Treatment approaches to nasopharyngeal carcinoma: a review

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Early-stage nasopharyngeal carcinoma (T1–2a;N0;M0) represents a small proportion of nasopharyngeal tumors. Radiotherapy alone is the current treatment approach for this tumor and the emerging role of new radiotherapy techniques will hopefully further improve the treatment outcome for these patients. The vast majority of patients with nasopharyngeal carcinoma is diagnosed with locally advanced disease. Concomitant chemoradiotherapy is now acknowledged as being a standard treatment option, even though it induces a considerable incidence of acute mucosal and hematologic toxicity. The issue of adding adjuvant chemotherapy is somewhat more controversial. Similarly, the role of neoadjuvant chemotherapy before concomitant chemoradiotherapy is a matter of interest. In patients with recurrent/metastatic nasopharyngeal carcinoma the prognosis is generally grim, as platinum-based chemotherapy results in a 50–70% response rate and in a median survival time of 11 months. Several trials have been performed on this subset of patients with both cytotoxic and biologic agents, but the results have not been particularly encouraging thus far. Epstein–Barr virus is associated with the vast majority of nasopharyngeal carcinoma. Concentrations of plasma Epstein–Barr virus DNA have been associated with treatment outcome in the clinic. Immunotherapy is generally well tolerated and can sometimes elicit significant immune response, which possibly induces clinical benefit in some patients. *Anti-Cancer Drugs* **21:471–477 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Nasopharyngeal carcinoma (NPC) is a tumor arising from the epithelial cells that cover the surface of the nasopharynx. Its incidence is relatively high in Southeast Asia, North Africa, and part of the Mediterranean basin where about 80 cases per 100 000 of population are reported. The World Health Organization recognizes three different histologic subtypes, namely squamous cell carcinoma, nonkeratinizing carcinoma, and undifferentiated carcinoma [1]. The last two types are nearly always associated with Epstein–Barr virus (EBV) infection [2]. NPC differs from other head and neck cancer (HNC) in terms of epidemiology, natural behavior, and chemoradiosensitivity [3]. The current review aims to cover the treatment approach and future perspectives for patients with early-stage, locally advanced, recurrent/metastatic disease. Finally, the increasingly important role of immunotherapy will be discussed.

Early-stage disease

Radiotherapy (RT) alone was the standard treatment for almost all stages of NPC until 1990 [4]. Patients presenting with early-stage disease (T1–2a;N0;M0) are a minority and may be effectively treated with RT alone to the nasopharynx and elective neck irradiation, as the addition of chemotherapy to RT has not yielded increased survival in clinical trials [5] and a 5-year local control ranging from 80 to 95% may be achieved in these good prognosis patients.

Patients with T2b disease (parapharyngeal infiltration) and N1, initially believed to be treatable with RT alone, have a worse survival and should therefore be treated with concomitant chemoradiotherapy (CCRT) [6–11]. Recently, many investigators have highlighted the role of brachytherapy given after external beam RT in early-stage disease and have suggested that this approach may be able to significantly improve survival when compared with external beam RT alone [12–15]. Intracavitary brachytherapy may be used even in patients with residual mass after exclusive upfront RT, especially when they had a T2b disease at initial diagnosis [16]. Furthermore, clinical evidence has shown that in patients with T2b disease interstitial brachytherapy may be a valid alternative to the endocavitary technique with a probably better therapeutic index [17]. Early-stage NPC can also benefit from intensity-modulated radiation therapy, which in clinical trials resulted in a lower toxicity rate when compared with conventional external beam RT [18–21].

Although efficacy of both the intensity modulated radiation therapy and brachytherapy in early-stage NPC is well known, their use is currently recommended only in highly dedicated and selected institutions.

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Locally advanced disease

The vast majority of patients with NPC presents with locally advanced disease. Until recently, RT has been the cornerstone of treatment. However, despite progress in treatment techniques, the outcome with RT alone is disappointing, since 5-year survival rates are 34–52%. Therefore, significant efforts have been made over the last few years with the aim of improving these results. Given the chemosensitivity of NPC, the most logical way has been considered the concurrent administration of chemoradiotherapy followed or not by adjuvant chemotherapy.

Clear and well-accepted superiority has been observed for concurrent chemoradiotherapy when compared with RT alone in several phase III clinical studies [22–24], even though it was at the expense of a higher incidence of acute mucosal and hematologic toxicities [25]. Zhang *et al.* [26] have recently presented the data of a meta-analysis of CCRT versus RT, which included only studies carried out in endemic regions. The results confirmed that CCRT was more beneficial compared with RT alone, although concerns about the costs of CCRT-related side effects were raised. Taken as a whole, the above studies lead to the assumption that concurrent chemoradiation should be adopted as standard therapy in patients with locally advanced NPC.

