

Review

Role of chemotherapy in stage IIb nasopharyngeal carcinoma

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Abstract

The efficacy of neoadjuvant chemotherapy and adjuvant chemotherapy on stage IIb nasopharyngeal carcinoma (NPC) remains unclear. Conventional two-dimensional radiotherapy combined with concurrent chemotherapy can improve the overall survival, progression-free survival, recurrence-free survival, and distant metastasis-free survival of patients with stage IIb NPC. Intensity-modulated radiotherapy without concurrent chemotherapy also provides good outcomes for patients with stage IIb NPC. This article summarizes the features of stage IIb NPC and reviews the role of chemotherapy in this subgroup of NPC.

Key words: Nasopharyngeal carcinoma, stage IIb, chemotherapy

With the advancement of diagnostic approaches for nasopharyngeal carcinoma (NPC), more and more NPC cases are diagnosed at early stage. Radiotherapy alone yields satisfactory efficacy on early-stage NPC^[1-4]. In most previous studies, early-stage NPC was considered as one group. However, the prognosis of stage IIb NPC is worse than that of other subgroups of early-stage NPC; in addition, the treatment responses of stage IIb NPC in various subgroups vary significantly^[1,2,5]. Therefore, subgroup analysis of stage IIb NPC for prognostic factors is significant in proposing individualized treatments for early-stage NPC patients. At present, most related studies have assessed the efficacy of chemotherapy on stage IIb NPC and observed disparate outcomes. Here, we review recent findings on the efficacy of chemotherapy on stage IIb NPC.

Clinical Characteristics of Stage IIb NPC

According to the 2002 Union for International Cancer Control (UICC) classification, stage IIb NPC is defined as T1-T2aN1M0 or T2bN0-N1M0. T2b and N1 are two key factors of stage IIb NPC. Survival analysis has indicated that categories T2 and N1 are high-risk factors of distant metastasis in patients with early-stage NPC,

especially stage IIb NPC^[1].

Parapharyngeal extension increases the risk of distant metastasis^[6-8]. When NPC invades beyond the skull base fascia barrier and infiltrates the loose parapharyngeal space, the incidence of distant metastasis will increase significantly. The severer the parapharyngeal extension, the higher the incidence of distant metastasis. Statistical analysis showed that the 5-year distant metastasis-free survival (DMFS) rate of patients with parapharyngeal extension was 12.6% lower than that of patients without parapharyngeal extension (73.6% vs. 86.2%)^[9]. Chua *et al.*^[8] demonstrated that the 5-year DMFS rate of patients with grade 0/1 parapharyngeal extension was significantly higher than that of those with grade 2/3 (87% vs. 68%, $P < 0.001$). Cervical lymph node metastasis is closely related with distant metastasis. However, Teo *et al.*^[6] observed that for patients without cervical lymph node metastasis (N0), the 3-year DMFS rate of patients with T2b NPC was 18% lower than that of those with T2a disease (4% vs. 22%). Cheng *et al.*^[10] further found that even with cervical lymph node metastasis (N1), the 5-year DMFS rate of patients with T1-T2a NPC was still significantly higher than that of patients with T2b NPC although both were subgroups at stage IIb. These findings thoroughly confirm that patients with parapharyngeal extension have a higher risk of distant metastasis than do those without parapharyngeal extension, whether complicated with cervical lymph node metastasis or not. The above results suggest that the parapharyngeal space contains an intensive network of vascular plexus and that parapharyngeal extension is more likely than cervical lymph node metastasis to cause an increased risk of distant metastasis. With the development and application

