Holistic Integrative Oncology

GUIDELINE

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CACA guidelines for holistic integrative management of nasopharyngeal carcinoma

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Abstract

Purpose Nasopharyngeal carcinoma (NPC) is a malignant epithelial tumor originating in the nasopharynx and is particularly prevalent in southern China. Unfortunately, international guidelines, such as NCCN or ESMO, fail to adequately coincide with clinical practice in China, making it difficult to achieve precision personalized therapy in China. The aim of this guideline is to better promote a "Multidisciplinary Team to Holistic Integrative Medicine" (MDT to HIM) system for the prevention, screening, diagnosis, treatment, and rehabilitation of NPC.

Methods The China Anti-Cancer Association (CACA) invited domestic multi-disciplinary experts, involving radiologists, oncologists, surgeons, pathologists, herbalists, physiatrists, and psychologists, to write, discuss, and revise the guidelines. Based on the integration of research evidence, clinical experience, and patient needs, the domestic experts have iteratively developed these guidelines to provide proper and feasible management of NPC.

Results and conclusion The CACA Guidelines for Holistic Integrative Management of Nasopharyngeal Carcinoma are more suitable for China's clinical practice, highlight Chinese characteristics, and have important clinical significance.

Keywords Nasopharyngeal carcinoma, China anti-Cancer Association (CACA), Integrated guideline

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1 Epidemiology

Nasopharyngeal carcinoma (NPC) is an epithelial cancer arising from the nasopharynx epithelium, mostly occurring in the parietal and lateral walls of the nasopharynx, especially in the pharyngeal fossa, and is one of the common malignant tumors in China [1, 2]. NPC is characterized by distinct geographical distribution, being particularly prevalent in southern China, as well as regional clustering, ethnic susceptibility, high familial incidence, and a relatively stable population incidence rate [3]. It is currently believed that the occurrence of NPC is mainly associated with Epstein-Barr virus (EBV) infection, genetics, and environmental factors [4]. Meanwhile, unhealthy lifestyles, such as heavy smoking, consumption of preserved foods, and air pollution, can also induce the occurrence of NPC [4]. In non-endemic areas, the incidence increases with age and shows a bimodal distribution: the first peak predominates in adolescents and young adults, and the second peak predominates in those older than 65 years. In endemic areas, the incidence increases after the age of 30 years, peaks at 40–59 years, and subsequently declines [5]. The male to female incidence ratio was 2.75:1. NPC in Asia appears to have a disease-specific survival advantage independent of sex, age, pathological grade, stage, and treatment [6]. The risk of mortality associated with different histological subtypes varies significantly [7]. Age has a significant impact on survival, with a 5-year survival rate of 72% in the 15–45 years group and only 36% in the 65–74 years group, and in general women have a better prognosis than men [1].

2 Etiology

EBV infection: The presence of EBV DNA, mRNA, or its expression products in NPC biopsies is detected by molecular hybridization as well as polymerase chain reaction (PCR). By infecting human oral epithelial cells and B cells, EBV integrates into the host cell DNA, prevents apoptosis of the infected cells, and activates their growth, causing NPC [8].

Individual factors: Although NPC can occur at any age, it is common at the age of 40–50 years, with a male predilection [9].

Environmental factors: Nickel content in food and water is high in areas with a high prevalence of NPC, and animal experiments have confirmed that nickel can induce NPC [10].

Dietary factors: Preserved foods, such as salted fish and sausage, are high-risk factors for NPC, as these foods all produce the class 2A carcinogen nitrite during their manufacture. Cancer induction assays in rats also found that nitrosamines could induce NPC [11].

Genetic factors: There is a distinct ethnic and familial clustering of NPC, with high incidence rates maintained by descendants who migrated overseas [12–14].

3 Early screening

The symptoms of early NPC are insidious and atypical, making it extremely difficult to self-detect until it has progressed to the locally advanced stage. In endemic areas, the screening modality of detecting blood EBV DNA, targeting the BamHI-W region, at least two times at an interval of 4 weeks combined with nasopharyngoscopy and magnetic resonance imaging (MRI), achieved a sensitivity and specificity 97.1% and 98.6%, respectively [15]. Screening of early, asymptomatic NPC in endemic areas is recommended in high-risk populations, such as men aged 40–62 years, given the detection of 1 case per 593 tested. Despite the insufficiency of overall survival (OS) data for the screened population, 3-year progression free survival (PFS) was significantly improved compared with that of a matched historical cohort [15]. However, the following issues need to be addressed. First, in terms of screening methods, screening in endemic areas is currently often based on EBV DNA [15] and EBV serum antibodies (VCA-IgA, EA-IgA, EBNA1-IgA) [16]; however, because of the prevalence of EBV infection, more than 90% of adults are seropositive for EBV antibodies, making false-positive results unavoidable and further causing a waste of medical resources [17]. In contrast, a large proportion of early-stage patients tested negative for EBV DNA because of low sensitivity, precluding the effective screening of early-stage patients. In addition, a lack of uniform standards in instruments, assays, and methods had led to data discrepancies and even inaccuracies. Electronic nasopharyngoscopy and nasopharynx MRI are two important methods that are required for screening in high-risk populations; however, using these methods, it is difficult to detect early lesions and they require high operator and reader skills [18]. Physicians' judgment of early NPC imaging, including nasopharyngoscopy and MRI, is mixed, which might lead to some cases of early NPC being missed. Second, it is difficult to detect intraepithelial neoplasia or early malignancy of the nasopharyngeal mucosal epithelium using common light electron nasopharyngeal endoscopy, which might also lead to a missed diagnosis [19].

4 Diagnosis

4.1 Clinical manifestations

The most frequent sites of NPC occurrence are the pharyngeal crypts, followed by the lateral nasopharyngeal wall, and the apical wall. The early stage, when the symptoms are insidious and atypical, is difficult to detect, and diagnosis mostly occurs at the locally

advanced stage. As the disease progresses, a series of symptoms, including tinnitus, hearing loss, nasal obstruction, epistaxis, headache, facial numbness, and diplopia can occur, as well as symptoms and signs associated to cervical mass or cranial nerve palsy [1].

Nasal symptoms: Intermittent epistaxis in the early stage; nasal obstruction can be caused by further tumor enlargement, at first unilateral, followed by bilateral obstruction.

Ear symptoms: Tumors located in the pharyngeal crypts can compress or obstruct the eustachian tube pharyngeal orifice at an early stage, causing tinnitus and hearing loss.

Cranial nerve symptoms: Patients in locally advanced stages might present with headache or cranial nerve palsies, such as facial anesthesia, diplopia, blurred vision, decreased or absent sense of smell, neural deafness, ptosis, eye fixation, reduced swallowing activity, deviation of the tongue, and hoarseness.

Cervical symptoms: About 70% of NPC have cervical lymph node metastasis at the time of diagnosis. About 40% of the patients who visited the hospital with cervical lymphadenopathy as the first symptom presented with painless masses. As the disease progresses, the cervical lymph nodes can increase in size, become rigid, and have poor mobility, first unilaterally then bilaterally, and can have local erythematous heat and pain if infected. In severe cases, compression of neck vessels might lead to head or neck pain on the affected side, sudden syncope, and even death.

Dermatomyositis: A small proportion of NPC can be combined with dermatomyositis, often in the facial, thoracic dorsal, and extremities. Usually no special management is required, with subsequent improvement in symptoms as the tumor is controlled. Dermatomyositis is a severe connective tissue disorder whose association with malignancy is not well defined, and the incidence of malignancy in patients with dermatomyositis is at least five times higher than in non-dermatomyositis individuals. Careful systemic examination is warranted in dermatomyositis to prevent asymptomatic malignancy.

Metastatic symptoms: At autopsy, more than half of patients are discovered to have distant metastases. The common sites are the bone, lung, and liver; however, brain metastases are rare. Metastatic lesions can cause tissue destruction or compression at metastatic sites and present with corresponding symptoms, such as bone pain, cough, and abdominal pain.

Symptoms such as tinnitus, hearing loss, epistaxis, nasal obstruction, diplopia, headache, or cervical mass should induce prompt medical attention.

4.2 Laboratory and imaging evaluation

4.2.1 General tests

Complete blood count, routine urine tests, routine stool tests, liver and kidney function tests, electrolytes, blood glucose, coagulation function, and infectious disease screening (hepatitis, syphilis, HIV, etc.) are necessary to understand the general condition of patients and develop a comprehensive treatment plan.

4.2.2 Tumor specific tests

Some cases of NPC present with increased DNA copy number of EBV in peripheral blood, as well as increased titers of serum EBV antibodies VCA-IgA and EA-IgA, both of which can be an auxiliary diagnostic method, and EBV-DNA levels correlate with prognosis.

4.2.3 Imaging evaluation

MRI MRI, with a higher resolution of soft tissues than computed tomography (CT), determines the tumor location, extent, and invasion of its adjacent structures, especially in the brain, parapharyngeal, and muscle more clearly [20]. MRI of the nasopharynx and neck with contrast enhancement should be recommended in all eligible patients to better define staging, treatment options, and the extent of the radiotherapy target. The submucosal infiltration of NPC, as well as the invasion of the pharyngeal skull base fascia, levator veli palatini, parapharyngeal space, bony mass of the skull base, and the intracranial mass are better understood using transverse, sagittal, and coronal reconstruction based on T1WI, T2WI and Gd-DTPA enhanced T1WI. Tumors in the nasopharynx have low T1WI signals and high T2WI signal intensity, which was obvious after Gd-DTPA enhancement. The T1WI signal was markedly reduced in the bone marrow cavity invaded by the tumor [21].

CT scan or X-ray CT scan of the nasopharynx and neck should be recommended for those illegible for MRI because of its advantage in resolving the extent of the lesion and invasion to surrounding structures, especially for parapharyngeal, skull base, and intracranial regions [20]. Enhanced scans are more helpful in the diagnosis of metastases in the carotid sheath region, cavernous sinus, and cervical lymph nodes. The scope of the scan should include the skull base, nasopharynx, and neck.

CT scan rather than chest X-ray is recommended routinely in patients aged > 50 years or in heavy smokers to clarify lung metastasis or mediastinal lymph node metastasis.

Ultrasound Abdominal ultrasound is used to assess the presence of abdominal metastases. Cervical ultrasound can help to determine the characteristics of cervical lymph nodes, according to the level and distribution of blood flow within them [22].

Bone scan A bone scan is commonly used to exclude the presence of bone metastases because of its high sensitivity; abnormal radiolucencies are detected as early as 3 months before the onset of symptoms of bone metastases or 3–6 months before radiographical detection of bone destruction [22]. However, false-positive results might occur with bone trauma or inflammation.

Positron emission tomography (PET)/CT PET/CT is recommended for locally advanced NPC, especially those with cervical or supraclavicular lymphadenopathy, to clarify the presence or absence of distant metastasis [23, 24].

4.3 Pathological diagnosis

NPC has a predilection for the parietal and lateral walls of the nasopharynx and the pharyngeal crypts, and on nasopharyngoscopy, the lesions appear as small nodules or granulomatous swellings with a rough and easily observed hemorrhagic surface. When there is a mass in both the nasopharynx and neck, the former should be preferred as the biopsy site. Cervical lymph node biopsy is considered only if multiple nasopharyngeal biopsies were pathologically negative or if lesions were not seen by nasopharyngoscopy. For cervical lymph node biopsy, single and completely resectable nodes should be selected. The most common type of NPC pathology is squamous carcinoma (SCC), accounting for more than 95% of cases [3]. Currently, NPC is classified into the following three categories: Keratinizing squamous cell carcinoma, non-keratinizing carcinoma, and basaloid squamous cell carcinoma. Among them, non-keratinizing carcinoma, associated with EBV infection, accounts for the vast majority of NPC in endemic areas and can be further subdivided into differentiated and undifferentiated non-keratinizing carcinoma. However, adenocarcinomas, carcinoids, and adenoid cystic carcinomas of the nasopharynx are rare. Keratinizing squamous cell carcinoma is more common in non-endemic areas [1, 25].

It is well documented that EBV is oncogenic for humans, which can be identified by detecting EBV encoding RNAs in NPC tissues using in situ hybridization (ISH) [26]. The presence of EBV latent infection was found in high-grade dysplasia and NPC cells, but not in the normal epithelium or low-grade dysplasia. In the latent phase, infected cells express a variety of proteins, including EB core antigens and latent membrane proteins, which are currently thought to be poorly immunogenic, partially explaining how NPCs evade immune recognition. The role of EBV genomic variations in the development of NPC has not been determined, although whole genome sequencing has revealed high variability in many genomic regions of EBV in NPC biopsies. EBV is necessary for nonkeratinizing NPC; however, its role in keratinizing NPC is not significant [27].

In endemic areas, p16 positivity and human papillomavirus (HPV) infection (an RNA probe detects 13 high-risk and 5 low-risk HPV types) in nonkeratinizing undifferentiated carcinomas is up to 8%, which is associated with a better prognosis than EBV infection. HPV data are limited in nonendemic areas, where positivity is higher in keratinizing carcinomas, and the relationship with prognosis is unclear. Whether HPV is involved in carcinogenesis and disease progression remains to be demonstrated [28, 29].

5 Multidisciplinary Team to Holistic Integrative Medicine (MDT to HIM)

5.1 General assessment

Specialist with expertise in the management of NPC from following department should be included for optimal treatment and follow-up: Radiation, Head and neck surgery, Medical oncology, Pathology, Radiology, Nuclear medicine, Ultrasonography, Endoscopic, Specialized nursing care, Psychiatry, Clinical nutrition, and Palliative care [30].

5.1.1 Clinical staging

The eighth edition staging developed jointly by the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) [31] is recommended for NPC staging, as shown in Tables 1 and 2.

5.1.2 Nutrition status

Nutrition care Rational nutritional care improves the tolerance to chemoradiotherapy and accelerates the post-treatment rehabilitation of patients. After the patient is admitted, clinical nutritionists should advise the patient and their family members to fully recognize the importance of nutrition for rehabilitation, and make an appropriate dietary plan according to the nutritional status of the patient.