The issue of adding adjuvant chemotherapy is somewhat more controversial. He *et al.* [27] ran a phase II study of paclitaxel and cisplatin administered concomitantly with RT and subsequently as adjuvant in patients with locally advanced NPC. The 3-year survival rate was 83.9% in that study. The Intergroup-0099 [28] was the first randomized study comparing concurrent chemoradiotherapy with RT alone. In this study, RT was administered according to standard fractionation and concurrent chemotherapy consisted of cisplatin (100 mg/m^2 every 21 days) for three cycles, followed by adjuvant cisplatin (80 mg/m^2 on day 1) and 5-fluorouracil (5-FU) (1000 mg/m^2 on days 1–4 every 4 weeks) for three cycles. This study showed the clear advantage of CCRT in terms of overall survival (OS), disease-free survival, locoregional failure, and appearance of distant metastases. In particular, 3-year OS was 76% in the CCRT arm and 46% in the RT arm ($P < 0.001$); 5-year survival was 67% versus 37% ($P = 0.001$). Despite these impressive data, Asian oncologists did not immediately accept the implications coming from this study, mainly because of the histologic subtype in the 0099 study, which included 25% keratinizing tumors; furthermore, compliance with adjuvant chemotherapy was suboptimal, with only 55% of patients completing treatment as planned. Finally, concerns were raised about the poor results of the RT-alone control arm. In the study by Wee *et al.* [29] the findings of the earlier trial were confirmed in Asian patients. In fact, disease-free survival, 2 and 3-year OS rates were significantly superior in the experimental arm. Conflicting results have been produced by other studies that compared CCRT followed by adjuvant CT versus RT alone. Completed and ongoing clinical trials of chemoradiotherapy in locally advanced disease are shown in Tables 1 and 2.

The role of neoadjuvant chemotherapy before RT or CCRT is a matter of outstanding interest. Initially, RT alone was considered as the control arm in randomized trials. Ma *et al.* [30] showed the lack of significant survival benefit with the addition of neoadjuvant chemotherapy (cisplatin, bleomycin, and 5-FU) to standard radiation therapy in patients with locoregionally advanced NPC. Al-Amro *et al.* [31] tested induction chemotherapy (cisplatin and epirubicin) followed by a radical course of RT with three cycles of concurrent cisplatin in the same patient population. This study, carried out in 110 patients, showed encouraging results in terms of safety and effectiveness. The same treatment schedule was also used by Italian investigators in a nonendemic population.

Table 1 Completed clinical trials using chemoradiotherapy

Reference number	Phase	Patients	Design	Endpoints	Results	Status
[22]	III	284	CRT (cDDP-5-FU)[a] vs. RT alone	5-year PFS	71.6[a] vs. 53% (significant)	Completed
[23]	III	350	CRT (cDDP)[a] vs. RT alone	2-year PFS	76[a] vs. 69% (not significant)	Completed
[24]	III	316	CRT (cDDP) followed by adjuv CT (cDDP-5-FU)[a] vs. RT alone	2-year OS	89.8[a] vs. 79.7% (significant)	Completed
[28]	III	147	CRT* (cDDP) followed by adjuv CT (cDDP-5-FU) vs. RT alone	3-year OS 3-year PFS	78[a] vs. 47% (significant) 69[a] vs. 24% (significant)	Completed
[29]	III	221	Concurrent CRT[a] (cDDP) followed by cDDP-5-FU vs. RT alone	3-year OS	80[a] vs. 65% (significant)	Completed
[30]	III	456	Neoadj CT[a] (cDDp-Bleo-5-FU) followed bt RT vs. RT alone	5-year OS	63[a] vs. 56% (significant)	Completed
[27]	II	31	Concurrent RT plus cDDP-taxol followed by adjuv CT (cDDP-taxol)	3-year OS	84%	Completed
[31]	II	110	neoadj CT (cDDP-DOX) followed by CRT (cDDP)	ORR	100%	Completed
[32]	II	65	Neoadj CT (cDDP-DOX) followed by CRT (cDDP)[a] vs. CRT (cDDP)	3-year OS	94.1[a] vs. 67.7% (significant)	Completed

Bleo, bleomycin; cDDP, cisplatin; CRT, chemoradiation; DOX, doxorubicin; CT, chemotherapy; 5-FU, 5-fluorouracil; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RT, radiation; TXT, docetaxel.
[a]The experimental arm.

Table 2 Ongoing clinical trials using chemoradiotherapy

Reference number	Phase	Patients	Design	Endpoints	Results	Status
[33]	II	93	Neoadj CT (cDDP-TXT) followed by RT	ORR	97.7%	Ongoing
[34]	II	45	Neoadj CT (TXT-cDDP-5-FU) followed by CRT (cDDP)	ORR	98%	Ongoing
[35]	II	19	Neoadj CT (TXT-cDDP-5-FU) followed by CRT (cDDP)	ORR	93%	Ongoing
[36]	II	40	Neoadj CT (TPX) (TXT-cDDP-Cap) followed by CRT (cDDP)	ORR	88% (after TPX)	Ongoing
[37]	II	34	Neoadj CT (cDDP-5-FU) followed by CRT (cDDP)	ORR	85.3%	Ongoing

Cap, capecitabine; cDDP, cisplatin; CRT, chemoradiation; DOX, doxorubicin; 5-FU, 5-fluorouracil; ORR, overall response rate; RT, radiation; TPX, taxotere, platinum, xeloda; TXT, docetaxel.

