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REVIEW

Emerging treatment options for nasopharyngeal carcinoma

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Lu Zhang[1,2]
Qiu-Yan Chen[1,2]
Huai Liu[1,2]
Lin-Quan Tang[1,2]
Hai-Qiang Mai[1,2]

[1]State Key Laboratory of Oncology in South China, [2]Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, Guangzhou, People's Republic of China

Abstract: Nasopharyngeal carcinoma is endemic in Asia and is etiologically associated with Epstein–Barr virus. Radiotherapy is the primary treatment modality. The role of systemic therapy has become more prominent. Based on multiple phase III studies and meta-analyses, concurrent cisplatin-based chemoradiotherapy is the current standard of care for locally advanced disease (American Joint Committee on Cancer manual [7th edition] stages II–IVb). The reported failure-free survival rates from phase II trials are encouraging for induction + concurrent chemoradiotherapy. Data from ongoing phase III trials comparing induction + concurrent chemoradiotherapy with concurrent chemoradiotherapy will validate the results of these phase II studies. Intensity-modulated radiotherapy techniques are recommended if the resources are available. Locoregional control exceeding 90% and reduced xerostomia-related toxicities can now be achieved using intensity-modulated radiotherapy, although distant control remains the most pressing research problem. The promising results of targeted therapy and Epstein–Barr virus-specific immunotherapy from early clinical trials should be validated in phase III clinical trials. New technology, more effective and less toxic chemotherapy regimens, and targeted therapy offer new opportunities for treating nasopharyngeal carcinoma.

Keywords: nasopharyngeal carcinoma, intensity-modulated radiotherapy, chemoradiotherapy, molecular targeted agents, immunotherapy, prognostic markers

Introduction

Nasopharyngeal carcinoma (NPC) is endemic in Southern China and Southeast Asia, with an annual incidence of 15–50 cases per 100,000.[1] According to global cancer statistics from the International Agency for Research on Cancer, there were over 84,000 new NPC cases in 2008, with 80% of the cases located in Asia and 5% in Europe. NPC is characterized by poorly or undifferentiated carcinoma. It differs from nonnasopharyngeal head and neck squamous cell carcinomas in several ways, including its association with the Epstein–Barr virus (EBV), increased radio- and chemosensitivity, and a greater propensity for distant metastases.[2] Because of its complex anatomic location and high radiosensitivity, radiotherapy (RT) is the recommended treatment for nonmetastatic disease. Technological advances in the fields of imaging and RT have improved our ability to visualize and accurately target the tumor with tumoricidal agents while simultaneously decreasing exposure to normal structures.[3]

RT has a high cure rate for patients in the early stages of NPC. However, the majority of NPC cases present with locally advanced stages, and these patients are rarely treated with RT alone.[4] Over the past 20 years, various modes of combined chemoradiotherapy (CRT) have been used to treat NPC patients with advanced-stage disease.[5]

Correspondence: Hai-Qiang Mai
Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, 651 Dongfeng Road East, Guangzhou, Guangdong 510060, People's Republic of China
Tel +86 20 8734 3380
Fax +86 20 8734 3392
Email maihq@mail.sysu.edu.cn

However, the treatment outcomes for locoregionally advanced NPC remain unsatisfactory. The overall survival (OS) rates at 5 years were 53%–80% and 28%–61% in NPC stages III and IV, respectively.[6–13] The current understanding of molecular targets in cancer has enabled the development of targeted NPC therapies. Combined chemotherapy with targeted therapy and immunotherapy may further improve the treatment results. This review describes several recent and notable developments in NPC treatment that have the potential to change treatment standards.

Investigations and staging system

TNM staging is fundamental for predicting outcomes and guiding treatment decisions. NPC is clinically staged according to the 7th edition of the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) staging-system manual.[14] Cross-sectional imaging is important for achieving an accurate delineation of the tumor and facilitating staging and treatment. Magnetic resonance imaging (MRI) is currently considered the best modality to assess NPC.[15] Imaging for distant metastases, including isotope bone scans and computed tomography (CT) scans of the chest and upper abdomen, could be considered in at-risk subsets (eg, node-positive, particularly stage N3) and patients with clinical or biochemical abnormalities.[16] Positron emission tomography (PET)/CT can replace the traditional workup for detecting distant metastatic disease because it has been proven to be the most sensitive, specific, and accurate diagnostic method.[17,18]

With the development and application of imaging technology, particularly MRI, several changes have been adopted in the 7th edition of the UICC/AJCC staging-system manual.[14] T2a in the 6th edition (a tumor that extends to the nasal cavity/oropharynx without parapharyngeal extension) is now classified as T1, and stage IIa is now classified as stage I, because there was no significant difference in the outcomes of these stages.[19] Unilateral or bilateral retropharyngeal lymph-node involvement is now classified as N1, because the prognosis was similar to unilateral cervical nodal involvement. Two retrospective studies showed that the 7th edition staging system for NPC is prognostically useful in patients treated with conformal/intensity-modulated radiotherapy (IMRT).[20,21] However, both studies suggest that further simplifying the staging system should be considered because of improvements in managing and treating NPC.

Prognostic and predictive biomarkers

As with most other tumors, the extent of an NPC as embodied in the TNM staging system is the most important prognostic factor. A large variation of tumor volume is present in T stages, primary tumor volume represents an independent prognostic factor of local control for NPC, and there is an estimated 1% increase in risk of local failure for every 1 cm^3 increase in primary tumor volume.[22] Validity of tumor volume has also been confirmed in patients with T3 and T4 stages.[23] Even in NPC patients treated with IMRT, the primary tumor volume is still highly significant in evaluating local control, distant metastasis, and OS.[24,25] The histological-type World Health Organization type I patients frequently seen among the Caucasian population were found to be associated with adverse prognosis.[26]

EBV plays an important role in the etiology of NPC, and viral status has prognostic implications. Pretreatment and posttradiotherapy plasma EBV DNA levels have been correlated with patient outcome and survival.[27–30] A case report of patients with three episodes of recurrent metastatic NPC illustrates that EBV DNA is a useful monitoring tool for NPC because it can detect early recurrence and has an excellent correlation with treatment response.[31] Chan et al showed that the relative risk for recurrence increased 11.9 times in patients with persistently elevated plasma EBV DNA levels at 6–8 weeks posttreatment compared to patients without increased EBV DNA levels.[29]

