REVIEW

Chinese expert consensus on diagnosis and treatment of nasopharyngeal carcinoma: evidence from current practice and future perspectives

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Abstract: Nasopharyngeal carcinoma (NPC) is a rare type of head and neck cancer, with a higher incidence reported only in Southeast Asia and Northern Africa. Owing to the rarity of NPC occurrence, no internationally accepted consensus or guideline for its diagnosis and treatment is available. Based on the current evidences and practices, the Chinese experts on multidisciplinary diagnosis and treatment of NPC were designated to develop a national consensus for the treatment strategy of NPC. In this consensus, we report the development for improving the treatment efficacy and quality of life of NPC patients in China. The consensus also describes and recommends the role of multidisciplinary management approach in the management of NPC. A multidisciplinary team should include experts from different domains who can cater to the individualized needs of patients with NPC in a much more efficient manner. In addition, the team may also play a key role in developing guiding principles for future research, contributing to the improvement in the management of NPC.
Keywords: Asian, Chinese, consensus, nasopharyngeal carcinoma, radiotherapy

Introduction

Nasopharyngeal carcinoma (NPC) is a relatively rare type of malignancy worldwide, with an age-standardized rate (ASR) of 1.2 per 1,00,000 person-year and a death rate of 0.7 per 1,00,000 person-year.[1] However, NPC is highly prevalent among the populations of the developing and underdeveloped countries in Southeast Asia, East Asia, and Northern Africa.[1–3] In China, the ASR and death rate of NPC are 2.0 and 1.2 per 1,00,000 person-years, respectively, which are much higher than the average rate worldwide. Furthermore, morbidity and mortality vary with race and geographical area in China. Southern China, especially Hong Kong and Guangdong, has reported an incidence rate of 20–30 per 1,00,000 person-year, which is over 10 times than the average.[4]

Although NPC is histopathologically classified as keratinizing squamous cell carcinoma (with varying degrees of differentiation), non-keratinizing carcinoma (differentiated and undifferentiated types), and basaloid squamous cell carcinoma by the World Health Organization,[5] its etiology is not completely known. The occurrence of NPC is considered to be the result of interactions between Epstein-Barr virus (EBV) infection, genetic and environmental factors such as alcohol consumption and smoking, and consumption of salted fish,[3,6,7] with EBV infection playing a major role.[6] Other than the conventionally known risk factors of NPC, nose/ear infections have been found to be associated with NPC in China.[8–10] Prognosis of NPC has been found to be

associated with TNM staging, primary tumor size, biomarkers such as circulating plasma DNA, EBV DNase-specific neutralizing antibody, lactate dehydrogenase (LDH), beclin-1, galectin-3, and other associated comorbidities.[11,12]

Accurate and appropriate clinical staging plays a key role in the diagnosis and management of cancer. Owning to the higher incidence of NPC reported in China and the advances in diagnostic and therapeutic area, the Chinese Committee for Staging of Nasopharyngeal Carcinoma (CCSNPC) revised the previously validated 1992 Chinese staging system on December 16, 2008 and a new version of the clinical staging was recommended in the same year by CCSNPC. However, further evidences are warranted to validate the effectiveness, and further improve the staging system used in China.[13] In order to facilitate the comparison and exchange of data and results between the different research centers, the TNM classification used the seventh edition of the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) staging system.[14] However, with the progress of radiodiagnosis and radiotherapy, the current AJCC/UICC staging system needs further evaluation for its applicability and improvement, especially for NPC.

The routine clinical staging identification in NPC includes medical history, physical examination (including cranial nerve examination), complete blood biochemical analysis including complete blood count, liver and kidney function tests, EBV DNA copy, chest computed tomography (CT), nasopharyngoscopy and CT or magnetic resonance imaging (MRI) of nasopharynx, skull base and neck. MRI is an initial choice; however, each center can choose the best imaging tools based on daily clinical practices and experiences. For high risk patients (those with N3 disease or biochemical abnormalities), isotope bone scans or CT scans of the upper abdomen and chest are recommended. Positron emission tomography (PET-CT), with better sensitivity, specificity and accuracy is a replacement of traditional techniques for the diagnosis of distant metastasis while PET-MRI may play a role in the staging of NPC.

According to the current TNM staging, NPC patient is diagnosed as N3 when there are unilateral or bilateral metastasis in cervical node(s), invading below the caudal border of cricoid cartilage including those extending to the supraclavicular fossa (SCF). SCF described by Ho is a triangular region which is bounded anatomically by the superior margin of the sternal head and the lateral edge of the clavicle and the area of shoulder and neck confluence.