Enteral nutrition Enteral nutrition should be administered as early as possible at the start and during treatment. For those with good gastrointestinal function, but who cannot be supplemented orally for anatomical or primary morbidity, tube feeding with enteral nutrition should be a preference. Patients on short-term supplementation can be managed with a nasogastric tube and, in the long-term,

Table 1 AJCC/UICC TNM staging system (8th edition)

Primary tumor (T)
Tx: The primary tumor cannot be assessed
T0: No tumor identified, but there is EBV-positive cervical lymph node(s) involvement
Tis: Carcinoma in situ
T1: Tumor confined to the nasopharynx, or extension to the oropharynx and/or the nasal cavity without parapharyngeal involvement
T2: Tumor with extension to the parapharyngeal space, and/or adjacent soft tissue involvement (medial pterygoid, lateral pterygoid, and prevertebral muscles)
T3: Tumor with infiltration of bony structures at the skull base, cervical vertebra, pterygoid structures, and/or paranasal sinuses
T4: Tumor with intracranial extension, involvement of cranial nerves, the hypopharynx, orbit, parotid gland, and/or extensive soft tissue infiltration beyond the lateral surface of the lateral pterygoid muscle
Regional lymph node (N)
Nx: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Unilateral metastasis in cervical lymph node(s) and/or unilateral or bilateral metastasis in retropharyngeal lymph node(s), 6 cm or smaller in their greatest dimension, above the caudal border of the cricoid cartilage
N2: Bilateral metastasis in cervical lymph node(s), 6 cm or smaller in their greatest dimension, above the caudal border of the cricoid cartilage
N3: Unilateral or bilateral metastasis in cervical lymph node(s), larger than 6 cm in their greatest dimension, and/or extension below the caudal border of the cricoid cartilage
Distant metastasis (M)
M0: No distant metastasis
M1: Distant metastasis

Table 2 Overall classification based on AJCC/UICC TNM staging system (8th edition)

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T0-1	N1	M0
	T2	N0-1	M0
III	T0-2	N2	M0
	T3	N0-2	M0
IVa	T4	N0-2	M0
	Any T	N3	M0
IVb	Any T	Any N	M1

percutaneous endoscopic gastrostomy (PEG) or jejunostomy is recommended, because long-term indwelling nasogastric feeding tubes might cause nasal, esophageal, and gastric mucosal erosions and could predispose the patients to aspiration pneumonia [32]. PEG can be used with an inexpensive, self-prepared homogenate, to reduce the economic burden and maintain or improve the nutritional status and quality of life of the patients. However, PEG is an invasive procedure that might affect the patient's life and appearance and is not easily accepted.

Parenteral nutrition Parenteral nutrition should be given promptly when patients have feeding difficulties and cannot meet their daily needs.

Table 3 Numerical ratings scale

Rate	Pain
0	Painless
1–3	Mild pain (not affecting sleep)
4–6	Moderate pain
7–9	Severe pain (inability to sleep or awaken from pain during sleep)
10	Extreme pain

5.1.3 Pain

The chief complaint of patient is the gold standard for pain assessment, and pain intensity must be assessed before analgesic treatment. Patients should be asked about their level of pain, making a mark or circling a number that best represents their level of pain. Commonly used methods of pain assessment include Numerical ratings scale (NRS) and verbal description scales (VDS) [33]. Detailed scales are listed below in Tables 3 and 4.

5.1.4 Pathology

Currently, the third edition of the World Health Organization (WHO) staging (2003) is used internationally and classifies NPC into the following three categories: Keratinizing squamous cell carcinoma, non-keratinizing carcinoma, and basaloid squamous cell carcinoma. Among them, non-keratinizing carcinoma accounts for the vast majority of NPC in China and can be further

Table 4 Verbal description scales

Level	Pain
0	Painless
I (mild)	Pain but tolerable, life and sleep undisturbed
II (moderate)	Pain intolerable, requested sedative medication, sleep disturbed
III (severe)	Pain intolerable, need for analgesic medication, sleep severely disturbed, may be accompanied by autonomic disturbances or passive body position

subdivided into differentiated and undifferentiated non-keratinizing carcinoma [34].

Based on the current staging system, a multicenter study with new classification of NPC pathology led by Jian-Yong Shao's group was able to significantly distinguish patients with different prognoses [34]. This study was divided into three cohorts: a training cohort, a retrospective validation cohort, and a prospective validation cohort. According to the cellular morphological appearance of NPC, four pathological types, epithelial carcinoma, mixed epithelial sarcoma carcinoma, sarcomatous carcinoma, and squamous cell carcinoma, were classified. Epithelioid carcinoma: Small round, ovoid, or plated cells in a road like arrangement; cells with a low nucleo-cytoplasmic ratio or abundant chromatin; poorly defined borders between large round cells with centrally placed nucleoli; large and round vesicular nuclei; and nucleoli significantly occupying more than 75% of tumor cells. Mixed cutaneous sarcoma carcinoma: Features of both epithelial and sarcomatous carcinoma. Sarcomatous type carcinomas: Irregular small cells, large cells with hyperchromatic chromatin, uniformly intermediate sized spindle cells with inconspicuous nucleoli, or hyperchromatic nuclei and oncocytes with eosinophilic cytoplasm. Squamous cell carcinoma: Well differentiated keratinized squamous carcinoma with prominent intercellular bridges and keratinized beads, and poorly or moderately differentiated squamous carcinoma; there are scattered small numbers of basal like cells. The 5-year survival rates for each pathological subtype were 78.9% for epithelial carcinoma, 68.3% for mixed epithelial sarcoma carcinoma, 59% for sarcomatous carcinoma, and 41.1% for squamous cell carcinoma.

5.1.5 Thrombotic risk

All admitted patients should undergo venous thromboembolism (VTE) risk assessment, especially in departments with a high risk of VTE. The assessment protocol recommends the use of the Padua prediction score (Table 5), which can be adapted according to the characteristics of each center and different clinical conditions [35].

5.2 Diagnosis and differentiation

5.2.1 Qualitative diagnosis

Pathological examination by electronic nasopharyngoscopy biopsy is recommended to clarify the character, classification, and differentiation of the tumor.

5.2.2 Staging

Please refer to Section 5.1.1 Clinical staging.

5.2.3 Differential diagnosis

Nasopharyngeal angiofibroma Nasopharyngeal angiofibroma, also known as nasopharynx fibroangioma, is the most common benign tumor in the nasopharynx, which is prone to hemorrhage because of the rich blood vessels contained in the tumor. The main differentiating points from NPC are the site of the lesion, and a history of multiple episodes of epistaxis.

Lymphadenitis Lymphadenitis is a nonspecific infection. The causative organism of lymphadenitis might be derived from inflammatory, subcutaneous foci of a pyogenic infection in the oropharynx. In contrast to NPC, lymphadenitis often presents as bilateral multiple enlarged lymph nodes; however, there is no obvious pathological change. After resolution of inflammation, lymph nodes often shrink to their original size.

Lymphoma Lymphoma refers to a malignancy originating in the lymphohematopoietic system and often occurs in adolescents or young adults. Lymphoma has a wide spectrum of invasion, including the nasal cavity and oropharynx. Enlargement of bilateral cervical or systemic lymph nodes with an elastic texture and a rubbery ball sensation are observed. Mucosal lines are seen on the surface of the mass; therefore, attention needs to be paid to the possibility of lymphoma, which can be used as a point of differentiation from NPC.

Table 5 Padua prediction score

Risk	Score
Active cancer; Previous VTE (with the exclusion of superficial vein thrombosis); Reduced mobility; Already known thrombophilic condition	3
Recent (≤ 1 month) trauma and/or surgery	2
Elderly age (≥ 70 years); Heart and/or respiratory failure; Acute myocardial infarction or ischemic stroke; Acute infection and/or rheumatologic disorder; Obesity (body mass index, BMI ≥ 30 kg/m^2); Ongoing hormonal treatment	1

low risk: < 4; high risk: ≥ 4

Nasopharynx tuberculosis These patients often have a history of tuberculosis (TB), which is frequently accompanied by low-grade fever, night sweats, and emaciation, in addition to nasal obstruction and epistaxis, nasal ulcers, edema, and lighter color on nasopharyngoscopy. Acid fast bacilli are visible on secretion smears. It is often accompanied by cervical lymph node TB, which manifests as lymphadenopathy, adhesions, and no tenderness, and cervical lymph node puncture can identify TB bacilli. The tuberculin test (PPD test) is strongly positive. Chest X-ray chest often suggests active TB foci in the lungs.

Other benign hyperplastic lesions Single or multiple nodules can often be found in the apical, posterior, or lateral parietal walls of the nasopharynx, which are 0.5–1 cm in size and have a smooth, reddish surface mucosa. They occur based on the mucosa or adenoids of the nasopharynx, and can also be caused by squamous transformation of the mucosal epithelium with retention of a keratinized epithelium, resulting in epidermoid cyst changes and, in part, retention cysts resulting from vigorous mucosal gland secretion. However, when the surface of a nodule appears rough, erosive, ulcerated, or oozing blood, the possibility of carcinogenesis must be considered, and should be confirmed by biopsy.

Key points: Comprehensive assessment of NPC requires a multidisciplinary team to holistic integrative medicine (MDT to HIM) approach to establish standard of care procedures for NPC (Fig. 1), which will help to achieve optimal and individualized integrative therapy. Comprehensive evaluation should include staging, nutritional status, pain, pathology, and thromboembolism. Either assessment requires a comprehensive dynamic that focuses on individual differences to select the best treatment.

5.3 Prognostic factors

5.3.1 Clinical factors associated with prognosis

The primary prognostic factor for NPC is clinical stage (tumor-node-metastasis (TNM) stage). Several studies have pointed out that lymph node capsule invasion, high pretreatment body mass index (BMI), and hepatitis virus infection are all independent poor prognostic factors for NPC. In addition, age, pathological grade, Karnofsky performance score (KPS), and skull base invasion are significant prognostic factors [36].

5.3.2 Biological factors associated with prognosis

The pretreatment serum EBV-DNA level and its dynamic change are widely accepted as NPC prognosis-related biological factors [37]. In addition, serum heme level; the hemoglobin level before radiotherapy; and the levels of epithelial cell adhesion molecule, cyclin dependent protein kinase regulatory subunit 1 (Cks1), p27, centromere protein-F (CENP-F), Rho-guanine nucleotide exchange factor 3 gene (ARHGEF3), and kelch domain containing 4 (KLHDC4); with promising clinical applications, have also shown to be associated with NPC prognosis [38].

5.4 Management

5.4.1 Radiotherapy

Naive nasopharyngeal carcinoma

Principles of radiotherapy

For stage I (T1N0M0) NPC, a satisfactory outcome can be achieved by administering radiotherapy alone [3]. For stage II (T0-2N0-1M0) NPC, it is controversial whether concurrent chemotherapy should be added to radiotherapy, in which T2N1 with a high incidence of distant metastasis should receive radiotherapy concurrent with platinum-based chemotherapy [39, 40]. For locally advanced (stages III to IVa) NPC, concurrent platinum-based chemotherapy is required [41]. Meanwhile, the intensity of chemotherapy (e.g., induction chemotherapy or adjuvant chemotherapy) can be further increased on the basis of concurrent chemoradiotherapy (CCRT) according to the stage and performance. In addition, radiotherapy concurrent with targeted therapies (e.g., cetuximab, nimotuzumab, and recombinant human endostatin) and immunotherapy are among the options for patients unable to tolerate or unwilling to receive chemotherapy [42–45]. Intensity modulated radiotherapy (IMRT) with daily image guidance should be offered. If IMRT is unavailable, patients should be transferred to institutions that could implement IMRT whenever possible.

Principles of immobilization and simulation

(1) Immobilization**,** the body position is generally taken as a supine position, with appropriate angles of head rest (standard resin headrest or a water-activated fixed pillow), the two arms are naturally placed on both sides of the body in parallel, the left and right shoulders are highly congruent, and the legs are held together and extended [46]. A head and neck shoulder thermoplastic film plus an individualized Styrofoam head and neck cushion are recommended, covering the range from the cranial roof to the shoulder joint.
(2) Simulation, the scan center is usually chosen at a site close to the center of the target, and the marker points are chosen in a flat position as much as possible (avoiding the nasal tip, and the submental

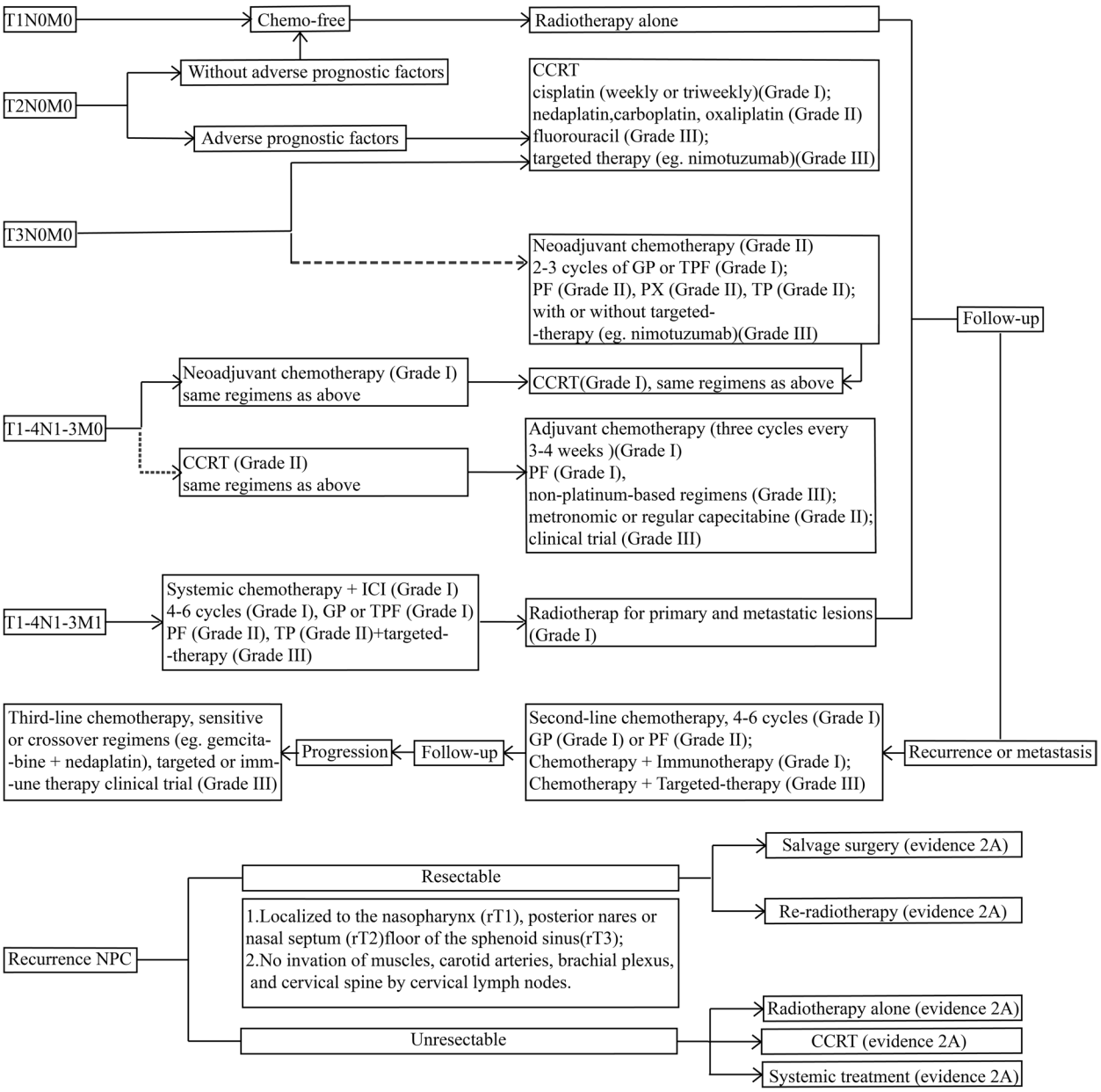

Fig. 1 Standard of care procedures for NPC

region) to ensure good postural repeatability. The recommended scanning and reconstruction layer thickness is 3 mm, ranging from 2 cm above the head to 2 cm below the sternal notch, and the width needs to include all skin over the shoulders bilaterally. In those without contraindications to contrast, intravenous contrast is necessary for simulation. MRI, as an important reference for the delineation of the NPC target volume, and MRI simulation, are recommended when available, and to perform target delineation after fusion of CT simulation with MRI simulation [47, 48]. If there is no contraindication, MRI simulation is carried out according to the simulated positioning position of CT as far as possible, and image fusion is carried out using skull base bone marker fusion method and positioning CT [48].