The excision repair cross-complementing 1 (ERCC1) enzyme plays a crucial role in the nucleotide excision-repair pathway. Impaired function of the nucleotide excision-repair pathway in tumor cells treated with cisplatin has been shown to lead to greater sensitivity to platinum-induced DNA damage with subsequent cell death.[32] ERCC1 is of particular interest in NPC patients because the primary treatment regimens often contain platinum-based chemotherapy. A study of 77 NPC patients showed that patients with ERCC1-negative tumors had longer disease-free survival (DFS) ($P = 0.076$) and OS ($P = 0.013$) than patients with ERCC1-positive tumors.[33] Chan et al reported that high ERCC1 expression predicts poor locoregional control in NPC.[34] However, chemotherapy responses are unaffected by ERCC1 expression. Recently, Huang et al reported that high tumor ERCC1 expression predicted a low chemotherapy response and poor survival, primarily because of an increase in metastasis in locoregionally advanced NPC treated with cisplatin-based induction chemotherapy.[35] Further validation studies are required to confirm the prognostic and predictive role of ERCC1 in NPC.

Radiation therapy

IMRT as the standard of care

Until the early 1990s, radical RT for NPC was delivered with two-dimensional RT (2D-RT), followed by three-dimensional

conformal RT. With technological advances, modern RT for NPC should be IMRT with inverse RT planning. IMRT allows the modification of each radiation beam by shaping the field or changing the intensity of the dose and provides highly conformal dose delivery. IMRT is becoming a standard RT technique for treating NPC by ensuring high local and regional control at reduced toxicity rates.[36] The advantages of IMRT over conventional radiation therapy include local–regional control and improved survival rates and quality of life in NPC patients. In a retrospective study by Lai et al, the treatment results were significantly improved with IMRT compared to 2D-RT by achieving a higher local tumor control rate in NPC patients, particularly in patients with stage T1 tumors (5-year local relapse-free survival rate 100% vs 94.4%, $P = 0.016$).[13] Combined with chemotherapy, all of the IMRT series have reported excellent results, with local control exceeding 90% at 2–5 years (Table 1).[37–50] However, the improvement in distant control was unsatisfactory despite the extensive use of chemotherapy. The 2-year distant metastasis rates ranged from 10% to 15%,[45,47,50] and the 4-year rates were as high as 32%.[37] Effective systemic therapy combined with IMRT is needed to treat NPC.

Target volume delineation

Although IMRT has been adopted as the standard of care at most major cancer centers, challenges remain regarding optimizing and refining treatment.[51] If the resources are available, IMRT is preferred for NPC. However, IMRT requires careful delineation of target volumes to prevent marginal recurrences. The target volumes should be defined in accordance with the International Commission on Radiation Units and Measurements reports 50 and 62. The delineation of gross tumor volume (GTV), which is based on a combination of clinical, endoscopic, and imaging findings that include the primary disease, lymph nodes > 1 cm in diameter, necrotic centers, or PET/CT-positive lesions, is relatively easy and less controversial. Because of the biological behavior of NPC, the optimal definition of the clinical target volume (CTV) has not been sufficiently addressed, and future research should include CTV delineation. The CTV varies more than the GTV between institutions because of the different methods of contouring, such as the margin around the GTV and the delineation of high-risk volumes. Useful RT guidelines – the Radiation Therapy Oncology Group (RTOG) 0225 study – can be referred to for additional information.[45] The RTOG 0225 study was the first to demonstrate the transportability of IMRT from large institutions to a multi-institutional setting. IMRT with or without chemotherapy produced excellent locoregional control and resulted in 2-year progression-free survival (PFS) and OS rates of 72.7% and 80.2%, respectively. The CTV denoted the subclinical regions at risk for involvement. Different CTVs were defined as follows: CTV_{70} = GTV + 5 mm margin; $CTV_{59.4} = CTV_{70} + 5$ mm margin plus areas at risk for microscopic involvement, including the entire nasopharynx, retropharyngeal nodal regions, skull base, clivus, pterygoid fossae, parapharyngeal space, sphenoid sinus, the posterior third of the nasal cavity/maxillary sinuses that includes the pterygopalatine fossae, and nodal regions levels I–V. To account for organ motion/daily treatment setup uncertainties, a planning target volume (PTV) was added (ie, additional margin of 3–5 mm) to each of the above CTVs. In areas

Table 1 Treatment parameters and outcomes of patients after intensity-modulated radiotherapy

Study	Year	n	Stage	Radiotherapy			Fraction	Time (years)	Outcome (%)		
				Dose (Gy)	Dose/Fr	Boost after IMRT			LFFR	DFFR	OS
Ma et al[42]	2012	30	III–IVb	66–74	2–2.11	Yes	33	2	93	93	90
Lee et al[50]	2012	44	IIb–IVb	70	2.12	No	33	2	83.7	90.8	90.9
Su et al[49]	2012	198	I–II	68	2.27	No	30	5	97	97.8	97
Xiao et al[48]	2011	81	III–IVa	68	2.27	No	30	5	95	83	75
Lai et al[13]	2011	512	III–IV	68	2.27	Yes	30	5	93	84	76
Ng et al[47]	2011	193	III–IV	70	2–2.12	Yes	33	2	95	90	92
Bakst et al[41]	2011	25	II–IVb	70.2	2.34	No	30	3	91	91	89
Wong et al[46]	2010	175	I–IVb	70	2.12	Yes	33	3	93.6	86.6	87.2
Lee et al[45]	2009	68	I–IVb	70	2.12	No	33	2	92.6	84.7	80.2
Tham et al[43]	2009	195	III–IV	70	2.12	Yes	33	3	90	89	94
Lin et al[44]	2009	323	II–IVb	66–70	2.2–2.25	Yes	30	3	95	90	90
Wolden et al[39]	2006	74	I–IV	70	2	No	35	3	91	78	83
Kwong et al[40]	2006	50	III–IVb	76	2.17	No	35	2	96	94	92
Kam et al[38]	2004	63	I–IV	66	2	Yes	33	3	92	79	90
Lee et al[37]	2002	67	I–IV	65–70	2.12–2.25	Yes	33	4	97	66	88

Abbreviations: Fr, fraction; IMRT, intensity-modulated radiotherapy; LFFR, local failure-free rate; DFFR, distant failure-free rate; OS, overall survival.

