with 5-FU/taxanes;
- Single-agent therapy with platinum-based agents, taxanes, methotrexate or cetuximab (combined therapy intolerance).

Recommended second-line therapies:

- Taxanes with cetuximab (taxane-naive patients);
- Single-agent treatment with cetuximab (cetuximab-naive patients);
- Other single-agent regimens that have not been used in previous first-line treatment.

Recommended treatment for patients with poor performance status (scores >2):

- Best supportive treatment (possible palliative RT, three-step analgesic treatment and appropriate nutritional support).

Treatment of NPC

NPCs are malignancies originating from the nasopharyngeal cavity. Despite their anatomical location, NPCs display unique features and are very different from other head and neck tumors.

First, their epidemiological characteristics differ markedly. Although NPCs are seen globally, areas that have a high incidence are south China and southeast Asia, Alaska and west Canada in North America, east Africa and several countries of north Africa. Guangdong province in south China and Hong Kong are areas with the highest incidences. The world population standardized incidences of NPC in Guangdong province for males and females are 30 per 100,000 and 13 per 100,000, respectively [51]. In Hong Kong, there were 5835 newly diagnosed cases between 1993 and 1997, and the world population standardized incidences reached 26.1 per 100,000 for males and 10.1 per 100,000 for females [52].

Second, the risk factors for tumorigenesis are different. Other than chemical and genetic factors, studies have found a close relationship

Figure 1. Treatment algorithm for patients with nasopharyngeal cancer. All supporting evidence is category IIa or above, unless otherwise stated. Recommendations based on category IIb evidence require further clarification in clinical trials.
†Surgery is preferred for nodular recurrences in the neck; for nasopharyngeal recurrences, surgery is indicated only in rT1 (without retropharyngeal lymph node metastasis) and some localized rT2 (without retropharyngeal lymph node metastasis and parapharyngeal lymph node clearance invasion) cases.
CR: Complete response; CT: Computed tomography; EBV: Epstein–Barr virus; ECT: Emission computed tomography; EGFR: EGF receptor; KPS: Karnofsky performance status; PR: Partial response; RT: Radiotherapy.

between NPC and EBV infection [53,11], which plays a critical role in the carcinogenesis process.

Third, the histological types of NPCs are unique. According to the 2005 classification [54], NPCs can be classified as keratinizing squamous cell carcinoma (type I), nonkeratinizing squamous cell carcinoma with differentiated (type IIa) and undifferentiated (type IIb) subtypes, and basaloid squamous cell carcinoma (type III). Type IIb and type I are major pathologies in high incidence areas and nonhigh incidence areas, respectively.

Fourth, treatment options also differ. RT is the major treatment option for patients with NPCs. RT alone can achieve a very favorable outcome in early stage patients, and radiochemotherapy-focused comprehensive therapy has become the standard treatment in advanced stage patients.

The clinical outcome of NPC depends on a solid diagnosis, accurate clinical staging, a reasonable treatment strategy and a proper follow-up scheme. In the current era of scientific explosion, evidence-based practice guidelines are vital for both physicians and patients to make appropriate treatment decisions. The management pathway for treatment of NPCs is shown in **Figure 1**.

• Changed & updated treatment recommendations

The updated recommendations for the management of NPS in China are as follows:

- Quantitative DNA testing for EBV: accumulating evidence has proven the critical role of such testing in the initial diagnosis, outcome evaluation and diagnosis of recurrences or metastases [55,56]. Therefore, quantitative DNA testing for EBV should be performed during the diagnosis, pretreatment examination and post-treatment follow-up of patients;
- Staging of NPC: the Chinese Committee on clinical staging of NPC revised the 1992 NPC staging system in December 2008 and published a new NPC staging system that year [57], which was not proven for rationality and accuracy. Subsequently, we recommended the 2010 American Joint Committee on Cancer clinical staging system for NPC (version 7) [13] as the current standard in order to facilitate comparisons of data and outcomes between different facilities, and promote international communication;
- Treatment for early stage patients: for T1–2N0M0 patients, radical RT alone can achieve a favorable outcome, but controversy still exists regarding the need for CT for patients with T1–2N1M0 NPC. Therefore, no recommendation for single therapy is made for T1–2N1M0 patients in the current consensus. Radical RT with or without concurrent platinum-based CT is reasonable, but further prospective clinical studies are warranted to clarify the role of CT;
- Treatment for locally advanced disease: RT with or without concurrent adjunctive platinum-based CT is the standard treatment. Although Phase II clinical studies have shown