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of high-resolution computed tomography (CT) and magnetic resonance imaging (MRI), the diagnostic accuracy of parapharyngeal extension has been enhanced. Whether parapharyngeal extension increases the risk of distant metastasis has been debated. CT-based parapharyngeal extension grading revealed that distant metastasis is significantly associated with parapharyngeal extension ($P = 0.002$). The risk ratios were higher in patients with grade 1/2 and grade 3 parapharyngeal extension than in patients with bilateral cervical lymph node metastases (15.97% and 45.84% vs. 4.04%)^[11]. MRI yields higher values in differentiating soft tissues like parapharyngeal space tissue than CT. Therefore, MRI-based parapharyngeal extension grading may be more accurate. Ng *et al.*^[12] classified parapharyngeal extension based on MRI results and analyzed the prognosis of patients treated with three-dimensional conformal radiotherapy. Their study indicated that the 5-year DMFS rates were 87% in patients with T2a NPC and 91% in patients with T2b NPC, and that parapharyngeal extension was not a poor prognostic factor of NPC. MRI provides great benefits in diagnosing parapharyngeal extension and precisely delineating target volume in the parapharyngeal space. CT-based diagnosis of parapharyngeal extension and conventional two-dimensional radiotherapy may be unsuitable in the era of precise radiotherapy. Thus, it is reasonable that the 2009 UICC classification (7th edition) does not contain the concept of stage IIb NPC. However, whether T2a and T2b should be kept for NPC classification must be investigated in more prospective and multi-center studies.

NPC patients with N1 tumors have a high risk of distant metastasis. Zong *et al.*^[5] analyzed 749 NPC patients in different T-N groups and found that the 5-year distant metastasis rate in the N1 group (T1-T2N1) was significantly higher than that in the N0 group (T1-T2N0) (10.8% vs. 0.1%, $P < 0.001$). The risk ratio of death in the N1 group was 3.8 times higher than that in the N0 group. Relevant studies have reported that patients with retropharyngeal lymph node metastasis but without cervical lymph node metastasis had an increased risk of distant metastasis, which was similar to the risk in patients with cervical lymph node metastasis (N1 stage)^[13,14]. Hence, it is feasible to categorize retropharyngeal lymph node metastasis as N1 in clinical classification. However, large-scale and multi-center prospective studies are warranted to determine the effect of retropharyngeal lymph node metastasis on the staging and treatment of NPC.

Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy can inhibit the implan-

tation of tumor cells, thereby eliminating cancer cells in the circulation and reducing subclinical metastasis. In addition, it can also lower locoregional tumor load and eventually increase locoregional control rate. Neoadjuvant chemotherapy has been primarily applied to treat local advanced NPC and provides benefits to these patients^[15-18]. But Hareyama *et al.*^[19] drew an opposite conclusion. Few studies on applying neoadjuvant chemotherapy to treat stage IIb NPC have been conducted, and the conclusions of these studies are inconsistent. Thus, to determine the effect of neoadjuvant chemotherapy on stage IIb NPC, large-scale and multi-center prospective investigations are needed.

In 2006, Chua *et al.*^[20] performed a meta-analysis of two randomized, prospective phase III clinical trials including 208 patients with stage IIb NPC, among whom 98 underwent neoadjuvant chemotherapy combined with radiotherapy and 110 underwent conventional radiotherapy alone. The chemotherapy scheme was based on the combination of cisplatin and epirubicin; some patients underwent chemotherapy with cisplatin, epirubicin, and 5-fluorouracil. Radiotherapy was performed after 2 to 3 cycles of chemotherapy. The results of the meta-analysis revealed that the 5-year overall survival (OS) rate in the combination therapy group was 12% higher than that in the radiotherapy alone group (79% vs. 67%, $P = 0.048$). Moreover, the 5-year DMFS rate in the combination therapy group was 15% higher than that in the radiotherapy alone group (86% vs. 71%, $P = 0.005$). Hence, the authors attributed the low OS rate of patients with stage IIb NPC in the radiotherapy alone group to distant metastasis, the main reason of treatment failure of stage IIb NPC. Neoadjuvant chemotherapy can evidently reduce distant metastasis and eventually prolong OS.

Nevertheless, neoadjuvant chemotherapy postpones local radiotherapy, accelerates the repopulation of cancer cells, yields no radiosensitization, and can hardly inhibit radioresistant tumor cells. Therefore, theoretically, neoadjuvant chemotherapy weakens the efficacy of subsequent radiotherapy.