where the GTV or the CTV was adjacent to critical normal structures (ie, brain stem) the margin could be reduced to 1 mm. PTV_{70} received 70 Gy in 2.12 Gy/fraction, and $PTV_{59.4}$ received 59.4 Gy in 1.8 Gy/fraction, over 33 days. The lower neck could be included in the IMRT fields by using proper contours of CTVs (1.8 Gy/fraction) and by keeping the dose to the larynx to as low as possible without compromising target coverage. Alternatively, a split-field IMRT technique was used, in which the low neck was treated with conventional anterior–posterior or anterior–posterior/posterior–anterior fields and received a total of 50.4 Gy. However, all involved nodes received a total dose of 70 Gy. Another useful reference, RTOG 0615,[50] suggested a dose prescription that was similar to RTOG 0225. With excellent locoregional control rates from IMRT, the current CTV margins may be too large. In the era of modern imaging and increased resolution, we may be able to reduce the margins and decrease toxicity without compromising patient outcomes. Lin et al proposed a reduced volume technique that produced an acceptable outcome compared to the targets in the RTOG 0225 and RTOG 0615 studies.[44] Future studies should focus on reducing target volumes to minimize toxicity while escalating the dose in high-risk patients.

Selective neck irradiation in N0 disease

Selective neck irradiation usually covers the whole-neck lymph-node drainage region of N0 disease.[52] Head and neck MRI is generally used in most cancer centers, because it can clearly detect lymph-node metastases in the clinically negative necks of NPC patients. A retrospective review of data from 924 NPC patients who underwent MRIs in Tang et al showed that lymph-node metastases spread in an orderly fashion from the higher-level lymph nodes to the lower-level lymph nodes. Prophylactic irradiation (excluding the level IV and supraclavicular regions) did not increase the risk of regional recurrence in N0 disease.[53] Gao et al reported that four patients developed neck recurrence, and only one (0.2%) of the 410 patients with lymph node-negative NPC (treated with elective levels II, III, and Va irradiation) experienced relapse outside the irradiation fields.[54] Ou et al reported that elective irradiation at levels II, III, and Va was not inferior to whole-neck irradiation in patients with retropharyngeal lymph-node metastasis in cases of rare out-of-field recurrence and good regional control.[55] Chen et al recently reported a phase II prospective study examining the effects of omitting elective neck irradiation to nodal levels IV and Vb in 212 NPC patients (128 N0 and 84 N1) who were treated with IMRT.[56] Only one patient (0.5%) developed nodal failure at level Vb; none of the patients developed nodal failure at level IV. The 5-year regional control rates, distant failure-free survival (FFS), and OS were 95.6%, 91.4%, and 89.8%, respectively. Based on these studies, it appears that the risks of regional recurrence and distant metastasis did not differ statistically between the patients with inferior borders in the neck-irradiation field at and below the cricoid cartilage in patients with N0 NPC. Reducing the volume of neck irradiation in N0 patients may potentially reduce skin, soft-tissue, and thyroid toxicity in the lower neck, maintain submandibular gland function, and minimize oral mucositis in the upper neck. This hypothesis would require further prospective phase III testing before becoming standard practice.

Toxicity and quality of life

Advances in radiation therapy, such as IMRT, have allowed high-dose delivery to tumors while sparing normal tissues. IMRT was shown to be superior to conventional RT by minimizing xerostomia and maintaining quality of life in a randomized study.[57] In another randomized trial by Kam et al, the incidence of observer-rated xerostomia was 39.3% with IMRT compared to 82.1% with conventional RT ($P = 0.01$).[58] The patients who received IMRT had increased stimulated whole-saliva and parotid flow rates. There is increasing evidence that toxicity to other critical organs (besides the salivary glands) may be moderated if tight dose constraints are applied during the IMRT planning process. A cross-sectional study by Fang et al showed that long-term survivors (>2 years) who were treated with IMRT had significantly better quality of life scores than those who were treated with 2D-RT in terms of swallowing, social eating, teeth, and mouth-opening domains.[59] Wang et al reported that compared to the conventional CRT technique, IMRT may protect middle-ear function, even with larger fraction sizes.[60] By limiting the dose to the middle-ear cavity to <34 Gy and the dose to the isthmus to <53 Gy with IMRT, we may decrease the radiation-induced otitis media with effusion, even with the larger 2.25 Gy fraction size. In a prospective study by Pan et al, the rate of hearing impairment decreased if the IMRT radiation dose in the inner ear was <50 Gy.[61] Lee et al also reported that cochlea that received > 50 Gy had significantly higher rates of deafness.[62] Temporal lobe necrosis (TLN) is one of the most debilitating late-stage complications after RT in NPC. Tuan et al showed that the cumulative incidence of TLN was 5% in 771 NPC patients who were treated with conventional RT alone.[63] However, Bakst et al used dose-painting IMRT to deliver 2.34 Gy/fraction to a total dose of 70.2 Gy with Intergroup

0099 chemotherapy.[41] The patients achieved excellent 3-year FFS and OS rates, but 12% of the patients developed TLN after a median follow-up of 33 months. This regimen is no longer recommended. Two retrospective studies by Lee et al showed that the dose per fraction did not affect local control, but was significantly associated with TLN.[64,65] More delayed neurologic toxicities such as cervicobulbar neuronopathy have also been reported.[66] The therapeutic margin for NPC is extremely narrow. Therefore, excessive dose escalation and large fractional doses should be avoided.

Primary treatment of NPC

Treatment for stage I NPC

Patients with stage I disease should be treated with RT alone. A large Hong Kong study reported 5-year local control and OS rates as high as 91% and 90%, respectively, for stage I NPC using predominantly conventional RT.[12] Two phase III studies of early stage NPC treated with IMRT showed no differences compared to the local controls while improving xerostomia.[57,58] None of the early stage patients who were treated with IMRT alone developed locoregional failure, with a median follow-up of 2.6 years in the RTOG 0225 trial.[45] IMRT alone is effective at treating over 90% of patients with stage I NPC.

