Review Article

Combination of precision radiotherapy with chemotherapy and immunotherapy in non-recurrent/metastatic nasopharyngeal carcinoma

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Abstract: Nasopharyngeal carcinoma (NPC) is a highly radiosensitive cancer with a unique geographical distribution pattern and a close relationship with Epstein-Barr virus infection. Over recent decades, the rapid development of precision radiotherapy techniques, such as intensity-modulated radiotherapy, proton therapy, and carbon-ion therapy, has not only achieved significantly improved clinical outcomes, but also reduced radiation-related toxicities in the management of NPC, especially for the early-stage disease. However, radiotherapy alone is not sufficiently effective for patients with locoregionally advanced NPC. Based on robust medical evidence from clinical trials, platinum-based concurrent chemotherapy has been established as the standard treatment option for patients with NPC at the intermediate-to-advanced stages. In addition, the combination of precision radiotherapy with different chemotherapy schedules and regimens is still under extensive investigation. Meanwhile, emerging immunotherapy techniques, especially immune checkpoint inhibitors, combined with precision radiotherapy, with or without chemotherapy, is considered a promising strategy to treat locoregionally advanced NPC. Apart from the validation of its therapeutic efficacy, a reliable strategy to select patients that would benefit from different combination therapies is highly anticipated in the future. This review presents a comprehensive summary of the evidence for various combination strategies based on precision radiotherapy in patients with non-recurrent/metastatic NPC, and provides an insight into the related ongoing and future clinical trials.

Keywords: Nasopharyngeal carcinoma (NPC); precision radiotherapy; chemotherapy; immunotherapy

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Introduction

Nasopharyngeal carcinoma (NPC) is a special type of head and neck cancer because of its unique epidemiology and association with Epstein-Barr virus (EBV) infection. NPC has a unique geographical distribution, being mainly prevalent in Southeast Asia. According to the International Agency for Research on Cancer, the incidence of NPC in 2018 was 129,079 worldwide, of which 60,558 (46.9%) cases were in China, and 34,639 (26.8%) cases occurred in the rest of Southeast Asia (1). Correspondingly, the age-standardized incidence of NPC in 2018 ranged from 2.0 to 6.6 in southeast Asia, while it ranged from 0.21 to

0.51 in non-endemic North America (1). In addition to environmental factors, ethnic and genetic factors also play an important role in the pathogenesis of NPC, which has been validated in second-generation immigrants from endemic regions (2).

Radiotherapy is the backbone of NPC treatment. Over recent decades, the precision of radiotherapy techniques has increased rapidly, from the conventional two-dimensional radiotherapy (2D-RT) to the three-dimensional radiotherapy (3D-RT), which includes three-dimensional conformal radiotherapy (3D-CRT, intensity-modulated radiotherapy (IMRT), and particle beam therapy (such as proton therapy and carbon-ion therapy). The progress of precision radiotherapy has brought appreciably better survival outcomes, with obviously decreased mortality rate observed in three NPC endemic regions (*Figure 1*) (3-8). From 1974 to 2013, the mortality rate of male patients with NPC decreases by 73.8% in Hong Kong, 64.9% in Singapore, and 65.7% in Mainland China. However, radiotherapy alone is not a high intensity treatment option for locoregionally advanced NPC (LANPC). A suitable way to achieve effective management of LANPC is to add chemotherapy to radiotherapy, such as concurrent chemoradiotherapy, which is regarded as the standard choice according to the National Comprehensive Cancer Network (NCCN) clinical guidelines. Besides, the emerging immunotherapy promises to be alternative to the current standard care in NPC.

The most suitable schedule and regimen of combination therapy comprising chemo-/immunotherapy based on precision radiotherapy are still under extensive investigation, and there is controversy surrounding the limited and heterogenous trial results. Therefore, this comprehensive review discusses the efficacy and safety of various combinations of precision radiotherapy with chemotherapy and immunotherapy in non-recurrent/metastatic NPC, with the aim of providing an insight into related ongoing and future clinical trials.

Precision radiotherapy

Radiotherapy has long been the backbone of the treatment modality for non-recurrent/metastatic NPC since 1965, because of its unique biological behaviour of high radiosensitivity and deep anatomical position. In the 1920s, only a few patients with NPC receiving radiotherapy alone survived for more than 3 years (9). Longer survival has been achieved since the development of the machine from kilo-voltage to mega-voltage, which yielded a 5-year overall survival (OS) of 25% by 1965 (10). Since then, although still in the era of conventional 2D-RT, the prognosis of patients with NPC gradually improved. Retrospective analysis of 5,037 patients with NPC treated between 1976 and 1985 in Hong Kong and 378 patients treated between 1954 and 1992 in M.D. Anderson Cancer Centre reported a similar 5-year OS of over 50% and a local control rate of 60–70% (11,12). Another study of 2,687 patients with NPC treated between 1996 and 2000 showed a 5-year OS of 75% and a local failure-free rate of 85% (13).

The nasopharynx lies in a special anatomical position adjacent to many critical structures, including salivary glands, ear, pharyngeal muscle, mandible, oral cavity, spinal cord, brain, and brainstem; therefore, unavoidable radiation to these structures results in life-related toxicities (e.g., xerostomia, mucositis, hearing loss, dysphagia, jaw osteonecrosis, or brain injury), which significantly impaired patients' quality of life. Considering that it is impossible to avoid casting the beam through the structures, highly precise methods that deliver most of the beam to the tumor while sparing more normal tissues are required. From the 1990s, along with the development of computer science, imaging techniques [e.g., computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography-CT (PET-CT)], and radiotherapy machines themselves, major radiotherapeutic techniques have gradually advanced from 2D-RT to the more precise 3D-RT. A series of 3D-RT techniques have been adopted to treat NPC over the past two decades, including 3D-CRT, IMRT, stereotactic radiotherapy, etc. In 3D-CRT, the development of CT enables the delineation of tumors in three dimensions, as opposed to the "flat" image from X-ray, and the advent of multileaf collimators has helped to arrange beams to optimally fit the outlines of the tumors at various angles. More precise than 3D-RCT, IMRT deliver a non-uniform fluence to the tumor, by dividing the beam into multiple "beamlets" with different intensities. Many publications have reported significantly improved therapeutic effects of IMRT compared with those of 2D-RT (14-21). The local control rate (LCR) has increased from 44–68% to 75–95% for LANPC (20,22-28). A meta-analysis including 3,570 participants in 8 studies showed that IMRT resulted in a better 5-year OS [odds ratio (OR) 1.51, 95% confidence interval (CI): 1.23–1.87] and 5-year LCR compared with those achieved by 2D-RT or 3D-CRT (29). Besides, a prospective randomized controlled trial showed that IMRT resulted in an improved 5-year OS (79.6%