Target delineation

(1) Definitive radiotherapy, the target volume for NPC irradiation includes the primary tumor, metastatic

cervical lymph nodes, subclinical areas, and draining cervical lymph nodes, while the irradiation of an organ at risk (OAR) should be avoided or reduced. Target delineation is based on MRI, combined with nasopharyngoscopy, physical examination of the neck, and is performed on CT simulation images, combined with PET/CT if necessary [49]. The Gross tumor volume of nasopharyngeal carcinoma (GTVnx) comprises regions of primary tumors in the nasopharynx, as determined by clinical and radiographical examination. The gross tumor volume of cervical node (GTVnd) comprises enlarged lymph nodes as determined by clinical and radiographical examination. The Clinical target volume (CTV) is based on the local invasion and is classified into high-, medium- and low-risk areas [50]. CTV1: Subclinical area including and around the GTVnx (generally 5 mm external to the GTVnx, the distance might be reduced to 1 mm immediately adjacent to the brainstem orientation). CTV2 and CTVnd: Includes the CTV1 and its outer 5 mm (the distance can be reduced to 2 mm immediately adjacent to the brainstem orientation), and includes the GTVnd as well as cervical lymph node drainage areas requiring prophylactic irradiation. If metastatic nodes have significant extranodal or surrounding muscles extension, CTV1 can be added depending on the location. For those with lymph node metastasis present bilaterally, prophylactic irradiation of the draining cervical lymph nodes includes level II, III, IV, Va and Vb bilaterally. Prophylactic irradiation of the draining cervical lymph nodes for those with lymph node metastasis on only one side includes level II, III, IV, Va, and Vb on the metastatic side, and level II, III, and Va on the contralateral side. For N0, prophylactic irradiation of the draining cervical lymph nodes includes bilateral level II, III, and Va. In addition, level Ib might be omitted from the prophylactic volume unless there is involvement of the anterior half of the nasal cavity or if there are level II lymph nodes with extranodal extensions or size > 2 cm or bilateral involvement [51, 52].

(2) Definitive radiotherapy after induction chemotherapy, the use of induction chemotherapy in the treatment of locally advanced NPC is becoming more prevalent, and the response rates to standard first-line induction chemotherapy regimens are all around 75%. Tumor volume and extent often undergo large changes after induction chemotherapy and thus are slightly different from the target delineation of definitive radiotherapy. For patients with NPC who have undergone induction chemotherapy, the pre-induction scan should be combined with the postinduction CT simulation data set to illustrate the initial disease extent. The gross tumor volume should generally follow the pre-induction tumor extent, especially within bony anatomy [53]. GTVnx: Tumors that bulge into the nasopharynx cavity or expand into the parapharyngeal space should be delineated according to the actual extent after chemotherapy; however, areas with osseous involvement of the skull base should be delineated according to the pre-chemotherapy range. GTVnd: Delineated by area seen on post chemotherapy imaging, but should contain the area with invasion of muscle if there is extranodal extension [53, 54]. CTV1 and CTV2: Identical in principle and definitive radiotherapy, except CTV1 must include the tumor invasion range before chemotherapy [50, 53].

Prescription doses and dose limitation

For all patients with NPC, a prescribed dose of 70 Gy in 33–35 fractions (2.0–2.12 Gy per fraction) delivered over 7 weeks (once daily, 5 fractions per week) should be offered. Different prescription doses are given according to the primary lesion of the nasopharynx, subclinical lesions, cervical lymph nodes, and cervical lymph drainage areas, and conventional fractionation is generally used [55, 56], with the prescription doses listed in Table 6.

The anatomy of the head and neck is complex and requires precise delineation with dose constraints. OARs that must be delineated for NPC radiotherapy include the brainstem, spinal cord, optic nerve, optic chiasm, lens, bilateral temporal lobes, pituitary gland, inner ear, parotid gland, temporomandibular joint, and mandible. Alternative organs include the eye, oral cavity, tongue, larynx, thyroid, pharyngeal constrictor muscles, submandibular glands, mastoids, brachial plexus, and others [57].

Table 6 Prescription dose

Location	Target	Dose	Fraction
Primary lesion	PTV-GTVnx	D_T 68-76 Gy	33-35f
	PTV-CTV1	D_T 60-64 Gy	33-35f
	PTV-CTV2	D_T 50-54 Gy	33-35f
Cervical lymph node	PTV-GTVnd	D_T 66-70 Gy	33-35f
	PTV-CTV2	D_T 50-54 Gy	33-35f

Dose limitation refers to Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) and critical OAR are listed in Table 7 [58]. When the tumor is locally advanced or the tumor invades the intracranial region and has developed symptoms of cranial nerve palsy, the target volume needs to be determined and the OAR dose instituted after discussion by the MDT. Studies have reported that in IMRT, to guarantee the dose to the target volume of the tumor invasion site and improve the local control rate, under the premise of informed consent, appropriate adjustment of the OAR limiting dose did not obviously increase the serious complications of radiotherapy [59, 60].

Key points: (1) Stage I NPC can obtain satisfactory outcome using definitive radiotherapy alone. (2) Stage II NPC can be treated with definitive radiotherapy concurrent with platinum-based chemotherapy. For patients not suitable for chemotherapy, radiotherapy alone can be used. (3) The combination of radiotherapy and systematic treatment is recommended for stage III–IVa NPC. For patients unable to tolerate or unwilling to accept chemotherapy, radiotherapy combined with targeted therapy or immunotherapy can be selected. (4) Before radiation, CT and MRI simulation with precise immobilization shall be carried out, and the target volume shall be delineated after image fusion. (5) The target volume and OAR need to be carefully delineated to minimize radiation to the OAR and meet the requirements.

Recurrent nasopharyngeal carcinoma

Principles of treatment

For recurrent NPC, MDT to HIM is recommended. For different recurrence patterns, radiotherapy, surgery, chemotherapy, targeted therapy, immunotherapy and other means should be used to develop individualized integrated treatment strategies, which can improve efficacy and ensure quality of life.

Table 7 Dose limitation

Organ	Dose
Brainstem	$D_{max} \leq 54$ Gy or $V_{60} \leq 1\%$
Spinal cord	$D_{max} \leq 45$ Gy
Optic nerve and chiasm	$D_{max} \leq 54$ Gy
Lens	$D_{max} \leq 12$ Gy
Temporal lobe	$D_{max} \leq 60$ Gy
Temporomandibular joint and mandible	$D_{max} \leq 60$ Gy
Parotid gland	
Total	$V_{40} \leq 50\%$
Superficial	$V_{30} \leq 50\%$
Inner ear	$D_{max} \leq 40$ Gy

Re-radiotherapy

The timing and implementation of re-radiotherapy should be determined with caution. Recurrent NPC usually requires second-line chemotherapy or targeted treatment first, followed by re-radiotherapy after the response of the recurrent lesion, in which IMRT is the first choice. Moreover, a comprehensive restaging assessment is needed to assess the recurrence or distant-metastasis before treatment [61]. The dose to an OAR should be strictly limited in re-radiotherapy, because of the increased possibility of complications such as nasopharyngeal necrosis, mucosal ulceration, skull base necrosis and hemorrhage. Thus, informed consent from patients and family members are critical before re-radiotherapy is delivered.

Stereotactic radiotherapy (SRT) and stereotactic radiosurgery (SRS) concentrate the high dose inside the target volume, while it decreases sharply outside the target volume, which is beneficial for normal tissue protection. Local control (LC) rates of SRT for selectively recurrent NPC range from 53.8% to 92.0% with a 5-year OS rate of around 40% [62]. SRT using multiple fractions is associated with better LC rates than SRS, despite there being no significant difference in survival [63]. SRT requires that the tumor volume is not large and is located at some distance from vital neural structures. This highly precise treatment method is technically demanding and only suitable for experienced centers.

Target delineation for re-radiotherapy

(1) GTV GTVnx includes the recurrent tumor found on imaging and clinical examination, GTVnd is the metastatic lymph node in the neck.
(2) CTV Prophylactic irradiation of lymph node drainage areas is not considered for recurrent NPC. The recommended CTV is GTVnx + (5–10) mm and the area of regional recurrent lymphatic drainage.
(3) PTV An external expansion of 3–5 mm is recommended, considering the oscillation error, systematic error, organ movement, and target volume change during irradiation.

Prescription doses and dose limitation

The biological effectiveness dose (BED) (according to tumor $\alpha/\beta = 10$) is < 60 Gy, and the LC rate was significantly worse when the BED was > 60 Gy [64]. However, with dose escalation, severe complications also increase significantly [65]. No significant difference in LC rate was

observed when BED = 60–70 Gy compared with > 70 Gy [66, 67]. A phase II trial compared the efficacy of low-dose IMRT (60 Gy/27 f) and high-dose IMRT (68 Gy/34 f) in the treatment of recurrent NPC [67]. It was found that there was no significant difference in the LC rate. The survival rate of the low-dose group was higher, and the late complication-related death was reduced. A small sample retrospective study found that hyperfractionation radiotherapy reduced the occurrence of massive nasopharyngeal hemorrhage with the potential to improve OS. However, there is still a lack of definitive evidence in recurrent NPC that hyperfractionation radiotherapy is superior to conventional fractionation. Therefore, under the guarantee of OAR dose limitation, PTV can be prescribed with 60–64 Gy/30–35f or $BED_{10} > 60$ Gy, and excessive doses should not be pursued.

No standards for the OAR dose limitation for re-radiotherapy are currently available. Obvious differences occur in the repair abilities of radiation injury among different tissues, which are related to the type of organ and tissue, the size of the previous irradiation range, and the time of the radiation interval. The afore-mentioned factors should be considered when setting the OAR dose limitation for re-radiotherapy. Current experience is with maximum tolerated doses in the brainstem and spinal cord of 40 Gy and 30 Gy, respectively, with re-radiotherapy. Other OAR limitation requirements are viable by the method of subtracting 30% of the first irradiation dose by the maximum tolerated dose ($TD_{5/5}$) [58]. Detailed dose limits are listed in Table 8.

Key points: (1) For recurrent NPC, the MDT should generate a comprehensive scheme for an individualized approach. (2) OAR doses should be strictly limited during re-radiotherapy. Treatment modalities are dominated by conventional fractionation, and hypofractionated or hyperfractionated radiotherapy requires further study. (3) Prescription doses may be considered at 60–64 Gy/30-35f or $BED_{10} > 60$ Gy, excessive doses should not be pursued. (4) The maximum tolerated dose to the brainstem and spinal cord at the time of re-radiotherapy is 40 Gy and 30 Gy, respectively. Other OAR limitation requirements are viable by the method of subtracting 30% of the first irradiation dose by the maximum tolerated dose ($TD_{5/5}$).

Table 8 Lifetime dose limitation

Organ	Dose limitation	PRV extension	PRV dose limitation
Brainstem	$D_{max} \leq 70.2$ Gy	≥ 1 mm	$D_{1\%} < 78$ Gy
Spinal cord	$D_{max} \leq 58.5$ Gy	≥ 5 mm	$D_{1cm}3 \leq 65$ Gy
Optic nerve	$D_{max} \leq 65$ Gy	≥ 1 mm	$D_{max} \leq 78$ Gy
Optic chiasm	$D_{max} \leq 65$ Gy	≥ 1 mm	$D_{max} \leq 78$ Gy
Temporal lobe	$D_{1cm}3 < 84.5$ Gy	/	/
Brachial plexus	$D_{1cm}3 < 85.8$ Gy		

Metastatic nasopharyngeal carcinoma

Radiotherapy of the primary lesion

A study of 718 patients with metastatic NPC from the National Cancer Database (NCDB) found that systemic chemotherapy combined with primary lesion radiation conferred a significant survival advantage compared with chemotherapy alone, both in the whole population (median OS 21.4 months *vs.* 5.5 months, $P < 0.001$) and the population after propensity value matched scoring (median OS 22.7 months *vs.* 16.0 months, $P < 0.001$) [68]. A study of 679 metastatic NPC cases from Shanghai also confirmed that radiotherapy of the primary lesion reduced the mortality risk by 50% ($P < 0.001$), and definitive effects might be achieved, especially in oligometastatic NPC. The survival benefit was more pronounced in the group with primary radiotherapy doses > 50 Gy, and long-term survival over 10 years appeared only in the radiotherapy group [69]. Therefore, for the management of metastatic NPC, systemic chemotherapy combined with high-dose primary lesion radiation is recommended.

Radiotherapy of oligometastatic lesions

Different local managements for different metastatic sites and numbers, such as local radiotherapy for bone metastases and stereotactic body radiotherapy (SBRT) for lung or liver metastases. Local treatment of patient with oligometastatic lesions confers a survival benefit [70].

Key points: (1) Long term survival is still possible with holistic integrative therapy in metastatic NPC. (2) High dose radiation targeting the primary lesion is recommended for metastatic NPC. (3) Local treatment of metastases NPC required holistic integrative thinking.

Recurrent metastatic NPC

Oligometastases

For metastases arising after definitive therapy, a significant survival benefit was observed with aggressive treatment of oligometastatic lesions. According to a report from Sun Yat-sen University Cancer Center of 105 patients with posttreatment lung oligometastases, chemotherapy ± surgery or radiotherapy of lung metastases versus chemotherapy alone improved the LC, as well as the OS and PFS [71]. Studies targeting radiation of bone metastases also reached the same conclusion.

Among 197 patients with post-treatment metastatic NPC from Fujian Cancer Hospital treated using different methods, the 2-year OS of chemotherapy combined with local radiotherapy of metastatic lesions was superior to that of chemotherapy alone and best supportive care (57.7%, 37.7%, 1.6%, respectively, $P < 0.001$), and this survival advantage was more pronounced in patients with oligometastatic lesions [72]. A complete response (CR) of metastases might occur after adequate palliative chemotherapy and local treatment cannot be performed; therefore, the management of metastases is facilitated by prechemotherapy or concurrent chemotherapy to maximize lesion elimination.

Multiple metastases

For patients with recurrent multiple metastases, systemic palliative therapy is required according to the individual patient**.** Local management can be added on a clinical basis to relieve symptoms.

Key points: (1) For metastases arising after definitive therapy, a significant survival benefit was observed with aggressive treatment of oligometastatic lesions. (2) For patients with recurrent multiple metastases, systemic palliative therapy is required. Local management was considered as clinically appropriate.