Treatment for stage II NPC

The prognoses of patients with stage I and II NPC are generally favorable. This group of patients has largely been excluded from clinical trials of the combined modality treatment. While most authors agree that the prognosis for stage I patients is excellent with RT alone, the outcomes in patients with stage II disease have been reported to be less favorable.[67–69] The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (version 2.2012) recommends concurrent chemoradiotherapy (CCRT) for patients with stage II NPC because the landmark Intergroup 0099 trial included patients with disease states that were equivalent to stage II based on the current TNM system.[70] The Society of Clinical Oncology terminology, the European Head and Neck Society–European Society for Medical Oncology–European Society for Radiotherapy and Oncology Clinical Practice Guidelines also considered CCRT for stage II NPC as level I evidence with a grade B recommendation.[16]

RT alone should be adequate for treating stage I NPC and has resulted in excellent survival rates. However, it may not be the optimal treatment for stage II disease. Two historical series have reported 5-year survival rates of only 75%–77% for stage II; both locoregional and distant recurrences were more common than in stage I disease.[11,67–69] Xiao et al found that patients with Chinese 1992 stage T2N1 are a unique subgroup in early stage NPC, with a 5-year OS rate of only 73.1%. Distant metastasis primarily accounts for treatment failure in this group.[68] Leung et al evaluated the results of 1070 patients who were primarily treated with RT alone between 1990 and 1998 and reported that isolated distant metastases occurred in only 5.7% of the patients with stage IIa but were observed in 14.9% of the patients with stage IIb NPC.[11] Su et al reported on the long-term survival outcomes and toxicity of early stage NPC patients who were treated with IMRT alone.[49] The 5-year distant metastases-free survival (DMFS) rate for T2N1 disease was 94% compared to 99%–100% for T1–2N0 or T2N0 NPC. In a study that evaluated patients with negative cervical nodes treated with IMRT, the patients without retropharyngeal node involvement had a DMFS rate of 95.9% compared to 88.1% for the patients with retropharyngeal lymphadenopathy ($P = 0.04$).[71]

Two retrospective analyses suggested that CRT appeared to be effective only in patients with early stage disease.[72,73] Chua et al studied the effects of induction chemotherapy on NPC patients.[72] The results showed that significant differences in the OS and DMFS rates were only observed in the T1–2N0–N1 group and favored the combined chemotherapy and RT arm. The 5-year OS was 79% in the combined arm and 67% in the RT-alone arm ($P = 0.048$). The corresponding 5-year DMFS rates were 86% and 74% ($P = 0.0053$); however, improved outcomes were not observed in the advanced NPC group. Lin et al divided NPC patients into high-risk and low-risk subgroups according to their grading system.[73] The high-risk patients met at least one of the following criteria: (1) nodal size $>$ 6 cm, (2) supraclavicular node metastases, (3) 1992 AJCC stage T4 N2, or (4) multiple neck-node metastases with one node $>$ 4 cm. The authors found that the OS (83.2% vs 59.7%, $P = 0.0041$) and PFS (87.3% vs 61.5%, $P = 0.0003$) were significantly improved in the patients receiving CCRT rather than RT alone in the low-risk group. No survival benefits were gained in the high-risk patients.

Cheng et al[74] showed that the DFS of stage II disease with CCRT was equal to that of stage I disease with RT alone, which suggested that CCRT reversed the unfavorable prognosis of patients with stage II NPC and reduced the risk of failure compared to the risk in patients with stage I disease. A recent phase III trial by Chen et al included 230 patients with stage II disease according to the Chinese 1992 staging system (equivalent to stage II–III in the 7th edition AJCC manual) and reported that RT plus concurrent weekly cisplatin (30 mg/m^2) achieved significantly improved OS compared to RT alone

(94.5% vs 85.8% at 5 years).[75] This result was mainly caused by an improved DMFS (94.8% vs 83.9%), although there was no significant difference in locoregional FFS (93% vs 91%). This randomized study supported the important role of concurrent chemotherapy for stage II NPC patients. It is possible that early stage disease may have a smaller distant tumor bulk that is more easily eradicated by concurrent chemotherapy. Because the earlier trials were performed using conventional radiation techniques, it is unclear whether the magnitude of the benefit is similar in patients who are treated with IMRT. The potential therapeutic gain of concurrent chemotherapy in stage II patients treated with IMRT should be explored in the future. Based on these studies, we hypothesized that stage II patients with cervical or retropharyngeal nodal metastases (particularly T1–2N1) may have higher risks for distant micrometastases that require systemic therapy, but local control may be adequate with RT alone.

Treatment for stages III–IVb NPC

Role of exclusive concurrent chemoradiotherapy

The current standard of care for locoregionally advanced (AJCC stages III–IVb) NPC is cisplatin-based CCRT. The US Intergroup 0099 trial was the first to demonstrate a 31% improvement in 3-year OS compared to RT alone using concurrent RT and high-dose cisplatin followed by adjuvant cisplatin and fluorouracil.[70] Although these benefits persisted at the 5-year follow-up, they were accompanied by severe toxicity, including mucositis and bone marrow suppression. The Intergroup 0099 trial regimen was cisplatin (100 mg/m^2) on days 1, 22, and 43 concurrent with RT at conventional fractionation (70 Gy in 35 fractions), followed by a combination of cisplatin (80 mg/m^2) and fluorouracil (1000 mg/m^2/day for 96 hours) on days 71, 99, and 127 during the post-RT phase. The results of four subsequent trials in endemic areas (one from Singapore, two from Hong Kong, and one from the People's Republic of China) supported the results of the Intergroup trial that used the same chemotherapeutic agents and the same or similar chemotherapy dose intensity.[76–79] The results from three trials[80–83] that compared CCRT vs RT alone with a different concurrent chemotherapy regimen favored the use of CCRT. As outlined in Table 2, this benefit was evident irrespective of the type or schedule of concurrent chemotherapy used, including high-dose cisplatin,[76–79] weekly low-dose cisplatin or oxaliplatin[81,82] and nonplatinum agents, such as tegafur-uracil.[83] A "noninferiority" study comparing cisplatin with carboplatin in concurrent and adjuvant therapy did not find any differences in OS or DFS after a relatively short median follow-up of 26.3 months, although carboplatin was better tolerated and resulted in fewer mucosal and renal toxicities.[84] However, only 59% and 42% of the patients treated with cisplatin were able to complete the concurrent and adjuvant therapies, respectively, compared with over 70% of the patients who received carboplatin. In contrast, an exploratory analysis from a phase II study reported that substituting cisplatin with carboplatin in CCRT adversely affected the clinical outcomes.[85] Until more definitive studies are available, carboplatin should not routinely replace cisplatin in clinical practice unless a patient cannot tolerate cisplatin.