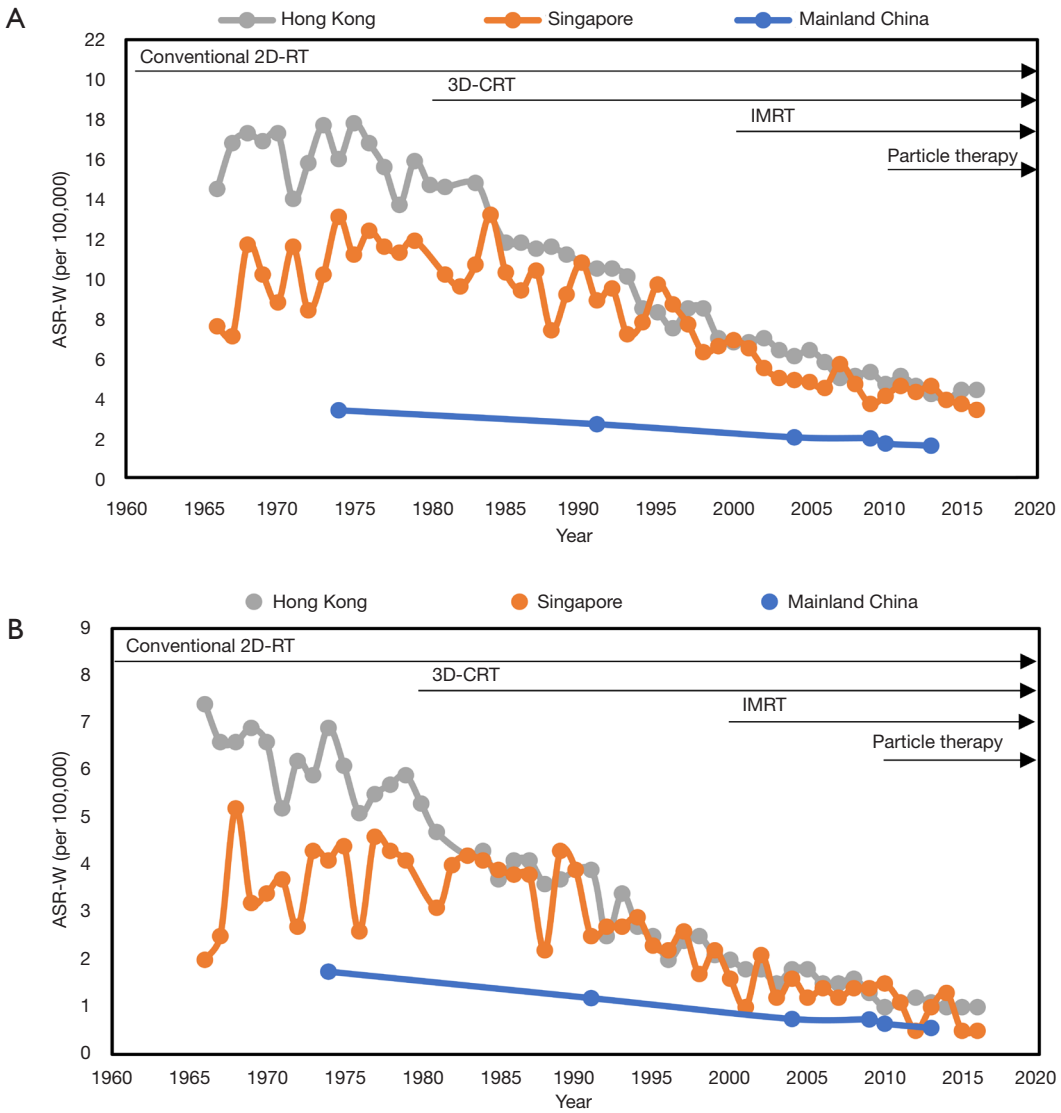

Figure 1 Trend of age-standardized mortality of patients with NPC in three endemic regions. (A) Male patients. (B) Female patients. ASR-W, age-standardized mortality rate using Segi's World Standard Population as a standard population. Data source: The data for Singapore and Hong Kong was obtained from the World Health Organization Cancer Mortality Database, and the data for mainland China was obtained from related publications.

vs. 67.1%) and LCR (90.5% *vs.* 84.7%) compared with that of 2D-RT (30). In addition to the survival benefit, IMRT improves quality of life by sparing more organs at risk (OARs) and reducing radiation-induced toxicities. A randomized clinical trial revealed that IMRT led to a significantly lower incidence of xerostomia than 2D-RT (39.3% *vs.* 82.1%) and a better preservation of parotid function (31). Another trial demonstrated a significantly lower incidence of both acute and late radiation-induced toxicities from IMRT (30). Based on these evidences, IMRT has become the most widely used radiotherapy technique in current clinical practice.

However, the intratreatment and intertreatment variation of the tumor poses a great threat to the precision of radiotherapy. Intratreatment variation results mainly from movement, while intertreatment variation is mainly from tumor shrinkage, soft-tissue change, and weight loss. Considering the very steep dose fall-off at the margin between the tumor and normal tissue in IMRT, these variations could lead to missing the target and an

overdosage in the OARs. Image-guided radiotherapy (IGRT) was introduced to cope with this issue, which uses imaging within the treatment room to change the position of the patient to match with the primary CT-simulation or change the planning dose. A prospective study of 197 patients with NPC reported a survival superiority in 5-year OS of IGRT over non-IGRT (91.8% *vs.* 74.3%) (32), while another study failed to detect a significant difference of the dose delivered to parotid glands between the IGRT and non-IGRT groups (33). Tomotherapy, an advanced form of IMRT that combines IGRT with a helical delivery pattern, is believed to have a better dosimetric distribution. A prospective phase II clinical trial comparing tomotherapy with IMRT in patients with NPC is still underway (NCT03588403). More recently, adaptive radiotherapy, an emerging concept that involves replanning during the treatment by changing either the dosage or outlines, is a promising technique to deal with these variations. Studies have demonstrated a survival benefit of adaptive radiotherapy in head and neck cancer, including NPC (34), and a prospective non-inferiority trial of the use of adaptive radiotherapy for head and neck cancer undergoing radiotherapy is proposed (NCT03096808); however, more studies on the details of implementation and identification of the benefits of adaptive radiotherapy are warranted.