The activity of the regimen was noteworthy in this study, since all of the 40 treated patients achieved an objective response; 5-year disease-free survival was 65% and 5-year OS was 77%. More recently, the results of a phase II trial of combination docetaxel and cisplatin in patients with locally advanced NPC have been presented. This combination was followed by radiation therapy and turned out to be active with an acceptable safety profile [33]. Bossi *et al.* [34] have recently presented the data of a study of docetaxel, cisplatin, 5-FU as induction chemotherapy followed by concomitant cisplatin/RT. After completion of treatment, complete response (CR) and partial response (PR) were observed in 78 and 20% of the patients, respectively. The same combination was studied by Eastern investigators and similar results were obtained, with a 93% response rate and median time to progression of 39 months [35]. Induction chemotherapy with the addition of capecitabine to docetaxel and cisplatin has also been tested in a phase II study in 40 patients. In this study a 48% CR rate and a 40% PR rate were observed [36]; data are awaited concerning responses after concurrent CCRT, which follows the induction phase. An Italian trial has tested the activity of induction chemotherapy with cisplatin and 5-FU followed by RT and concurrent cisplatin. The results of this study were very encouraging, as response rates were about 80 and 85% after induction chemotherapy and chemoradiation, respectively. At a median follow-up of 29 months, 3-year OS and progression-free survival rates were 80 and 54%, respectively [37]. Hui *et al.* [32] have recently published the results of a randomized phase II trial in which stage III to IVB NPC untreated earlier were randomly assigned to receive either neoadjuvant docetaxel and cisplatin for two cycles followed by CCRT, or CCRT alone. The neoadjuvant regimen was well tolerated with a manageable toxicity profile that allowed subsequent delivery of full-dose CRT; more importantly, a positive impact on survival was observed, since 3-year OS for neoadjuvant versus control arm was 94.1 versus 67.7% ($P = 0.012$), thus warranting a phase III trial.

Recurrent/metastatic disease

In patients with recurrent/metastatic NPC the prognosis is generally grim, as platinum-based combination chemotherapy results in a 50–70% response rate and in a median survival time of approximately 11 months. The treatment options for patients who fail the platinum-based combinations are even fewer and frequently second-line chemotherapy is recommended only in selected patients. The combination of cisplatin and capecitabine has been tested as first-line chemotherapy in a phase II trial in patients with recurrent/metastatic NPC [38]. The overall response rate was 54% in this study, whereas the 1-year survival rate was 73%. Airoldi *et al.* [39] reported a small trial with carboplatin and paclitaxel in patients with progressive disease after cisplatin and 5-FU. The treatment was well tolerated and moderately active, as three patients obtained a PR and median OS time was 9.5 months. Weekly docetaxel has shown activity against platinum-refractory disseminated NPC in a phase II study, as a PR was achieved in 37% of patients, whereas median progression-free survival was 5.3 months and median OS was 12.8 months [40]. Chua *et al.* [41] have also published a small phase II study with oral capecitabine after platinum-based chemotherapy. Toxicity was moderate in this study, and activity was encouraging, as the overall response rate was 23.5%, and the median OS time was 7.6 months. Given the frequent overexpression of epidermal growth factor receptor (EGFR) in NPC, clinical trials with EGFR-targeted compounds have been undertaken. Cetuximab, a monoclonal antibody targeting EGFR, has been tested in combination with carboplatin in patients with recurrent/metastatic NPC [42]. The toxicity profile was acceptable. PR rate was 11.7%, stable disease was observed in 48.3% of patients for a disease control rate (DCR) of 60%; median OS time was 233 days. Gefitinib, an oral small molecule, which inhibits EGFR-specific tyrosine kinases, has shown negative results in a phase II study in patients with NPC pretreated with platinum-based chemotherapy. In fact, no objective responses were recorded in 19 patients; median time to progression was 4 months and median survival was 16 months [43]. Sorafenib is an oral inhibitor of the serine/threonine kinases C-raf and B-raf and of the receptor tyrosine kinases of vascular endothelial growth factor. Sorafenib has undergone a phase II trial in patients with recurrent/metastatic squamous cell HNC and NPC [44]. Despite fair tolerance, the study results were negative, as the response data were lower than the historical controls. In the seven patients with NPC treated in the study time to progression was 3.2 months and OS was 7.7 months. A phase II randomized study of

oral seliciclib, a selective inhibitor of cyclin-dependent kinases 2, 7, and 9 in patients with nasopharyngeal cancer treated earlier, is currently ongoing and very preliminary data have been presented [45].