Proton and heavy ion radiation Malyapa et al. demonstrated that intensity-modulated proton radiotherapy (IMPT) is effective for head and neck cancer, especially with dosimetric advantages [73]. Widesott et al. suggested that for NPC radiotherapy, IMPT provides better protection of OARs than tomographic intensity modulated radiotherapy [74]. Lewis and Jakobi et al. compared IMRT and IMPT dosimetric parameters and determined that NPC might benefit from IMPT dosimetric advantages, particularly a reduction in swallowing-related side effects after treatment [75, 76]. The dosimetric advantages of IMPT, in younger patients or in patients with T4 staging where the tumor is in close to an OAR, reduced the occurrence of acute and late toxic effects and were associated with a favorable near-term prognosis.

The higher relative biological effect (RBE) of heavy ion radiotherapy (e.g., carbon ions) leads to more effective eradication of cancer cells that are resistant to photon irradiation. The Shanghai Proton and Heavy Ion Center applied intensity-modulated carbon ion radiotherapy (CIRT) to 75 patients with locally recurrent NPC, and the 1-year survival rate was over 98.1% [77]. In general, salvage CIRT is effective for locally recurrent NPC and its toxicity is acceptable. With a median follow-up of 22.8 months, the 2-year OS rate was 83.7% [78]. The use of proton radiotherapy in recurrent NPC initially proved safe and feasible; however, whether heavy ion radiotherapy confers a survival benefit and reduces complications compared with other radiotherapy needs to be further studied.

Key points: Proton and heavy ion radiotherapy has been applied in NPC and initially proved to be safe and feasible, with low side effects; however, its long-term efficacy requires further study.

5.4.2 Chemotherapy

Populations unsuitable for chemotherapy For patients with T1-2N0, chemotherapy is not routinely recommended, but might be offered if there are adverse features in T2N0, such as bulky tumor volumes or high EBV DNA copy number [1].

For patients with T1-2N1, concurrent chemotherapy might be offered, particularly for T2N1. The role of concurrent chemotherapy is not absolutely defined for stage II NPC, given the paucity of randomly assigned data in the IMRT era. Stage II consists of three subgroups (T2N0, and T1-2N1), among which N1 patients are at higher risk of distant metastasis. However, the results of a phase III randomized controlled trail (RCT) evaluating additional concurrent chemotherapy to IMRT confirmed the efficacy of IMRT alone for low-risk patients including stage II and T3N0 with lymph node longest diameter (< 3 cm), no extranodal extension and EBV-DNA (< 4000 copies / ml), making it possible in the future to omit some stage II patients from chemotherapy incorporating other prognosticators [39].

Chemotherapy for non-metastatic NPC

Induction chemotherapy

For treatment-naïve NPC staged III–IVa (except T3N0M0), if there are no contraindications, 2–3 cycles of platinum-based induction chemotherapy should be offered, followed by CCRT [7, 79–82]. The chemotherapy is administered every 21–28 days (calculated from the first day of the last cycle). The following regimens might be used in the absence of medical contraindications: GP (gemcitabine 1000 mg/m^2 day 1, 8; cisplatin 80 mg/m^2 day 1) [7] or TPF (docetaxel 60–75 mg/m^2, day1; cisplatin 60–75 mg/m^2, day 1; fluorouracil 600–750 mg/m^2, daily, continuous intravenous drip day1–5) [80]. Other regimens include PF (cisplatin 80–100 mg/m^2, day 1; fluorouracil 800–1000 mg/m^2, continuous intravenous drip day

1–5) [82], PX (cisplatin 100 mg/m^2 day 1; capecitabine 2000 mg/m^2, day 1–14) [83] and TP (docetaxel 75 mg/m^2, day 1; cisplatin 75 mg/m^2, day 1) [81]. For patients with distant metastasis (TxNxM1, IVb), systemic treatment should be given priority, and local treatment (such as radiotherapy for primary and metastatic lesions) should be given after 4–6 cycles. The recommended induction regimens are listed in Table 9.

Despite CCRT being the backbone of treatment for locally advanced NPC (stages III–IVa), the value of induction chemotherapy has been demonstrated in several multicenter trials [7, 79–82]. Induction chemotherapy plus CCRT was superior to CCRT alone in terms of OS, PFS, and distant metastasis free survival (DMFS), whereas a benefit in terms of locoregional recurrence free survival (LRFS) was demonstrated only in the induction chemotherapy group in a clinical trial using the three drug TPF regimen [80]. A pooled analysis showed that induction chemotherapy plus CCRT significantly improved OS (hazard ratio (HR) 0.75, 95% confidence interval (CI) 0.57–0.99) and PFS (HR 0.70, 95% CI 0.51–0.9) [84]. Based on previous trials, we recommended GP or TPF as the preferred induction chemotherapy regimens, both of which have been confirmed by large phase III trials. Other alternative regimens include PF, PX, and TP. Holistic integrative thinking in terms of efficacy, adherence, and tolerability is required to select the appropriate regimen. In addition, trials on whether the use of other platinum-based agents, such as nedaplatin and carboplatin, instead of cisplatin or other fluorouracil-based agents, such as capecitabine, could achieve non-inferior efficacy while improving quality of life are ongoing (ChiCTR-TRC-13003285, NCT03503136).

Concurrent chemotherapy

For T1-2N1M0, as well as for stage III–IVA locally advanced NPC, chemotherapy with at least seven weekly regimens (cisplatin 40 mg/m^2) or three triweekly regimens (cisplatin 80–100 mg/m^2) should be administered concurrently to achieve a cumulative cisplatin dose of at least 200 mg/m^2 [40, 85–87]. For those intolerant to cisplatin, nedaplatin (100 mg/m^2, triweekly) [88] or carboplatin (area under the curve (AUC) 5–6, triweekly) [89], oxaliplatin (70 mg/m^2, weekly) [90] might be considered. For those intolerant to platinum-based chemotherapy, administration of fluoropyrimidine-based chemotherapy (e.g., capecitabine, fluorouracil, and tegafur) might also be considered [91]. The recommended concurrent regimens are listed in Table 10.

No significant difference was observed in efficacy between the weekly and the triweekly regimens; however, the former was superior in terms of adherence [87]. A head to head study comparing two chemotherapy regimens showed that the cisplatin weekly regimen appeared to be superior in terms of quality of life compared to the triweekly regimen. A similar large sample study showed no difference in survival outcomes, but higher rates of leukopenia and thrombocytopenia in the weekly regimen group [92].

Adjuvant chemotherapy

For stage III–IVa (except T3N0M0) NPC receiving only definitive CCRT, PF (cisplatin 80–100 mg/m^2, day 1 or 20 mg/m^2, daily; fluorouracil 1000 mg/m^2, continuous intravenous drip day 1–4 or 800 mg/m^2, continuous intravenous drip day 1–5) administered every 4 weeks for a total of 3 cycles should be offered [55, 86, 93]. For those with a contraindication to cisplatin, carboplatin (AUC 5) might be alternatively combined with fluorouracil [94]. For those who cannot tolerate platinum-based adjuvant chemotherapy, the use of non–platinum-based regimen remains experimental at this time and should not be offered routinely outside the context of a clinical trial. The completion rate of adjuvant chemotherapy is generally around 50%, and the relatively low completion rate is the main reason for no clear benefit of adjuvant chemotherapy versus concurrent chemoradiotherapy in previous studies. Plasma EBV DNA after radiotherapy was used to select the adjuvant chemotherapy population, and the subgroup patients who would possibly benefit from adjuvant chemotherapy was defined based on postradiotherapy risk stratification in the ongoing NRG-HN001 trial

Table 9 Induction regimens for NPC

Indication	Cycle	Regimen
III-IVa (except T3N0M0)	2–3 cycles (every 21–28 days)	GP (gemcitabine 1000 mg/m^2 day1, 8; cisplatin 80 mg/m^2 day1) [7]; TPF (docetaxel 60-75 mg/m^2, day1; cisplatin 60-75 mg/m^2, day1; fluorouracil 600-750 mg/m^2, daily, continuous intravenous drip day1-5) [80]; PF (cisplatin 80-100 mg/m^2, day1; fluorouracil 800-1000 mg/m^2, continuous intravenous drip day1-5) [82]; PX (cisplatin 100 mg/m^2 day1; capecitabine 2000 mg/m^2, day1-14) [83]; TP (docetaxel 75 mg/m^2, day1; cisplatin 75 mg/m^2, day1) [81]

Table 10 Concurrent regimens for NPC

Indication	Cycle	Regimen
T1-2N1M0 and III-IVA	≥ seven weekly regimens or ≥ three triweekly regimens	cisplatin (40 mg/m^2, weekly or 80-100 mg/m^2, triweekly) [87]; nedaplatin (100 mg/m^2, triweekly) [88]; carboplatin (AUC 5–6, triweekly) [89]; oxaliplatin (70 mg/m^2, weekly) [90]; fluoropyrimidines (e.g., capecitabine, fluorouracil, tegafur, etc.) [91]

(NCT02135042). Another phase III RCT (NCT0295811) exploring metronomic adjuvant capecitabine for locoregionally advanced NPC showed significantly higher 3-year failure free survival in the capecitabine group than in the standard therapy group [95]. The recommended adjuvant regimens are listed in Table 11.

T3N0M0

Patients with this stage of NPC are often excluded from large clinical trials that explore the induction or adjuvant chemotherapy; thus, data from clinical trials of this stage are currently lacking. In patients with T3N0M0, whether induction or adjuvant chemotherapy is added to CCRT should be considered holistically in combination with pre- and post-treatment status.

Key points: (1) NPC with T1N0M0 and T2N0M0 without adverse prognostic factors (large tumor volume, high EBV-DNA expression) do not require chemotherapy. (2) T1–2N1M0, as well as stage III–IVa locally advanced NPC, should be given platinum-based chemotherapy concurrent with radiotherapy. (3) Stage III–IVa (except T3N0M0) NPC, should receive 2–3 cycles of platinum-based induction chemotherapy before CCRT. (4) Stage III–IVa (except T3N0M0) NPC, which received only CCRT, should be followed by 3 cycles of adjuvant chemotherapy.

First-line chemotherapy for recurrent/metastatic NPC For patients with distant metastasis (TxNxM1, IVb), systemic treatment should be given priority, and local treatment (such as radiotherapy for primary and metastatic lesions) should be given after 4–6 cycles after [96]. GP alone or combined with immunotherapy represents the first-line treatment regimen for metastatic NPC [97–99]. If intolerable, PF or other regimens can be considered [100–102]. In past decades, PF has been the commonly recommended regimen for recurrent/metastatic NPC. However, it was recently found that GP was superior to PF to treat recurrent/metastatic NPC. Zhang et al. compared the efficacy and safety of the two treatments for recurrent/metastatic NPC, and as a result, the GP group achieved a higher proportion of objective response than the PF group (64% *vs.* 42%, $P<0.0001$) in addition to prolonged PFS and more tolerable toxicity [99]. Chemotherapy and chemotherapy plus Camrelizumab in patients with recurrent/metastatic NPC achieved an objective response rate of 64.1% and 90.9%, respectively. Chemotherapy combined with PD-1/PD-L1 immunotherapy improved the short-term outcome of recurrent/metastatic NPC [97–99]. The recommended first-line regimens were listed in Table 12.

Key points: (1) For recurrent/metastatic NPC, systemic treatment is the primary management, and the combination of chemotherapy and PD-1/PD-L1 immunotherapy is effective to improve the short-term outcome. (2) The GP regimen is recommended as the preferred regimen, rather than PF, for first-line treatment of recurrent/metastatic NPC.

Second- and further-line chemotherapy The optimal chemotherapy for patients with the first-line platinum-containing regimen failure is still a matter of debate, with

Table 11 Adjuvant regimens for NPC

Indication	Cycle	Regimen
III-IVa (except T3N0M0) receiving only concurrent chemoradiotherapy	3 cycles (every 21–28 days)	PF (cisplatin 80-100 mg/m^2, day1 or 20 mg/m^2, daily; fluorouracil 1000 mg/m^2, continuous intravenous drip day1-4 or 800 mg/m^2, continuous intravenous drip day1-5) [55, 86, 93]; carboplatin (AUC 5) + fluorouracil 1000 mg/m^2, continuous intravenous drip day1-4 or 800 mg/m2, continuous intravenous drip day1-5 [94]; non-platinum-based adjuvant or clinical trial; metronomic or regular adjuvant capecitabine [95]

Table 12 First-line regimens for NPC

Indication	Cycle	Regimen
recurrent/metastatic NPC	4–6 cycles (triweekly)	GP (gemcitabine 1000 mg/m^2 day1, 8; cisplatin 80 mg/m^2 day1) ± Immunotherapy (Toripalimab, Camrelizumab) [97–99]; PF (cisplatin 80-100 mg/m^2, day1; fluorouracil 800-1000 mg/m^2, continuous intravenous drip day1-5) [100]; TP (docetaxel 75 mg/m^2, day1; cisplatin 75 mg/m^2, day1) [101]; PX (cisplatin 100 mg/m^2 day1; capecitabine 2000 mg/m^2, day1-14) [102];

no standard salvage plan. Sensitive or crossover regimens should be selected based on previous drug usage and are usually selected for single-agent treatment. Studies have shown that capecitabine [103], docetaxel [104], gemcitabine [105], vinorelbine combined with gemcitabine [106], and irinotecan [107] have a certain limited efficacy as salvage treatment after the failure of platinum-containing regimens. A multicenter phase II trial (CAPTAIN) investigating the efficacy of Camrelizumab in patients who experienced failure of first- and second-line chemotherapy showed that the ORR was 28.2%, the median PFS was 3.7 months, and the median OS was 17.4 months [108]. Another phase II trial (POLARIS-02) from the Sun Yat-sen University Cancer Center showed that for patients ($n=190$) with recurrent or metastatic NPC who received Toripalimab monotherapy (51.6% as second-line treatment, 48.4% as third- or further-line treatment), their ORR was 20.5%, the median PFS was 1.9 months, and the median OS was 17.4 months [109]. Currently, there are no phase III trial results for anti-PD-1/PD-L1 antibodies in treating NPC after first-line platinum-containing regimen failure.

Key points: Limited options for salvage chemotherapy in NPC after first-line platinum-containing regimen failure are current available. Immunotherapy has shown some potential; however, further studies are required. Clinical trials are encouraged to explore novel regimens.

5.4.3 Targeted therapy and immunotherapy

Targeted therapy Targeted therapy is based on the specific conjunction of antibody/ligand and tumor cell target molecule to block the signaling pathway that plays a key role in tumor cell growth. Targeted therapy applicable to locally advanced or recurrent and/or metastatic NPC include anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (mAbs) and anti-angiogenesis drugs.

Anti-EGFR

In 2017, a study demonstrated that CCRT combined with nimotuzumab or cetuximab significantly improved the OS and DMFS compared with CCRT alone [43]. A retrospective study from Sun Yat-sen University Cancer Center in 2018 reported that induction chemotherapy combined with nimotuzumab or cetuximab prolonged OS and DFS in locoregionally advanced NPC compared with induction chemotherapy alone [110]. Sequential intensity-modulated radiotherapy with concurrent nimotuzumab after induction chemotherapy compared with concurrent chemoradiotherapy for locally advanced NPC showed similar PFS and OS between the two groups, and the long-term follow-up results are expected [111]. A single arm multicenter phase II trial of nimotuzumab in combination with the PF regimen for the treatment of post-radiation metastatic NPC showed an overall response rate (ORR) and disease control rate (DCR) of 71.4% and 85.7%, respectively, and median PFS and OS of 7.0 months and 16.3 months [112]. Anti-EGFR mAbs in combination with chemotherapy might be explored as a new treatment for recurrent metastatic NPC, which still needs to be validated in large sample trials.