However the definition of N3 is mostly based on clinical examination[15] and there are some concerns while demarcating the SCF radiologically as the area may extend to lower neck including the IV and Vb areas.[16] Evidences from recent studies have reported an assessment of radiological lower levels (LL) IV and Vb as a potential replacement for the SCF in the demarcating criteria for the N3 category.[16,17] This newly defined area can be assessed by imaging tools and will not influence the overall prognosis of N3. Similarly, there is a lack of universal consensus on the significance of involvement of various muscles in defining the T4 stage in NPC, thereby affecting the treatment and prognosis. According to the current definition, NPC with intracranial extension and/or involvement of cranial nerves, hypopharynx, or orbit, parotid gland, and/or extensive soft tissue infiltration beyond the lateral surface of the lateral pterygoid are defined as stage T4. Even though the patients with tumor invasion limited to the exoskeleton muscle are categorized as T4, they have a better prognosis, comparable to that of T2 phase. Hence clarification and the need to redefine the criteria are considered necessary.[5,18] As per the consensus, we recommend the T-staging as suggested by Ng et al (Box 1).[5]

Box 1: Tumor staging in nasopharyngeal carcinoma

Recommendations

T1: Nasopharynx, adjacent soft tissue extension.

T2: Bony structure, paranasal sinuses.

T3: Intracranial extension, cranial nerve, hypopharynx, orbit, infra-temporal fossa (masticatory space).

Pan et al (2016) analyzed 1609 NPC patients treated with IMRT using the seventh AJCC/UICC staging system and suggested that the difference between adjacent stages in patients with non-metastatic cancer need to be improved. Based on these findings, the author proposed the changes for the eighth edition of the AJCC/UICC staging system for NPC. The changes recommended are changing medial pterygoid/lateral pterygoid involvement from T4 to T2, adding prevertebral muscle involvement as T2, replacing the SCF with the lower neck, merging this with a maximum nodal diameter of >6 cm as N3, and classifying T4 and N3 collectively as stage IVA.[19] The Pan et al study results were unanimously approved and relevant recommendations were incorporated into the AJCC/UICC 8th edition of staging[20] and the 2017 China NPC staging system, thereby achieving unification in the internal and domestic NPC staging.

The management of NPC has undergone dramatic evolution as a result of advances in radiotherapy technology, including the transition from 2-dimensional to 3-dimensional conformal and intensity-modulated radiotherapy (IMRT), improvement in concurrent chemotherapy, and accurate disease staging. This article is a consensus on treatment strategies for NPC, which was developed by the domestic experts after several group discussions on their own experiences along with published reference. The consensus aims to update the clinicians and provide guidance for the management of NPC, thereby improving the overall survival (OS) and quality of life with minimal complications. Further, the recommendations put forward in this consensus was arrived when there was ≥80% level of agreement between the members of the consensus group.

Consensus recommendations

Recommended treatment options for stage I and stage II NPC are presented below, along with the recommended therapy regimen, doses, and evidence from previous studies.

Treatment options for stage I NPC

Radiotherapy is the main treatment for the NPC patients without distant metastasis. For stage I, a radical dose of 66–70 Gy and 56 Gy administered to the primary tumor and the upper neck, respectively, is necessary for tumor control and prevention of local recurrence, and the local control rate is over 90% for patients with stage T1N0M0.[21,22] A single-center retrospective study by Gao et al reported a 5-year OS of 85% and a local control rate of 90% in stage N0 cases without irradiating the lower cervical region. The study reported a very low failure rate of <0.2%. This evidence suggested that radiotherapy is not necessary in the lower cervical region in stage N0 cases.[23]

Treatment options for stage II NPC

Radiotherapy to primary tumor and lymphatic drainage are the standard treatment options for stage II NPC, including T2N0 and T1N1.[24,25] A retrospective study by Su et al that included patients with early-stage (T1-T2bN0-N1M0) NPC who underwent only IMRT (N=198) reported a 5-year estimated disease-specific survival of 97.3% and a distant metastasis-free survival rate of 97.8%. It was noted that patients with T2b had a relatively greater risk of local recurrence, whereas those with T2bN1 disease had a greater risk of distant metastasis. Therefore, patients with T2bN1 NPC were considered requiring intensified therapy.[25] Cheng et al also reported a high 3-year

locoregional control rate of 91.7% and 100% in the groups receiving only radiotherapy and concurrent chemotherapy and radiotherapy (CCRT) (*P*=0.10), respectively. In addition, the authors also reported a similar 3-year disease-free survival (DFS) rate in the groups receiving radiotherapy and CCRT (91.7% and 96.9%, *P*=0.66).[26] Evidence from the concerned studies showed that synchronized radiotherapy as the first choice of treatment for stage II NPC, especially for patients with T2N1, for the local control and distant metastasis. Supporting the evidence, a phase III randomized trial that compared CCRT with 2-dimensional radiotherapy (RT) in 230 patients with stage II NPC reported that CCRT significantly improved the 5-year OS rate of patients (94.5% vs 85.5%, hazard ratio [HR]: 0.30; 95% CI: 0.12–0.76; *P*=0.007) and distant metastasis-free survival rate (94.8% vs 83.9%, HR: 0.27; 95% CI: 0.10–0.74; *P*=0.007).[27] However, it should be noted that in these studies, 2-dimensional RT was administered to the control group, and currently IMRT is widely used. These data indicate toward an important question: whether chemotherapy is still necessary in patients treated with IMRT.