Four phase III trials comparing induction chemotherapy to RT alone failed to show an improvement in OS, despite a significant reduction in local and distant failures.[86–89] Only two randomized trials have specifically compared RT alone with or without adjuvant chemotherapy, and no survival benefits were observed.[90,91] The meta-analysis by Baujat et al confirmed the value of adding chemotherapy and showed that concurrent chemotherapy is the most potent sequence for combining the two modalities. Induction chemotherapy could significantly reduce the risk of locoregional and distant failures, resulting in a significant improvement in FFS, but no statistically significant benefit in OS. Adjuvant chemotherapy failed to achieve significant benefits at any of the end points.[92] The Clinical Practice Guidelines in Oncology by the NCCN recommended the Intergroup 0099 regimen as the standard treatment for locoregionally advanced NPC (category 1 evidence). Zhang et al performed a meta-analysis of CCRT vs RT alone in NPC treatment,[93] including studies (six randomized controlled trials with 1483 patients) performed in endemic areas. Risk ratios of 0.63 (95% confidence interval [CI] 0.50–0.80), 0.76 (95% CI 0.61–0.93), and 0.74 (95% CI 0.62–0.89) were observed for 2, 3, and 5 years OS, respectively, in favor of the CCRT group. In addition, CCRT was also associated with improved locoregional and distant control. The results confirmed that CCRT was beneficial compared to RT alone. However, the relative benefits of CCRT in endemic populations may not be as significant as the benefits that were observed in previous meta-analyses. The current study has helped to establish CCRT as a standard practice for NPC patients with locally advanced disease in endemic regions. To our knowledge, no published data are available from randomized trials to address the role of concurrent CT and IMRT vs IMRT alone for locally advanced NPC.

Role of adjuvant chemotherapy following concurrent chemoradiotherapy

One major question regarding the design of the Intergroup 0099 regimen is the contribution of the adjuvant phase.

Table 2 Randomized trials of concurrent chemoradiotherapy in patients with nasopharyngeal carcinoma

Study	Year	Stage	n	Regimen	Radiotherapy dose (Gy)	Result (%)			
						Time (years)	LRFFR	DFFR	OS
Concurrent chemoradiotherapy									
Lin et al[80]	2003	III–IV (AJCC manual, 4th edition)	284	RT alone RT + PF	70–74	5	92.9 96.8 *P* = 0.1716	69.9 78.7 *P* = 0.0577	54.2 72.3 *P* = 0.0022
Chan et al[81]	2005	Ho's N2/N3 or node ≥ 4 cm (N1)	350	RT alone RT + P	66	5	–	–	59 70 *P* = 0.049
Zhang et al[82]	2005	III–IV (AJCC manual, 5th edition)	115	RT alone RT + O	70–74	2	–	80 92 *P* = 0.02	77 100 *P* = 0.01
Chen et al[75,*]	2011	II (Chinese 1992)	230	RT alone RT + P	68–70	5	91.9 93 *P* = 0.29	83.9 94.8 *P* = 0.007	85.5 94.5 *P* = 0.007
Concurrent + adjuvant chemotherapy									
Al-Sarraf et al[70]	1998	III–IV (AJCC manual, 4th edition)	147	RT alone RT + P → PF		5	–	–	37 63 *P* = 0.001
Wee et al[76]	2005	III–IV (AJCC manual, 5th edition)	221	RT alone RT + P → PF	70	2	–	70 83 *P* = 0.0029	78 85 *P* = 0.0061
Chen et al[78]	2008	III–IVb (AJCC manual, 5th edition)	316	RT alone RT + P → PF	70	2	91.9 98 *P* = 0.007	78.7 86.5 *P* = 0.024	79.7 89.8 *P* = 0.003
Lee et al[77]	2010	III–IVb (AJCC manual, 5th edition)	348	RT alone RT + P → PF	66	5	78 88 *P* = 0.005	68 74 *P* = 0.32	64 68 *P* = 0.22
Lee et al[79]	2011	T3–T4, N0–N1 (AJCC manual, 5th edition)	189	RT alone RT + P → P ART alone ART + P → P	69	5	85 81 *P* = 0.96 75 *P* = 0.3 90 *P* = 0.31	75 75 *P* = 0.94 74 *P* = 0.94 95 *P* = 0.046	66 78 *P* = 0.45 66 *P* = 0.43 85 *P* = 0.058
Chen et al[94]	2012	III–IV (AJCC manual, 6th edition)	251	CCRT CCRT → PF	66	2	95 98 *P* = 0.1	86 88 *P* = 0.12	92 94 *P* = 0.32
Induction + concurrent chemoradiotherapy									
Hui et al[102]	2009	III–IVb (AJCC manual, 5th edition)	65	CCRT T* P → CCRT	66	2	–	–	68 94 *P* = 0.012
Fountzilas et al[103]	2012	IIb–IVb (AJCC manual, 6th edition)	141	CCRT PET → CCRT	66–70	3	–	–	72 67 *P* = 0.052

Note: *Chinese 1992 stage II patients.

Abbreviations: RT, radiotherapy; CCRT, concurrent chemoradiotherapy; P, cisplatin; F, 5-fluorouracil; O, oxaliplatin; T*, docetaxel; E, epirubicin; T, paclitaxel; LRFFR, locoregional failure-free rate; DFFR, distant failure-free rate; OS, overall survival; U, uracil and tegafur; V, vincristine; B, bleomycin; M, methotrexate; AJCC, American Joint Committee on Cancer; PET, positron emission tomography.

Of the eight randomized trials that supported the use of CCRT, three were all concurrent trials, whereas five had both concurrent and adjuvant components, which made it difficult to identify the exact benefit of adjuvant chemotherapy. Based on the lack of benefit shown using adjuvant chemotherapy in meta-analyses, it is possible that the concurrent components of chemotherapy accounted for the observed survival benefit in the Intergroup 0099 and other Asian studies with similar designs. Poor compliance with adjuvant chemotherapy limits its broader application. Additional administration of chemotherapy after completing the CCRT phase may provide added benefit in advanced-stage patients. A recent phase III randomized trial by Chen et al showed that adjuvant cisplatin and fluorouracil chemotherapy did

not significantly improve FFS after CCRT in locoregionally advanced NPC; the risk of treatment failure was not significantly decreased.[94] In this study, the estimated 2-year FFS after a median follow-up of 37.8 months was 86% in the CCRT-plus-adjuvant chemotherapy group and 84% in the CCRT-only group ($P = 0.13$). However, the results must be interpreted with caution, because 18% of the patients in the CCRT-plus-adjuvant chemotherapy group were actually treated with CCRT alone, 20% of the patients discontinued the trial after starting adjuvant chemotherapy, 49% had a dose reduction, and 69% experienced delays in treatment. Longer follow-ups are needed to fully assess patient survival and late toxic effects. Furthermore, this trial was not designed as a noninferiority trial against the current standard of the US Intergroup 0099 trial; therefore, the negative result is difficult to interpret. A combined analysis of two large studies (NPC 9901 and NPC 9902) revealed that the dose of cisplatin during the concurrent phase of CCRT had a significant impact on locoregional control, while additional adjuvant chemotherapy with a fluorouracil-containing combination contributed to improved distant control.[95] However, the positive findings of the combined analysis are also difficult to interpret, as they were based on a per-protocol analysis. The value of adjuvant chemotherapy after CCRT has been extensively debated, because many patients will not be able to tolerate this treatment phase accurately and its benefit seems to be limited if existing at all but will lead to considerable toxicity. Only 55%–76% of the patients completed three cycles of adjuvant chemotherapy, and grade 3–4 toxicity occurred in 23%–43% of patients in phase III trials.[70,76–79] Additional external validation is needed before a definitive change in the Intergroup 0099-recommended regimen is appropriate.

