World Journal of Clinical Oncology

Online Submissions: http://www.wjgnet.com/2218-4333office
wjco@wjgnet.com
doi:10.5306/wjco.v2.i12.377

World J Clin Oncol 2011 December 10; 2(12): 377-383
ISSN 2218-4333 (online)

EDITORIAL

Locally advanced nasopharyngeal carcinoma: Current and emerging treatment strategies

Francesco Perri, Davide Bosso, Carlo Buonerba, Giuseppe Di Lorenzo, Giuseppina Della Vittoria Scarpati

Francesco Perri, Oncology Division, Division INT Fondazione "G. Pascale", 80131 Naples, Italy
Davide Bosso, Carlo Buonerba, Giuseppe Di Lorenzo, Giuseppina Della Vittoria Scarpati, Oncology and Rare Cancer Center, Federico Ⅱ University, 80131 Naples, Italy
Author contributions: Perri F and Della Vittoria Scarpati G collected literature and drafted the first version; Bosso D and Buonerba C critically revised the paper and added additional references; Di Lorenzo G critically revised the paper.
Correspondence to: Giuseppe Di Lorenzo, MD, PhD, Oncology and Rare Cancer Center, Federico Ⅱ University, 80131 Naples, Italy. giuseppedilorenzoncol@hotmail.com
Telephone: +39-081-7463660 Fax: +39-081-8997370
Received: September 5, 2011 Revised: October 15, 2011
Accepted: October 22, 2011
Published online: December 10, 2011

Key words: Chemotherapy; Nasopharyngeal carcinoma; Radiotherapy; Treatment

Peer reviewer: Robert Mandic, MD, Associate Professor, Head of Research Laboratory, Department of Otolaryngology, Head and Neck Surgery, University Hospital Giessen and Marburg, Campus Marburg, Deutschhausstrasse 3, D-35037 Marburg, Germany

Perri F, Bosso D, Buonerba C, Di Lorenzo G, Della Vittoria Scarpati G. Locally advanced nasopharyngeal carcinoma: Current and emerging treatment strategies. *World J Clin Oncol* 2011; 2(12): 377-383 Available from: URL: http://www.wjgnet.com/2218-4333/full/v2/i12/377.htm DOI: http://dx.doi.org/10.5306/wjco.v2.i12.377

Abstract

Although nasopharyngeal carcinoma (NPC) is a widespread malignant tumor, it is particularly frequent in Southeast Asia. Although T1 tumors can be effectively controlled with exclusive radiotherapy, this treatment modality is insufficient for most NPC patients, who present with locally advanced disease at diagnosis. In fact, for stages ranging from T2b N0 to T4 N3, definitive scientific evidence supports the use of concurrent platinum-based chemotherapy with standard external beam radiotherapy. This treatment approach has shown a statistically significant advantage in terms of overall survival, with respect to radiotherapy alone. Several trials have also investigated the use of neoadjuvant and adjuvant chemotherapy in combination with radiotherapy or chemo-radiotherapy. Platinum compounds, anthracyclines and taxanes are among the chemotherapy agents employed. This review focuses on the clinical results obtained in the field of adjuvant/concurrent/neoadjuvant chemotherapy for locally advanced NPC, for which exclusive concurrent chemo-radiotherapy currently represents the standard treatment approach.

INTRODUCTION

Nasopharyngeal carcinoma (NPC), a malignant tumor originating from the epithelium of the nasopharynx, is particularly frequent in Southeast Asia and can be divided into three different histological types, that is, non-keratinizing squamous cell carcinoma, keratinizing squamous cell carcinoma and undifferentiated carcinoma[1]. At diagnosis, most NPC patients have locally advanced disease, which includes stages ranging from T2b N0 to T4 N3 (Table 1).

Radiotherapy (RT) can control early stage NPC effectively, yielding an excellent 90%-95% 5-year local control rate in clinical trials. However, radiotherapy alone is not the optimal treatment for patients with locally advanced disease, which is the most frequent clinical presentation at diagnosis, since it yields an unsatisfactory 5-year survival rate of about 50%[2]. For this reason, concurrent platinum-based chemotherapy and radiotherapy has become the standard treatment for locally advanced NPC. While in early stage NPC (T1-2a N0), the addition of chemotherapy to standard radiotherapy has not provided

Table 1 Standard approach to nasopharyngeal carcinoma

Stage	Denomination	Gold standard therapy
T1-2a N0 M0	Early stage	- IMRT alone - Conventional RT alone
From T2b N0 M0 to T4b N3 M0 also every T N2/3 M0	Locally advanced	- Neoadjuvant platinum-based CT followed by IMRT or CCRT (platinum-based) - Concurrent cDDP and RT
Every T every N M1	Metastatic	- Exclusive CT

RT: Radiotherapy; IMRT: Intensity modulated RT; CCRT: Concurrent chemoradiotherapy; CT: Comptued tomography.

a survival advantage in clinical trials[3], a clear superiority has emerged for concurrent chemoradiotherapy when compared to RT alone in patients with locally advanced disease[4-5].