Anti-angiogenesis drugs

Vascular endothelial growth factor (VEGF) and its receptor, VEGFR, are highly expressed in NPC, and are associated with intratumoral angiogenesis, and lymph node and distant metastasis. Antiangiogenic regimens such as bevacizumab, apatinib, sunitinib, and anlotinib in combination with concurrent chemoradiotherapy or chemo/radiotherapy for locally advanced or recurrent metastatic NPC have shown some efficacy, but still require further exploration. Multiple clinical trials of recombinant human endostatin have demonstrated a synergistic effect on NPC when combined with radiotherapy and chemotherapy, but only a slight improvement in ORR was observed when combined with a standard CCRT, and no survival benefit was observed; however, some trials also suggested the improvement of prognosis in recurrent metastatic NPC with tolerable adverse effects [45].

Immunotherapy Immunotherapy for NPC mainly refers to immune checkpoint inhibitors (ICIs) including programmed death receptor-1 (PD-1), programmed death receptor ligand 1 (PDL1), and cytotoxic T lymphocyte

associated antigen 4 (CTLA-4), represented by anti-PD-1 mAbs, including pembrolizumab, nivolumab, camrelizumab, toripalimab, sintilimab, tislelizumab, and penpulimab and the anti-CTLA-4 mAb, ipilimumab.

The JUPITER-02 and the CAPTAIN trials confirmed that treatment of recurrent metastatic NPC with a combination of Toripalimab or Camrelizumab plus the GP regimen significantly improved median PFS and median OS [107, 108]. Pathological type, baseline lactate dehydrogenase (LDH) level, baseline EBV, and changes in plasma EBV DNA copy number are suggested as predictors of prognosis for patients considering the use of ICIs. A phase II trial (NCT03097939) investigating the efficacy and safety of ipilimumab plus nivolumab in EBV-associated advanced NPC is awaited.

Key points: (1) For locally advanced NPC (III–IVa), the combination of anti-EGFR mAbs with definitive CCRT is recommended. (2) For stage III–IVa NPC unsuited to chemotherapy, concurrent radiotherapy with anti-EGFR mAbs is recommended. (3) For metastatic NPC, anti-PD-1 immunotherapy combined with GP chemotherapy is recommended. However, anti-EGFR mAbs combined with chemotherapy needs further exploration.

5.4.4 Surgery

Surgery is not the primary definitive treatment for NPC; however, its value becomes increasingly important in some cases, such as nasopharynx recurrence, cervical or retropharyngeal lymph node recurrence, residual NPC, and those intolerable to radiotherapy. Surgical approaches to the nasopharynx include open surgery (lateral, inferior, inferolateral, anterolateral, and anterior approaches) and endoscopic approaches (ablation and nasopharyngectomy). Highly invasive conventional open surgery has been replaced by endoscopic surgery. In addition, endoscopic nasopharyngectomy has become the mainstream mode because of its definitive and minimally invasive nature.

Salvage surgery for locoregionally recurrence For resectable locoregionally recurrent NPC, endoscopic nasopharyngectomy is preferred. Currently accepted indications for surgical resection of locoregionally NPC are: The tumor is located within 5 mm of the medial to the internal carotid artery, including the nasopharynx cavity, or invades the nasal septum or posterior nares, or mildly invades the parapharyngeal space, or is confined to the floor of the sphenoid sinus or the base of the pterygoid process. For recurrence of NPC confined to the above range, surgery performed better than re-radiotherapy and a multicenter phase III trial confirmed that resectable recurrent NPC had a significantly higher 3-year survival rate when treated with nasoendoscopic surgery compared with re-radiotherapy [113]. Another study also demonstrated that surgery was associated with lower costs and fewer long-term toxicities [114].

Salvage surgery for cervical nodal recurrence The surgical treatment of cervical lymph nodes recurrences includes radical neck dissection, modified radical neck dissection, selective neck dissection, and endoscopic neck dissection. The evaluation of the efficacy of surgical treatment for cervical lymph node recurrence focuses on whether dissection is complete. The major differences in the different surgical modalities are in the extent of dissection and the size of the trauma, with thorough dissection being more important than wide excision [115, 116].

Salvage surgery for retropharyngeal nodal recurrence Re-irradiation of the retropharynx for nodal failures is associated with significant radiation toxicities. Currently, minimally invasive salvage surgery is used for retropharyngeal lymph node failure, including transoral robotic retropharyngeal lymph node dissection and nasoendoscopic retropharyngeal lymphadenectomy via submandibular parapharyngeal approach [117, 118]. Both procedures have been reported in retrospective studies with better outcomes and fewer complications.

Surgery for post-radiation nasopharyngeal necrosis Post-radiation nasopharyngeal necrosis (PRNN) is a severe complication after radiotherapy in NPC, which can severely affect the quality of life and threaten the patient's life [119]. Repeated endoscopic debridement was reported as an effective traditional treatment of PRNN, with only a minority of these patients being cured, reflecting the possibility that the necrotic tissue could not be completely removed with or without efficient re-epithelialization of the nasopharyngeal defect [120]. A novel curative-intent endoscopic surgery comprising radical endoscopic necrectomy and reconstruction of the nasopharyngeal defect using the nasal septum and floor mucoperiosteum flap has been proven by other retrospective study [121].

Minimally invasive surgery A novel surgical procedure of endoscopic nasopharyngectomy + repairing nasopharyngeal mucosa with vascularized free flap was first proposed by Professor Chen, which is beneficial for relieving the limitation of nasopharyngeal stenosis on manipulation difficulties, achieving en bloc resection of the tumor and promoting rapid wound healing [122]. For patients with tumors adjacent to the

internal carotid artery, the advanced concept of "surgical target volume" was proposed. The resectable extent of recurrent nasopharyngeal carcinoma was clarified, and the principles of postoperative evaluation were formulated. This novel method incorporates the precision of radiation therapy, the radical treatment by open surgery, and the minimally invasive treatment by endoscopic ablation, such that the minimally invasive surgery of the nasopharynx basically achieves the maximum resection of the tumor and the maximum protection of normal tissues. Minimally invasive surgery in highly selected patients improves survival in recurrent NPC with fewer complications and costs compared with re-radiotherapy. Patients with retropharyngeal lymph node recurrence, transoral minimally invasive resection of retropharyngeal lymph nodes can be performed using Da Vinci robotic surgery in qualified hospitals to overcome the difficulties of deep location and adjacent blood vessels for retropharyngeal lymph node recurrence.

Surgery of radiation toxicity Long term toxicity of radiation (radiation-induced brain injury, paranasal inflammation, and choanal atresia) can be controlled by choosing the appropriate surgical approach and procedure, resulting in improved quality of life.

5.4.5 Supportive care

Nutrition therapy Nutritional support is given to those with an indication for nutrition therapy after timely and accurate assessment of the nutritional status of the patients, with ongoing reassessment and adjustment of the treatment regimen.

(1) Once malignancy is diagnosed, nutritional risk screening should be performed.
(2) The NRS 2002 [123]and PG-SGA [124] are currently the most commonly used screening scales.
(3) Screening should be performed weekly during hospitalization for patients with an NRS < 3, even without nutritional risk. For patients with NRS ≥ 3, an individualized nutrition plan should be developed based on the clinical situation to perform nutrition intervention.
(4) Patients with a PG-SGA score of 0 to 1 require no intervention, and follow-up and reassessment should go on during treatment; patients scoring 2–3 should receive nutritional education together with their families from dietitians, nurses, and physicians, and undergo pharmacological intervention depending on the presence of symptoms and laboratory results; patients scoring 4–8 should receive prompt intervention by dietitians, which might be combined with physicians and nurses depending on the degree of symptoms; those scoring 9 have an urgent need for symptomatic improvement and concurrent nutritional intervention.
(5) A comprehensive nutritional evaluation according to medical history, physical examination, and laboratory tests clarifies the cause and extent of malnutrition.
(6) Comprehensive nutritional risk screening and nutritional assessment should be performed in parallel with imaging efficacy evaluation of antitumor therapy to comprehensively assess antitumor benefit.

Traditional Chinese medicine Patients with NPC suffer from impaired immunity because of long-term tumor consumption, which, together with the related side effects, such as xerostomia, nausea, vomiting, decreased appetite, and poor natriuresis caused by the treatment, might be alleviated by traditional Chinese medicine (TCM) treatments to reduce the adverse effects of chemoradiotherapy and improve the quality of life. For patients of advanced age, poor physical fitness, and critical illness who cannot tolerate treatment, TCM can be used as an alternative adjuvant treatment.

Supportive/palliative care Supportive/palliative care aims at relieving symptoms, alleviating distress, improving quality of life, managing treatment-related adverse effects, and improving adherence. Patients should receive ongoing symptomatic screening, evaluation, and treatment by supportive/palliative care for symptoms related to the disease and treatment, such as pain, diplopia, facial anesthesia, hearing loss, nausea and vomiting, as well as psychological disorders such as insomnia, anxiety and depression. Intensive rehabilitation guidance and follow-up should also be provided, including nasal irrigation, mouth opening training, and neck muscle function exercises.

Basic principle

Supportive/palliative care should be holistically integrated into the treatment, with all patients participating as early as treatment is initiated and should be adjusted at the appropriate time or as clinically indicated, by the MDT, formed by oncologists, supportive / palliative care physicians, nurses, dietitians, social workers, pharmacists, mental health, and other specialties.

Specific managements

Pain

The chief complaint is the gold standard for pain assessment, and pain intensity must be assessed before analgesic treatment. Commonly used methods of pain assessment include the Numerical ratings scale (NRS). The evaluation includes pain etiology, characteristics, nature, aggravating or alleviating factors, impact of pain on daily life, efficacy of analgesia, and side effects, in addition to clarifying the presence or absence of pain attributed to a tumor emergency. The WHO Analgesic Ladder remains the most basic principle to follow, with opioids as the cornerstone of cancer pain treatment and the addition of glucocorticoids and anticonvulsants if necessary, while concern should be raised about the adverse effects of analgesics [125]. More than 80% of cancer-related pain can be relieved by pharmacological treatment, only a few require nonpharmacological means of analgesia, including surgery, radiotherapy, or other interventions, such that the analgesic effect should be dynamically assessed and interdisciplinary collaboration should be encouraged.

Nausea/vomiting

Management of chemotherapy-induced nausea/vomiting should be based on the emetic risk of the regimen, prior antiemetic experience, and the patient's own factors, with dynamic assessment. For nausea/vomiting potentially caused by radiotherapy, the choice of medication might be made with reference to chemotherapy-induced nausea/vomiting, along with strengthening of psychological distancing efforts. Other potential emetogenic factors should be considered, including vestibular dysfunction, brain metastases, electrolyte disorders, supportive care medications (including opioids), and psychophysiology (including anxiety, anticipatory nausea/vomiting). Lifestyle management helps to reduce nausea/vomiting, such as eating fewer or more meals, choosing a light diet, and avoiding food that is too cold or too hot.

Anorexia/cachexia

The cause and degree of weight loss should be assessed to manage possible causes (oral infections, psychological causes, pain, constipation, nausea/vomiting, or medication). An appropriate plan is made to give enteral or parenteral nutrition actively.

Psychotherapy Patients often experience fear, anxiety, depression, and other negative emotions, which will affect their physiological functions. Family members should implement psychological distancing to establish confidence in overcoming the disease, maintaining optimism, and creating a good mood for recovery.

Psychological distress is an unpleasant experience triggered by multiple factors, in which psychological (including cognitive, behavioral, and emotional factors), social, spiritual, and/or somatic factors might affect a patient's ability to cope with oncological and somatic symptoms, and compliance with treatment. Psychological distress includes depression, anxiety, panic, social isolation and existential crises. Psychological distress should be promptly identified, monitored, documented, and addressed at all stages of the disease and in all settings. An MDT should be formed according to clinical practice guidelines to assess and manage psychological distress.

Interventional therapy Interventional therapy, including radiofrequency ablation therapy, transcatheter arterial embolization (TAE), Transarterial chemoembolization (TACE), and transcatheter arterial infusion (TAI) might be used as a local treatment option for liver metastases in addition to surgical resection.

Interventional therapies are uniquely advantageous for NPC-related hemorrhage, including ruptured hemorrhage because of cervical great vessel involvement and post-radiation nasopharyngeal ulceration involving the internal carotid vessels. The bleeding location is first clarified by selective or superselective arteriography, followed appropriate embolic material for occlusive hemostasis. NPC-related hemorrhage is mostly caused by the rupture of large vessels in the neck, with an extremely aggressive blood volume that easily causes asphyxia and shock, thus timely and effective interventional hemostatic treatment is extremely important.

Key points: A holistically integrated MDT should be formed to rationally develop individualized treatment plans, appropriately utilize nutritional support, traditional Chinese medicine conditioning, and psychological support, to improve efficacy and quality of life.

5.4.6 Prevention and management of complications

Radiotherapy-related complications

Radiation-induced oral mucositis (RTOM)

(1) Non-medication

Avoid irritation of the oral mucosa by spicy food. Oral examination is routinely performed before radiotherapy, and oral hygiene is maintained during radiotherapy, such as using a soft toothbrush, cleaning the mouth with fluoride free toothpaste, flossing, and normal saline or alkaline (sodium bicarbonate) mouthwash. Lubricate the mouth with moisturizers or artificial saliva, and use water-soluble jelly or gums. Protective materials should be placed between the oral mucosa and metallic teeth to reduce friction [126, 127].

Low level laser therapy (LLLT) functions as a treatment for RTOM by regulating reactive oxygen species as well as proinflammatory cytokine production [128].

Oral ulcer protectants significantly reduced the incidence and severity of oral mucositis in chemoradiotherapy for locally advanced NPC, delaying the progression of oral mucositis, promoting oral mucosal healing, and reducing oral and throat pain, as confirmed by a domestic trial using scales evaluating oral mucositis, oral pain, and quality of life [129].

(2) Medication

Cytokines: A trial showed that prophylactic application of recombinant human epidermal growth factor (rh-EGF) delayed the development of radiation-induced mucositis and reduced grade 3 and 4 mucositis [130]. Another Korean multicenter randomized double-blind prospective trial also showed that topical rh-EGF administration alleviated the occurrence and extent of RTOM [131].

Mucosal protective agents: These include free radical scavengers, oral mucosal coatings, essential amino acids, and supersaturated calcium phosphates. In 2013, a systematic analysis of 30 publications dealing with buccal mucositis and amifostine showed that amifostine reduced the severity of buccal mucositis [132]. Tsujimot et al. found that L-glutamine (10 g/day) had a prophylactic effect against RTOM in patients with head and neck cancer, with incidences of grade 2 mucositis of 0 and 10% ($P=0.023$) and grade 4 of 0 and 25%, respectively, in the glutamine group versus placebo [133].