A major goal of adjuvant chemotherapy is to reduce the subsequent occurrence of distant metastasis. No other regimens have been reported to be as effective as cisplatin and fluorouracil for treating NPC in an adjuvant setting. Another promising intensification strategy could be the addition of a fluoropyrimidine as a maintenance therapy. Fluoropyrimidines are thought to also function as angiogenesis inhibitors.[96] Results from studies in Taiwan[97] and Singapore[98] have shown great promise in terms of median survival rates in metastatic NPC. The use of biomarkers has provided new possibilities for tailoring treatments for patients who are most likely to benefit. Future studies should focus on using biomarkers in selecting patients who are at risk of distant failure after CCRT for additional adjuvant treatment. Chan et al reported that patients with elevated posttreatment EBV DNA loads had a high risk of tumor recurrence.[29] The NPC 0502 study in Hong Kong was designed to address whether patients with a detectable level of plasma EBV DNA at 6 weeks following CCRT should be offered adjuvant chemotherapy. Only those patients with a detectable level of plasma EBV DNA after completing RT were randomized to undergo observation either alone or with six cycles of adjuvant cisplatin and gemcitabine therapies.

Role of induction chemotherapy followed by concurrent chemoradiotherapy

One strategy to improve the efficacy of chemotherapy further is to use an induction-concurrent sequence. The NCCN guidelines currently include induction + CCRT as an option (category 3). Adjuvant chemotherapy is poorly tolerated, and compliance is limited because patients suffer substantial toxicities from CCRT. In the Intergroup trial, only 45% of patients fully complied with the planned concurrent and adjuvant chemotherapy schedule (primarily because of toxicity).[70] Similarly, only 57% of patients received all three cycles of adjuvant chemotherapy in the Singapore trial.[76] Compared with adjuvant chemotherapy, induction chemotherapy appears to be better tolerated, even with more aggressive regimens. A review of phase II studies of induction-concurrent sequences showed that the tolerance and compliance of induction chemotherapy are substantially better.[99] Nearly 100% of patients tolerated at least two cycles, and more than 85% completed all three intended cycles. Early use of a potent combination of cytotoxic drugs at a full dose would theoretically be more effective for eradicating micrometastases. In addition, this regimen could shrink the primary tumor to give a wider margin for irradiation, an advantage that is particularly needed in patients with extensive cranial involvement. Lee et al reported on 20 patients who received induction and CCRT with accelerated (six fractions per week) IMRT.[100] While the efficacy results were encouraging, with only one distant failure and no locoregional recurrences, all but one of the patients suffered severe (grade 3–4) acute toxicity.

In 2002, Rischin et al reported encouraging estimated 4-year PFS and OS rates of 90% and 81%, respectively, in patients with locally advanced NPC treated with induction + CCRT.[101] To the best of our knowledge, at least 16 single-arm phase II studies and three randomized trials evaluating induction + CCRT have been published. Various induction schemes using doublet or triplet regimens (containing platinum plus fluorouracil, epirubicin, gemcitabine and/or taxanes/docetaxel) have been tested.[99] However, the first three randomized phase II studies that evaluated induction + CCRT showed conflicting early results. Two randomized

phase II studies compared induction chemotherapy followed by CCRT with CCRT alone (Table 2).[102,103] A phase II trial by Hui et al suggested that induction docetaxel and cisplatin chemotherapy followed by CCRT was a highly feasible sequential strategy for treating advanced NPC.[102] The 3-year OS for the induction versus the control arm was 94.1% and 67.7% (hazard ratio 0.24, 95% CI 0.078–0.73; $P = 0.012$). Preliminary patterns of failure analysis suggested that this benefit is derived from the reduced number of distant failures. Another randomized phase II study comparing induction chemotherapy (cisplatin, epirubicin, and paclitaxel) followed by CCRT with CCRT alone was conducted by the Hellenic Cooperative Oncology Group.[103] After a median follow-up of 55 months, the 3-year PFS rates were 64.5% in the investigational group and 63.5% in the control arm ($P = 0.708$), with respective 3-year OS rates of 66.6% and 71.8% ($P = 0.652$). Huang et al showed that adding carboplatin to concurrent chemotherapy did not improve 3-year OS compared with induction chemotherapy alone using carboplatin and floxuridine.[104] The benefit of adding induction chemotherapy to CCRT remains uncertain. Phase III studies to test definitively the efficacy and feasibility of induction + CCRT should be encouraged. This strategy is being investigated by several groups in a phase III setting, and the studies are being performed in an induction setting to overcome poor compliance when chemotherapy is administered after RT (NCT00201396, NCT00997906, NCT00828386, NCT01245959).

Treatment for stage IVc NPC

Patients who present with distant metastasis (stage IVc disease) might account for approximately 10% of all NPC cases in the endemic area of NPC.[105] Choosing the appropriate primary treatment modality is based on several factors, mainly the survival impact, treatment-related complications, and quality of life. A major controversy concerns the necessity of treating the primary nasopharyngeal tumors. In a study of 125 patients with stage IVc NPC, Yeh et al[105] found improved 1-year OS in patients receiving RT alone versus chemotherapy alone or versus no treatment (48% vs 36% vs 25%, respectively), despite using conventional RT. This study might support the opinion that RT to the primary tumor sites offers certain survival benefits at the cost of mild radiation-related complications. In light of the poor prognosis in stage IVc NPC, treatment has conventionally been palliative in nature. However, improved therapies, including wider use of combined modality therapy and the development of modern RT techniques, are allowing selected patients to survive long-term. Lin et al[106] recently reported the 2- and 5-year OS rates were 50% and 17%, respectively, in 105 stage IVc NPC patients treated with platinum-based chemotherapy and RT. Radiation doses of greater than 65 Gy to the primary region and number of organs with metastases (single vs multiple) were independent predictive factors for OS. Setton et al[107] also reported the results of five stage IVc NPC patients underwent chemotherapy and definitive IMRT. Two have no evidence of disease as of their last follow-up (29 and 91 months). It is reasonable to assume that a combination of chemotherapy and RT might have potential survival benefits for selected patients with stage IVc NPC. Prospective randomized studies are needed to optimize treatment strategy.