In locally advanced NPC patients, there are presently few data regarding the use of neoadjuvant/adjuvant chemotherapy, as an alternative to concurrent chemoradiotherapy. The role of neoadjuvant chemotherapy before RT or concurrent chemoradiotherapy is a matter of great interest. In fact, induction chemotherapy is an effective way to control subclinical metastatic foci, especially in patients with lymph node metastasis. Moreover, in some patients with large tumors infiltrating the brain stem, it is often difficult to deliver the total required dose to the clinical target volume (CTV) with preservation of critical tissues. Neoadjuvant chemotherapy is often able to provide objective responses in tumor lesions, which offers the possibility to shrink the CTV and reduce toxicity[6].

Retrospective studies that used RT alone for NPC indicated that local control was closely linked to the radiation dose delivered to target tissues[7-8]. Intensity modulated RT (IMRT) is a special type of conformal RT that creates a high dose volume that is precisely shaped around the target volume in order to minimize the radiation dose delivered to surrounding healthy tissues. Investigators compared dosimetric plans of IMRT with conventional RT techniques and concluded that IMRT provided improved tumor coverage and preservation of normal tissues. The proximity of the nasopharynx to critical normal tissues, such as the brainstem and optic structures, makes it challenging for radiotherapists to deliver the optimal radiation dose to the tumor using conventional conformal RT, and underdosing of affected areas is often necessary to preserve healthy tissues. IMRT for locally advanced NPC spares critical portions of the brain stem and of the parotid glands, avoiding neurologic toxicity and permanent xerostomia, respectively. While IMRT has completely replaced conventional conformal RT and has become the standard practice for early stage NPC, its role in the locally advanced setting is not yet well defined[9].

Intracavitary brachytherapy may be used in patients with residual mass after exclusive upfront radiotherapy, especially in the case of a T2b tumor (parapharyngeal infiltration) at initial diagnosis[10]. The combination of external beam RT followed by endocavitary brachytherapy may play an important role in patients with T2b disease. In this review, the treatment of patients with locally advanced NPC is reviewed and discussed, with a special focus on novel experimental therapeutic options.

ROLE OF EXCLUSIVE CONCURRENT CHEMORADIOTHERAPY

In several phase Ⅲ trials, radiotherapy with concurrent platinum-based chemotherapy has been compared to standard external beam radiotherapy alone in patients with locally advanced NPC. Concurrent chemo-radiotherapy has shown a statistically significant advantage in terms of survival and response rate when compared with radiotherapy alone, but at the expense of more severe toxicity, mainly mucositis and bone marrow suppression[4,5,11]. Results of a large meta analysis carried out by Zhang *et al*[12] which included 1608 patients enrolled in seven studies confirmed the superiority of concurrent chemo-radiotherapy with respect to RT alone. Of note, this meta-analysis was the first to include studies conducted in endemic areas only.

Another meta-analysis included 18 trials enrolling a total of 1993 patients from China. A comparison between concurrent chemo-radiotherapy and RT alone showed that concurrent chemo-radiotherapy was able to obtain a 3-year overall survival rate of 68.5%, compared with 56.4% in the RT alone arm[13].

More recently, the association of cisplatin and paclitaxel given concurrently with standard radiotherapy was evaluated in a phase Ⅱ trial. Thirty-one patients with locally advanced NPC received three-weekly 120 mg/m2 of paclitaxel and 75 mg/m2 of cisplatin concurrently with standard 70 Gy external beam radiotherapy. Three-year overall survival rate was 83.9% and the main grade 3/4 toxicity was neutropenia, reported in 12.9% of patients[14]. Another way of improving the effectiveness of standard concurrent chemo-radiotherapy may be to modify the radiotherapy scheme. In a phase Ⅱ trial, Jian *et al*[15] investigated the activity of hyperfractionated radiotherapy and concomitant platinum-based chemotherapy. As a result, three-year overall survival rate was 72%, with 73% of patients showing grade 3 mucositis, 31% of patients experiencing severe weight loss and 15% requiring a feeding tube. In view of such an unfavorable toxicity profile, further investigation in this direction does not seem justified.