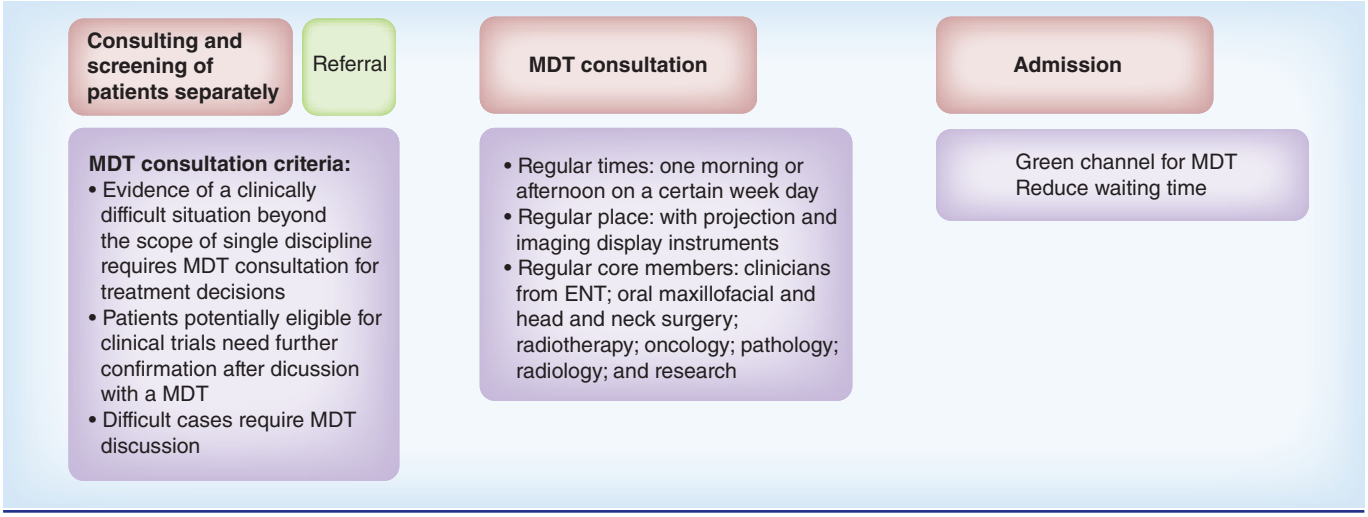

Figure 2. Multidisciplinary team diagnosis and treatment algorithm.
ENT: Ear, nose and throat; MDT: Multidisciplinary team.

that the addition of ICT with docetaxel/cisplatin to RT and concurrent cisplatin CT can provide a significant survival benefit over concurrent radiochemotherapy alone in patients with locally advanced NPC (stage III–IVb) [58], this regimen has not been proven in Phase III studies. Thus, it is only recommended as category IIb evidence for patients with locally advanced disease. Further prospective clinical studies of this treatment are also warranted;

- IMRT: this technique can significantly increase the primary tumor control rate, provide better protection for normal surrounding tissue and improve QoL in patients surviving long term [59,60]. It is recommended that all centers with proper resources adopt IMRT as the main RT modality in the treatment of patients with NPCs;
- Clinical importance of EGFR monoclonal antibody treatment: EGFR is expressed in more than 80–90% of patients with NPCs [61–64]. Accumulating evidence from research studies have shown that an EGFR monoclonal antibody alone or combined with RT or RT plus CT can markedly inhibit the growth and proliferation of NPC cell strains and increase cell sensitivity to RT and CT [65–67]. Two recent multicenter, uncontrolled Phase II clinical studies of the EGFR monoclonal antibody cetuximab in the treatment of patients with locally advanced NPC have been completed, and preliminary results have revealed a favorable short-term outcome and favorable tolerability [68,69]. Therefore, in selected patients with locally advanced disease, it is recommended that an EGFR monoclonal antibody (such as cetuximab) be added to standard radiochemotherapy (category IIb evidence).

Reasons for the recommendation to use cetuximab in selected patients with locally advanced disease include the following: first, studies have shown that cetuximab can remarkably enhance the cell-killing effect of docetaxel and cisplatin on NPC cells. Thus, ICT combined with cetuximab can further amplify the induction effect. Second, CT can upregulate the expression of EGFR in NPC cells, and the use of ICT combined with cetuximab is likely to downregulate the expression of EGFR in residual tumor cells, which potentially increases the sensitivity of NPC cells to future RT. Third, many Phase II clinical studies have shown that ICT combined with cetuximab in patients with SCCHN has a low incidence of serious acute toxicity, and is effective in reducing the tumor load and protecting organ function [70–72]. In a multicenter Phase II clinical study conducted in Hong Kong that evaluated the role of a carboplatin/cetuximab regimen in patients with recurrent/metastatic NPC, most of whom had disease progression after one or more cycles of CT, it was found that the tumor control rate was 60% and the median OS was 7.7 months [73]. Although this result was not satisfactory, the treatment regimen had low toxicity and was well tolerated. In addition, a retrospective study of 20 patients from the Tumor Hospital of Fudan University that investigated the effect of cetuximab combined with radiochemotherapy in the treatment of SCCHN found that the response rate in eight patients with recurrent/metastatic NPC reached 87.5% (complete response in one patient and partial response in six patients) [74]. Moreover, many expert opinions have suggested that first-line CT with additional cetuximab might achieve a satisfactory outcome in NPC patients with remote metastases.