EBV role in nasopharyngeal carcinoma

EBV is associated with several malignancies, among which is NPC. EBV is present in virtually all undifferentiated and poorly differentiated nasopharyngeal carcinomas and the viral antigens expressed by tumor cells are potential targets for immunotherapy [46]. All EBV-related malignancies involve the virus latent infection; however, three different types of latency are known and each type is characterized by a different expression of viral antigens [47–49], as shown in Table 3.

Concentrations of plasma EBV-DNA have been associated with treatment outcome in the clinic. Lin *et al.* [50] have shown that patients with relapse had a higher basal plasma EBV-DNA concentration than those who did not experience a relapse. Furthermore, plasma EBV-DNA concentrations were very low or even undetectable in patients with CR. As a consequence, investigators have speculated that plasma EBV-DNA concentrations can be used as a biomarker for screening, monitoring, and prognostic assessment in NPC. NPC expresses a restricted set of immunogenic viral antigens, namely Epstein–Barr nuclear antigen 1 and latent membrane proteins (LMPs) 1 and 2. LMPs 1 and 2 are immunogenic and detectable in about 50% of NPCs [51–55]. These antigens are able to elicit an immune cytotoxic T-lymphocyte (CTL)-mediated response directed against NPC cells [51].

In fact, it has been asserted that NPC cells, which are capable of immunologic processing for CTL recognition [56], stimulate a boost colony of CTL $CD8^+$, which is able to attack tumor cells leading to tumor debulking. These features have prompted the adoption of several immunotherapy techniques, which are, however, still in a research stage and whose efficacy cannot be presently stated. In particular, two distinct approaches are being developed to treat NPC, namely adoptive immunotherapy and active immunotherapy. The first one consists in the direct activation of effector cells as CTLs. The use of allogenic CTLs to treat NPC has not been further evaluated, as it is associated with the need of human leukocyte antigen-matched donor, the risk of CTLs rejection, and the short-term persistence of infused allogenic CTLs [57]. In contrast, autologous CTL therapy has produced somewhat more encouraging results. Comoli *et al.* [58] carried out a clinical trial including 10 patients with stage IV NPC in progression after conventional RT and chemotherapy. The patients received autologus EBV-specific CTLs intravenously, which reactivated and expanded *ex vivo* from peripheral blood lymphocytes through stimulation with autologous EBV-infected antigen-presenting cells. As a result, EBV-specific CTLs were generated in all patients studied and were able to specifically kill in-vitro autologous EBV-infected cells. A 60% DCR was obtained and two PRs were seen. Another similar study [59] enrolled 10 patients with NPC treated with autologous EBV-specific CTLs. Four of the 10 patients were in complete remission after a conventional therapy (chemo or radiation or both), whereas the other six had a recurrent/metastatic disease. Even in this case, an encouraging DCR was reached, as all four patients, who were in complete remission, remained disease free with a follow-up of about 27 months. Among the six patients with refractory disease, two had CR and remained disease free for 11–23 months after treatment, one had partial remission that persisted for 12 months, one had a stable disease for more than 14 months, and two patients did not respond. Interestingly, one of the two patients, who had no response to CTL infusion, subsequently developed a PR to palliative chemotherapy to which the disease had been unresponsive earlier. Toxicity reported in both the trials was mild; in fact, a weak swelling at the tumor site was the only side effect, and it might be suggestive of CTL trafficking at the tumor site. More recently, Whirt *et al.* [60] presented a similar trial enrolling 10 patients with refractory NPC. Data about objective clinical response are not yet available but by analyzing the viral EBV-DNA load before and after treatment, a substantial tumor cellular lysis has been probably obtained.

Table 3 Different latency types and expression of viral genes in EBV-related malignancies

Latency type	Viral genes expressed	Tumor
Type I	EBNA-1	Endemic Burkitt's lymphoma
Type II	EBNA-1	Nasopharyngeal carcinoma
	LMP-1	Hodgkin's lymphoma
	LMP2	Nasal T/K lymphoma
Type III	All EBNAs	Lymphoproliferative disorders in immunocompromised patients
	LMP1	
	LMP2	

EBNA, Epstein–Barr nuclear antigen; EBV, Epstein–Barr virus; LMP, latent membrane protein.

Active immunotherapy consists of delivering selected tumor-associated antigens to patients with the aim of inducing an immune response that may result in the eradication of malignant cells. Two strategies have been developed: dendritic cell (DCs) vaccination and viral vector-introduced peptides. DCs are professional antigen-presenting cells that are able to activate naive $CD4^+$ and $CD8^+$ T cells.