IMRT is widely employed as an alternative to conventional RT in NPC patients with stage Ⅰ-Ⅱ disease, but its role in association with chemotherapy is still unknown. Lu *et al*[16] evaluated the feasibility and efficacy of a weekly cisplatin (40 mg/m^2/wk) regimen given concurrently with definitive IMRT in twenty-one locally advanced NPC patients, obtaining a good safety profile and an excellent one-year overall survival of 95.5%[17]. In another similar trial, the association of three-weekly cisplatin and weekly cetuximab was employed together with standard IMRT

Table 2 Chemo-radiation trials

Trial	Phase	Pts	Study design	Main end-point	Results
Lin JC *et al*[4]	Ⅲ	284	Exclusive RT alone *vs* cDDP-5FU + RT	5-year DFS	Experimental arm better ($P < 0.0012$)
Chan AT *et al*[5]	Ⅲ	350	Exclusive RT alone *vs* cDDP-5FU + RT	2-year PFS	Experimental arm better ($P < 0.016$)
Zhang L *et al*[12]	Ⅲ(m)	1608	Exclusive RT alone *vs* cDDP based CT + RT	5-year OS	Experimental arm better ($P < 0.001$)
Yang AK *et al*[13]	Ⅲ(m)	1993	Exclusive RT alone *vs* cDDP based CT + RT	5-year OS	Experimental arm better ($P < 0.05$)
Lu H *et al*[17]	Ⅱ	22	IMRT + cDDP	1 year OS	96%
Ekenel M *et al*[34]	Ⅱ	100	IMRT+ cDDP-Cet	ORR	100%

RT: Radiotherapy; IMRT: Intensity modulated RT; CT: Comptued tomography; ORR: Overall response rate; DFS: Disease-free survival.

in 100 locally advanced NPC patients. The complete + partial response rate achieved was 100% and the toxicity profile was very low, except for a 64% rate of grade 2 acneiform rash. Clinical studies assessing the efficacy and activity of exclusive concurrent chemo-radiotherapy in locally advanced NPC patients are shown in Table 2.

ROLE OF ADJUVANT CHEMOTHERAPY FOLLOWING CONCURRENT CHEMO-RADIOTHERAPY

The Intergroup-0099 was the first randomized trial to compare concurrent chemo-radiotherapy followed by adjuvant chemotherapy with RT alone[18]. In this study, concurrent chemo-radiotherapy consisted of cisplatin (100 mg/m^2 every 21 d) for three cycles, followed by adjuvant cisplatin (80 mg/m^2 on day 1) and 5-fluorouracil (1000 mg/m^2 on days 1-4 every 4 wk). A clear and statistically significant advantage in the chemo-radiation arm was seen in terms of overall survival, disease-free-survival, locoregional failure rate and time to distant metastases. However, these encouraging results did not translate into a change in clinical practice for many Asian oncologists, in view of the high rate of well differentiated carcinomas enrolled in both treatment arms (about 25%) which does not reflect common clinical practice. Furthermore, a particularly low compliance was reported, with only 55% undergoing adjuvant treatment and a particularly poor survival observed in the RT-alone arm.

A comparison between concurrent chemo-radiotherapy followed by adjuvant chemotherapy and RT alone was performed in 316 locally advanced NPC patients enrolled in a phase Ⅲ trial conducted by Chen *et al*[19]. Patients were assigned to receive concurrent chemo-radiotherapy, consisting of a standard radiation dose of 70 Gy plus cisplatin followed by three adjuvant cycles of cisplatin and 5-fluorouracil, or RT alone. Concurrent chemo-radiotherapy plus adjuvant chemotherapy yielded better results with respect to RT alone in terms of survival and activity, at the cost of higher toxicity. Similar results were seen in another phase Ⅲ trial enrolling only non-keratinizing locally advanced NPC patients randomized to concurrent chemo-radiotherapy followed by adjuvant cisplatin and 5-fluorouracil or to RT alone. In this trial, concurrent chemo-radiotherapy was superior in terms of efficacy but also more toxic than RT alone[20].

Park *et al*[21] carried out a retrospective analysis in forty-three locally advanced NPC patients treated with concurrent chemo-radiotherapy using cisplatin and 5-fluorouracil followed by adjuvant chemotherapy consisting of three cycles of cisplatin, epirubicin and bleomycin. The overall response rate (ORR) was 95% after concurrent chemo-radiotherapy and 100% after adjuvant therapy. The main toxicities observed were grade 3/4 neutropenia and mucositis occurring during concurrent chemo-radiotherapy.