Song *et al.*^[21] retrospectively analyzed the efficacy of neoadjuvant chemotherapy on NPC, and the results significantly differed from those reported by Chua *et al.*^[20]. Forty-three patients with stage IIb NPC were enrolled in this investigation, among whom 22 underwent conventional radiotherapy alone and 21 underwent neoadjuvant chemotherapy plus radiotherapy. The chemotherapy scheme was based on cisplatin (100 mg/m², day 1) plus 5-fluorouracil (1000 mg/m², day 1 to day 5). Radical radiotherapy was given after 3 cycles of chemotherapy. The results revealed that the 5-year DMFS and disease-free survival (DFS) rates were similar between the two groups. In addition, multivariate analysis indicated that postponing radiotherapy for more than 81

days was an independent risk factor of locoregional relapse of NPC ($P = 0.044$). The authors concluded that neoadjuvant chemotherapy failed to provide therapeutic gains for patients with stage IIb NPC. In contrast, delayed local radiotherapy and accelerated proliferation of tumor cells significantly reduced the efficacy of radiotherapy and increased the risk of locoregional relapse.

Previous studies did not use novel chemotherapeutic agents and did not apply concurrent chemotherapy while applying radiotherapy. Therefore, although the efficacy of neoadjuvant chemotherapy on stage IIb NPC is unclear, the role of neoadjuvant chemotherapy deserves further investigation. Whether neoadjuvant chemotherapy plus concurrent chemoradiotherapy can increase the efficacy on stage IIb NPC is an important topic for subsequent analysis.

Concurrent Chemoradiotherapy

In concurrent chemoradiotherapy, radiotherapy can be classified into conventional radiotherapy and intensity-modulated radiotherapy (IMRT). The local control rates of stage IIb NPC treated with the two techniques differ. Hence, whether the two techniques should be used in combination with chemotherapy is under debate.

Conventional radiotherapy with chemotherapy

Previous studies on the efficacy of conventional radiotherapy alone on stage IIb NPC have consistently shown that patients with N1 and T2b tumors should undergo comprehensive chemoradiotherapy to enhance efficacy^[1,2,5,22]. However, these studies did not include a comparison with concurrent chemoradiotherapy. Thus, this conclusion is not quite tenable in the clinic and should be seen as a reference at most. Concurrent chemoradiotherapy has two major advantages. First, chemotherapy and radiotherapy exert a synergistic effect. Chemotherapeutic agents directly kill cancer cells, or cause G₂/M arrest in cancer cell cycle to enhance tumor cell sensitivity to radiotherapy, or inhibit the repair of sublethal injuries in cancer cells to enhance the effect of radiotherapy on tumors. Second, chemotherapy could eliminate potential subclinical metastatic lesions and circulating metastatic cells. Thus, in theory, concurrent chemotherapy could not only increase the local control rate but also reduce distant metastasis.

Xu *et al.*^[23] confirmed this conclusion by retrospectively analyzing 392 patients with T2N1M0 NPC, among whom 181 underwent conventional radiotherapy and concurrent chemotherapy (cisplatin, 100 mg/m² per day) on the 1st, 22nd, and 43rd days during the course

of radiotherapy, 211 underwent conventional radiotherapy alone. The results showed that the 5-year OS and DFS rates were higher in the concurrent chemoradiotherapy group than in the radiotherapy alone group (80.2% vs. 76.6%, $P = 0.778$; 70.5% vs. 64.2%, $P = 0.413$), whereas the 5-year DMFS rate was lower in the concurrent chemoradiotherapy group than in the radiotherapy alone group (76.9% vs. 81.5%, $P = 0.336$), though they failed to reach statistical significance. However, a significant improvement of 5-year relapse-free survival (RFS) rate was detected in the concurrent chemoradiotherapy group as compared with the conventional radiotherapy alone group (91.5% vs. 77.3%, $P = 0.008$). Multivariate analysis indicated that concurrent chemotherapy was an independent risk factor of 5-year RFS ($P = 0.007$). The above studies showed that concurrent chemoradiotherapy has the tendency to increase OS rate as compared with radiotherapy alone. These results were further validated by a randomized trial conducted by Chen *et al.*^[24], who found that the 5-year OS rate (94.5% vs. 85.8%, $P = 0.007$), progression-free survival (PFS) rate (87.9% vs. 77.8%, $P = 0.017$), and DMFS rate (94.8% vs. 83.9%, $P = 0.007$) in the concurrent chemoradiotherapy group ($n = 116$) were significantly higher than those in the radiotherapy alone group ($n = 114$), respectively. However, the concurrent chemoradiotherapy group had a significantly higher incidence of acute toxic reactions, including hematological system toxicity, mucositis, and gastrointestinal tract reactions, than did the radiotherapy alone group. Although acute toxic reactions may decrease compliance, the patients presented with good tolerance and successfully completed the whole treatment.