Owing to the greater toxicity associated with CCRT, physicians should be more cautious while prescribing chemotherapy to patients. In the INT-0099 trial, 63% patients receiving cisplatin 100 mg/m^2 for 3 cycles completed the trial. The major reason for withdrawal from the study was toxicity to the therapy.[2] A phase III randomized control study by Chen et al also reported that patients receiving CCRT experienced more severe grades 3–4 acute toxicities, including adverse events (AEs) of blood, gastrointestinal system, and mucositis in comparison with those receiving radiotherapy alone.[27] Therefore, IMRT has replaced the conventional 2-dimensional radiotherapy techniques as the standard therapy for stage 2 NPC (Box 2).

Treatment options for locally advanced NPC (Box 3)

CCRT with or without adjuvant chemotherapy is the standard therapy in patients with locally advanced (LA) NPC (stages III, IVA, or IVB). The patients may also be prescribed induction/neoadjuvant chemotherapy sequential CCRT, cetuximab targeted therapy, and chemoradiation combination. In addition, cervical lymph node dissection is recommended for refractory or recurrent lymph node enlargements.[28] Lately, there has been a major focus on the treatment of LA NPC with combined radiotherapy and

Box 2: Treatment recommendations in stage II NPC

Recommendations

(i) For conventional radical radiotherapy, a dose fraction of 2.0 Gy/fx and a total dose of 66–70 Gy/33–35fx are recommended. For IMRT, a fractioned dose of 2.12–2.25 Gy/fx and a total dose of 66–72 Gy (30–33 times) are recommended. Patients with a significant residual disease after irradiation should be administered local extended-dose irradiation or additional 6 Gy external irradiation or stereotactic radiotherapy or breech-loading intracavitary brachytherapy with an additional 6–10 Gy dose.

(ii) Patients with parapharyngeal obvious invasion/enlarged neck lymph nodes or retropharyngeal lymph nodes (diameter ≥2.0 cm) are recommended cisplatin monotherapy 35–40 mg/m^2/week or 80–100 mg/m^2/3 weeks.

Abbreviation: IMRT, intensity-modulated radiotherapy.

chemotherapy showing improved clinical outcomes. This treatment strategy has been an important milestone in the treatment of LA NPC. To date, at least 5 phase III randomized controlled trials (RCTs) that compared the efficacy of concurrent chemoradiation with radiotherapy alone in LA NPC[25,29–33] have reported concurrent chemoradiotherapy significantly improved DFS, while other phase III RCTs have reported a significant improvement in progression-free survival (PFS) and OS.[34–38] The HR for OS in these studies ranged from 0.4 to 0.71, with a follow-up period of 2–5 years. Not only RCTs, but more robust evidence from several meta-analyses (n>8000 patients with LA NPC) have also shown a significant benefit of CCRT in clinical outcomes in comparison to radiotherapy alone.[39–41] A recent meta-analysis of 19 trials (n=4806) and patients treated with CCRT reported a significantly improved PFS (HR: 0.75; 95% CI: 0.69–0.81), OS (HR: 0.79; 95% CI: 0.73–0.86; $P<0.0001$), locoregional control (HR: 0.74; 95% CI: 0.65–0.85), and distant control (HR: 0.68; 95% CI: 0.60–0.76).[41] Based on these findings, CCRT is currently recommended as the standard treatment option for LA NPC. Although the beneficial clinical outcome of CCRT is not related to the type of chemotherapy used, a few exploratory analyses have shown the beneficial effect of cisplatin in both local control and OS.[42,43] Although cisplatin-based regimens are commonly used in CCRT and have shown benefits in relapse-free survival and OS rates, cisplatin is associated with significantly increased toxicity, and hence, there is reduced patient compliance, which must also be taken into account while prescribing cisplatin. Hence, carboplatin may be considered for use in CCRT because of its lower nephrotoxicity.

Box 3: Treatment recommendations for locally advanced NPC

Recommendations

1.Chemotherapy regimen (specific therapeutic dose) and radiotherapy dose

For patients undergoing radical radiotherapy with two dimensional technique, a fractioned dose of 2.0 Gy/fx and a total dose of 66–70 Gy/33–35 fx are recommended. For IMRT, a fractioned dose of 2.12–2.25 Gy/fx and a total dose of 66–72 Gy (30–33 times of fractioned dose) are recommended. Patients with a significant residual disease after radiation therapy should be administered local extended-dose irradiation or an additional external irradiation dose of 6 Gy or stereotactic radiotherapy with an additional dose of 6–10 Gy. Patients without contraindications to chemotherapy are recommended to be prescribed with concurrent chemotherapy, with cisplatin monotherapy 35–40 mg/m^2/week or 80–100 mg/m^2 ETW as the mainstay.