Nonsteroidal anti-inflammatory drugs (NSAIDs): A randomized, double-blind study of 135 head and neck cancers cases conducted by Epstein et al. found that benzydamine hydrochloride reduced the incidence of erythema and ulceration by approximately 30% ($P=0.037$) and consequently reduced the use of systemic analgesics ($P<0.05$) [134]. A clinical trial including 100 cases of head and neck cancer found that the incidence of RTOM in the placebo group was 26 times higher than that in the benzydamine hydrochloride mouthwash group [135]. Benzydamine has been recommended in Europe as a level I evidence-based recommendation for the prevention of RTOM from head and neck cancer.

TCM: Several studies on the prevention of RTOM with Chinese patent formulations have been published, including clove-based herbal [136], Shuanghua Baihe Tablets [137], and Kangfuxin Liquid [138]. A multicenter randomized, double-blind, prospective clinical trial of 240 patients with NPC showed that Shuanghua Baihe tablets significantly reduced the incidence of RTOM, delayed the onset of oral mucositis, and reduced the incidence of severe RTOM ($P<0.01$) [137]. Another randomized, parallel, multicenter clinical trial included 240 patients randomized to receive either Kangfuxin Liquid or compound borax gargle to prevent RTOM. The incidence, severity, and mouth cavity pain of RTOM were significantly lower in the Kangfuxin Liquid group ($P<0.01$) [138].

Analgesics: In RTOM with mild pain, a mouthwash, such as lidocaine or morphine, can be used. Studies have confirmed that 2% morphine-containing rinses can effectively control mucositis-related pain and reduce systemic morphine requirements. Systemic administration of strong opioids, such as morphine or fentanyl, is recommended for severe pain.

Antimicrobials: Antimicrobials for RTOM coinfection. Before treatment, buccal mucosal swabs were sent for bacterial and fungal culture and susceptibility testing to guide antimicrobial use.

Glucocorticoids: Topical use of glucocorticoids reduces edema, inhibits the inflammatory response, and relieves symptoms; however, long-term use has the risk of increasing oral fungal infection.

Radiation-induced salivary gland injury

Symptoms usually appear 1 to 3 days after the start of radiotherapy and often present as swelling and pain in the parotid region on one or both sides, and in severe cases, the skin appears reddish and warm. Radiation-induced salivary gland injury is generally self-healing without special treatment. If fever is present, secondary infection is suspected, and special oral care should be given, together with anti-infection and analgesic therapy, with suspension of radiotherapy if necessary [139].

Radiation-induced xerostomia

Radiation-induced salivary gland injury is a direct cause of xerostomia. NPC develops symptoms of significant xerostomia in up to 30% of cases after radiation and management should focus on prevention, such as using intensity-modulated conformal radiotherapy and adaptive radiotherapy to improve the precision of radiation, while TCM has some therapeutic effect on it [140].

Radiation-induced otitis media

Radiation-induced otitis media usually presents with tinnitus, hearing loss, and is a common toxicity during radiotherapy, which generally does not need to be treated. In case of eardrum perforation or fluid loss, irrigation and anti-infection treatment are indicated [141].

Radiation-induced brain injury

Radiation-induced brain injury has a long latency and occurs mostly in the bilateral temporal lobes. Clinical manifestations vary from asymptomatic to death, and there is currently no specific treatment, thus we should focus on prevention. For stage T4 NPC with severe intracranial invasion, induction chemotherapy is recommended to minimize the tumor volume, with the aim of reducing the dose and volume to the temporal lobe and brainstem as much as possible, eventually preventing radiation-induced brain injury [141]. The traditional treatment of radiation induced brain injury is to administer large doses of vitamins, vasodilators, neurotrophic agents, and glucocorticoids. Bevacizumab has been suggested in prospective clinical studies to ameliorate edema resulting from radiation-induced brain injury, with a higher treatment response rate than conventional hormone therapy, with nerve growth factor combined with intermittent glucocorticoids being able to repair 20% of temporal lobe injuries [142].

Key points: (1) Nonpharmacological management of RTOM includes prophylaxis before and during radiotherapy, oral care, LLLT, and oral ulcer protectants. (2) The pharmacological management of RTOM includes mucosal protective agents, benzydamine hydrochloride mouthwash, Shuanghua Baihe tablets, and Kangfuxin Liquid. (3) Severe pain due to RTOM should be managed systemically with opioids, such as morphine or fentanyl. (4) Antimicrobials and glucocorticoids should be used in RTOM co-infection. (5) Improving the precision of radiotherapy and organ protection of salivary glands remain the primary method of preventing of radiation-induced xerostomia. (6) Radiation-induced otitis media is a common toxicity during radiotherapy, and severe symptoms require specialist otolaryngology management. (7) Radiation-induced brain injury has a long latency and occurs mostly in the bilateral temporal lobes, which currently has no specific treatment, thus we should focus on prevention.

Chemotherapy-related complications

Hematological toxicity

Myelosuppression is the most common hematological toxicity of chemotherapy. The severity and duration correlates with the type of chemotherapy, dose, combination drugs, as well as patients' own factors, such as: age, liver and kidney function, immune status, surgical history, previous chemoradiotherapy and so on. Myelosuppression is classified into four grades according to the Common Terminology Criteria for Adverse Events (CTCAE-Version 5.0).

Prevention of myelosuppression:

(1) Febrile neutropenia (FN). The prophylactic use of granulocyte colony-stimulating factor (G-CSF) is indicated in patients with agranulocytosis with > 20% risk of developing FN and might be used after the risk is evaluable in 10% to 20% of cases. If FN or a dose limiting neutropenia event occurs with the previous cycle of chemotherapy, the next cycle requires prophylactic G-CSF, warranting a full course of standard chemotherapy
(2) For patients with previous grade III–IV thrombocytopenia, who had a tendency of declining platelets (PLT) after the end of this cycle of chemotherapy and had high risk factors for bleeding, prophylactic administration of thrombopoietic agents starting at 6–24 h after chemotherapy is recommended. For patients without high-risk factors for bleeding, initiation of a pro-thrombopoietic agent is recommended at PLT < 75, until the myelosuppressive effects of chemotherapy disappear and PLT ≥ 100. Recombinant human interleukin-11 (rhIL-11) is recommended at a dose of 50 μg/kg by subcutaneous injection once daily, but should not be used until 2 days before the start of chemotherapy and during chemotherapy.
(3) For mild anemia (hemoglobin 100–110 g/L), an iron test is required, and the presence or absence of iron deficiency is judged as transferrin saturation (TSAT) < 20% or serum ferritin (SF) < 100 ng/ml, followed by iron supplementation (i.v., 1000 mg). Oral iron is reserved for patients with

ferritin < 30 ng/ml and no inflammation [C-reactive protein < 5 mg/L]. Vitamin B12 or folic acid supplementation is also indicated if considered deficient.

Treatment of myelosuppression:

(1) G-CSF may be used prophylactically in patients at higher risk for FN. Whereas prophylaxis is not recommended for low to intermediate risk patients. G-CSF can be given again after the occurrence of neutropenia.
(2) Subcutaneous erythropoietin (EPO) with concomitant iron supplementation is recommended for hemoglobin < 100 g/l. Red blood cell transfusion, along with iron supplementation, oral medications and nutritional support supplementation is recommended for hemoglobin < 80 g/ll. When hemoglobin is 80–100 g/l, vitamin B12 or folic acid supplementation is also indicated, if vitamin B12 or folic acid deficiency is considered. Iron supplementation is administered intravenously in the presence of absolute iron deficiency (SF < 100 ng/ml and TSAT < 20%), and, if hemoglobin remained < 100 g/L after iron supplementation, the addition of an erythropoiesis stimulating agent (ESA) (epoetin alfa or darbepoetin alfa, approximately 450 IU/week/kg). ESA in combination with iron is administered if there is functional iron deficiency (TSAT < 20% but normal SF). If iron deficiency is not present (both TSAT and SF are normal), ESA only is used, and if iron deficiency develops during follow-up, iron is added. Hemoglobin < 80 g/l indicates a state of severe anemia requiring rapid recovery by transfusion.
(3) Treatment of chemotherapy-induced thrombocytopenia (CIT) consists of platelet transfusion and administration of pro-platelet growth factors such as rhIL-11, recombinant human thrombopoietin (rhTPO), and the TPO receptor agonists romiplostim and eltrombopag. When CIT occurs with bleeding symptoms, platelet transfusion or concomitant administration of rhTPO is indicated. CIT without bleeding symptoms and with platelets $\leq 10 \times 10^9$/l requires platelet transfusion or concomitant rhTPO administration. Platelet transfusion is not recommended when platelets are $> 10 \times 10^9$/l.

Non-hematological toxicity

(1) Gastrointestinal reactions

Chemotherapy induced nausea and vomiting (CINV) is a common, often predictable, and preventable adverse effect of chemotherapy, and is divided into acute, delayed, and anticipatory states. For acute CINV, antiemetic agents such as NK-1 receptor blockers, metoclopramide, 5-HT3 receptor antagonists, and dexamethasone should be used prophylactically in combination before chemotherapy. For delayed CINV, no effective management is recommended currently, and combination therapy with 1–2 antiemetics is indicated if it occurs. Anxiolytic or antidepressant medication is recommended for anticipatory CINV [143].

For patients treated with highly emetogenic risk chemotherapy regimens, a triple regimen of 5-HT3 receptor antagonist + NK-1 receptor antagonist + dexamethasone, or a quadruplet regimen of 5-HT3 receptor antagonist + NK-1 receptor antagonist + dexamethasone + olanzapine is recommended. Antiemetic therapy with a 5-HT3 receptor antagonist + NK-1 receptor antagonist (for carboplatin containing chemotherapy) or 5-HT3 receptor antagonist + dexamethasone (for carboplatin free chemotherapy) is recommended for patients treated with moderate emetogenic risk chemotherapy regimens.

For patients with diarrhea more than five times a day or bloody diarrhea, chemotherapy should be stopped in parallel with symptomatic treatment. Diarrhea ceased after cessation of chemotherapy or with antidiarrheal medications in some patients. Patients with more frequent diarrhea or the elderly and weak need to supplement adequate energy and maintain water electrolyte balance, especially to prevent the occurrence of hypokalemia. Those with a positive stool culture should be treated with antibiotics, mainly for *Escherichia coli* infections.

(2) Oral mucositis

Chemotherapy causes or aggravates pre-existing oral mucositis, except for prevention and treatment according to RTOM, more attention should be paid to oral hygiene during chemotherapy, brushing teeth with a soft toothbrush, selecting non-irritating scalers, gargling with compound boric acid solution, Kangfuxin Liquid, 3% sodium bicarbonate or 3% dioxygen 30 min after eating, avoiding excessive heat, cooling, spicy and rough irritating food. TCM conditioning also reduces the occurrence and severity of oral mucositis associated with chemoradiotherapy.

(3) Alopecia

In patients with alopecia, psychological grooming should be practiced, with advice to cut their hair short or wear a wig, and inform them that hair will regrow after chemotherapy has been completed. Hair lotions with a moderate nature and protein predominance are recommended. Strong irritant shampoos, electro hair blowing, hair coilers, hair gels, hair dye, and excessive hair brushing should be avoided, tourniquets and ice caps are available before chemotherapy.

(4) Anaphylaxis

Drug allergy occurrence should be minimized by effective prophylactic anti-allergic therapy. If drug-related anaphylaxis occurs, the severity of the anaphylaxis should be fully assessed and effective treatment measures instituted. The continuation of chemotherapy under close monitoring might be considered after local urticaria has improved with close monitoring and anti-allergic therapy. If systemic anaphylaxis occurs, chemotherapy should be stopped immediately and a histamine 1 (H-1) and H-2 receptor antagonist administered in combination with glucocorticoids, vasopressors, or bronchodilators, as appropriate, depending on the condition.

Toxicity during concurrent chemoradiotherapy

During CCRT, the associated hematological and non-hematological toxicities were greater than during radiotherapy or chemotherapy alone. Among them, the occurrence of oral mucositis and esophagitis was significantly aggravated by the increase in radiotherapy dose and chemotherapy course. Oral mucositis and esophagitis should be effectively prevented and treated in NPC patients receiving CCRT, referring to the prevention and treatment of RTOM section.

For oral mucositis or esophagitis, grade I–II patients can continue the current chemoradiotherapy regimen; For grade III patients, prolonging the interval or adjusting the dosage and regimen of drugs; Chemotherapy should be withheld or suspended for grade IV patients.

Toxicity and drug reduction

Adjusting the dosage of drugs and the interval between their administration according to chemotherapy-related toxicities allow patients to receive an adequate course and amount of chemotherapy with greater benefits. The basic principle of drug reduction is that chemotherapy drugs should not be reduced unless necessary. In response to chemotherapy-induced adverse effects, prolonging the interval between chemotherapy cycles and changing the way chemotherapy drugs are administered should be considered first. Dose titration where appropriate is based on the grading of adverse effects of chemotherapy. Those over 70 years of age or with poor general physical fitness should reduce the dosage as appropriate. In cases of severe liver and kidney function and myocardial injury, chemotherapy should be stopped [144].

Titration of dose reduction according to the grading of adverse effects of chemotherapy is recommended, depending on the patient's grade of adverse effects after chemotherapy, either by extending the interval between chemotherapy administrations (e.g., extending the interval after the three-week regimen until day 28) or by reducing the dose by 10%, 25%, 50%, or 100% based on the standard dose.

Titration step: First, calculate the standard dose or empirically determine the dosing based on the currently employed body surface area. Second, appropriately adjust the drug dose in combination with the patient's risk factors that can affect drug metabolism or drug clearance, such as liver and kidney function. Finally, based on the drug dose effect determined in the second step of the patient's individual post-treatment situation, adverse effects are weighed, and the post-treatment dose is determined. The dose is adjusted in real time so that sufficient chemotherapy under the premise of tolerable toxicity is guaranteed.

Key points: (1) An adequate assessment of patient tolerance (physical fitness, age, cardiopulmonary function, laboratory tests) should be carried out before chemotherapy. (2) Prevention and treatment of chemotherapy-related toxicity are important, and toxicity of grade III and above seen in the previous chemotherapy should be fully considered, and the next chemotherapy regimen, dosage, and interval should be reconsidered if necessary, and necessary preventive treatment should administered. (3) CCRT increases toxicities and their prevention and management should be enhanced. (4) The impact of chemoradiotherapy-related toxicity on dose titration of the next cycle of chemotherapeutic agents varies due to toxicity (hematological/non-hematological), recovery of the patient, and the stage of treatment being administered.