The inconsistent conclusions among the above studies can potentially be attributed to two causes. (1) In the investigation by Xu *et al.*^[23], the proportion of patients who underwent lymph node biopsy was significantly higher in the concurrent chemoradiotherapy group than in the radiotherapy alone group (23.2% vs. 14.2%, $P = 0.02$). Lymph node biopsy might enhance the risk of distant metastasis and eventually decrease the OS rate^[25,26]. The role that lymph node biopsy played in enhancing the risk of distant metastasis counteracted the therapeutic gains provided by concurrent chemoradiotherapy in controlling distant metastasis. Hence, 5-year DMFS rate decreased and therefore OS and other outcomes showed no significant differences between the concurrent chemoradiotherapy group and the radiotherapy alone group. (2) Various studies adopted different chemotherapy schemes. Once-a-week chemotherapy may have more therapeutic gains than conventional 3-week chemotherapy may have, though this hypothesis requires more testing.

IMRT with chemotherapy

IMRT, an precise radiotherapy technique, can increase target dose, enhance the local control rate, and thereby decrease the incidence of distant metastasis. Wong *et al.*^[27] performed a 3-year follow-up of 40 patients with N1 NPC who underwent IMRT and found that the 3-year DMFS rate reached 100%. However, Xu *et al.*^[23] used conventional two-dimensional radiotherapy to treat N1 NPC and found that the 5-year DMFS rate was only 81.5%. These two studies differed in terms of enrollment time, examination tools for tumor staging (Xu *et al.*^[23] used CT, whereas Wong *et al.*^[27] used MRI), and radiotherapy dose. Thus, it is untenable to conclude that IMRT prolongs DMFS than does two-dimensional radiotherapy merely based upon statistical data. However, IMRT distributed target dose in a highly conformal pattern, allocating more doses to cover gross tumor volume (GTV) of cervical lymph node metastasis and parapharyngeal extension to increase the local control rate. The increased local control rate enhanced the 5-year DMFS rate by 11% in IMRT group than in two-dimensional radiotherapy group^[4]. In addition, two-dimensional radiotherapy distributed target doses into cervical lymph node metastasis and parapharyngeal extension in a poor conformal manner. This probably leads to insufficient delivery of the dose required by radical radiotherapy in certain tumor sites and a decrease in the local control rate, and finally lower the DMFS rate.

Su *et al.*^[26] conducted a follow-up of 198 patients with early-stage NPC (141 at stage IIb) who underwent IMRT. The median follow-up time was 50.9 months, and the longest follow-up time was 104 months. No patients underwent neoadjuvant, concurrent, or adjuvant chemotherapies. The 5-year tumor-related survival, locoregional recurrence-free survival, and DMFS rates were 97.3%, 97.7%, and 97.8%, respectively. Subgroup analysis revealed that the 5-year DMFS rates for patients with T1N0, T2N0, T1N1, and T2N1 cancer were 100%, 98.8%, 100%, and 93.8% ($P = 0.125$), respectively, indicating that the efficacy of IMRT was equivalent in patients with stages IIb and I NPC. Despite this, T2b and N1 remain risk factors of distant metastasis in patients with stage IIb NPC. The failure rate of the whole group was 6.1%. Distant metastasis or locoregional relapse was observed in 12 cases at stage IIb, which accounted for 9% of all stage IIb cases, and 7 of the 12 patients died. During follow-up, the patients with T1N0 disease had no treatment failure. Wong *et al.*^[27] also found that for early-stage NPC patients underwent IMRT, all cases of death occurred during stage IIb. Regarding the question whether concurrent chemotherapy should be used to lower the incidence of distant metastasis, Su *et al.*^[26] provided no answer, whereas Tham *et al.*^[29] refuted

this application. They found that IMRT plus concurrent chemotherapy group and IMRT group did not differ in terms of 3-year local control, regional control, DMFS, DFS, and OS rates by log-rank test^[29]. IMRT had desirable efficacy in patients with stage IIb NPC because of small target tumor size, low proportion of hypoxic cells within tumors, and dosimetric advantages of IMRT^[29]. The limitation of this study was small sample size in the concurrent chemotherapy group, probably inducing unreasonable statistical data. Hence, the efficacy of IMRT on stage IIb NPC requires large-scale, prospective, multi-center, randomized trials to validate.