In a prospective phase Ⅱ trial conducted by Hu *et al*[22] fifty-four patients were treated with concomitant weekly paclitaxel and external beam radiation therapy (concurrent chemo-radiotherapy) followed by three cycles of cisplatin (30 mg/m^2 on days 1-3) and paclitaxel (135 mg/m^2 on day 1), both given every three weeks. An excellent 100% ORR was obtained after the entire treatment with a complete response (CR) rate of 85%. An acceptable toxicity profile was seen with no grade 3/4 side effects.

In view of the conflicting results reported on the role of adjuvant chemotherapy after concurrent chemo-radiotherapy, it is presently unclear whether the addition of adjuvant therapy may improve the efficacy of concurrent chemo-radiotherapy. Interestingly, a combined analysis of two large studies (NPC-9901 and the NPC-9902) revealed that the dose of cisplatin during the concurrent phase of concurrent chemo-radiotherapy had a significant impact on locoregional control, while additional adjuvant chemotherapy with a fluorouracil-containing combination contributed to improving distant control. Table 3 shows the results of clinical trials assessing the efficacy and/or activity of adjuvant chemotherapy following concurrent chemo-radiotherapy.

ROLE OF NEOADJUVANT CHEMOTHERAPY FOLLOWED BY CONCURRENT CHEMO-RADIOTHERAPY

The role of neoadjuvant chemotherapy followed by concurrent chemo-radiotherapy or RT is a matter of outstanding interest. Several clinical phase Ⅲ trials from Western countries have proved that induction chemotherapy based on the administration of cisplatin, 5-fluorouracil and taxanes, may significantly improve treatment outcomes in patients with squamous cell carcinoma of the head and neck. An interesting approach may be to employ the same chemotherapy or a similar regimen in locally advanced NPC patients. Amro *et al*[23] treated 110

Table 3 Adjuvant chemotherapy trials

Trial	Phase	Pts	Study design	Main end-point	Results
Al-Sarraf M *et al*[18]	Ⅲ	147	Exclusive RT alone *vs* CCRT followed by cDDP-5FU	3-year PFS	Experimental arm better ($P < 0.01$)
Chen Y *et al*[19]	Ⅲ	316	Exclusive RT alone *vs* CCRT followed by cDDP-5FU	2-year OS	Experimental arm better ($P < 0.003$)
Lee AW *et al*[20]	Ⅲ	348	Exclusive RT alone *vs* CCRT followed by cDDP-5FU	5-year PFS	Experimental arm better ($P < 0.035$)
Park KH *et al*[21]	Ⅱ	43	cDDP-5-FU + RT followed by cDDP-Epi-Ble CT	ORR	100%
Hu W *et al*[22]	Ⅱ	54	w Pac + RT followed by cDDP-Pac CT	ORR	100%
Leung TW *et al*[10]	Ⅱ	48	HFRT + cDDP based CT followed by cDDP-5FU CT	3-year DFS	71%

RT: Radiotherapy; CT: Comptued tomography; ORR: Overall response rate; CCRT: Concurrent chemoradiotherapy; DFS: Disease-free survival.

patients with induction cisplatin and epirubicin followed by a radical course of radiotherapy with three cycles of concurrent cisplatin, and obtained encouraging results in terms of safety and effectiveness. Italian investigators used the same treatment schedule in 40 patients and obtained an overall response rate of 100% and a 5-year disease-free survival of 77%[24]. In another Italian phase Ⅱ study, Ferrari *et al*[25] treated thirty-four patients with three cycles of neoadjuvant cisplatin and 5-fluorouracil followed by concurrent cisplatin and RT. As a result, the overall response rate obtained was a satisfactory 85.3% and the 3-year overall survival rate was 80%.