Over the past decade, emerging particle radiotherapy techniques, including proton therapy and carbon ion radiotherapy, have made great progress and attracted increased interest in their application to treat NPC, as an alternative to the traditional photon-based radiotherapy mentioned above. Particle beams establish a unique distribution of dose in depth, known as the "Brag Peak", creating a much sharper dose fall-off by releasing most of the energy over a short range of depth, depending on the initial energy level, and releasing only a little outside the peak, which provides a much more precisely controlled dose distribution. The dosimetric advantage of intensity-modulated proton therapy brings a significant improvement in tumor conformation and a reduction in both the mean dose to the OARs and the relevant radiation-induced toxicities, compared with those of IMRT (35-42). Favorable clinical outcomes of proton therapy have been reported in many publications. Preliminary results of a phase II trial of proton therapy with chemotherapy for NPC in Massachusetts General Hospital (NCT00592501) showed a 2-year LCR, OS, and disease-specific survival of 100%, 100%, and 90%, respectively (43). A similar result was reported in MD Anderson Cancer Center, with a 2-year LCR of 100% and OS of 88.9% (35). Intensity-modulated carbon-ion radiation therapy also shows a dosimetric advantage over IMRT in sparing more critical OARs (44). Studies of carbon ion radiotherapy are mainly limited to high-risk or recurrent NPC, mainly because of its high cost and limited availability. A study including 24 patients with high-risk NPC receiving bimodal treatment comprising IMRT plus carbon ion radiotherapy reported a 2-year LCR and OS of 95% and 100%, respectively (45). The first prospective trial evaluating the efficacy and safety of intensity-modulated carbon-ion radiation therapy in locoregional recurrent NPC has reported preliminary results. It showed an increase of 1-year OS from the historical 82% to 95% for intensity-modulated carbon-ion radiation therapy (46,47), which is in line with the value (98.1%) published in a retrospective study (48). Results of a phase I/II trial evaluating carbon ion radiation therapy for locally recurrent NPC is due imminently (NCT02795195). Currently, the availability of particle radiotherapy is limited, mainly because of the high cost and large size of the machines. There are only 5 countries and 13 centers that provide carbon ion radiotherapy and there are fewer than 100 proton therapy centers worldwide (49), which has also limited the evidence supporting particle therapy in NPC. No randomized trials evaluating particle therapy in NPC are available yet; therefore, further study of particle therapy is expected, especially trials with both a larger sample size and a randomized setting.

Precise dose planning is crucial to precision radiotherapy, in addition to the radiation techniques. Significant inter-observer variation was observed in manual contouring for all OARs of NPC, which affected dosimetric parameters significantly (50). To reduce the intra- and inter-observer variation, the idea of an automated artificial intelligence contouring system based on deep learning, especially convolutional neural networks, has been proposed against the background of booming artificial intelligence techniques. Findings showed that the artificial intelligence contouring system to automate delineation of the primary gross tumor volume could significantly improve accuracy and reduce variation and contouring time (51).

Combining chemotherapy with precision radiotherapy

With rapidly increasing precision, very satisfactory clinical outcomes have been achieved using radiotherapy alone for patients with early-stage NPC in the era of IMRT.

Radiotherapy alone is recommended as the first choice for patients with T1N0M0 NPC (52). For patients with NPC other than stage I, radiotherapy alone might be insufficient; thus, at least one type of systematic therapy is recommended to be added to radiotherapy for these patients, according to the 2020 NCCN clinical guidelines (52). However, consensus has yet to be achieved for the management of stage II non-metastatic NPC. The 10-year survival outcomes of a phase III randomized clinical trial indicated that concurrent chemoradiotherapy (CCRT) significantly improves OS, progression-free survival (PFS), and distant metastasis-free survival (DMFS), compared with those achieved by 2D-RT alone (53), while a meta-analysis showed that IMRT alone achieved similar survival outcomes compared with those of CCRT in stage II NPC (54). Another retrospective study demonstrated that CCRT only shows a survival advantage over 2D-RT, but not IMRT (55). A phase III multicenter randomized clinical trial (NCT02633202) focusing on this issue is underway. In this study, a total of 338 patients with stage T1–2N1M0/T2–3N0M0 NPC were randomly assigned into an IMRT group or a CCRT group, which might provide a clearer answer to whether chemotherapy is necessary for stage II NPC in the era of IMRT.

Concurrent chemoradiotherapy

Definitive CCRT is recognized as the standard treatment modality for LANPC, based on the evidence derived from many clinical trials; however, these were mainly performed in the era of 2D-RT (*Table 1*) (56,59,63,64). A meta-analysis conducted by Blanchard and colleagues in 2015 revealed that an OS benefit was only observed in CCRT [hazard ratio (HR) 0.65, 95% CI: 0.56–0.76] or CCRT plus adjuvant chemotherapy (AC; HR 0.65, 95% CI: 0.56–0.76) in comparison with radiotherapy alone (65). Meanwhile, another meta-analysis demonstrated a significantly improved 5-year OS (relative risk 0.64, 95% CI: 0.45–0.91) and overall response rate (0.53; 95% CI: 0.43–0.66) in CCRT versus IMRT alone (66). Besides, an ongoing multicenter clinical trial might provide more evidence of the superiority of CCRT over radiotherapy alone (NCT01817023).

Cisplatin is regarded as the classic chemotherapy regimen for NPC in the CCRT regimen, and is also the only drug that the 2020 NCCN clinical guidelines recommended for CCRT (52,57,63). The efficacy of drugs other than cisplatin, including other platinum-based drugs like carboplatin, oxaliplatin, lobaplatin, or nedaplatin (62,67-69), and non-platinum drugs like uracil plus tegafur, docetaxel, or 5-fluorouracil plus hydroxyurea (70-72), has been widely explored. Some studies showed that the non-platinum regimen has a comparable therapeutic effect to cisplatin, which might offer more alternatives for NPC. A recent retrospective cohort study revealed that CCRT based on non-platinum regimens was inferior in terms of OS and disease-free survival (DFS) to the platinum-based CCRT, although the differences were not significant (73). Regarding the dose of cisplatin in clinical practice, either 80–100 mg/m^2 every 3 weeks or 40 mg/m^2 once a week is acceptable (8), and a cumulative cisplatin dose of 230–270 mg/m^2 is recommended for patients with LANPC (74).