2. Adjuvant chemotherapy recommendations

(i) Cisplatin + Fluorouracil (PF regimen):[2,34–36,45] 5-fluorouracil (5-FU) 1000 mg/m^2/day for 4 days [96 hr continuous intravenous (IV) infusion] or 5-FU 800 mg/m^2/day IV infusion for 5 days [120 hrs IV infusion]; Cisplatin (DDP) 80 mg/m^2 IV on day 1 or DDP 20 mg/m^2/day IV infusion on days 1–4; repeat the cycle every 28 days for 2–4 courses.

(ii) Fluorouracil + Carboplatin (FC regimen):[38] 5-FU 1000 mg/m^2, 96 hr continuous IV infusion; carboplatin AUC 5 IV on day 1; repeat the cycle every 21 days for 2–4 courses,

3. Induction chemotherapy (neoadjuvant chemotherapy) recommendations

(i) Docetaxel, cisplatin, fluorouracil (TPF regimen): Docetaxel 70 mg/m^2 IV on day 1; DDP 75 mg/m^2 IV on day 1; 5-FU 1000 mg/m^2 96 hr continuous infusion; repeat the cycle every 28 days for 2–4 courses[71] or docetaxel 60 mg/m^2 IV on day 1; DDP 60 mg/m^2, IV on day 1; 5-FU 600 mg/m^2, 120 hr continuous infusion; repeat the cycle every 3 weeks for three cycles before CCRT.[72]

(ii) Gemcitabine + Carboplatin (GC regimen):[48] Gemcitabine 1000 mg/m^2 IV on days 1 and 8; carboplatin AUC 5 IV on day 1; repeat the cycle every 21 days for 2–4 courses

(iii) Docetaxel + Cisplatin (DP regimen):[49] Docetaxel 75 mg/m^2 IV and DDP 75 mg/m^2 IV on day 1; repeat the cycle every 21 days for 2–4 courses

(iv) Cisplatin + Fluorouracil (PF regimen):[73] DDP 100 mg/m^2 IV on day 1; 5-FU 1000 mg/m^2 96 hr continuous infusion; repeat the cycle every 3 weeks for 3 cycles.

(v) EGFR monoclonal antibody combined with CRT/RT:[61] Cetuximab IV at a starting dose of 400 mg/m^2 on day 1 about 7–10 days before starting CRT/RT; further weekly infusion at a maintenance dose of 250 mg/m^2 used with CRT/RT.

Abbreviations: IMRT, intensity-modulated radiotherapy; ETW, every 3-weeks; CCRT, concurrent chemotherapy and radiotherapy.

The dose of chemotherapy to be used in CCRT is still under exploration in clinical research. A phase III, non-inferiority, multicenter RCT involving 526 patients with LA NPC was conducted to assess the efficacy and toxicity

profiles of CCRT between every 3-week (ETW) versus once-in-a-week (OAW) schedule of cisplatin. After 24 months, the failure-free survival (FFS) and 2-year OS of OAW compared with ETW were similar in both groups; 93.1% vs 89.1% (HR: 1.217; 0.684–2.163; P=0.504) and 98.6% vs 97.4% (HR: 1.271; 0.441–3.664; P=0.657), respectively. However, the incidence of grades 3–4 leukopenia and thrombocytopenia were significantly higher in the group receiving weekly OAW cisplatin in comparison to the group receiving ETW cisplatin (27.3% vs 16.2%; 4.8% vs 1.2%). However, more evidences are warranted to conclude on the efficacy of the therapies after longer follow-up.[44]

To date, RCTs showing survival benefit with CCRT in combination with adjuvant chemotherapy are scarce and the significance of adjuvant chemotherapy for LA NPC remains to be determined. Previous meta-analysis has shown that compared to CCRT, the addition of adjuvant chemotherapy did not show a significant improvement on local control rate, distant metastasis rate and OS.[37] However, based on the previous study comparing between CCRT and radiotherapy, it could be speculated that CCRT combined with adjuvant chemotherapy may improve clinical outcomes in LA NPC. As CCRT has proven to be superior to radiotherapy alone, an unmet need to increase the significance of adjuvant chemotherapy on this basis exists. The largest phase III study to date comparing adjuvant chemotherapy (cisplatin and 5-fluorouracil [5-FU]) + CCRT and CCRT alone reported an estimated 2-year FFS rate of 86% in the adjuvant chemotherapy + CCRT group in comparison to 84% in the CCRT alone group (HR: 0.74; 95% CI: 0.49–1.10; P=0.13). In addition, patient compliance was lower in the group receiving adjuvant chemotherapy + CCRT, with 63% of the patients receiving adjuvant chemotherapy and 49% receiving reduced doses of chemotherapy.[45] However, meta-analyses of MACH-NPC showed that CCRT combined with adjuvant chemotherapy is more effective (n=1267; HR: 0.65; 95% CI: 0.56–0.76) for OS than radiotherapy alone (n=1834; HR: 0.80; 95% CI: 0.70–0.93).[41] Nevertheless, it should be noted that the above-mentioned comparison between the two groups was indirect. On the basis of the current literature data, CCRT sequential adjuvant chemotherapy has not been specifically recommended for the treatment of LA NPC. Further studies should be performed to determine subsequent directions and identify subgroups that can derive the maximum benefit from CCRT and adjuvant chemotherapy. The ongoing RCTs (NCT00370890 and NCT02135042) are evaluating the role of persistent infection of EBV DNA after treatment to guide subsequent adjuvant chemotherapy, which is one of the patient groups considered to be beneficial from the CCRT and adjuvant chemotherapy. Another potential group of patients likely to benefit from adjuvant chemotherapy is NPC patients with large cervical lymph nodes (N2, N3). In a recent study involving 547 NPC patients with N2-3, no significant benefit was observed in the adjuvant chemotherapy subgroup analyses of patients with N3. However, the patient subgroup had a significantly lower risk of distant metastases (HR: 0.413; 95% CI: 0.194–0.881; P=0.022) and survival benefit (HR: 0.398; 95% CI: 0.187–0.848; P=0.017) after adjuvant chemotherapy. More evidence is therefore required to confirm the efficacy of CCRT and adjuvant chemotherapy in these subpopulations.[46]