Lin *et al.* [61] performed a clinical trial using DCs against NPC patients. Sixteen patients with advanced NPC were enrolled in this study; autologous monocyte-derived DCs were cultured from patients, matured with cytokine,

Table 4 Completed clinical trials using immunotherapy

Reference number	Immunotherapy technique	Number of patients	Stage disease	Number of infusions	Objectives	Results
[48]	Autologous CTLs	10	4 Ned 6 R/M	2	PFS DCR[a] Toxicity Immune response elicited	23 months 70% 1/10 swelling at tumor site 10/10
[58]	Autologous CTLs	10	10 R/M	10	PFS DCR Toxicity Immune response elicited	5 months 60% 2/10 swelling at tumor site 5/10
[62]	Vaccination with autologous DCs LMP2-specific HLA-restricted	16	16 R/M	4	PFS DCR Toxicity Immune response elicited	3 months 13% 4/16 swelling at tumor site 9/16

CTLs, cytotoxic T-lymphocytes; DCR, disease control rate; HLA, human leukocyte antigen; LMP, latent membrane protein; Ned, nonevidence of disease; OR, objective response; PFS, progression free survival; R/M, recurrent/metastatic.
[a]In 6/10 patients.

pulsed with human leukocyte antigen-restricted LMP2 epitope peptides, and injected into inguinal lymph nodes. All of the patients tolerated treatment without serious side effects. Only two PRs were obtained whereas the other 14 patients developed disease progression. Nevertheless, a substantial immune response was elicited as EBV epitope-specific CTLs were generated in the peripheral blood of almost all patients.

Viral vector loading with EBV peptides is as yet an experimental approach and, at present, it has been used only in preclinical models [62]. Completed clinical trials of immunotherapy are detailed in Table 4.

Conclusion

NPC is unique among the HNC, mainly in terms of radio and chemosensitivity. The optimal integration of the different treatment modalities may induce an improvement in survival in patients with locally advanced disease, who represent the vast majority. In contrast, the search of new drugs, both cytotoxic and biologic, is the strongest effort to be pursued in recurrent/metastatic disease. The role of immunotherapy in the treatment of NPC is the most appealing issue.

Preliminary clinical data have shown that immunotherapy is well tolerated and can sometimes induce significant immune response that is associated with clinical benefit in some patients. Strategies to improve immunotherapy are warranted and some ideas have been suggested. For example, preclinical trials have shown that lytic EBV infection in NPC cells leads to greater expression of viral antigens on cell surface sensitizing such cells to specific CTL killing. In addition, other studies indicate that chemotherapy and RT are able to induce the expression of lytic cycle antigens in EBV infected cells [63,64], thus bearing the potential for a synergistic effect to be possibly exploited in clinical trials. Despite the lack of significant clinical data, this probably represents the most exciting way forward in the clinical research of NPC.

References

1 Brennan B. Nasopharyngeal carcinoma. *Orphanet J Rare Dis* 2006; **1**:23.
2 Takeshita H, Furukawa M, Fujieda S, Shoujaku H, Ookura T, Sakaguchi M, *et al.* Epidemiological research into nasopharyngeal carcinoma in the Chubu region of Japan. *Auris Nasus Larynx* 1999; **26**:277–286.
3 Chan AT, Teo PM, Johnson PJ. Nasopharyngeal cancer. *Cancer Treat Res* 2003; **114**:275–293.
4 Wang CC. *Radiation therapy for head and neck neoplasms*. 3rd ed. New York: Wiley-Liss; 1997. p. 274.
5 Song CH, Wu HG, Heo DS, Kim KH, Sung MW, Park CI. Treatment outcomes for radiotherapy alone are comparable with neoadjuvant chemotherapy followed by radiotherapy in early-stage nasopharyngeal carcinoma. *Laryngoscope* 2008; **118**:663–670.
6 Ma BB, Mo FK, Chan AT, Hui E, Leung S, Lo Y, *et al.* The prognostic significance of tumor vascular invasion and its association with plasma Epstein–Barr virus DNA, tumor volume and metabolic activity in locoregionally advanced nasopharyngeal carcinoma. *Oral Oncol* 2008; **44**:1067–1072.
7 Ho HC, Lee MS, Hsiao SH, Hwang JH, Hung SK, Lee CC, *et al.* Prognostic influence of parapharyngeal extension in nasopharyngeal carcinoma. *Acta Otolaryngol* 2008; **128**:790–798.
8 Xiao GL, Gao L, Xu GZ. Prognostic influence of parapharyngeal space involvement in nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2002; **52**:957–963.
9 Cheng SH, Tsai SY, Yen KL, Jian J, Feng A, Chan K, *et al.* Prognostic significance of parapharyngeal space venous plexus and marrow involvement: potential landmarks of dissemination for stage I-III nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2005; **61**:456–465.
10 Liu MT, Hsieh CY, Chang TH, Lin JP, Huang CC, Wang AY. Prognostic factors affecting the outcome of nasopharyngeal carcinoma. *Jpn J Clin Oncol* 2003; **33**:501–508.
11 Chua DT, Sham JS, Leung LH, Tai KS, Au GK. Tumor volume is not an independent prognostic factor in early-stage nasopharyngeal carcinoma treated by radiotherapy alone. *Int J Radiat Oncol Biol Phys* 2004; **58**:1437–1444.
12 Leung TW, Wong VY, Sze WK, Lui CM, Tung SY. High-dose rate intracavitary brachytherapy boost for early T stage nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2008; **70**:361–367.
13 Lin SJ, Pan JJ, Wu JX, Han L, Pan CZ. Long-term efficacy of external radiotherapy plus intracavitary hyperfractionated brachytherapy on nasopharyngeal carcinoma. *Ai Zheng* 2007; **26**:208–211.
14 Cao XP, Lu TX, Ye WJ, Cui NJ. Prospective study on long-term efficacy of external plus intracavitary radiotherapy on stage I–II nasopharyngeal carcinoma. *Ai Zheng* 2007; **26**:204–207.
15 Lu JJ, Shakespeare TP, Tan LK, Goh BC, Cooper JS. Adjuvant fractionated high-dose rate intracavitary brachytherapy after external beam radiotherapy in TI and T2 nasopharyngeal carcinoma. *Head Neck* 2004; **26**:389–395.
16 Leung TW, Tung SY, Wong VWY, Sze WK, Lui CMM, Wong FCS, *et al.* Nasopharyngeal intracavitary brachytherapy: the controversy of T2b disease. *Cancer* 2005; **104**:1648–1655.