Adjuvant chemotherapy (AC)

Although CCRT has been proven to be highly effective in locoregional control, distant metastasis is still an unresolved problem that requires additional cycles of chemotherapy to strengthen treatment intensity. However, no evidence supporting AC alone has been reported yet. Several studies reported that AC following radiotherapy could not bring survival benefits, but induced increased toxicities (58,60,65,75).

More attention has been paid to the combination of AC and CCRT. In 1998, the landmark American Intergroup-0099 Study (INT-0099) demonstrated a significant improvement in 3-year OS and PFS in concurrent-adjuvant chemoradiotherapy compared with that of radiotherapy alone (63). However, there are two major flaws in the INT-0099 study. First, as radiotherapy alone was set as the control group in comparison with CCRT plus AC, it is difficult to definitively determine which one of the two chemotherapy schedules, or both of them, was the real and effective modality. Second, the INT-0099 trial was conducted in North America, where the major pathological type of NPC is World Health Organization type I, which is different from the endemic regions, where type II/III dominate. Therefore, the results of the INT-0099 study might be inapplicable to endemic regions. Since then, the efficacy of the INT-0099 regimen (cisplatin plus 5-fluorouracil as AC) has been validated in three endemic regions, including Hong Kong (NPC-9901 and NPC-9902 trials), Singapore (SQNP01 trial), and Mainland China (*Table 2*) (58,76-80). A combined analysis of NPC-9901 and NPC-9902 revealed that the CCRT phase and AC phase had a significant impact on locoregional failure-free survival and distant failure-free survival, respectively (83).

Table 1 Phase 3 randomized controlled trials evaluating concurrent chemoradiotherapy versus radiotherapy alone or different regimens of concurrent chemoradiotherapy

Reference	Experimental chemotherapy	Control chemotherapy	Inclusion period	Sample size	Overall survival		Other survival outcome measurements	
					Experimental *vs.* control	HR (95% CI); P value	Experimental *vs.* control	HR (95% CI); P value
Concurrent chemoradiotherapy *vs.* radiotherapy alone								
Lin *et al.* (56)	Concurrent: cisplatin 20 mg/m^2 d1–4; fluorouracil 400 mg/m^2 d1–4; q4wks × 2	–	1993–1999	284	5-year: 72% *vs.* 54%	NR; P=0.0022	5-year PFS: 72% *vs.* 53%	NR; P=0.0012
Chan *et al.* (57)	Concurrent: cisplatin 40 mg/m^2 d1; q1wk × 8	–	1994–1999	350	5-year: 70% *vs.* 59%	0.71 (0.5–1.0); P=0.049	5-year PFS: 60% *vs.* 52%	0.74 (0.54–1.0); P=0.06
Kwong *et al.* (58)	Concurrent: uracil plus tegafur 600 mg d1–7; concurrent with radiotherapy	–	1995–2001	219	5-year: 81% *vs.* 73%	NR; P=0.075	5-year FFS: 68% *vs.* 54%	NR; P=0.038
Wu *et al.* (59)	Concurrent: oxaliplatin 70 mg/m^2 d1; q1wk × 8	–	2001–2003	115	7-year: 71% *vs.* 56%	0.54 (0.31–0.94); P=0.028	5-year DMFS: 75% *vs.* 63%	0.52(0.29–0.94); P=0.027
Li *et al.* (53)	Concurrent: cisplatin 30 mg/m^2 d1; q1wk × 8	–	2003–2007	230	10-year: 84% *vs.* 66%	0.30 (0.23–0.68); P=0.001	10-year PFS: 77% *vs.* 64%	0.55 (0.34–0.89); P=0.014
Different regimens of concurrent chemoradiotherapy								
Chen *et al.* (60,61)	Concurrent: cisplatin 40 mg/m^2 d1; q3wks × 7; Adjuvant: cisplatin 80 mg/m^2 d1; fluorouracil 800 mg/m^2 d1–5; q4wks × 3	Concurrent: cisplatin 40 mg/m^2 d1; q3wks × 7	2006–2010	508	5-year: 83% *vs.* 80%	0.83 (0.57–1.22); P=0.35	5-year FFS: 75% *vs.* 71%	0.88 (0.64–1.22); P=0.45
Tang *et al.* (62)	Concurrent: Nedaplatin 100 mg/m^2 d1; q3wks × 3	Concurrent: cisplatin 100 mg/m^2 d1; q3wks × 3	2012–2014	402	NR	1.41 (0.67–2.94); P=0.37	2-year PFS: 90% *vs.* 88%	1.21 (0.75–1.96); P=0.42

PFS, progress-free survival; FFS, failure-free survival; DMFS, distant metastasis-free survival; CI, confidence interval; HR, hazard ratio; NR, not reported; q1/3/4wks, every 1/3/4 weeks; d1–4: day 1 to day 4.

However, consensus on whether AC following CCRT will achieve more survival benefits compared with those of CCRT alone, without increasing toxicity, has yet to be achieved. A robust phase III trial showed that CCRT followed by AC (cisplatin and 5-fluorouracil) failed to improve FFS, OS, DMFS, and LFFS compared with those achieved by CCRT alone in LANPC (*Table 3*) (60,61). Blanchard's meta-analysis also presented a similar result (65). It seems that applying concurrent-adjuvant chemoradiotherapy to patients with LANPC at a high risk of treatment failure might provide a survival benefit. A cohort study generating a risk stratification using age, T/N classification, and serum albumin level suggested that CCRT followed by AC (cisplatin and 5-fluorouracil, cisplatin and docetaxel, or cisplatin, 5-fluorouracil and docetaxel) could improve OS compared with the use of CCRT alone in high-risk LANPC (94). Besides, the post-treatment plasma EBV DNA level has become the most promising biomarker for risk stratification (95,96). A retrospective cohort defined high-risk patients as those with persistently detectable plasma EBV DNA 1 week after radiotherapy, and treated them with oral tegafur-uracil, with or without intravenous mitomycin-C, epirubicin, and cisplatin, while the control group was only placed under surveillance. This study showed a significant improvement of 5-year OS (71.6% *vs.* 28.7%; HR 0.27, 95% CI: 0.17–0.55) and a reduction in distant failure (97). However, in the phase III NPC-0502 trial, high-risk patients were defined as carrying detectable plasma EBV DNA at 6 to 8 weeks after radiotherapy and received AC comprising gemcitabine plus cisplatin (GP), while the rest of the patients were only placed under surveillance. No improvement in 5-year recurrence-free survival (49% *vs.* 55%; HR 1.09, 95% CI: 0.63–1.89) or OS (64% *vs.* 68%; HR 1.09, 95% CI: 0.56–2.11) was observed for AC compared with observation (98). The ongoing phase II/III NRG-HN001 trial (NCT02135042) defines high-risk patients as those with detectable plasma EBV DNA 1 week after IMRT. It is attempting to evaluate whether using adjuvant gemcitabine and paclitaxel could yield better survival outcomes than the standard regimen of cisplatin and 5-fluorouracil, which might provide further support for the application of AC. A recent new risk stratification model integrating the TNM staging system and post-treatment plasma EBV DNA showed improved effectiveness to screen patients with NPC, which could aid the selection of the AC beneficiaries in clinical practice (99).