Neoadjuvant or induction chemotherapy shrinks the tumor, which increases the likelihood of curative dose to be used in subsequent radiotherapy regimens. In addition, induction chemotherapy may also reduce distant metastasis of head and neck cancer. Therefore, in the past few years, efficacy of chemoradiotherapy (CRT) in combination with induction chemotherapy has been determined in patients with LA NPC. Efficacy of induction chemotherapy has been evaluated in two phase II, single-arm studies in patients with LA NPC (n=33, n=28, respectively).[47,48] In both studies, patients achieved good clinical outcomes with carboplatin + gemcitabine or docetaxel, cisplatin, and 5-FU induction chemotherapy regimens with 3-year OS rate ranging from 86.1% to 89.3%. Owing to the limited evidence from only 2 studies, efficacy of both induction regimens warrants further investigation. The phase II trial that compared the effect of CRT and CRT combined with docetaxel and cisplatin as induction chemotherapy lacked the power to observe a statistically significant OS. However, the results at 3 years indicated a much higher OS rate with induction chemotherapy (94.1% vs 67.7%, HR: 0.24; 95% CI: 0.078–0.73; P=0.012).[49] The promising results from this phase II study is not yet confirmed in larger phase III RCTs. In another two phase II/III studies, the regimen of induction chemotherapy are paclitaxel, cisplatin, epirubicin or paclitaxel, carboplatin, and gemcitabine.[50,51] In comparison with CCRT, induction chemotherapy did not show any significant benefit in terms of response rates, PFS, and OS in either of the studies. The multi-arm trial NPC-0501 compared CCRT with CCRT induction chemotherapy, capecitabine versus 5-FU, and accelerated radiotherapy versus conventional

RT in 706 patients randomized to 6 treatment groups, with concurrent cisplatin and RT followed by cisplatin and 5-FU adjuvant treatment as the standard control group. Over 3 years, the OS rate increased from 85% to 91%, with preliminary analysis showing no significant difference in PFS between cisplatin + fluorouracil (PF) induction chemotherapy and PF-adjuvant therapy. However, the subgroup analysis showed less toxicity and better efficacy with capecitabine in comparison with 5-fluorouracil (FU).[52] Based on the results, the patients were not recommended to use the accelerated fraction radiotherapy due to toxicity considerations. The study involved a relatively short follow-up period of 3 years and further long-term follow-up results are required to determine the role of induction chemotherapy.

Another recent phase III RCT showed a significant improvement in 3-year FFS with induction chemotherapy + CCRT compared with CCRT alone (80% vs 72%, HR: 0.68; P=0.034). This evidence suggested that for patients with LA NPC, docetaxel + cisplatin + fluorouracil (TPF)-induced radiotherapy in addition to concurrent chemoradiotherapy may benefit in prolonging the survival. In terms of safety, induction chemotherapy + CCRT resulted in a greater incidence of AEs, with the most common grade 3 or 4/severe adverse reactions being neutropenia (42% vs 7%), leukopenia (41% vs 17%), and stomatitis (41% vs 35%).[53] More long-term follow-ups of the study can further clarify the long-term efficacy and safety of the therapy. A report released in the American Society of Clinical Oncology Assembly in 2017 concluded similarly, wherein the intent-to-treat population analysis showed that the addition of a 2-courses PF regimen to the CCRT significantly improved DFS (P=0.028) in comparison with CCRT only, with no significant difference in OS and distant metastases-free survival (DMFS) between the two groups.