In the last five years, taxanes have been employed in several phase Ⅱ and Ⅲ clinical trials in patients with squamous cell carcinoma of the head and neck, showing a good activity and manageable toxicity profile. Lu *et al*[26] carried out a trial to compare two different schedules of induction chemotherapy, namely carboplatin-5-fluorouracil (CF) *vs* docetaxel-carboplatin (TC). Fifty-eight patients with locally advanced NPC were enrolled and randomized to receive CF or TC induction chemotherapy, both followed by concurrent carboplatin and RT. There was no significant difference in terms of response rate and 1-year survival rate. More grade 3/4 neutropenia events were reported in the TC group than in the CF group, whereas less grade 3/4 thrombocytopenia and emesis occurred with the TC regimen than with the CF regimen. An egyptian study enrolled thirty-six patients who were treated with three cycles of induction paclitaxel (175 mg/m^2) and cisplatin (80 mg/m^2) given every three weeks, followed by concomitant cisplatin-radiotherapy. The overall response rate after the entire treatment schedule was 89% and the 3-year overall survival was 68%. The main toxicity encountered was grade 3/4 neutropenia which was observed in 25% of patients[27]. Hui *et al*[28] published the results of a randomized phase II trial in which stage III-IVb NPC patients, not previously treated, were randomly assigned to receive either neoadjuvant docetaxel and cisplatin for two cycles followed by concurrent chemo-radiotherapy, or concurrent chemo-radiotherapy alone. A positive impact on survival was observed, since the 3-year overall survival for the neoadjuvant *versus* the control arm was 94.1% *versus* 67.7% ($P = 0.012$). Bossi *et al*[29] recently presented data of a study on docetaxel, cisplatin and 5-fluorouracil as induction chemotherapy followed by concomitant cisplatin/RT. After completion of treatment, the ORR was 98%, with a complete response rate of 70%. Other authors showed that the same combination had similar results with a 93% response rate and a median time to progression of 39 months[30]. In a phase II study, induction docetaxel, cisplatin and capecitabine followed by chemo-radiation was tested in 40 patients, and resulted in an ORR of 98% and a complete response rate of 48%[31]. In a phase Ⅱ clinical study, Bae *et al*[32] treated thirty-three patients with induction cisplatin (70 mg/m^2), 5-fluorouracil (1000 mg/m^2 in i.c of 4 d) and docetaxel (75 mg/m^2) followed by cisplatin (100 mg/m^2) and RT. Twenty-seven patients achieved a partial response and five patients a complete response. An excellent ORR of 98% was achieved and the three-year overall survival rate was 86.1%. Nevertheless, a 72.7% rate of grade 2/3 neutropenia and a 9.1% rate of febrile neutropenia were reported. Xie *et al*[33] administered induction cisplatin (80 mg/m^2) and docetaxel (70 mg/m^2) to fifty-seven patients and randomized them to receive either concomitant RT and single agent cisplatin (80 mg/m^2) or concomitant cisplatin (80 mg/m^2) and docetaxel (60 mg/m^2) with RT. After completion of treatment, the complete response rates were very similar in both treatment arms (about 93%), but the occurrence of grade 3/4 neutropenia was significantly higher in the concomitant docetaxel, cisplatin and RT group ($P > 0.05$). In a recent phase Ⅱ clinical study, fifty-nine locally advanced NPC patients were treated with neoadjuvant cisplatin (75 mg/m^2), docetaxel (75 mg/m^2) and 5-fluorouracil (500 mg/m^2 on days 1-5 in i.c) for three cycles, followed by concomitant weekly cisplatin (40 mg/m^2) and conventional RT or IMRT. The overall response rate three months after RT was 90.2% and the 1-year overall survival was 100%. The rate of grade 3/4 myelosuppression during induction CT was 55.9% and the corresponding rate during concomitant chemotherapy and RT was 11.9%[6]. More recently, Ekenel *et al*[34] published the preliminary results of a phase Ⅱ trial in which patients with locally advanced NPC received induction cisplatin (75 mg/m^2) and docetaxel (75 mg/m^2) for three cycles, followed by definitive RT and concomitant cisplatin (100 mg/m^2). Fifty-nine patients were evaluable and the ORR obtained after RT was 95%. Three-year overall survival was 93% and the treatment was generally well tolerated with a 10% rate of grade 3/4

Table 4 Neoadjuvant chemotherapy trials

Trial	Phase	Pts	Study design	Main end-point	Results
Al-Amro A *et al*[23]	Ⅱ	110	Neo cDDP-Epi and followed by cDDP + RT	ORR	100%
Airoldi M *et al*[24]	Ⅱ	30	Neo cbdca-Pac followed by RT + cbdca-Pac	ORR	87%
Ferrari D *et al*[25]	Ⅱ	34	Neo cDDP-5FU followed by RT + cDDP	ORR	85.3%
Lu X *et al*[26]	Ⅱ	58	Neo cbdca-Tax followed by cbdca + RT (arm A) *vs* neo cbdca-5FU followed by cbdca + RT (armB)	1-year DFS	no difference between arm A and B
Mosatafa E *et al*[27]	Ⅱ	36	Neo cDDP-Pac followed by cDDP-RT	ORR	89%
Hui EP *et al*[28]	Ⅱ	65	Neo cDDP-Tax followed by cDDP + RT (arm A) *vs* cDDP + RT (arm B)	3-year OS	Arm A better than arm B ($P < 0.012$)
Bossi P *et al*[29]	Ⅱ	45	Neo cDDP-Tax-5FU followed by cDDP + RT	ORR	98%
Cho S *et al*[30]	Ⅱ	19	Neo cDDP-Tax-5FU followed by cDDP + RT	ORR	93%
Bae WK *et al*[32]	Ⅱ	33	Neo cDDP-Tax-5FU followed by cDDP + RT	ORR	99%
Kong L *et al*[6]	Ⅱ	52	Neo cDDP-Tax-5FU followed by cDDP + RT	ORR	90.2%
Ekenel M *et al*[34]	Ⅱ	59	Neo cDDP-Tax followed by cDDP + RT	ORR	95%
Lin S *et al*[35]	Ⅱ	370	Neo cDDP based CT followed by IMRT	3-year OS	90%