17 Chen MY, Cao XP, Sun R, Hua YJ, Li AJ, Liu YY, *et al.* Application of interstitial brachytherapy via parapharynx involvement transnasal approach to enhance dose in radiotherapy for nasopharyngeal carcinoma. *Ai Zheng* 2007; **26**:513–518.

18 Pow EH, Kwong DL, McMillan AS, Wong MCM, Sham JST, Leung LHT, *et al.* Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. *Int J Radiat Oncol Biol Phys* 2006; **66**:981–991.

19 Fang FM, Tsai WL, Chen HC, Hsu HC, Hsiung CY, Chien CY, *et al.* Intensity-modulated or conformal radiotherapy improves the quality of life of patients with nasopharyngeal carcinoma: comparisons of four radiotherapy techniques. *Cancer* 2007; **109**:313–321.

20 Kwong DL, Pow EH, Sham JS, Mcmillan AS, Leung LHT, Leung WK, *et al.* Intensity-modulated radiotherapy for early-stage nasopharyngeal carcinoma: a prospective study on disease control and preservation of salivary function. *Cancer* 2004; **101**:1584–1593.

21 Sultanem K, Shu HK, Xia P, Akazawa C, Quivey JM, Verhey LJ, *et al.* Three-dimensional intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: the University of California–San Francisco experience. *Int J Radiat Oncol Biol Phys* 2000; **48**:711–722.

22 Lin JC, Jan JS, Hsu CY, Liang WM, Jiang RS, Wang WY. Phase III study of concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: positive effect on overall and progression-free survival. *J Clin Oncol* 2003; **21**:631–637.

23 Chan AT, Teo PM, Ngan RK, Leung TW, Lau WH, Zee B, *et al.* Concurrent chemotherapy–radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: progression-free survival analysis of a phase III randomized trial. *J Clin Oncol* 2002; **20**:2038–2044.

24 Chen Y, Liu MZ, Liang SB, Zong J, Mao Y, Tang L, *et al.* Preliminary results of a prospective randomized trial comparing concurrent chemoradiotherapy plus adjuvant chemotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma in endemic regions of china. *Int J Radiat Oncol Biol Phys* 2008; **71**:1356–1364.

25 Lu H, Peng L, Yuan X, Hao Y, Lu Z, Chen J, *et al.* Concurrent chemoradiotherapy in locally advanced nasopharyngeal carcinoma: a treatment paradigm also applicable to patients in Southeast Asia. *Cancer Treat Rev* 2009; **35**:345–353.

26 Zhang L, Zhao C, Ghimire BR, Guo Y, Guan ZZ. The role of concurrent chemoradiation in the treatment of locally advanced nasopharyngeal carcinoma among endemic area: a meta-analysis of the phase III randomized trial. *J Clin Oncol* 2008; **26**:6032.

27 He XY, Hu CS, Ying HM, Wu YR, Zhu GP, Liu TF. Paclitaxel with cisplatin in concurrent chemoradiotherapy for locally advanced nasopharyngeal carcinoma. *Eur Arch Otorhinolaryngol* 2009. doi: 10.1007/s00405-009-1112-7.

28 Al-Sarraf M, LeBlanc M, Giri PG, Fu KK, Cooper J, Vuong T, *et al.* Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *J Clin Oncol* 1998; **16**:1310–1317.

29 Wee J, Tan EH, Tai BC, Wong HB, Leong SS, Tan T, *et al.* Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union against cancer stage III and IV nasopharyngeal cancer of the endemic variety. *J Clin Oncol* 2005; **23**:6730–6738.