Targeted therapy-related complications

Cutaneous toxicity

Cutaneous toxicities rank highest among EGFR targeted therapy-related toxicities. Inhibition of EGFR affects the

proliferation, differentiation, migration, and adhesion of keratinocytes in the skin, leading to the formation of skin eruptions, including acneiform eruptions, pruritus, dry skin, skin fissures, hyperpigmentation, paronychia, mucositis, hair changes, and photosensitivity [145]. Preventive measures are as follows: before administering EGFR targeted therapy, patients and their families should be well advised, including that the rash resulting from EGFR targeted therapy is noninfectious and is indistinguishable from common acne, for which some therapeutic agents lack efficacy. During targeted therapy, patients should be instructed to take proper preventive measures, such as eating a healthy diet, eating more fresh vegetables and fruit, paying attention to sun protection, and recommending broad-spectrum sunscreen with a sun protection factor (SPF) ≥ 30. Besides, it is necessary to keep the skin clean and moist, apply moisturizing cream properly after warm bathing, wear loose and breathable shoe stockings during treatment, wash the body and feet with warm water and apply moisturizing cream to treat primary diseases, such as tinea pedis [146].

(1) Acneiform eruptions

Cutaneous adverse effects, most commonly acneiform eruption, occur with EGFR targeted medications and limit their tolerability. Acneiform eruption mostly appears at 1–2 weeks after administration and gradually subsides after peaking at about 14 days. It mostly occurs in the sebaceous rich areas of the head and face, anterior chest, and upper back. Acneiform eruption resulting from EGFR targeted agents is distinct from acne vulgaris, presenting as monomorphic, and rarely showing comedones, with mainly papulopustular, and may be accompanied by pruritus. Symptoms might be exacerbated by sun exposure, concurrent radiotherapy, and inadequate skin moisturization. Preventive measures include sun protection, using broad-spectrum sunscreens with a SPF ≥ 30, and appropriate application of moisturizing creams to keep the skin clean and moist. Mild symptoms do not require specific treatment and do not affect treatment, but crushing the rash by the hands should be avoided. Grade 1–2 rash during nimotuzumab administration should be slowed down by 50% when topical hydrocortisone ointment or erythromycin ointment is administered, with evaluation after 2 weeks. If it is still not in remission, or if a grade 3–4 rash occurs, Loratadine Tablets in addition to the above measures might be added. A shock dose of prednisolone might be administered with a 25% reduction in the nimotuzumab dose if necessary. For coinfections, use appropriate antibiotics.

(2) Xerosis cutis and pruritus cutis

Patients treated with EGFR targeted therapies can present with dry, desquamated, and even fissured skin, which causes pain or even infection, and some can have skin itching. Warm bathing, sun protection, keeping moist with creams, instead of scratching, facilitate recovery. Anti-allergic drugs (diphenhydramine, loratadine, etc.) can be selected when the effect of daily care is poor, and gabapentin, pregabalin, and other drugs can be added in severe cases.

(3) Paronychia

Often occurring at 4–8 weeks after drug administration, starting with redness and pain on the skin around the nail, followed by progressive infection, ulceration, and purulent granulation tissue on both sides of the paronychial sulcus, leading to pain and then affecting activity. Precautions include: loose shoes, clean skin, and avoidance of nail injuries. Antibiotics, glucocorticoids, antifungal drugs, and iodine tincture might also be added, if necessary.

Gastrointestinal toxicity

The possibility of diarrhea caused by EGFR targeted therapy should be considered in patients who do not have diarrhea before treatment but present after treatment, or who have diarrhea before EGFR targeted therapy that is significantly aggravated after treatment [147]. Preventive and therapeutic measures include: obtaining stool information for 6 weeks before treatment to better assess the condition leading to diarrhea with EGFR targeted therapy; concomitant medications and other clinical conditions before treatment are obtained to allow assessment of the potential effects of the medications on the digestive system. During EGFR targeted therapy, a low-fat, low-fiber diet should be recommended, with avoidance of caffeine, alcohol, dairy products, fat, fiber, orange juice, grape juice, and spicy food, and eat fewer meals with larger servings; No laxatives should be taken without relevant medical advice. For mild or moderate diarrhea, targeted therapy can be continued, but with the use of mucosal protective drugs such as montmorillonite, antidiarrheal drugs such as loperamide, and antimicrobials and microecological agents. For severe diarrhea leading to dehydration or that tends to worsen, targeted therapy should be suspended. In the case of grade 3–4 nausea and vomiting caused by nimotuzumab, which in not resolved after symptomatic management, nimotuzumab should be discontinued.

Hemorrhage

Hemorrhage is commonly seen in patients using VEGF/VEGFR inhibitors [148]. On the one hand, VEGF blocking leads to downregulation of nitric oxide (NO) levels, which affects platelet activation [149]. On the other hand, inhibition of the VEGF pathway affects endothelial cell survival and proliferation [150], both leading to impaired vascular integrity and then triggering hemorrhage. The potential risk should be evaluated before treatment to identify high-risk populations such as those with long-term or high-dose use of antirheumatic/anti-inflammatory drugs or anticoagulant therapy, those with a history of arteriosclerosis or peptic ulcers, those with signs of bleeding in the mass, those with severe cardiovascular disease (e.g., coronary heart disease or congestive heart failure), and those who have developed pulmonary hemorrhage and hemoptysis (> 3 ml of fresh red blood) within 3 months. Antiangiogenic therapy should not be initiated for at least 28 days after surgery [151].

Bleeding symptoms and signs should be closely monitored during treatment, and treatment should be interrupted once intracranial hemorrhage occurs. Different treatments should be given according to the grading after bleeding events occurs. No adjustment of antiangiogenic dosage is needed for Grade 1, besides smeared or orally administrated with Sanqi Powder or Yunnan Baiyao [152]. For Grade 2, antiangiogenic drug therapy needs to be suspended and continuation only be considered after effective hemostasis. For grade ≥ 3, antiangiogenic drugs should be permanently discontinued.

Hypertension

Hypertension is commonly seen in patients using VEGF/VEGFR inhibitors [149]. VEGF blocking leads to downregulation of NO levels, which further resulted in a failure of vessel dilation and increased peripheral resistance. In addition, lower NO levels also reduce renal excretion, which in turn leads to water and sodium retention. Thus, ambulatory monitoring of blood pressure is required. If hypertension occurs, or blood pressure values are markedly elevated from baseline, antihypertensive medication is recommended to achieve good blood pressure control. The goal for low-risk patients is 140/90 mmHg and for high-risk should be 130/80 mmHg. Recommended drugs include angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blocker (ARB), β Receptor blockers, and calcium channel blockers. If more than moderate hypertension develops (above 160/100 mmHg) and cannot be controlled by antihypertensive agents, antiangiogenic therapy should be suspended and antihypertensive therapy continued until the blood pressure returns to control levels. If hypertension remains uncontrolled or presents with hypertensive crisis or hypertensive encephalopathy, permanent discontinuation is indicated.

Immunotherapy-related complications

Prevention

Patients and their families should be educated about pre -, mid -, and post-treatment-related adverse effects that might occur and should be aware of their history and family history about autoimmune diseases. Physicians must be familiar with the characteristics and risk factors of immune related adverse events (irAEs), which can occur at any time and are recommended to be monitored from the start of immunotherapy until 1 year after discontinuation of therapy. Early recognition and management can reduce the duration and severity of irAEs. Although studies have shown that treatment of irAEs with glucocorticoids does not reduce the efficacy of immunotherapy, prophylactic use of glucocorticoids is still not recommended because of their immunosuppressive effects [153].

Management

Medical history, including previous autoimmune diseases, infectious diseases, and organ specific diseases, should be recorded in detail before treatment, and a baseline assessment of bowel function (e.g., peristaltic capacity, constipation) should be performed, along with a well-established physical examination and laboratory and imaging evaluation as baseline references. When new symptoms occur or original symptoms worsen after medication, they might be caused by disease progression, incidental events, or the occurrence of irAEs. Patients should be judged based on their specific history, symptoms, or concomitant diseases, and compared with baseline values, to rule out the possibility of disease progression or irAEs [153, 154].

The overall management of irAEs is guided by the grading of adverse events. Generally, patients with grade I toxicities, except for neurological and hematological toxicities, may continue treatment under close monitoring. In patients with grade II toxicities, except for only cutaneous or endocrine toxicities, immunotherapy should be suspended until symptoms and/or laboratory tests return to grade I or less and glucocorticoids can be administered (initial dose: prednisone 0.5–1 mg/kg/day or equivalent doses of other hormones). Grade III, treatment should be discontinued, and high-dose glucocorticoids (prednisone 1–2 mg/kg/day, or methylprednisolone 1–2 mg/kg/day) should be

given immediately, with glucocorticoid reductions lasting more than 4 to 6 weeks. If glucocorticoid treatment fails to relieve symptoms for 3 to 5 days, other immunosuppressive agents under the guidance of a specialist should be considered. When symptoms and/or laboratory tests return to grade I or less, treatment can be resumed but with caution, especially in those who experience adverse events early in treatment. For patients with grade IV toxicities, except endocrine adverse events that have been controlled with hormone replacement therapy, permanent discontinuation of therapy and institution of systemic hormone therapy with intravenous methylprednisolone at 1 to 2 mg/kg/day for 3 days is generally recommended, with tapering to approximately 6 weeks if symptoms diminish. In those who do not achieve remission of symptoms for 3 to 5 days with glucocorticoid therapy, other immunosuppressive agents, such as infliximab, might be considered, under the guidance of a specialist [155–157].

Management of common complications is as follows:

(1) Cutaneous toxicity

Cutaneous toxicities are the most common and are mostly maculopapular/rash and pruritus [158]. Other cutaneous manifestations including dermatomyositis, eosinophilia with systemic symptoms, granulomas, lichenoid, panniculitis like, and lupus like reactions are uncommon. Reactive cutaneous capillary endothelial proliferation (RCCEP) was frequent (77%) in the Camrelizumab arms and pathologically confirmed to be a benign capillary proliferative lesion. Skin toxicity was more common in patients receiving anti-CTLA-4 and anti-PD-1 [97]. Some studies argue that cutaneous irAEs are predictive of PD-1 inhibitor treatment efficacy. It usually occurs early in treatment, but might also appear days, weeks or months after treatment. Most cutaneous toxicity courses are short-lasting and might be managed with appropriate intervention without compromising immunotherapy. Prednisone is used therapeutically until symptoms improved to a toxicity grade of ≤ 1 and tapered over 4 to 6 weeks. Pneumocystis pneumonia should be prevented with antibiotics in patients who have used more than 20 mg prednisolone or equivalent for more than 4 weeks. Long term glucocorticoid users require calcium and vitamin D supplementation, but also proton pump inhibitors to prevent gastrointestinal bleeding.

(2) Gastrointestinal (GI) toxicity

The median time to onset of GI toxicity with PD-1/PD-L1 inhibitors is 3 months after administration, and combining CTLA-4 inhibitors not only elevates the risk, but also might lead to earlier onset. Sigmoidoscopy or colonoscopy is recommended in cases of severe diarrhea or diarrhea of grade 2 with higher duration. Grade 1 toxicities may continue immunotherapy with oral iron supplementation and antidiarrheal medications if necessary. Grade 2 toxicities lead to suspended immunotherapy and use oral prednisone, 1 mg/kg/day. Grade 3 toxicities also necessitate suspension of immunotherapy. Grade 4 toxicities require permanent discontinuation of ICIs with systemic methylprednisolone 2 mg/kg/day, if no improvement by 48 h, continuation of hormone therapy concomitant with infliximab, or if resistant, consider vedolizumab.

(3) Endocrine toxicity

Thyrotoxicity is the most common irAEs of the endocrine system, mainly characterized by hypothyroidism, hyperthyroidism, and thyroiditis, usually associated with anti-PD-1 inhibitors, rarely occurring above grade 3, and rarely causing lethal thyroid crisis through prompt examination and hormone replacement therapy [159]. Although adverse events such as primary hypoadrenalism and hypophysitis are rare, 20% to 35% of them may be grade 3 or higher. Endocrine toxicity appears later compared with other systemic toxicities, and PD-1 inhibitor monotherapy-related endocrine toxicity usually occurs around weeks 10 to 24; however, endocrine toxicity caused by combination therapy with ICIs is significantly advanced, to about 12 weeks. A previous family history of hyperthyroidism, excessive or insufficient iodine intake, or metabolic diseases are risk factors for the development of hyperthyroidism. Patients who present with hyperthyroidism might continue immune checkpoint inhibitors. A previous history of thyroid surgery is a risk factor for the development of hypothyroidism. For those with hypothyroidism, immune checkpoint inhibitors might also be continued, and for grade ≥ 2 toxicity, patients should be started on levothyroxine replacement after ruling out adrenal insufficiency.

(4) Respiratory toxicity

Compared with other irAEs, pneumonitis occurs at a median time of around 2.8 months, but with an earlier onset in those on combination therapy. Patients receiving PD-1 inhibitors are more likely to develop immune-related pneumonitis than those receiving CTLA-4 inhibitors, and are often life-threatening [150–162]. The clinical manifestations of immune-related pneumonitis are fever,

cough, chest pain, and dyspnea, and in severe cases, respiratory failure, with variable imaging findings, which can be cryptogenic organizing pneumonitis, hypersensitivity pneumonitis, acute interstitial pneumonitis, nodular reaction, and ground glass pneumonitis. Among all pneumonia cases, 72% were grade 1–2. Unlike self-limiting immune responses, such as thyroiditis and hepatitis, a large proportion of immune-related pneumonitis require glucocorticoid or immunosuppressant therapy. In patients with grade 1 toxicity, chest CT and lung function should be reviewed 3 to 4 weeks later, and if symptoms progress, ICIs should be suspended. Patients with grade 2 toxicities required discontinuation of ICIs until resolution to grade 1 and below, along with intravenous methylprednisolone, 1 to 2 mg/kg/day for 48 to 72 h, and tapering at 5 to 10 mg per week over 4 to 6 weeks if symptoms improved. If symptoms do not improve, treatment should be enhanced with reference to grade 3 or 4 toxicities. If infection cannot be completely ruled out, empirical anti-infection therapy should be combined. For patients with grade 3–4 toxicities, immunotherapy should be permanently discontinued, and patients should be treated with intravenous methylprednisolone 2 mg/kg/day with pulmonary ventilation as appropriate. After 48 h of glucocorticoid treatment, if symptoms improve, continue treatment to grade I and below, then taper over 4–6 weeks. In addition, infliximab, mycophenolate mofetil, or intravenous immunoglobulins might be considered for patients without significant improvement after glucocorticoid treatment, with empiric anti-infection therapy for those in whom infection cannot be completely excluded. Prophylaxis for pneumocystis pneumonia should be considered for those on prednisone greater than 20 mg or equivalent for four weeks and longer. Long term glucocorticoid users require calcium and vitamin supplementation, but also proton pump inhibitor use to prevent gastrointestinal reactions. Tuberculosis should be excluded before treatment with TNF-α inhibitors.

Traditional Chinese medicine Basic treatment is based on the strengthening the body (Fuzheng) and the rehabilitation principle. Avoidance of spicy food, tobacco, and alcohol is recommended, as is the consumption of small but frequent meals and the adjustment of emotions toward happiness. If conditions permit, participation in gentle activities such Tai Chi, yoga, and Wu Qin Xi are encouraged so that qi can be guided and adjusted. Acupuncture treatment at the following acupoints: Xiaguan, Renying, Jiache, and Zusanli, is beneficial to restore the difficulty in mouth opening [163]. Since TCM holds that radiation belongs to "hot heat toxic", Yuwu Decoction and Yintiao Mabu San are also beneficial for alleviating the radiation mucosal response. Myosuppression after chemoradiotherapy can be treated with drugs that affect Qi, represented by Bazhen Decoction [164].