RT: Radiotherapy; IMRT: Intensity modulated RT; CT: Comptued tomography; ORR: Overall response rate; DFS: Disease-free survival.

hematologic toxicity.

In the last three years, a significant effort has been made to incorporate IMRT in treatment protocols for locally advanced NPC. In a phase Ⅱ study, Lin *et al*[35] treated a total of 370 patients with locally advanced NPC, with stages ranging from Ⅱb to Ⅳ, with induction cisplatin-based chemotherapy followed by exclusive IMRT or the association of IMRT and concomitant cisplatin. Drugs more frequently used in combination with cisplatin were paclitaxel and 5-fluorouracil. With a median follow-up of 31 mo, the three-year disease-free-survival and overall survival were 81% and 89%, respectively. A subgroup analysis revealed that concurrent chemotherapy provided no significant benefit to IMRT but was responsible for higher rates of grade 3/4 toxicities[35]. A recent Italian phase Ⅱ trial carried out by Palazzi *et al*[36] enrolled 87 patients with locally advanced NPC and treated them with either conventional RT or with IMRT. Of these patients, 26% received only concurrent cisplatin and the other 74% received both induction and concurrent CT. Three-year disease-free survival (DFS) and overall survival were 82% and 90%, respectively. Interestingly, a multivariate analysis revealed that histology, N-stage, RT-technique and total dose of RT had the strongest independent impact on DFS.

Further clinical trials assessing activity, efficacy and toxicity of the combination of induction taxane-based chemotherapy followed by exclusive IMRT in locally advanced NPC are warranted. At the present time, this treatment strategy is recommended only in experienced centers. Table 4 shows clinical trials assessing the activity and efficacy of neoadjuvant chemotherapy followed by radiation or chemo-radiation.

CONCLUSION

This review reported in detail the available clinical data regarding the use of chemotherapy in combination with radiotherapy for locally advanced NPC. Although several cytotoxic agents have been used both in the neoadjuvant and adjuvant setting with promising results, exclusive concurrent chemo-radiotherapy remains the recommended approach at the present time, as additional evidence is required to support the use of chemotherapy in the adjuvant/neoadjuvant setting.

REFERENCES

1 **Caponigro F**, Longo F, Ionna F, Perri F. Treatment approaches to nasopharyngeal carcinoma: a review. *Anticancer Drugs* 2010; **21**: 471-477

2 **Wang CC**. Radiation therapy for head and neck neoplasms. 3rd edition. New York: Wiley-Liss, 1987: 274

3 **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

4 **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

5 **Chan AT**, Teo PM, Ngan RK, Leung TW, Lau WH, Zee B, Leung SF, Cheung FY, Yeo W, Yiu HH, Yu KH, Chiu KW, Chan DT, Mok T, Yuen KT, Mo F, Lai M, Kwan WH, Choi P, Johnson PJ. 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

6 **Kong L**, Zhang YW, Hu CS, Guo Y. Neoadjuvant chemotherapy followed by concurrent chemoradiation for locally advanced nasopharyngeal carcinoma. *Chin J Cancer* 2010; **29**: 551-555

7 **Vikram B**, Mishra UB, Strong EW, Manolatos S. Patterns of failure in carcinoma of the nasopharynx: I. Failure at the primary site. *Int J Radiat Oncol Biol Phys*. 1985; **11**: 1455-1459