30 Ma J, Mai HQ, Hong MH, Min HQ, Mao ZD, Cui NJ, *et al.* Results of a prospective randomized trial comparing neoadjuvant chemotherapy plus radiotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma. *J Clin Oncol* 2001; **19**:1350–1357.

31 Al-Amro A, Al-Rajhi N, Khafaga Y, Memon M, Al-Hebshi A, El-Enbabi A, *et al.* Neoadjuvant chemotherapy followed by concurrent chemo-radiation therapy in locally advanced nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2005; **62**:508–513.

32 Hui EP, Ma BB, Leung SF, King AD, Mo F, Kam MK, *et al.* Randomized phase II trial of concurrent cisplatin–radiotherapy with or without neoadjuvant docetaxel and cisplatin in advanced nasopharyngeal carcinoma. *J Clin Oncol* 2009; **27**:242–249.

33 Yamouni M, Benhadji KA, Beldjilali Y, Lahfa I, Khellafi H, Abdelaoui A, *et al.* Phase II trial of combination docetaxel and cisplatin in patients with locally advanced nasopharyngeal carcinoma [abstract 6044]. *J Clin Oncol* 2009; **27**.

34 Bossi P, Parolini D, Bergamini C, Locati LD, Orlandi E, Franceschini M, *et al.* TPF induction chemotherapy (CT) followed by concomitant cisplatin/radiotherapy (cCTRT) in locally advanced nasopharyngeal cancer (LANPC) [abstract 6046]. *J Clin Oncol* 2009; **27**.

35 Cho S, Bae W, Hwang J, Shim H, Lee J, Lim S, *et al.* Phase II study of docetaxel, cisplatin and 5-FU induction chemotherapy followed by concurrent chemoradiotherapy for advanced nasopharyngeal cancer [abstract 17010]. *J Clin Oncol* 2008; **26**.

36 Beldjilali Y, Benhadji KA, Boukerche A, Khellafi H, Abdelaoui A, Betkaoui F, *et al.* First results of induction chemotherapy with cisplatin, docetaxel, and capecitabine for the treatment of nasopharyngeal carcinoma [abstract 6045]. *J Clin Oncol* 2009; **27**.

37 Ferrari D, Chiesa F, Codèca C, Calabrese L, Jereczek-Fossac BA, Alterio D, *et al.* Locoregionally advanced nasopharyngeal carcinoma: induction chemotherapy with cisplatin and 5-fluorouracil followed by radiotherapy and concurrent cisplatin: a phase II study. *Oncology* 2008; **74**:158–166.

38 Chua D, Ng W, Yiu H, Seetalarom K, Kurnianda J, Sze W, *et al.* Phase II trial of first-line capecitabine plus cisplatin in patients with advanced/metastatic nasopharyngeal cancer (NPC) [abstract 6033]. *J Clin Oncol* 2008; **26**.

39 Airoldi M, Pedani F, Marchionatti S, Gabriele AM, Succo G, Gabriele P, *et al.* Carboplatin plus taxol is an effective third-line regimen in recurrent undifferentiated nasopharyngeal carcinoma. *Tumori* 2002; **88**:273–276.

40 Ngeow JY, Gao F, Leong SS, Lim W, Toh C, Tan EH. Phase II study of weekly docetaxel as salvage therapy for disseminated nasopharyngeal carcinoma [abstract 6057]. *J Clin Oncol* 2008; **26**.

41 Chua D, Wei WI, Sharm JS, Au GK. Capecitabine monotherapy for recurrent and metastatic nasopharyngeal cancer. *Jpn J Clin Oncol* 2008; **38**:244–249.

42 Chan ATC, Hsu MM, Goh BC, Hui EP, Liu TW, Millward MJ, *et al.* Multicenter, phase II study of cetuximab in combination with carboplatin in patients with recurrent or metastatic nasopharyngeal carcinoma. *J Clin Oncol* 2005; **23**:3568–3576.

43 Chua DT, Wei WI, Wong MP, Sham JS, Nicholls J, Au GK. Phase II study of gefitinib for the treatment of recurrent and metastatic nasopharyngeal carcinoma. *Head and Neck* 2008; **30**:863–867.

44 Elser C, Siu LL, Winquist E, Agulnik M, Pond GR, Chin SF, *et al.* Phase II trial of sorafenib in patients with recurrent or metastatic squamous cell carcinoma of the head and neck or nasopharyngeal carcinoma. *J Clin Oncol* 2007; **25**:3766–3773.

45 Yeo W, Goh B, Le Tourneau C, Green SR, Chiao JH, Siu LL. A phase II randomized study of oral seliciclib in patients with previously treated nasopharyngeal carcinoma [abstract 6026]. *J Clin Oncol* 2009; **27**.

46 Masmoudi A, Toumi N, Khanfir A, Kallel-Slimi L, Daoud J, Karray H, *et al.* Epstein–Barr virus-targeted immunotherapy for nasopharyngeal carcinoma. *Cancer Treat Rev* 2007; **33**:499–505.