Adjuvant Chemotherapy

The main purpose of adjuvant chemotherapy is to reduce distant metastasis. Because the efficacy of concurrent chemotherapy on distant metastasis remains unclear due to low dosage, multiple studies collectively applied these two methods to treat advanced NPC. Concurrent chemoradiotherapy plus adjuvant chemotherapy is currently a standard approach for NPC treatment in Tai Wan, Hong Kong, and other districts; however, it has been seldom applied to treat early-stage NPC, and the corresponding cost-effectiveness ratio is elusive.

Cheng *et al.*^[30] reported 44 cases of stages I and II NPC. Among these, 12 patients (11 with stage I and 1 with stage II NPC) underwent radiotherapy alone, and 32 (30 with stage IIb, 29 with N1, and 9 with T2b NPC) underwent concurrent chemoradiotherapy plus adjuvant chemotherapy. Concurrent chemotherapy was based on cisplatin plus 5-fluorouracil, given on the first and sixth weeks during radiotherapy, followed by 2 courses of adjuvant chemotherapy (cisplatin plus 5-fluorouracil) when concurrent radiotherapy was finished. The results indicated that 3-year locoregional control and DFS rates in the radiotherapy alone group and concurrent chemoradiotherapy plus adjuvant chemotherapy groups were 91.7% vs. 100% ($P = 0.10$) and 91.7% vs. 96.9% ($P = 0.66$), respectively. The results also revealed that concurrent chemoradiotherapy plus adjuvant chemotherapy had increased efficacy in patients with stage IIb NPC, similar to that in patients with stage I NPC that underwent radiotherapy alone. Nevertheless, the study was limited by small sample size, and the observed efficacy of concurrent chemoradiotherapy plus adjuvant chemotherapy was mainly ascribed to concurrent chemoradiotherapy. In this study population, 2 patients (T2bN1M0) had developed distant metastasis, suggesting that there is a risk of distant metastasis even if highly intensive chemotherapy was given to patients with stage IIb NPC. Furthermore, concurrent chemoradiotherapy plus adjuvant chemotherapy yields

poor patient compliance and tolerance. Indeed, the incidence of related adverse events was high, with grade III mucosa reactions and grade IV adverse events occurring in 62.5% and 6% of cases, respectively.

Prospective analysis showed that concurrent chemoradiotherapy plus adjuvant chemotherapy can enhance the OS rate of patients with locoregional advanced NPC [30-33]. However, Kwong *et al.* [34] performed Cox regression analysis and noted that concurrent chemoradiotherapy was an independent influencing factor of OS, whereas adjuvant chemotherapy exerts no significant effect on local control rate or OS. Few studies focusing on adjuvant chemotherapy for stage IIb NPC have been conducted. Therefore, large-scale and multi-center prospective studies are warranted to determine the effect of adjuvant chemotherapy on stage IIb NPC.

Current Problems and Future Study Orientation

At present, many studies have been conducted retrospectively for an overall analysis of early-stage NPC patients. There are few studies focusing on the overall and subgroup analysis of stage IIb NPC. These overall studies suggest that the efficacy of neoadjuvant and adjuvant chemotherapies on stage IIb NPC is unclear, whereas concurrent chemoradiotherapy could elevate the

OS, DFS, RFS, and DMFS rates for patients with stage IIb NPC. Subsequent subgroup analysis of stage IIb NPC showed that conventional two-dimensional radiotherapy combined with concurrent chemotherapy can improve the prognosis of patients with N1 NPC (T1N1, T2aN1, and T2bN1). IMRT can produce desirable 5-year OS and RFS rates for patients with T1N1, T2aN1, and T2bN0 diseases and only causes mild adverse events. For patients with T2bN1 NPC, IMRT also yield similar desirable outcomes. Whether concurrent chemotherapy combined with IMRT can increase the efficacy requires large-scale prospective investigations.