Considering the controversies identified to date, it is difficult to draw a definitive conclusion regarding the utility of AC. On the one hand, marked between-study heterogeneity exists in study design, AC regimens and schedules, risk stratification methods, and even the timing of detection of post-treatment plasma EBV DNA levels. On the other hand, patients showed generally low compliance with the completion rate of whole-course AC, ranging from 50% to 76%, which was caused by poor fidelity to treatment resulting from severe toxicities (25,63,76,78-80). This greatly impaired the practicability and generalizability of the study results. The introduction of metronomic chemotherapy, a new method of delivering chemotherapeutic drugs in a continuous and dose-dense way, might help solve the latter problem by reducing toxicity and improving compliance (100). A retrospective analysis reported that the metronomic use of tegafur-uracil as AC significantly improved the 5-year DFS (91.89% *vs.* 57.58%), without compromising safety, compared with that of observation after radiotherapy (101). A prospective phase II trial came to a similar conclusion using metronomic delivery of capecitabine as AC (102). Three ongoing phase III randomized controlled trials evaluating the efficacy and toxicity of capecitabine following CCRT in patients with LANPC have attracted considerable attention, as one of them (NCT02958111) is delivered in a metronomic way (1,300 mg/m^2 per day for 1 year) and the other two trials (NCT02973386 and NCT02143388) use a traditional method of treatment delivery. The results of these trials will provide more insight into the efficacy of the adjuvant regimen using single-capecitabine and the impact of metronomic AC on the prognosis of patients with NPC.

Induction chemotherapy (IC)

IC is thought to be better tolerated than AC (103,104). The upfront use of chemotherapeutic drugs is not only more effective in reducing micrometastases, but also provides a wider safety zone and flexibility for radiotherapy planning by shrinking the tumors before radiotherapy (105). However, whether the combination of IC and radiotherapy is superior to radiotherapy alone remains controversial, because inconsistent results were reported by a series of studies comparing IC followed by radiotherapy with radiotherapy alone in LANPC. In 1996, a phase II trial reported that the combination of IC (bleomycin, epirubicin, and cisplatin) and radiotherapy improved DFS compared with that achieved by radiotherapy alone (106). Similarly, a pooled analysis of two phase III trials showed that adding cisplatin-based IC to radiotherapy led to a significantly improved disease-specific

Table 2 Phase 3 randomized controlled trials comparing radiotherapy alone as the control group with other treatment strategies

Reference	Experimental chemotherapy	Inclusion period	Sample size	Overall survival		Other survival outcome measurements	
				Experimental *vs.* control	HR (95% CI); P value	Experimental *vs.* control	HR (95% CI); P value
Concurrent chemoradiotherapy plus adjuvant chemotherapy *vs.* radiotherapy alone							
Al-Sarraf *et al.* (63)	Concurrent: cisplatin 100 mg/m^2 d1, q3wks × 3; Adjuvant: cisplatin 80 mg/m^2 d1, fluorouracil 1,000 mg/m^2 d1–4, q4wks × 3	1989–1995	147	3-year: 78% *vs.* 47%	2.50 (1.29–4.84); P=0.005	3-year PFS: 69% *vs.* 24%	4.34 (2.47–7.69); P<0.001
Wee *et al.* (76)	Concurrent: cisplatin 25 mg/m^2 d1–4, q3wks × 3; Adjuvant: cisplatin 20 mg/m^2 d1–4, fluorouracil 1,000 mg/m^2 d1–4, q4wks × 3	1997–2003	221	3-year: 80% *vs.* 65%	0.51 (0.31–0.81); P=0.0061	3-year DFS: 72% *vs.* 53%	0.57 (0.4–0.9); P=0.093
Lee *et al.* (77,78)	Concurrent: cisplatin 100 mg/m^2 d1, q3wks × 3; Adjuvant: cisplatin 80 mg/m^2 d1, fluorouracil 1,000 mg/m^2 d1–4, q4wks × 3	1999–2004	348	10-year: 62% *vs.* 49%	0.74 (0.56–0.997); P=0.047	10-year PFS: 56% *vs.* 42%	0.68 (0.51–0.90); P=0.006
Lee *et al.* (79)	Concurrent: cisplatin 100 mg/m^2 d1, q3wks × 3; Adjuvant: cisplatin 80 mg/m^2 d1, fluorouracil 1,000 mg/m^2 d1–4, q4wks × 3	1999–2004	189	5-year: 78% *vs.* 66%	0.76 (0.38–1.54); P=0.45	5-year PFS: 60% *vs.* 62%	0.98 (0.53–1.81); P=0.93
Chen *et al.* (80)	Concurrent: cisplatin 40 mg/m^2 d1, q3wks × 7; Adjuvant: cisplatin 80 mg/m^2 d1, fluorouracil 800 mg/m^2 d1–5, q4wks × 3	2002–2005	316	5-year: 72% *vs.* 62%	0.69 (0.48–0.99); P=0.043	5-year PFS: 68% *vs.* 57%	0.65 (0.46–0.92); P=0.015
Induction chemotherapy followed by radiotherapy *vs.* radiotherapy alone							
Chua *et al.* (81)	Induction: epirubicin 100mg/m^2, d1, cisplatin 60 mg/m^2, d1, q3wks × 2–3	1998–1993	334	3-year: 78% *vs.* 71%	NR; P=0.57	3-year RFS: 48% *vs.* 42%	NR; P=0.45
Ma *et al.* (82)	Induction: bleomycin 10 mg/m^2 d1, d5, cisplatin 100 mg/m^2 d1, fluorouracil 800 mg/m^2 d1–5, q3wks × 2–3	1993–1994	456	5-year: 63% *vs.* 56%	NR; P=0.11	5-year RFS: 82% *vs.* 74%	NR; P=0.05

PFS, progress-free survival; DFS, disease-free survival; FFS, failure-free survival; RFS, recurrence-free survival; DMFS, distant metastasis-free survival; CI, confidence interval; HR, hazard ratio; NR, not reported; q3/4wks, every 3/4 weeks.