The epidermal growth factor receptor (EGFR) monoclonal antibody cetuximab has found clinically significant application in the treatment of NPC as it is expressed in more than 80–90% of patients with NPC.[54–56] Cetuximab monotherapy or combination with chemotherapy or radiotherapy has shown to significantly inhibit tumor growth and proliferation and increase the sensitivity of NPC tumor cell lines to radiotherapy or chemotherapy, and therefore have a synergistic effect.[57,58] Collecting the evidence from preclinical studies, some phase II trials investigated the use of cetuximab therapy in combination with or without chemotherapy. Recently 2 phase II trials that evaluated the efficacy of IMRT in combination with cetuximab and cisplatin in 130 patients with LA NPC reported good short-term effects, with 2-year DFS rates of 86.5–89%. One of the studies even reported a 2-year OS rate of 91%. Cetuximab combined with chemotherapy or radiotherapy was well tolerated with very few controllable and reversible cutaneous AEs and mucositis.[59–61] However, the phase II RCT that evaluated the efficacy and safety of IMRT in combination with cetuximab or cisplatin after 2 courses of induction chemotherapy (docetaxel + cisplatin) was terminated prematurely because of higher rates of mucositis and skin reactions. Nevertheless, in terms of efficacy, the combination of cetuximab and IMRT reported a higher 3-year DFS rate of 85.7% in comparison to 78.3% reported in the group receiving cisplatin + IMRT. Similarly, multiple single-arm clinical studies of cetuximab + radiotherapy/chemotherapy (with or without induction chemotherapy) have also been performed in LA NPC patients.[62–64] In accordance with the results from previous trials, the 2-year DFS was around 89% while the 3 year OS reached approximately 90%. On the basis of the results from these studies, it is evident that cetuximab in combination with CRT or radiotherapy is a viable treatment regimen in patients with LA NPC with acceptable toxicity. Therefore, for some patients with LA NPC, it may be advisable to add cetuximab to the standard CRT regimens. However, there is a need for further prospective phase III clinical trials to confirm the efficacy and safety of cetuximab in patients with LA NPC. Another targeted therapy that has been explored for NPC is bevacizumab. In a phase II one-arm study among the 44 patients with NPC, the estimated 2 year locoregional PFS, distant metastasis-free survival, PFS, and OS rates were 83.7% (95% CI: 72.6–94.9), 90.8% (82.2–99.5), 74.7% (61.8–87.6), and 90.9% (82.3–99.4), respectively. Addition of bevacizumab to chemoradiation was feasible for NPC treatment and the combination also delayed distant metastasis.[65] IMRT being the standard radiotherapy for NPC reported a significant reduction in the risk of dry mouth and improved local control and safety in comparison to conventional 2-dimensional radiotherapy in RCTs.[66–68] It is also reported that with IMRT, patients with T3 and T4 disease generally have a 5-year local control rate of ≥90% and 74–80%, respectively,[69,70] along with long-term toxicity and damage to the nervous system. Hence, the overall treatment principle is to consider the risk-benefit profile of the largest dose of the drug. The dose should have a tolerable risk to the vital organs, balance the local control of the tumor, and prevent the occurrence of organ complications.

Treatment of recurrent or metastatic NPC (Box 4 and 5)

NPC patients who experience recurrence after treatment are required to undergo a pathological biopsy and MRI restaging, and then choose a different treatment mode according to the type of staging and patient status. A salvage surgery for disease recurrence can be performed in patients with no comorbidities who are otherwise in good health.[74] If the disease relapses after >1 year of radiotherapy, re-radiation therapy should be considered.[75,76]

Box 4: Treatment recommendations for recurrent or metastatic NPC

> **Recommendations**
> **Locally recurrent disease**
> (i) The total dose of radiotherapy administered in patients with locally recurrent nasopharyngeal carcinoma (NPC) should be recalculated after considering the patient's condition, the extent of tumor invasion, and tumor volume. At present, there is no consensus on the best dose fraction and total doses. Generally, larger dose fractions and the total dose lead to a higher local control rate, but also more toxicities. The local control rate of total dose ≥60 Gy with regular dose fractions is significantly better than <60 Gy.

Platinum-based chemotherapeutic combinations are commonly used as first-line treatment in patients contraindicated for re-radiation or surgery and in patients with recurrent or metastatic (R/M) NPC who are otherwise in good condition. In the Taiwanese population, a multicenter phase II study showed gemcitabine plus cisplatin as an effective, well tolerated, first-line treatment regimen for R/M NPC. The response rate, median PFS, and median OS reported in ITT were 51.9%, 9.8 months, and 14.6 months, respectively.[77] In another recently reported multicenter phase III RCT in China, the efficacy and safety of gemcitabine plus cisplatin (GP) compared with 5-FU plus cisplatin (FP) showed that the GP regimen significantly prolonged the median PFS (7 vs 5.6 months, HR: 0.55; 95% CI: 0.44–0.68; $P<0.001$) and OS (29.1 vs 20.9 months, HR: 0.62; 95% CI: 0.45–0.84; $P=0.0025$) in comparison with the FP regimen. Overall safety of GP regimen was acceptable and manageable despite major hematologic grade 3/4 AEs, including leukopenia (29%), neutropenia (23%), and thrombocytopenia (13%).[78] Although platinum-based chemotherapy has rarely been evaluated in a larger phase III clinical trial, it is still recommended because of its efficacy and lesser side effects. The most commonly recommended