6 Follow-up and surveillance

6.1 General goal

The main purpose for post-treatment follow-up and surveillance is to detect metastases or recurrences that are amenable to potential radical cure, to detect tumor progression or a second primary tumor as early as possible, and to intervene in a timely manner to improve overall survival and promote functional rehabilitation [25, 165]. There is currently no evidence to support which follow-up and surveillance strategy is optimal. Individualized protocols should be made to ensure timely detection of tumor recurrence events, without blindly increasing the frequency of follow-up and examination items.

Guidance on health lifestyles for NPC survivors: (1) The irradiated skin is not exposed to sun exposure or frostbite. Nasopharyngeal irrigation should be intensified to avoid infected necrosis during and after radiotherapy. Strengthening mouth opening training avoids late emergence of mouth opening limitation. Strengthening neck muscle function exercises to avoid fibrotic stiffness of the neck. (2) Pay attention to a healthy diet, encourage eating small but frequent meals, monitor weight regularly, refer to a dietitian or nutrition department for individualized counselling, and focus on positively managing medical and/or psychosocial factors causing weight loss. (3) Adopt a healthy lifestyle and engage in physical activity appropriately. (4) Smoking cessation and alcohol cessation.

6.2 Follow-up

6.2.1 Frequency

Follow-up should comprise at least the first 2 years after the end of treatment, with at least 1 follow-up visit every 3 months. Patients were followed for 3 to 5 years at least every 6 months. After 5 years, patients were followed up at least annually [25].

6.2.2 Follow-up evaluation items

The following examinations should be performed: EBV-DNA, thyroid function, pituitary function, electronic nasopharyngoscopy, enhancement MRI of the nasopharynx and neck, chest X-ray or CT scan, whole-body bone scan, abdominal ultrasound, and, if available, PET/CT [25].

The following items should to be documented: (1) Tumor, including time to regression, residual sites, and treatments; (2) Recurrence, including site, time, examination, management, and outcome; (3) metastasis,

including site, time, examination, management, and outcome; (4) Complications, including radiation-induced brain/spinal cord injury, radiation ear injury, osteonecrosis, mucocutaneous injury, cervical fibrosis, difficulty in mouth opening, secondary tumors; (5) Survival, including the cause and time of death; and (6) Other important clinical manifestations.

6.2.3 Management

Regular follow-up visits enable timely detection of recurrent metastatic lesions, which leads to targeted early intervention and management to improve efficacy. Recurrence and metastasis need to be treated aggressively and promptly according to the principle of advanced tumor treatment.

(1) Radiation-related caries

The mouth and all salivary glands are damaged by irradiation, which leads to reduced salivary secretion as well as an altered oral microenvironment in affected individuals, which can easily induce dental caries [166, 167]. Therefore, tooth extraction or implant placement should be avoided until 2–3 years after radiotherapy because of the susceptibility to osteonecrosis of the mandible. Before radiotherapy, all patients should undergo oral evaluation and extraction of pre- or probable caries at least 2 weeks before radiotherapy. Tooth extraction within 2–-3 years of radiotherapy should be assessed by a joint of radiology and stomatology team.

(2) Radiation-induced otitis media

Most of structures of the ear are located within the radiation field at the time of radiotherapy, which can cause symptoms such as hearing loss and, especially, otitis media, making it a common complication of radiotherapy for NPC. Colds should be prevented, periauricular cleanliness should be maintained, and visits made to specialists if necessary.

(3) Radiation-induced brain injury

For tumors with a large volume or with intracranial involvement before treatment, the probability of brain injury after radiotherapy is high and can occur as early as 2 to 3 years after radiotherapy [141]. Patients with severe radiation-induced brain injury usually have obvious symptoms, such as headache with nausea and vomiting, and even limb movement disorders, and the larger range of brain injury may require surgical treatment. Regular follow-up after NPC radiotherapy is recommended, which can effectively detect early radiation-induced brain injury and provide opportunities for active intervention.

(4) Facial numbness

Facial numbness is one of the common symptoms of NPC with damage to the cranial nerves, mainly the trigeminal nerve, and about 20% can present with facial numbness. In some patients, after tumor regression, the function of trigeminal nerve with short-term compression can recover, and facial anesthesia can be significantly reduced or eliminated. However, some patients suffer irreversible damage because of long-term compression or invasion of the trigeminal nerve, and the symptoms of anesthesia persist after the end of treatment.

(5) Diplopia and other ocular symptoms

When the tumor is large and involves the intracranial cavernous sinus or the back of the eyeball, it might invade the optic, oculomotor, trochlear, and abducens nerves, resulting in diplopia, decreased visual acuity, fixation of the eyeball, and other ocular symptoms [168]. In some patients, the symptoms might diminish or disappear after treatment; however, if irreversible damage is caused by prolonged compression or invasion of the nerve, the above symptoms might persist after treatment.

6.2.4 Prevention

Posttreatment prophylaxis refers to measures to improve quality of life and promote recovery. The ultimate goal of oncology rehabilitation should be complete remission of the tumor with complete psychological, physical, and physical recovery and competence at work [25]. Under the present conditions, the goal of rehabilitation is to target the primary or secondary functional impairment of the patient caused by the tumor, through comprehensive measures that enable as gradual a recovery as possible, thereby improving their quality of life and survival, and helping their return to society.

7 Special types of NPC

NPC in children and young adults. Childhood NPC is rare, with an incidence of < 5% among childhood malignancies [169, 170]. NPC in young adults has tended to increase in recent years, and the pathogenesis is mainly related to genetic factors. Most tumors are in the locally advanced stage, but are more sensitive to chemoradiotherapy [170, 171]. Treatment for NPC in children and young adults is the same as that for adults, with induction chemotherapy combined with concurrent chemoradiotherapy for locally advanced stages, and IMRT recommended for radiotherapy; however, long-term

toxic side effects should be minimized to improve quality of life [172].

Nasopharyngeal adenocarcinoma and adenoid cystic carcinoma. Adenocarcinomas and adenoid cystic carcinomas of the nasopharynx have a low incidence, predominantly occur in men, are slow growing, and are prone to distant metastasis [173, 174]. The complex anatomy around the nasopharynx and the difficulty of surgery make it difficult to achieve radical resection, and the treatment and prognosis of adenocarcinoma is similar to that of squamous cell carcinoma. There is no recommended chemotherapy regimen, and platinum-based regimens remain the current mainstay.

Nasopharyngeal neuroendocrine neoplasms. Neuroendocrine neoplasms originating in the nasopharynx are very rare and have only been reported on a case by case basis; therefore, it remains to be determined whether treatment is the same as that for conventional SCC of the nasopharynx and whether lower dose radiotherapy can be used [175–177].

NPC in pregnancy. For pregnant women with NPC, abortion, induction of labor, or cesarean section is recommended as the first step, followed by anti-tumor therapy; however, their prognosis is poor and distant metastasis often occurs [178, 179]. The principle of treatment is the same as for general NPC, and the toxic side effects of chemoradiotherapy should be minimized, and reproduction is recommended with a 2-year interval from the end of treatment [178].

NPC in elderly patients. Current guidelines recommend the same treatment options for elderly patients and general populations; however, there is insufficient evidence on the effectiveness of these strategies in elderly NPC patients [25, 165]. Opinions are divided on whether standard aggressive treatment can bring benefit to this vulnerable population. Several retrospective studies suggest that elderly NPC patients should receive CCRT to improve survival outcomes [180–182]. However, it has also been shown that CCRT provides similar survival and higher grade 3 toxicity in NPC patients aged $\geq$70 years compared with radiotherapy alone. Therefore, most experts usually recommend radiotherapy alone for elderly patients, which can be combined with concurrent targeted therapy.

8 Future of NPC

For our country, NPC has its special characteristics. First, from a national perspective: China has the highest incidence, with 80% of all patients with NPC patient. Results from China continually refresh international guidelines. Second, in terms of radiotherapy technology development: NPCs are a 'model system' of the radiotherapy industry. Finally, from an institutional perspective: the level of radiation therapy delivered at a hospital (Center) or a radiation facility is focused on NPC treatment.

NPC radiotherapy began in the 1920s, and the earliest report of the efficacy of radiotherapy for NPC in China was by Professor Qubing Zhang, who employed radium therapy and deep external X-ray irradiation in the 1950s; unfortunately, the 5-year survival rate was only around 20%. With advances in radiotherapy equipment, in 1983, Zhang et al. reported the efficacy of Co-60 in the treatment of NPC, and the 5-year survival rate improved to around 50%. Later, with the combination of 3D imaging, IMRT, and chemotherapy, the 5-year survival rate further improved to more than 85%. In recent years, with the application of molecular targeting and immunotherapy, the curative effect is expected to further improve.

With the advent of the era of precision medicine, the need for optimal NPC diagnosis and treatment is increasingly urgent for three reasons. First, because patients with NPC survive longer, the demand for quality of life is increasing. This requires clinicians to consider not only the local control rate and survival, but also to protect normal tissues as much as possible and mitigate radiation injury. To achieve this, optimal treatment decisions and implementation must be carried out. Secondly, recent years have witness rapid progress in new techniques for radiotherapy, with a diversity of combination modes of chemotherapy, molecular targeting, and immunotherapy, and it is necessary to choose the optimal treatment mode according to the individual's condition. Finally, spending the least and achieving the best results is now the mainstream pursuit in the era of precision medicine, so-called "clinical optimization", i.e., which is the least costly and the best curative, including three aspects: First, among several alternatives, the choice of the most positive one is the one with the best efficacy, the least pain, the least danger, and the lowest cost. The second is to control negative consequences to a minimum, especially when the damage is inevitable. Third, we should comprehensively consider the factors of disease diagnosis and treatment, the means of disease treatment and impact, and their consequences, striving for the overall optimization of diagnosis and treatment. Optimization is a dynamically developing concept, and different levels of medical development, different social history backgrounds, different cultures, and people who identify with values, mean that the judgment of medical optimization is often quite different.

8.1 Precision staging

At present, the anatomy-based TNM staging system guides clinical treatment relatively well; however, it

also has certain shortcomings, including: non-uniqueness; coexistence of multiple staging versions; and low level of evidence (mostly retrospective trials and level III / IV evidence). In addition, information is not comprehensive: we only consider anatomical information, excluding important biological information such as circulating tumor DNA, circulating tumor cells, exosomes, and EBV replication within body fluids (blood, urine, saliva). Guidance is also imprecise, including failure to precisely map the tumor biology of different patients. In our opinion, staging should provide a precise reflection of the tumor and ideally, staging should be based on precise anatomical progression, precise prognosis, should guide individualized diagnosis and treatment, be feasible and easy to operate, based on big data validation, and should be updated as technology advances.

8.2 Target delineation

Target delineation is the first step toward achieving precision radiotherapy; however, current standards for target delineation are not uniform. Problems with target delineation include: Lack of uniform standards and high-level evidence-based support; time-consuming manual delineation; large variation among physicians; and imprecision in biological target identification. We believe that with future target delineation will evolve from the following five aspects. The first is that the target is more individualized. Target delineation not only depends on the tumor location, volume, stage, and differentiation, but also fully accounts for differences in individual radiosensitivity. The second is that the target is more physically rationalized. When lesions are close to high-risk OARs, such as the brainstem, an adequate space for physical optimization of the PRV is to be left when delineating the target volume. The third is that the target is more biologically plausible. Based on the information obtained by functional imaging, more precise dosing is delivered. The fourth is that the target is more clinically optimized. With the premise that high-risk OARs are maximally tolerable, efforts should be made to increase the dose within tumor volume, without the limitation of the dose of functional organs. The last is that the delineation of the target is more dependent on integrating information from multiple sources. Integrating multi-omics technologies, multimodal imaging, immune and bioinformatic technologies will improve radiotherapy precision and titer ratios. Intelligent delineation of the target volume is a reliable technique to maximize the efficient use of clinicians' time and effort; however, currently, it cannot replace clinician thinking, and hybrid intelligence from human–machine integration is the ultimate goal.

8.3 Recurrent NPC

Local recurrence in the nasopharynx or neck occurs in 10 to 20% of patients. Except for a few early-stage cases for which surgery is an option, the majority of locally recurrent NPC will require re-course radiotherapy. Severe radiotherapy toxicity is a major cause of re-course treatment failure. How to select suitable cases for re-course radiotherapy is the key issue that needs to be solved clinically. Coping strategies include precision grouping in precision models and precision treatment in precision groupings. Studies have established a quantitative model by analyzing the survival prognosis of 558 patients with locally recurrent NPC, using which patients can be divided into low—and high-risk groups by scoring five independent prognostic factors. In the low-risk group, the side effects of re-course radiotherapy were low, and re-course radiotherapy was recommended. In high-risk individuals, the prognosis is suboptimal and the side effects of re-course radiotherapy are severe, so combination chemotherapy, targeted therapy, or immunotherapy should be considered [61]. In clinical practice, there is usually no best plan, but only a more suitable plan. Where normal tissue is as tolerant as possible, tumor tissue should be given the most effective hit. Radiotherapy dose is often the result of compromise to preserve OARs.

8.4 Combination therapy

Current treatments for NPC include radiation therapy, chemotherapy, molecular targeting, and immunotherapy. Treatment modalities can also comprise various combinations, including induction, concurrent, adjuvant therapies, with two or three combinations. Nevertheless, many open questions remain in the treatment of NPC, including what combination modality is optimal? Is there still a need for concurrent chemotherapy for stage II NPC in the IMRT era? Are induction and adjuvant chemotherapy still meaningful? Which patients will benefit from molecularly targeted therapy and immunotherapy? There are some preliminary results that attempt to answer these questions. A meta-analysis of 2138 patients with stage II NPC from 11 clinical studies suggested that concurrent chemotherapy failed to benefit this subset of patients [183]. Long-term follow-up of 508 patients with stage III-IVb (without T3-4N0) NPC suggested that adjuvant chemotherapy failed to confer clinical benefit to patients with locally advanced NPC. Induction chemotherapy has improved survival for high-risk patients, e.g., TPF and GP induction chemotherapy improves 3-year survival by 4 to 8% [93].

Reviewing the 70-year development of the diagnosis and treatment of NPC, the 5-year survival rate has exceeded 90% because of breakthrough advances in

radiotherapy techniques, with a major change in local control rates and long-term survival. This has also led to a reduced space for further improvement. Radio-physical technology has also entered a plateau in recent years, and it is difficult to make a large breakthroughs in the short term. In addition, for patients who relapse after precision radiotherapy, the chance of re-course radiotherapy is significantly reduced. In response to this current status, we believe that the next breakthrough of NPC lies in "clinical optimization", which includes precise tumor staging, AI based precision delineation of the target volume, quantitative models, precision grouping of recurrent NPC, and individualized decision making based on multimodality omics and liquid biopsy.

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