Management of local or regional recurrent NPC

With the application of IMRT and appropriate chemotherapeutic agents, there was marked improvement in the outcome of NPC. Despite this, about 10% of patients still develop recurrent disease either in the neck or at the primary site.[39,41,43] The best salvage treatment for local recurrent NPC remains to be determined. The options include brachytherapy,[108] external RT,[109] stereotactic radiosurgery,[110] nasopharyngectomy,[111] and microwave coagulation therapy,[112] either alone or in different combinations. The role of chemotherapy alone is primarily reserved for palliation in patients not suitable for radical radiation therapy or a nasopharyngectomy. Treatment techniques should be highly individualized, and depend on the site and extent of recurrence, previous treatment, and the availability of equipment and expertise. Surgery or RT gives similar outcomes for small lesions, whereas either therapy has its own morbidities in both immediate and late periods.[113] Salvage nasopharyngectomy carried out for 246 selected patients showed a 5-year local control of disease of 74% and the 5-year disease-free survival was 56%.[111] Endoscopic nasopharyngectomy is a choice for recurrent NPC with central roof or floor lesions with minimal lateral extension. Short-term outcomes of endoscopic nasopharyngectomy for early stage recurrences are promising, but long-term follow-up is needed.[114,115] For recurrences involving the skull base or those too extensive for curative surgical salvage, external beam reirradiation sometimes with chemotherapy is applicable. Recent reports indicated that reirradiation by IMRT for recurrent NPC resulted in encouraging local control.[109,116] Hua et al[116] reported the long-term treatment outcome of 151 recurrent NPC patients treated with salvage IMRT. The 5-year local control rate and OS for restage I, II,

III, and IV were 80.0%, 85.0%, 80.0%, 78.7% and 71.4%, 62.9%, 35.5%, 30.2%, respectively. However, 39.0% of patients with restage III or IV disease experienced grade 3 or 4 late toxicities.

When the recurrent disease is only in the neck lymph nodes, salvage surgery is the optimal treatment method. Radical neck dissection is currently an accepted surgical management for recurrent nodal disease in patients with NPC, with well-proven efficacy and safety.[117,118] Radical neck dissection as the salvage procedure gave 55.8% 5-year local control of disease and 19.9% 5-year OS in 285 patients who had recurrent neck disease.[118] Recent reports have suggested that less extensive neck dissection is applicable in patients with localized involvement of the neck lymph nodes.[119,120]

Novel systemic therapies for nasopharyngeal carcinoma

Targeted therapy

Despite initial responses, the benefits of conventional chemotherapy are seldom long-term and the toxicities are intolerable for most patients. Therefore, novel therapies based on molecular targets of NPC have become the focus of development. Targeted therapy is still relatively underdeveloped for NPC. Epidermal growth-factor receptor (EGFR) and vascular endothelial growth-factor receptor (VEGFR) targeted therapies have been clinically studied in NPC patients.

EGFR has been evaluated as a therapeutic target in NPC because there is evidence to suggest that EGFR signaling may be important in the pathogenesis of NPC. EGFR is highly expressed in NPC (up to 90%), which is associated with a poor survival outcome.[121] Cetuximab is a chimeric anti-EGFR immunoglobulin G_1 monoclonal antibody, which is, to our knowledge, the first EGFR inhibitor that is clinically tested to treat NPC. Initial studies were performed on patients with recurrent and/or metastatic disease. In a multicenter study of 60 patients with progressive recurrent or metastatic NPC despite multiple lines of chemotherapy, the combination of cetuximab and carboplatin resulted in a partial response of 11.7% and a stable disease rate of 48.3%.[122] The median time to progression was 2.7 months for this patient cohort, in which 70% and 30% of the patients had one line and more than one line of prior chemotherapy, respectively. The treatment was well tolerated, with grade 3–4 leucopenia and thrombocytopenia occurring in 5% and 10% of patients, respectively. Gefitinib is a small molecule that acts against the EGFR tyrosine kinase. Two phase II studies of patients with recurrent or metastatic NPC conducted in Hong Kong failed to find any objective response to gefitinib at a dose of 500 mg daily.[123,124] One patient reportedly had prolonged disease stabilization for >8 months; this stabilization was associated with decreased plasma EBV DNA levels.[111]

Attempts were made to further improve the efficacy of primary treatment by integrating EGFR-targeted therapy with a current CCRT regimen. Because the predominant failure of locally advanced NPC with CCRT is distant metastasis, newer systemic strategies are being studied with the use of IMRT. A phase II study by Ma et al recently evaluated the feasibility of adding cetuximab to current cisplatin and IMRT in locoregionally advanced NPC.[42] The study showed the 2-year PFS was 86.5% (95% CI 74.3%–98.8%), with a median follow-up of 31.8 months. Another phase II trial by Chen et al obtained similar results.[125] With a median follow-up time of 23.5 months, the 2-year OS, DFS, local recurrence-free survival, regional recurrence-free survival, and DMFS rates were 91%, 89%, 90%, 90%, and 89%, respectively. In patients with locoregionally advanced NPC, cetuximab combined with IMRT plus concurrent cisplatin showed satisfactory 2-year locoregional control rates and 2-year OS. This combination appeared to be well tolerated with a manageable side-effect profile.

Angiogenesis is another attractive target, particularly because it may be associated with the metastatic process. In NPC, the expression of VEGF was found to have a significant association with angiogenesis and metastases.[126,127] Sunitinib is an orally administered small molecule that inhibits the tyrosine kinase activities of the VEGFR (VEGFR1–3), platelet-derived growth-factor receptor, stem cell-factor receptor (KIT), fms-like tyrosine kinase receptor-3, and rearrangement during transfection. One study in Hong Kong showed that sunitinib demonstrated modest clinical activity in heavily pretreated NPC patients.[128] However, the high incidence of hemorrhage from the upper aerodigestive tract in NPC patients who received prior high-dose RT in the region is concerning. In general, antiangiogenic therapy should be avoided in patients with recurrent nasopharyngeal tumors located close to major vessels or within a previously irradiated field.