47 Thompson MP, Kurzrock R. Epstein-Barr virus and cancer. *Clin Cancer Res* 2004; **10**:803–821.

48 Straathof KC, Bollard CM, Rooney CM, Heslop HE. Immunotherapy for Epstein–Barr virus-associated cancers in children. *Oncologist* 2003; **8**:83–98.

49 Khanna R, Tellam J, Duraiswamy J, Cooper L. Immunotherapeutic strategies for EBV-associated malignancies. *Trends Mol Med* 2001; **7**:270–276.

50 Lin JC, Wang JY, Chen KY, Wei YH, Liang WM, Jan JS, *et al.* Quantification of plasma Epstein–Barr virus DNA in patients with advanced nasopharyngeal carcinoma. *N Engl J Med* 2004; **350**:2461–2470.

51 Rickinson AB, Moss DJ. Human cytotoxic T lymphocyte responses to Epstein–Barr virus infection. *Annu Rev Immunol* 1997; **15**:405–431.

52 Moss DJ, Burrows SR, Khanna R, Misko IS, Sculley TB. Immune surveillance against Epstein–Barr virus. *Semin Immunol* 1992; **4**:97–104.

53 Chang KL, Chen YY, Shibata D, Weiss LM. Description of an in situ hybridization methodology for detection of Epstein–Barr virus RNA in paraffin-embedded tissues, with a survey of normal and neoplastic tissues. *Diagn Mol Pathol* 1992; **1**:246–255.

54 Pathmanathan R, Prasad U, Chandrika G, Sadler R, Flynn K, Raab-Traub N. Undifferentiated, nonkeratinizing, and squamous cell carcinoma of the nasopharynx. Variants of Epstein–Barr virus-infected neoplasia. *Am J Pathol* 1995; **146**:1355–1367.

55 Brooks L, Yao QY, Rickinson AB, Young LS. Epstein–Barr virus latent gene transcription in nasopharyngeal carcinoma cells: coexpression of EBNA1, LMP1, and LMP2 transcripts. *J Virol* 1992; **66**:2689–2697.

56 Khanna R, Busson P, Burrows SR, Raffoux C, Moss DJ, Nicholls JM, *et al.* Molecular characterization of antigen-processing function in nasopharyngeal carcinoma (NPC): evidence for efficient presentation of Epstein–Barr virus cytotoxic T-cell epitopes by NPC cells. *Cancer Res* 1998; **58**:310–314.

57 Murray RJ, Kurilla MG, Brooks JM, Thomas WA, Rowe M, Kieff E, *et al.* Identification of target antigens for the human cytotoxic T cell response to Epstein–Barr virus (EBV): implications for the immune

control of EBV-positive malignancies. *J Exp Med* 1992; **176**: 157–168.
58 Comoli P, Pedrazzoli P, Maccario R, Basso S, Carminati O, Labirio M, *et al.* Cell therapy of stage IV nasopharyngeal carcinoma with autologous Epstein–Barr virus-targeted cytotoxic T lymphocytes. *J Clin Oncol* 2005; **23**:8942–8949.
59 Straathof KC, Bollard CM, Popat U, Huls MH, Lopez T, Morriss MC, *et al.* Treatment of nasopharyngeal carcinoma with Epstein–Barr virus specific T lymphocytes. *Blood* 2005; **105**:1898–1904.
60 Wirth LJ, Fogg M, Wang F, Lork J, Haddad RI, Posner MR. Epstein Barr virus (EBV)-specific immunotherapy in nasopharyngeal carcinoma (NPC) [abstract 6025]. *J Clin Oncol* 2009.
61 Lin CL, Lo WF, Lee TH, Ren Y, Hwang SL, Cheng YF, *et al.* Immunization with Epstein–Barr virus (EBV) peptide-pulsed dendritic cells induces functional CD8+ T-cell immunity and may lead to tumor regression in patients with EBV-positive nasopharyngeal carcinoma. *Cancer Res* 2002; **62**:6952–6958.
62 Duraiswamy J, Sherritt M, Thomson S, Tellam J, Cooper L, Connolly G, *et al.* Therapeutic LMP1 polyepitope vaccine for EBV-associated Hodgkin disease and nasopharyngeal carcinoma. *Blood* 2003; **101**:3150–3156.
63 Feng WH, Israel B, Raab-Traub N, Busson P, Kenney SC. Chemotherapy induces lytic EBV replication and confers ganciclovir susceptibility to EBV-positive epithelial cell tumors. *Cancer Res* 2002; **62**:1920–1926.
64 Westphal EM, Blackstock W, Feng W, Israel B, Kenney SC. Activation of lytic Epstein–Barr virus (EBV) infection by radiation and sodium butyrate in vitro and in vivo: a potential method for treating EBV-positive malignancies. *Cancer Res* 2000; **60**:5781–5788.