There is no standard scheme for neoadjuvant, concurrent, or adjuvant chemotherapy. Most studies used cisplatin-based chemotherapy. Chemotherapeutic agents, doses, duration, courses, interval time, and other factors greatly vary among studies, which is likely to cause statistical bias among them. More studies regarding extended chemotherapy schemes as major variables are urgently required to screen an optimal chemotherapy scheme.

To advance the field, the goals of subsequent studies should include actively seeking prognostic factors for subgroups of stage IIb NPC, enhancing the efficacy of subgroups, and applying individual treatment.

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References

- [1] Xiao WW, Han F, Lu TX, et al. Treatment outcomes after radiotherapy alone for patients with early-stage nasopharyngeal carcinoma. *Int J Radiat Oncol*, 2009,74:1070-1076.
- [2] Chua DT, Sham JS, Kwong DL, et al. Treatment outcome after radiotherapy alone for patients with stage I-II nasopharyngeal carcinoma. *Cancer*, 2003,98:74-80.
- [3] Yi JL, Gao L, Huang XD, et al. Nasopharyngeal carcinoma treated by radical radiotherapy alone: ten-year experience of a single institution. *Int J Radiat Oncol Biol Phys*, 2006,65:161-168.
- [4] Lee AW, Sze WM, Au JS, et al. Treatment results for nasopharyngeal carcinoma in the modern era: the Hong Kong experience. *Int J Radiat Oncol Biol Phys*, 2005,61:1107-1116.
- [5] Zong JF, Ma J, Tang LL, et al. A study of the combined treatment strategy for patients with nasopharyngeal carcinoma based on the analysis of the treatment results from 749 cases. *China Cancer*, 2005,14:538-542. [in Chinese]
- [6] Teo P, Lee WY, Yu P. The prognostic significance of parapharyngeal extension in nasopharyngeal carcinoma. *Radiother Oncol*, 1996,39:209-221.
- [7] 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.
- [8] Chua DT, Sham JS, Kwong DL, et al. Prognostic value of parapharyngeal extension of nasopharyngeal carcinoma: a significant factor in local control and distant metastasis. *Cancer*, 1996,78:202-210.
- [9] Zhang DG, Lu TX, Chen CY, et al. Prognostic significance of parapharyngeal space involvement on distant metastasis in nasopharyngeal carcinoma. *Chin J Cancer Prev Treat*, 2008,15:541-543. [in Chinese]
- [10] Cheng SH, Tsai SY, Yen KL, 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.
- [11] Ho HC, Lee MS, Hsiao SH, et al. Prognostic influence of parapharyngeal extension in nasopharyngeal carcinoma. *Acta Otolaryngol*, 2008,128:790-798.
- [12] Ng WT, Chan SH, Lee AW, et al. Parapharyngeal extension of nasopharyngeal carcinoma: still a significant factor in era of modern radiotherapy? *Int J Radiat Oncol Biol Phys*, 2008,72:1082-1089.
- [13] Ma J, Liu L, Tang L, et al. Retropharyngeal lymph node metastasis in nasopharyngeal carcinoma: prognostic value and staging categories. *Clin Cancer Res*, 2007,13:1445-1452.
- [14] Tham IW, Hee SW, Yap SP, et al. Retropharyngeal nodal metastasis related to higher rate of distant metastasis in patients with N0 and N1 nasopharyngeal cancer. *Head Neck*, 2009,31:468-474.
- [15] O'Sullivan B. Nasopharynx cancer: therapeutic value of chemoradiotherapy. *Int J Radiat Oncol Biol Phys*, 2007,69:S118-S121.
- [16] Preliminary results of a randomized trial comparing neoadjuvant