Table 3 Phase 3 randomized controlled trials comparing concurrent chemoradiotherapy as the control group with other treatment strategies

Reference	Experimental chemotherapy	Control chemotherapy	Inclusion period	Sample size	Overall survival		Other survival outcome measurements	
					Experimental *vs.* control	HR (95% CI); P value	Experimental *vs.* control	HR (95% CI); P value
Induction chemotherapy plus concurrent chemoradiotherapy *vs.* concurrent chemoradiotherapy								
Tan *et al.* (84)	Induction: gemcitabine 1,000 mg/m^2 d1, d8, carboplatin AUC = 2.5 d1, d8, paclitaxel 70 mg/m^2 d1, d8, q3wks × 3; Concurrent: cisplatin 40 mg/m^2 d1, q1wk × 8	Concurrent: cisplatin 40 mg/m^2 d1, q1wk × 8	2004–2012	172	3-year: 94% *vs.* 92%	1.05 (0–2.19); P=0.49	3-year DFS: 75% *vs.* 67%	0.77 (0.44–1.35); P=0.36
Li *et al.* (85,86)	Induction: docetaxel 60 mg/m^2 d1, cisplatin 60 mg/m^2 d1, fluorouracil 600 mg/m^2 d1–5, q3wks × 3; Concurrent: cisplatin 100 mg/m^2 d1, q3wks × 3	Concurrent: cisplatin 100 mg/m^2 d1, q3wks × 3	2011–2013	480	5-year: 86% *vs.* 78%	0.65 (0.43–0.98); P=0.042	5-year FFS: 77% *vs.* 66%	0.65 (0.43–0.98); P=0.019
Yang *et al.* (87,88)	Induction: cisplatin 80 mg/m^2 d1, fluorouracil 800 mg/m^2 d1–5, q3wks × 2; Concurrent: cisplatin 80 mg/m^2 d1, q3wks × 3	Concurrent: cisplatin 80 mg/m^2 d1, q3wks × 3	2008–2015	476	5-year: 80.8% *vs.* 76.8%	0.69 (0.49–0.98); P=0.040	5-year DFS: 73.4% *vs.* 63.1%	0.66 (0.48–089); P=0.007
Hong *et al.* (89)	Induction: mitomycin 8 mg/m^2 d1, epirubicin 60 mg/m^2 d1, cisplatin 60 mg/m^2 d1, fluorouracil 450 mg/m^2 d8, leucovorin 30 mg/m^2 d8; Concurrent: cisplatin 30 mg/m^2 d1, q1wk	Concurrent: cisplatin 30 mg/m^2 d1, q1wk	2003–2009	479	5-year: 72% *vs.* 68%	0.92 (0.67–1.27); P=0.62	5-year DFS: 61% *vs.* 50%	0.74 (0.57–0.97); P=0.026
Frikha *et al.* (90)	Induction: docetaxel 75 mg/m^2 d1, cisplatin 75 mg/m^2 d1, fluorouracil 750 mg/m^2 d1–5, q3wks × 3; Concurrent: cisplatin 40 mg/m^2 d1, q1wk × 7	Concurrent: cisplatin 40 mg/m^2 d1, q1wk × 7	2009–2012	81	3-year: 86% *vs.* 69%	0.40 (0.15–1.04); P=0.059	3-year PFS: 74% *vs.* 57%	0.44 (0.20–0.97); P=0.042
Zhang *et al.* (91)	Induction: gemcitabine 1,000 mg/m^2 d1, d8, cisplatin 80 mg/m^2 d1, q3wks × 3; Concurrent: cisplatin 100 mg/m^2 d1, q3wks × 3	Concurrent: cisplatin 100 mg/m^2 d1; q3wks × 3	2013–2016	480	3-year: 94.6% *vs.* 90.3%	0.43 (0.24–0.77); P=NR	3-year RFS: 85.3% *vs.* 76.5%	0.51 (0.34–0.77); P=0.002
Concurrent chemoradiotherapy plus adjuvant chemotherapy *vs.* concurrent chemoradiotherapy								
Chen *et al.* (60,61)	Concurrent: cisplatin 40 mg/m^2 d1; Adjuvant: cisplatin 80 mg/m^2 d1, fluorouracil 800 mg/m^2 d1–5, q4wks × 3	Concurrent: cisplatin 40 mg/m^2 d1	2006–2010	251	5-year: 83% *vs.* 80%	0.86 (0.57–1.22); P=0.35	5-year FFS: 75% *vs.* 71%	0.88 (0.64–1.22); P=0.45

Table 3 (*continued*)

Table 3 (*continued*)

Reference	Experimental chemotherapy	Control chemotherapy	Inclusion period	Sample size	Overall survival		Other survival outcome measurements	
Induction chemotherapy followed by radiotherapy *vs.* concurrent chemoradiotherapy								
Xu *et al.* (92,93)	Induction: cisplatin 90 mg/m^2, fluorouracil 1,500 mg/m^2, q3wks × 2; Adjuvant: cisplatin 90 mg/m^2, fluorouracil 1,500 mg/m^2, q3wks ×4	Concurrent: cisplatin 90 mg/m^2, fluorouracil 1,500 mg/m^2, q3wks ×2; Adjuvant: cisplatin 90 mg/m^2, fluorouracil 1,500 mg/m^2, q3wks ×4	–	338	5-year: 79% *vs.* 76%	0.84 (0.53–1.33); P=0.47	5-year DMFS: 77% *vs.* 87%	0.59 (0.35–1.00); P=0.05

PFS, progress-free survival; DFS, disease-free survival; FFS, failure-free survival; RFS, recurrence-free survival; DMFS, distant metastasis-free survival; CI, confidence interval; HR, hazard ratio; NR, not reported; q3/4wks, every 3/4 weeks.