Thus, in selected patients with recurrent/metastatic NPC, first-line CT with additional cetuximab treatment might be an option (category IIb evidence). However, further prospective clinical studies are again warranted.

Multidisciplinary collaboration

A 'multidisciplinary team' (MDT) is a relatively fixed board of experts from multiple related fields who may gather regularly at symposia on various diseases to determine clinical solutions. This process is actually a new model for diagnosis and treatment. For head and neck diseases, a typical MDT is a close collaboration of clinical departments such as ear, nose and throat, oral maxillofacial and head and neck surgery, radiation therapy, medical oncology, pathology, and radiology, as well as adjunctive groups including nursing, physiological therapy and rehabilitation, language and swallowing training, clinical/social support, nutritional support, and adjunctive therapy groups [4,75].

• Target & purpose of MDTs

Head and neck diseases are anatomically unique with highly diversified histopathological types, and functional preservation and QoL are important considerations in their management. The

diagnosis and treatment of these diseases are complicated. In addition, there is limited category I evidence to support a treatment of choice in SCCHN. Therefore, the development of multidisciplinary collaboration is an urgent requirement.

MDTs are helpful for optimizing tumor staging, evaluating the appropriateness of the treatment plan, promoting individualized therapy, preserving patients' breathing, speech and feeding functions, improving QoL, and providing the most effective therapy for patients **(Figure 2)**. In addition, MDTs can significantly shorten the time from diagnosis to treatment. Clinicians from different specialties can share the clinical data simultaneously to determine the best individualized treatment strategy according to clinical

EXECUTIVE SUMMARY

Background

- Surgery, radiotherapy (RT) and chemotherapy (CT) are the principal treatment modalities for squamous cell cancer of the head and neck (SCCHN), but these treatments can also damage patients' head and neck organs and their functions and reduce quality of life (QoL).
- To achieve maximum preservation of physiological features and QoL while achieving the goal of tumor control, a comprehensive evaluation that includes patients' general status, tumor location, TNM stage and pathological type, and a weighing of the advantages and disadvantages of all treatment modalities is needed before deciding upon treatment.

Treatment of early stage & locally advanced SCCHN

- Surgery can be recommended initially for early stage disease if it will have little impact on function and cosmetic appearance; otherwise, RT is preferred.
- For resectable, locally advanced carcinoma of the larynx, oropharynx and hypopharynx:
  - Surgery plus RT (for patients with laryngocarcinoma and those in whom laryngeal function can be preserved or reconstructed after resection of the primary tumor);
  - Concurrent chemoradiotherapy (with cisplatin) plus salvage surgery (for patients with residual disease);
  - Induction CT plus RT or concurrent chemoradiotherapy plus surgery.
- For unresectable, locally advanced cancers: RT with concurrent CT or induction CT plus RT with or without concurrent CT.
- For patients considered poor candidates for the above treatments, cetuximab plus RT remains the best alternative treatment option.

Treatment of recurrent and/or metastatic SCCHN

- Recommended first-line therapies: platinum/5-fluorouracil (5-FU) plus cetuximab; platinum/taxanes plus cetuximab (5-FU intolerance); taxanes plus cetuximab (platinum intolerance); platinum plus 5-FU/taxanes; or single-agent therapy with platinum-based agents, taxanes, methotrexate or cetuximab (combined therapy intolerance).
- Recommended second-line therapies: taxanes plus cetuximab (taxane-naive patients); single-agent cetuximab treatment (cetuximab-naive patients); other single-agent regimens that have not been used in previous first-line treatment.
- Recommended treatment for patients with poor performance status (scores >2): best supportive treatment.

Treatment of nasopharyngeal cancer

- For early stage patients: radical RT with or without concurrent platinum-based CT is reasonable, but further prospective clinical studies are warranted to clarify the role of CT.
- For locally advanced disease: RT with or without concurrent adjunctive platinum-based CT. In selected patients, cetuximab can be added to standard radiochemotherapy.

Importance of multidisciplinary collaboration

- Multidisciplinary teams are valuable for optimizing tumor staging, evaluating the treatment plan, preserving patient functioning, improving QoL and providing the most effective individualized therapy.
- Multidisciplinary collaboration should involve specialists in several disciplines to integrate medical resources.

principles and guidelines. Moreover, MDTs can enhance communication between clinical disciplines, improve mutual understanding, expand knowledge on diseases, help make more reasonable treatment decisions and achieve better outcomes [76,77].

MDTs are also beneficial in conducting basic and clinical research, and rapidly refreshing knowledge. The National Comprehensive Cancer Network guidelines [4] state that tumor patients should receive the best treatment based on clinical studies. Therefore, clinical trials are useful for tumor patients.

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