8 **Lee AW**, Tung SY, Chan AT, Chappell R, Fu YT, Lu TX, Tan T, Chua DT, O'sullivan B, Xu SL, Pang ES, Sze WM, Leung TW, Kwan WH, Chan PT, Liu XF, Tan EH, Sham JS, Siu L, Lau WH. Preliminary results of a randomized

study (NPC-9902 Trial) on therapeutic gain by concurrent chemotherapy and/or accelerated fractionation for locally advanced nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2006; **66**: 142-151
9 **Lu H**, Yao M. The current status of intensity-modulated radiation therapy in the treatment of nasopharyngeal carcinoma. *Cancer Treat Rev* 2008; **34**: 27-36
10 **Leung TW**, Tung SY, Wong VY, Sze WK, Lui CM, Wong FC, Lee AS, O SK. Nasopharyngeal intracavitary brachytherapy: the controversy of T2b disease. *Cancer* 2005; **104**: 1648-1655
11 **Chua DT**, Sham JS, Au GK, Choy D. Concomitant chemo-irradiation for stage III-IV nasopharyngeal carcinoma in Chinese patients: results of a matched cohort analysis. *Int J Radiat Oncol Biol Phys* 2002; **53**: 334-343
12 **Zhang L**, Zhao C, Ghimire B, Hong MH, Liu Q, Zhang Y, Guo Y, Huang YJ, Guan ZZ. The role of concurrent chemo-radiotherapy in the treatment of locoregionally advanced nasopharyngeal carcinoma among endemic population: a meta-analysis of the phase III randomized trials. *BMC Cancer* 2010; **10**: 558
13 **Yang AK**, Liu TR, Guo X, Qi GL, Chen FJ, Guo ZM, Zhang Q, Zeng ZY, Chen WC, Li QL. [Concurrent chemoradiotherapy versus radiotherapy alone for locoregionally advanced nasopharyngeal carcinoma: a meta-analysis]. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi* 2008; **43**: 218-223
14 **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* 2010; **267**: 773-778
15 **Jian JJ**, Cheng SH, Tsai SY, Yen KC, Chu NM, Chan KY, Tan TD, Cheng JC, Lin YC, Leu SY, Hsieh CI, Tsou MH, Lin CY, Huang AT. Improvement of local control of T3 and T4 nasopharyngeal carcinoma by hyperfractionated radiotherapy and concomitant chemotherapy. *Int J Radiat Oncol Biol Phys*. 2002; **53**: 344-52
16 **Lu T**, Zhao C, Gao L, Lang J, Pan J, Hu C . Open, multicenter clinical study on cetuximab combined with intensity modulated radiotherapy (IMRT) plus concurrent chemotherapy in nasopharyngeal carcinoma (NPC); preliminary report. *J Clin Oncol* 28: 15s, 2010 (suppl abstr 5577)
17 **Lu H**, Chen J, Huang B, Cheng J, Peng L, Hao Y, Liao C, Mo Y, Wu D, Qin J. Feasibility and efficacy study of weekly cisplatin with concurrent intensity-modulated radiation therapy for nasopharyngeal carcinoma: preliminary results. *Oral Oncol* 2010; **46**: 743-747
18 **Al-Sarraf M**, LeBlanc M, Giri PG, Fu KK, Cooper J, Vuong T, Forastiere AA, Adams G, Sakr WA, Schuller DE, Ensley JF. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *J Clin Oncol* 1998; **16**: 1310-1317
19 **Chen Y**, Liu MZ, Liang SB, Zong JF, Mao YP, Tang LL, Guo Y, Lin AH, Zeng XF, Ma J. 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
20 **Lee AW**, Tung SY, Chua DT, Ngan RK, Chappell R, Tung R, Siu L, Ng WT, Sze WK, Au GK, Law SC, O'Sullivan B, Yau TK, Leung TW, Au JS, Sze WM, Choi CW, Fung KK, Lau JT, Lau WH. Randomized trial of radiotherapy plus concurrent-adjuvant chemotherapy vs radiotherapy alone for regionally advanced nasopharyngeal carcinoma. *J Natl Cancer Inst* 2010; **102**: 1188-1198
21 **Park KH**, Kim JS, Park Y, Seo HY, Park YJ, Choi IK, Oh SC, Seo JH, Kim CY, Jung KY, Shin SW, Kim YH, Kim JS, Lee NJ. Concurrent chemoradiation followed by adjuvant chemotherapy in patients with locoregionally advanced nasopharyngeal carcinoma in Korea. *Cancer Chemother Pharmacol* 2010; **66**: 643-651
22 **Hu W**, Ding W, Yang H, Shao M, Wang B, Wang J, Wu S, Wu S, Jin L, Ma CC. Weekly paclitaxel with concurrent radiotherapy followed by adjuvant chemotherapy in locally advanced nasopharyngeal carcinoma. *Radiother Oncol* 2009; **93**: 488-491