survival in LANPC (*Table 2*) (81,82,103). By contrast, a cohort study showed that IC (cisplatin and 5-fluorouracil) followed by radiotherapy significantly improved 5-year OS and DFS (107). However, a clinical trial adopting the same IC regimen did not find any significant differences in 5-year OS and DFS (108). Based on the studies conducted using 2D-RT, a meta-analysis concluded that IC could decrease the risk of recurrence and metastasis, but not improve OS and DFS, compared with that achieved by radiotherapy alone (109). However, the insignificant survival superiority of IC followed by radiotherapy was not validated in the era of IMRT (110). A retrospective study showed that patients with stage II NPC could benefit from adding IC (cisplatin plus docetaxel or 5-fluorouracil) to IMRT (111). Considering that CCRT is now the mainstay treatment of LANPC, it is more meaningful to perform a direct comparison of IC followed by radiotherapy with CCRT. However, past studies indicated that the differences in survival were not significant between the two treatment modalities, regardless of what kind of IC drugs were used (*Table 3*) (92,93,112-115). An ongoing phase III randomized controlled trial (NCT02434614) has the potential to deliver critical medical information concerning whether concurrent chemotherapy could be omitted when IC is combined with IMRT.

IC followed by CCRT is a more promising strategy to treat NPC, which has been studied in many randomized controlled trials (*Table 3*). A phase II clinical trial showed that IC (cisplatin and docetaxel) followed by CCRT significantly improved 3-year OS compared with that achieved by CCRT alone (116), while the other two phase II trials using different IC regimens (cisplatin-epirubicin and carboplatin-gemcitabine-paclitaxel) failed to detect a survival difference (84,117). The conflicting results might result from the small sample size and the natural flaw of the phase II trial design. Two multicenter phase III clinical trials, the GZ2011 trial adopting the IC regimen of docetaxel, cisplatin, and 5-fluorouracil (TPF); and the GZ2008 trial using cisplatin and 5-fluorouracil, reported a significant survival benefit in terms of PFS of IC followed by CCRT versus CCRT alone in LANPC (85,87). In addition, the GORTEC 2006 phase III trial showed that the addition of the TPF IC regimen significantly improved 3-year PFS (90). The long-term results of the GZ2011 and GZ2008 trials further validated the survival advantage of IC followed by CCRT (86,88). Meanwhile, improved 5-year DFS achieved by additional IC using mitomycin, epirubicin, cisplatin, 5-fluorouracil, and leucovorin was

observed in the phase III TCOG 1303 study (89). A pooled analysis of four randomized controlled trials found that IC followed by CCRT improved OS and PFS, and reduced locoregional and distant failures in LANPC (118). These results have been validated in a recent meta-analysis (119). Considering the survival benefits and good tolerance of IC, the recommendation evidence of IC followed by CCRT has been upgraded from level 3 to 2A in the NCCN clinical guidelines since 2018, which is the same level as CCRT followed by AC (120), indicating that IC will play an increasingly important role in LANPC treatment.

However, the optimal IC regimen has yet to be established. The effectiveness and toxicity of the TPF IC regimen have been validated in two phase III trials (121,122). A pooled analysis demonstrated no significant differences in survival outcomes among the TPF, docetaxel-cisplatin, and cisplatin-5-fluorouracil IC regimens; however, only the TPF regimen significantly improved OS and PFS compared with that achieved by the group without IC (118). A meta-analysis reported that TPF IC followed by CCRT led to better survival with tolerable toxicities compared with that of CCRT alone or double-drug-based IC plus CCRT (123). Recently, the GP regimen, which had proven its efficacy in recurrent or metastatic NPC (124), has been studied in LANPC as an alternative to the TPF regimen. A multicenter phase III randomized controlled trial reported that GP IC followed by CCRT improved 3-year recurrence-free survival (94.6% *vs.* 90.3%; HR 0.43; 95% CI: 0.24–0.77) and OS (85.3% *vs.* 76.5%; HR 0.51; 95% CI: 0.34–0.77) compared with that of CCRT alone in LANPC, and the high compliance of 96.7% supported its good toleration (91). A retrospective cohort study showed that the GP and TPF regimens achieved similar efficacy; however, the GP regimen is associated with increased hepatotoxicity (125). Further prospective studies or clinical trials comparing the roles of TPF, GP, and other regimens in IC are warranted. An ongoing phase III clinical trial (NCT03840421) comparing GP with cisplatin-5-fluorouracil as the IC regimen followed by CCRT in LANPC might provide more evidence.

Combining immunotherapy with radiotherapy

The unique characteristics of NPC, including its association with EBV infection, abundant tumor-infiltrating lymphocytes (TIL) in NPC tissues, and high expression of programmed cell death-ligand 1 (PD-L1) of up to 90%, make immunotherapy a promising treatment modality for NPC (126-129). Generally, anti-cancer immunotherapy consists of cancer vaccination, monoclonal antibodies, immune checkpoint inhibitors, adoptive T-cell therapy, and cytokines. Among them, vaccination and adoptive T-cell therapy targeting EBV-specific antigens were tested in patients with recurrent or metastatic NPC, and showed potential clinical efficacy (130-133); however, the combination of these therapeutic strategies with radiotherapy has not been explored.

Considering the high expression of PD-L1 and abundant TIL in NPC, applying immune checkpoint inhibitors, such as programmed cell death-1 (PD-1) and PD-L1 monoclonal antibodies, to LANPC is very appealing, especially with the emerging evidence of the synergistic radiotherapy-immunity interaction. On the one hand, experiments showed that radiotherapy could alter the immune context and microenvironment of the tumor to trigger an anti-tumor immune response. Two preclinical studies revealed an upregulation of PD-L1 levels in the tumors of mice after radiotherapy (134,135). The increased level of immunosuppressive regulatory T cells (Tregs) were found within the tumor after radiotherapy *in vivo* (136). Thus, the pro-immune effect induced by radiotherapy might not emerge without the help of immunotherapy. On the other hand, the role of PD-L1 blockade as a radiosensitizer has been observed both *in vivo* and *in vitro* (134,137), which might improve the efficacy of radiotherapy in patients with radioresistant NPC and reduce the irradiation dosage of radiotherapy to preserve more OARs. KEYNOTE-028 is a phase Ib trial evaluating the efficacy of PD-1 blockade using pembrolizumab. The results showed that pembrolizumab had satisfactory outcomes in 27 patients with PD-L1-positive, treatment-naïve, locally advanced or metastatic NPC, with an objective response rate (ORR) of 26%, a 1-year OS of 63%, a 1-year PFS of 33%, and manageable toxicity (138). A phase II trial evaluating nivolumab in 44 patients with previously treated recurrent or metastatic NPC demonstrated comparable results (ORR 20%, 1-year OS 59%, 1-year PFS 19%) (139). In addition, the combination of PD-1 blockade using camrelizumab with GP chemotherapy sharply increased the ORR from 34% to 91% in recurrent or metastatic NPC (140). These results support the extension of immune checkpoint inhibitors into combination with radiotherapy or chemoradiotherapy. Several ongoing randomized controlled trials evaluating the efficacy of combination therapy comprising immune checkpoint inhibitors with IMRT or CCRT are highly anticipated (*Table 4*). A phase II trial (NCT03383094)