Attempts have also been made to improve further the efficacy of primary treatment by integrating VEGF-targeted therapy with a current CCRT regimen. A recent phase II multi-institutional trial (RTOG 0615) demonstrated that the addition of bevacizumab (an anti-VEGF drug) to standard CCRT for locoregionally advanced NPC is feasible and might delay the progression of subclinical distant disease.[50] With a median follow-up of 2.5 years, the estimated 2-year locoregional progression-free interval was 83.7% (95% CI 72.6–94.9);

the 2-year DMFS was 90.8% (95% CI 82.2–99.5), the 2-year PFS was 74.7% (95% CI 61.8–87.6), and the 2-year OS was 90.9% (95% CI 82.3–99.4).

Because control of distant metastasis should be the main objective when combining CCRT with targeted therapy, it is encouraging that all the phase II trials that combined CCRT with targeted therapy resulted in a 2-year DMFS of approximately 90%. This result appeared to be an improvement compared with the expected DMFS of 70%–80%. These outcomes are promising and provide new hope to patients with NPC. Randomized phase III studies are needed to assess the magnitude of the benefits and cost-effectiveness of targeted agents.

Immunotherapy

The outcome of patients with NPC who present with advanced-stage disease or who have failed conventional CRT is poor. Additional effective low-toxicity treatments are warranted to improve the prognosis for NPC. EBV is present in virtually all cases of poorly differentiated and undifferentiated nonkeratinizing NPC (World Health Organization types II and III).[129] Consequently, the presence of EBV antigens in NPC provides a target for immunotherapeutic approaches.[130] Immunotherapy with EBV-specific cytotoxic T cells (CTLs) has proven effective in posttransplant lymphoproliferative disorders (PTLDs), which are highly immunogenic tumors expressing type III latency, including the immunodominant EBV nuclear antigens (EBNA)-3A, -3B, and -3C.[131] Autologous EBV-transformed B-lymphoblastoid cell line (LCL) reactivated T cells were generated in vitro and used to treat advanced cases of NPC. Several phase I and II studies that have generated CTLs for PTLD have shown potential efficacies against NPC.[132–135] Comoli et al reported that autologous CTL therapy has been used to treat ten NPC patients with promising results.[133] In this study, ten patients with documented progression of advanced-stage NPC were treated with EBV-specific CTLs. Disease control was achieved in six of the patients; two patients displayed partial responses, and four exhibited documented stable disease. Straathof et al reported that EBV-specific CTLs demonstrated promising efficacy and safety in six patients with refractory disease: two complete responses, one partial response, and one long-term stable disease.[134] These results demonstrated that administering EBV-specific CTLs in patients with advanced NPC was feasible and tolerable and may be associated with significant antineoplastic activity.

Current approaches using LCLs predominantly generate CTLs, which target the immunodominant EBNA3–6 antigens. However, unlike PTLD, NPC cells express a limited array of EBV antigens (latency type II), including latent membrane proteins (LMP)-1 and -2 and EBNA1.[136,137] In previous studies, the EBV-specific CTL lines were generated by stimulation with EBV-LCL, which favored the outgrowth of CTL responses to the immunodominant EBNA-3 proteins rather than the subdominant EBV proteins LMP1 and LMP2 expressed in NPC. In the context of NPC, immunotherapeutic approaches that only target LMP1, LMP2, and EBNA1 should improve the specificity of CTL lines and avoid the requirement to generate LCLs. Antitumor responses could be further enhanced by strategies that increase the specificities of the CTL lines for the EBV latency II antigens expressed in NPC.[138–144] Smith et al recently reported the effectiveness of a phase I study involving adenoviral-based EBV vaccine (referred to as AdE1-LMPpoly)-stimulated T-cell immunotherapy for EBV-associated recurrent and metastatic NPC.[144] AdE1-LMPpoly encodes EBNA1 fused to multiple $CD8^+$ T-cell epitopes from the EBV latent membrane proteins LMP1 and LMP2. Of 24 NPC patients, EBV-specific T cells were successfully expanded from 16 patients (72.7%). The time to progression in these patients ranged from 38 to 420 days, with a mean time to progression of 136 days. Compared with the patients who did not receive T cells, the median OS increased from 220 to 523 days. This study showed that adoptive immunotherapy with AdE1-LMPpoly-stimulated T cells is safe and may provide long-term clinical benefits. In future studies, AdE1-LMPpoly vectors should be considered for potential use as a prophylactic vaccine to prevent recurrent or metastatic disease in high-risk individuals after CCRT.

New RT technology

The development of new technology brings more opportunities for maximizing protection of normal structures and further improvement of locoregional control. Irradiation with protons instead of the currently used photons generally results in a significantly lower physical dose in the coirradiated healthy tissues, due to its superior beam properties. The advantages of intensity-modulated proton therapy over state-of-the art IMRT in NPC have been demonstrated by comparative planning studies,[145,146] revealing dosimetric benefits, essentially by lowering the integral dose in organs at risk and noncritical normal tissues. Whether the theoretic advantage of proton-beam RT can translate into a clinical benefit needs to be confirmed. To help answer this question for NPC, two phase II trials have been performed in the US (NCT00592501 and NCT00797290).

Conclusion

This review details the available clinical data regarding treatment of NPC. The treatment used for stage I NPC was RT alone, while the treatment for stage II and locally advanced NPC was cisplatin-based CCRT. Locoregional control exceeding 90% and reduced xerostomia-related toxicities can be achieved with IMRT; distant control was the most pressing research issue. However, additional improvements are still needed to improve the quantity and quality of life of NPC patients. The strategy of induction + CCRT is appealing, particularly for patients with extensive locoregional disease that infiltrates critical structures. Data from ongoing phase III trials must be available before the current standard (Intergroup 0099 regimen) is replaced. Additional prognostic and predictive biomarkers are needed to identify the patients at the greatest risk of distant failure who would benefit from adjuvant chemotherapy. With the emergence of new RT techniques, such as IMRT and image-guided RT, the role of CCRT combined with these new techniques should be tested. For targeted therapy and EBV-specific immunotherapy, promising results in early clinical trials should be validated in phase III clinical trials.

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Disclosure

The authors report no conflicts of interest in this work.

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