23 **Al-Amro A**, Al-Rajhi N, Khafaga Y, Memon M, Al-Hebshi A, El-Enbabi A, El-Husseiny G, Radawi A, Belal A, Allam A, El-Sebaie M. Neoadjuvant chemotherapy followed by concurrent chemo-radiation therapy in locally advanced nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2005; **62**: 508-513
24 **Airoldi M**, Gabriele P, Gabriele AM, Garzaro M, Raimondo L, Pedani F, Beatrice F, Pecorari G, Giordano C. Induction chemotherapy with carboplatin and taxol followed by radiotherapy and concurrent weekly carboplatin taxol in locally advanced nasopharyngeal carcinoma. *Cancer Chemother Pharmacol* 2010 Jul 20. [Epub ahead of print]
25 **Ferrari D**, Chiesa F, Codecà C, Calabrese L, Jereczek-Fossa BA, Alterio D, Fiore J, Luciani A, Floriani I, Orecchia R, Foa P. 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
26 **Lu X**, Guo X, Hong MH, Chen QY, Zeng Q, Xiang YQ. Comparison of the short-term efficacy of two inductive chemotherapy regimens for locally advanced nasopharyngeal caricinoma: docetaxal plus carboplatin versus 5-fluorouracil plus carboplatin. *Chin J Cancer* 2010; **29**: 140-144
27 **Mostafa E**, Nasar MN, Rabie NA, Ibrahim SA, Barakat HM, Rabie AN. Induction chemotherapy with paclitaxel and cisplatin, followed by concomitant cisplatin and radiotherapy for the treatment of locally advanced nasopharyngeal carcinoma. *J Egypt Natl Canc Inst* 2006; **18**: 348-356
28 **Hui EP**, Ma BB, Leung SF, King AD, Mo F, Kam MK, Yu BK, Chiu SK, Kwan WH, Ho R, Chan I, Ahuja AT, Zee BC, Chan AT. 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
29 **Bossi P**, Parolini D, Bergamini C, Locati LD, Orlandini E, Franceschini M.TPF induction chemotherapy (CT) followed by concomitant cisplatin/radiotherapy (cCTRT) in locally advanced nasopharyngeal cancer (LANPC). abstract 6046. *J Clin Oncol* 2009; 27
30 **Cho S**, Bae W, Hwang J, Shim H, Lee J, Lim S. Phase II study of docetaxel, cisplatin and 5-FU induction chemotherapy followed by concurrent radiotherapy for locally advanced nasopharyngeal cancer. Abstract 17010. *J Clin Oncol* 2008; 26
31 **Beldjiladji Y**, Beldjiladji KA, Boukerche A, Kellafi H, Abdelaoui A, Betkaoui Fabstract. First results of induction chemotherapy with cisplatin, docetaxel and capecitabine for the treatment of nasopharynfeal carcinoma. Abstract 6045. *J Clin Oncol* 2009; 27.
32 **Bae WK**, Hwang JE, Shim HJ, Cho SH, Lee JK, Lim SC, Chung WK, Chung IJ. Phase II study of docetaxel, cisplatin, and 5-FU induction chemotherapy followed by chemoradiotherapy in locoregionally advanced nasopharyngeal cancer. *Cancer Chemother Pharmacol* 2010; **65**: 589-595
33 **Xie FY**, Qi SN, Hu WH, Zou GR, Peng M, Li JS. [Comparison of efficacy of docetaxel combined cisplatin (TP regimen) and cisplatin combined 5-fluorouracil (PF regimen) on locally advanced nasopharyngeal carcinoma]. *Ai Zheng* 2007; **26**: 880-884
34 **Ekenel M**, Keskin S, Basaran M, Bavbek E, Ozdemir C, Meral R. Clinical outcomes in patients with locally advanced nasopharyngeal cancer treated with neoadjuvant docetaxel and cisplatin followed by radiation treatmentand concomitant cisplatin. *J Clin Oncol* abstract 16017. 2010; 28
35 **Lin S**, Lu JJ, Han L, Chen Q, Pan J. Sequential chemotherapy and intensity-modulated radiation therapy in the manage-

ment of locoregionally advanced nasopharyngeal carcinoma: experience of 370 consecutive cases. *BMC Cancer* 2010; **10**: 39
36 **Palazzi M**, Orlandi E, Bossi P, Pignoli E, Potepan P, Guzzo M, Franceschini M, Scaramellini G, Cantù G, Licitra L, Olmi P, Tomatis S. Further improvement in outcomes of nasopharyngeal carcinoma with optimized radiotherapy and induction plus concomitant chemotherapy: an update of the Milan experience. *Int J Radiat Oncol Biol Phys* 2009; **74**: 774-780

S- Editor Yang XC **L- Editor** Webster JR **E- Editor** Yang XC