Table 4 Clinical trials evaluating immune checkpoint inhibitors combined with radiotherapy in non-metastatic nasopharyngeal carcinoma

Trials	Phase	Sample size	Multicenter	Key eligibility criteria	Experimental regimen	Control regimen
Ma *et al.* (NCT03984357)	II	146	Yes	Stage III–IVA (except T3–4N0 and T3N1)	Induction: gemcitabine 1,000 mg/m^2 d1, d8; cisplatin 80 mg/m^2 d1; nivolumab 360 mg d1; q3wks × 3 Concurrent: nivolumab 360 mg d1, q3wks × 3; IMRT: 70 Gy, 33 fractions, 5 fractions/wk, 1 fraction/d Adjuvant: nivolumab 480 mg d1; q4wks × 6	NA
Ma *et al.* (NCT03427827)	III	417	Yes	Stage III–IVA (except T3–4N0 and T3N1)	Induction: gemcitabine 1,000 mg/m^2 d1, d8; cisplatin 80 mg/m^2 d1; q3wks × 3 Concurrent: cisplatin 100 mg/m^2 d1; q3wks × 2; q3wks × 3; IMRT: 70 Gy, 6–7 wks Adjuvant: camrelizumab 3 mg/kg (≤200 mg) d1, q4wks × 12	Induction: gemcitabine 1,000 mg/m^2 d1, d8; cisplatin 80 mg/m^2 d1; q3wks × 3; Concurrent: cisplatin 100 mg/m^2 d1; q3wks × 2; q3wks × 3; IMRT: 70 Gy, 6–7 wks
Ma *et al.* (NCT03700476)	III	417	Yes	Stage III–IVA (except T3–4N0 and T3N1)	Induction: gemcitabine 1,000 mg/m^2 d1, d8; cisplatin 80 mg/m^2 d1; sintilimab 200 mg d1, q3wks × 3 Concurrent: cisplatin 100 mg/m^2 d1, sintilimab 200 mg d1, q3wks × 3; IMRT: 70 Gy, 6–7 wks Adjuvant: sintilimab 200 mg d1, q3wks × 6	Induction: gemcitabine 1,000 mg/m^2 d1, d8; cisplatin 80 mg/m^2 d1; q3wks × 3; Concurrent: cisplatin 100 mg/m^2 d1; q3wks × 2; q3wks × 3; IMRT: 70 Gy, 6–7 wks
Mell *et al.* (NCT03383094)	II	114	Yes	stage III–IVB (T1–2N2–3M0 or T3–4N0–3M0) p16+ squamous cell nasopharyngeal carcinoma	Concurrent: pembrolizumab 200 mg q3wks × 3; IMRT: 70 Gy, 33-35 fractions, 6.5 wks Adjuvant: pembrolizumab 200 mg q3wks × 17	Concurrent: cisplatin 100 mg q3wks × 3; IMRT: 70 Gy, 33–35 fractions, 6.5 wks
Yom *et al.* (NCT03267498)	II	40	Yes	stage II–IV; WHO type II/III	Induction: nivolumab 240 mg, d1 Concurrent: nivolumab 240 mg, d1, q2wks ×11; cisplatin 40 mg/m^2, d1, q1wk × 22; RT: 7 0Gy, 33 fractions, 5 d/wk	NA
Lu *et al.* (NCT04143984)	II/III	180	No	Recurrent non-metastatic; completed a definitive course of IMRT to a total dose of ≥66 Gy	Arm-C: Concurrent: camrelizumab 200 mg, q2wks × 27; carbon-ion radiotherapy: 63–69 GyE, 21–23 fractions Arm-CA: Concurrent: camrelizumab 200 mg, q2wks × 27; apatinib, 250 mg, qd × 365; carbon-ion radiotherapy: 63–69 GyE, 21–23 fractions	Carbon-ion radiotherapy: 63–69 GyE, 21–23 fractions
NCT03734809	II	46	Yes	Stage IVA; WHO type II/III	Induction: pembrolizumab 200 mg, q3wks × 2; gemcitabine-cisplatin Concurrent: pembrolizumab 200 mg, q3wks × 3; cisplatin; IMRT Adjuvant: pembrolizumab 200 mg, q3wks × 12	NA

NA, not applicable; PD-L1, programmed death-ligand 1; q2/3/4wks, every 2/3/4 weeks; d1, day 1; wks, weeks; RT, radiotherapy; IMRT, intensity-modulated radiotherapy.

comparing concurrent pembrolizumab and radiotherapy with CCRT in p16-positive locoregionally advanced head and neck squamous cell carcinoma including NPC is ongoing. A single-arm multicenter phase II clinical trial (NCT03984357) is evaluating the efficacy and safety of whole-course concurrent and adjuvant nivolumab combined with IC followed by radiotherapy alone in LANPC. This is the first attempt to develop a de-intensification therapy by sparing the cisplatin-based concurrent chemotherapy and adopting PD-1 blockade based on IC followed by IMRT alone in LANPC. Meanwhile, two phase III clinical trials conducted by Ma *et al.* will investigate the value of concurrent PD-1 blockade using sintilimab (NCT03700476) and adjuvant PD-1 blockade using camrelizumab (NCT03427827) when added to standard chemoradiotherapy in LANPC. Given the additional toxicities induced by immunotherapy, selection of the beneficiaries of the combination of immunotherapy and radiotherapy is expected to be important; however, no effective biomarkers have yet been identified.

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Footnote

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