- chemotherapy (cisplatin, epirubicin, bleomycin) plus radiotherapy vs. radiotherapy alone in stage IV(> or = N2, M0) undifferentiated nasopharyngeal carcinoma: a positive effect on progression-free survival. International Nasopharynx Cancer Study Group. VUMCA I trial. *Int J Radiat Oncol Biol Phys*, 1996,35:463–469.
- [17] Chua DT, Sham JS, Choy D, et al. Preliminary report of the Asian-Oceania Clinical Oncology Association randomized trial comparing cisplatin and epirubicin followed by radiotherapy versus radiotherapy alone in the treatment of patients with locoregionally advanced nasopharyngeal carcinoma. Asian-Oceania Clinical Oncology Association Nasopharynx Cancer Study Group. *Cancer*, 1998,83:2270–2283.
- [18] Ma J, Mai HQ, Hong MH, 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.
- [19] Hareyama M, Sakata K, Shirato H, et al. A prospective, randomized trial comparing neoadjuvant chemotherapy with radiotherapy alone in patients with advanced nasopharyngeal carcinoma. *Cancer*, 2002,94:2217–2223.
- [20] Chua DT, Ma J, Sham JS, et al. Improvement of survival after addition of induction chemotherapy to radiotherapy in patients with early-stage nasopharyngeal carcinoma: subgroup analysis of two phase III trials. *Int J Radiat Oncol Biol Phys*, 2006,65:1300–1306.
- [21] Song CH, Wu HG, Heo DS, et al. Treatment outcomes for radiotherapy alone are comparable with neoadjuvant chemotherapy followed by radiotherapy in early-stage nasopharyngeal carcinoma. *Laryngoscope*, 2008,118:663–670.
- [22] Yi JL, Gao L, Huang XD, et al. The outcome of stage II nasopharyngeal carcinoma treated by definitive conventional fractionation radiotherapy. *Clin J Radiat Oncol*, 2009,18:83–86.
- [23] Xu T, Hu C, Wang X, et al. Role of chemoradiotherapy in intermediate prognosis nasopharyngeal carcinoma. *Oral Oncol*, 2011,47:408–413.
- [24] Chen QY, Wen YF, Guo L, et al. Concurrent chemoradiotherapy vs radiotherapy alone in stage II nasopharyngeal carcinoma: phase III randomized trial. *J Nat Cancer Ins*, 2011,103:1761–1770.
- [25] Tang SG, Lin FJ, Chen MS, et al. Prognostic factors of nasopharyngeal carcinoma: a multivariate analysis. *Int J Radiat Oncol Biol Phys*, 1990,19:1143–1149.
- [26] Tang SG, See LC, Chen WC, et al. The effect of nodal status on determinants of initial treatment response and patterns of relapse-free survival in nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*, 2000,47:867–873.
- [27] Wong FC, Ng AW, Lee VH, et al. Whole-field simultaneous integrated-boost intensity-modulated radiotherapy for patients with nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*, 2010,76:138–145.
- [28] Su SF, Han F, Zhao C, et al. Long-term outcomes of early-stage nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy alone. *Int J Radiat Oncol Biol Phys*, 2012,82:327–333.
- [29] Tham IW, Lin S, Pan J, et al. Intensity-modulated radiation therapy without concurrent chemotherapy for stage IIb nasopharyngeal cancer. *Am J Clin Oncol*, 2010,33:294–249.
- [30] Cheng SH, Tsai SY, Yen KL, et al. Concomitant radiotherapy and chemotherapy for early-stage nasopharyngeal carcinoma. *J Clin Oncol*, 2000,18:2040–2045.
- [31] Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *J Clin Oncol*, 1998,16:1310–1317.
- [32] Wee J, Tan EH, Tai BC, 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.
- [33] Lee AW, Lau WH, Tung SY, et al. Preliminary results of a randomized study on therapeutic gain by concurrent chemotherapy for regionally-advanced nasopharyngeal carcinoma: NPC-9901 trial by the Hong Kong Nasopharyngeal Cancer Study Group. *J Clin Oncol*, 2005,23:6966–6975.
- [34] Kwong DL, Sham JS, Au GK, et al. Concurrent and adjuvant chemotherapy for nasopharyngeal carcinoma: a factorial study. *J Clin Oncol*, 2004,22:2643–2653.