Box 5: Treatment recommendations for recurrent/metastatic NPC not suitable for radiotherapy/surgery

> **Recommendations**
> (a) **Patients with Locally recurrent and metastatic nasopharyngeal carcinoma (NPC) who are not suitable for radiotherapy/surgery**
> 1. GP regimen: Gemcitabine 1250 mg/m^2 IV on days 1 and 8; DDP 75 mg/m^2 IV on day 1; repeat the cycle every 21 days for 6 courses[77] or gemcitabine 1000 mg/m^2 IV on days 1 and 8; DDP 80 mg/m^2 IV on day 1; repeat the cycle every 21 days for 6 courses.[78]
> 2. Docetaxel + Carboplatin [DC regimen]:[79] Docetaxel 65 mg/m^2 IV on day 1; carboplatin AUC 6 IV on day 1; repeat the cycle every 21 days for 6 courses.
> 3. TC regimen:[80] Paclitaxel 175 mg/m^2 IV on day 1; carboplatin AUC 6 IV on day 1; repeat the cycle every 21 days for 6 courses
> 4. TPF regimen:[82] Paclitaxel 135 mg/m^2 IV on day 1; DDP 25 mg/m^2 IV on days 1 to day 3; 5-FU 600–1000 mg/m^2/day 120 hr continuous infusion; repeat the cycle every three weeks for 6 courses
> 5. CC regimen:[85] Capecitabine 1000 mg/m^2 PO BID on days 1–14 and DDP 80 mg/m^2 IV on day 1; repeat the cycle every 21 days for 6 courses
> 6. Gemox regimen:[86] Gemcitabine 1000 mg/m^2 continuous IV infusion at a constant rate of 10 mg/m^2·min on day 1; oxaliplatin 100 mg/m^2 IV on day 2; repeat the cycle every 14 days for 12 courses
>
> **Regimen for resistant platinum-based chemotherapy**
> 1. Gemcitabine regimen:[88] Gemcitabine 1000 mg/m^2 IV on days 1, 8, and 15; repeat the cycle every 28 days for 6 courses
> 2. GN regimen:[87] Gemcitabine 1000 mg/m^2 IV on days 1 and 8; vinorelbine 25 mg/m^2 IV on days 1 and 8; repeat the cycle every 21 days for 6 courses
> 3. Capecitabine regimen:[89] Capecitabine 1250 mg/m^2 PO BID on days 1–14, repeat the cycle every 21 days
> 4. Docetaxel regimen:[90] Docetaxel 30 mg/m^2 IV on days 1, 8, and 15, followed by 1 week rest; repeat the cycle every 28 days for 6 courses
> 5. Cetuximab + Carboplatin regimen:[91] Cetuximab, IV at a starting dose of 400 mg/m^2 on day 1; further weekly infusion at a maintenance dose of 250 mg/m^2; carboplatin AUC 5 IV on day 1, repeat the cycle every 21 days for 6–8 courses

regimens include cisplatin or carboplatin in combination with docetaxel or paclitaxel, cisplatin/5-FU chemotherapy, and paclitaxel in combination with cisplatin and 5-FU as triple regimen therapy.[79–83] The response rates of these regimens have been reported to be between 25% and 78.9%, of which TPF triple regimen had the highest response rate.[84,85] In addition, the combination of gemcitabine and oxaliplatin has also shown certain effects on patients with R/M NPC. The efficacy of this regimen was 56.1% in a single-arm phase II study that included

42 patients with R/M NPC, with a median OS and time to progression (TTP) of 19.6 and 14.8 months, respectively.[86,87] In patients who had previously received platinum-based chemotherapy, the option of combined chemotherapy or single-agent chemotherapy that included gemcitabine in combination with vinorelbine, capecitabine, and oxaliplatin has been explored in clinical studies.[87–89] The response rates reported in these studies ranged from 23.5% to 43.8% and the median PFS ranged from 4.9 m to 5.1 m. In addition, a study that included 30 patients with R/M NPC suggested that docetaxel monotherapy [30 mg/m^2 on days 1, 8, and 15, quarterly every 4 weeks (q4w)] has an active role in treatment of patients with disseminated NPC and those previously exposed and largely refractory to platinum-based chemotherapy.[90]

Also, the use of cetuximab combined with chemotherapy for patients with R/M NPC has been evaluated in a multicenter phase II study, where efficacy and toxicity of cetuximab plus carboplatin was evaluated in the platinum-resistant patients with R/M NPC. The results showed that cetuximab combined with carboplatin achieved considerable clinical efficacy, with a response rate of 11.7%, and approximately 50% of patients achieving stable disease (SD).[91] The median TTP was 3months while the median OS was 8months. The study showed the efficacy of the combination particularly in patients who had been treated with multiline chemotherapy, and hence, the regimen is also recommended in the National Comprehensive Cancer Network guideline. In another retrospective study, cetuximab and chemotherapy were administered in 30 patients with R/M NPC with or without IMRT and yielded a response rate of 70% and median OS of 23.6 months.[92] Based on the above-mentioned findings, cetuximab combined with chemotherapy is recommended as one of the treatment options for patients with R/M NPC. In order to reach an agreement for the use of cetuximab, more evidence from RCTs are warranted. A phase III RCT (NCT02633176), which compares cisplatin plus docetaxel with or without cetuximab followed by concurrent chemoradiation in previously untreated patients with metastatic NPC (mNPC), is ongoing to determine whether the addition of cetuximab to induction chemotherapy and chemoradiation could improve therapeutic efficacy in mNPC. The interim results showed that a response rate of 77.3% has been achieved in 17 patients, which shows

a great efficacy of the cetuximab and chemotherapy combination. Among other small-molecule- or monoclonal antibody (MAB) targeted therapies, gefitinib failed to demonstrate its efficacy in previous phase II clinical studies. Another small-molecule targeted drug pazopanib used as the second-line treatment option in a phase II study of 33 patients with R/M NPC has reported a clinical benefit in 54.5% of patients, with 6.1%, 48.5% and 21.2% of patients achieving partial responses (PRs), stable disease (SD), and PR/SD, respectively, that lasted ≥6 months.[93] Pazopanib has shown encouraging outcome in NPC with an acceptable toxicity profile. Targeted therapies with sorafenib and denosumab and immunotherapy are still under study, and there is a need for clinical trials to further validate their efficacy and safety.

A number of RCTs have been conducted to evaluate the efficacy and safety of immunotherapy in NPC. The KEYNOTE-028 trial (NCT02054806) assessed the efficacy and safety of 10 mg/kg biweekly pembrolizumab (MK-3475) given intravenously in patients with advanced NPC and PD-L1 expression (n=27). The study showed an overall response rate (ORR), DCR, SD, median response time, and median PFS of 22.2%, 77.8%, 55.6%, 10.3 months, and 5.6 months (3.6–11.0 months), respectively. The regimen was safe with a few grade 3–4 AEs of hepatitis (7.4%) and pneumonia (7.4%).[94] The CheckMate 358 enrolled patients with R/M NPC and with ≤2 prior systemic therapies in the R/M setting. The patients received nivolumab 240 mg every 2 weeks until progression or unacceptable toxicity. The study reported about 20.8% of patients achieving partial response (PRs) while 25% patients had confirmed SD, with a median response time of 4.4 months and 8.3% grades 3–4 AE.[95] In the Ma et al study (NCI-9742), 44 R/M NPC patients who were not amenable to curative treatment were treated with nivolumab at a dosage of 3 mg/kg intravenously every 2 weeks until they experienced disease progression. The study reported an overall ORR of 20.5% with 1 patient achieving confirmed complete response (CR) and 8 patients having PR. The one-year OS rate was 59% while PFS rate was 19.3% and reported no unexpected toxicity among the patients.[96]

Multidisciplinary approach for NPC management

The NPC consensus recommended a multidisciplinary approach for the management of NPC, which includes constituting a multidisciplinary team (MDT), which in turn

includes a fixed panel of experts in various fields. The panel holds regular meetings to discuss and formulate treatment plans for various diseases including cancers. In order to facilitate timely and appropriate evidence-based management of cases with NPC, most centers have now established MDTs and conduct meetings in which each of the medical and allied health specialties are represented, so that accurate tumor staging and treatment plans can be best tailored to meet the need of individual patients. This will help to optimize tumor staging, assess the rationality of treatment options, facilitate individualized treatment, protect a patient's breathing, speech, and eating functions, improve the patient's quality of life, and develop the most appropriate treatment for the patient. In addition, an MDT greatly shortens the time from diagnosis to treatment. A typical MDT should include experts from the fields of otolaryngology, oral and maxillo-facial-head and neck surgery, radiotherapy, radiation diagnosis, oncology, pathology, and adjuvant treatment group including nursing, psychotherapy, rehabilitation, clinical, and social support and nutritional support groups. Clinicians in various fields can share the clinical data and determine the best individualized treatment strategy based on treatment principles and guidelines. An MDT has a positive impact on communication among doctors in different fields, thereby expanding the knowledge about various diseases, which in turn improves the diagnosis and clinical outcomes of the disease. It can also have an impact on guiding preclinical and clinical research, helping to update field information, and ultimately benefit more NPC patients.

Conclusion

On the basis of this consensus, we have laid down a few treatment recommendations for patients in different NPC stages. These recommendations based on our clinical experience and literature review have been jointly agreed upon by our team of experts. With this consensus, we aim to improve the diagnosis and management of NPC, especially in the Chinese population.

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Author contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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