

## Original Article

# Effective radiotherapy dose for suspicious positive cervical lymph nodes for NO nasopharyngeal carcinoma patients: a prospective cohort study

Jun Lv, Lingjiang Pan, Jiamei Lu, Wen Qin, Tingting Zhang

Department of Radiation Oncology, First Affiliated Hospital of Guangxi Medical University, Guangxi Province, Nanning 530021, China

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**Abstract:** Nasopharyngeal carcinoma (NPC) is a malignant tumor, with a high rate of incidence in Southern China. This study explored the most appropriate radiotherapy dose for suspicious positive cervical lymph nodes in patients with NO NPC. Ninety-six patients with suspicious positive cervical lymph nodes were randomized into low-dose group (64 Gy) and high-dose group (68-70 Gy). Among these, T3/T4-stage patients were given concomitant chemo-radiotherapy and were followed-up for 28-44 months, with a median of 36 months, during which the regression of cervical lymph nodes, radiation injury of cervical skin and muscle, regional control rate, distant metastases rate, overall survival (OS), and other indicators were observed. Intergroup comparisons were performed using *t*-test. The treatment efficiencies for suspicious positive cervical lymph nodes of the experiment and control groups were 90.1% and 93.3%, respectively ( $P < 0.05$ ), and the incidences of cervical mucocutaneous reactions were 12.5% and 33.3% ( $P < 0.05$ ), respectively. The 3-year OS rates of the groups were 93.5% and 89.1% ( $P < 0.05$ ), respectively, while the tumor-free survival (TFS) rates were 87.0% and 80.4% ( $P < 0.05$ ), respectively. Treatment efficiency of cervical lymph nodes, OS, and other indicators did not show significant differences between the two groups, while the incidences of radiation dermatitis of neck skin and cervical soft tissue fibrosis were significantly lower in the experiment group than the control group. Therefore, a radiotherapy dose of 64 Gy for suspicious positive cervical lymph nodes of NPC is safe and reliable.

**Keywords:** Nasopharyngeal carcinoma, stage NO, suspicious positive lymph nodes, radiotherapy dose, prospective cohort study

## Introduction

Nasopharyngeal carcinoma (NPC) is a malignant tumor with a high incidence in Guangdong and Guangxi, China. Radiotherapy has been considered as the main treatment protocol for NPC. Cervical lymph node enlargement is an important manifestation of NPC. More than 85% of patients, with initially diagnosed NPC, are accompanied by regional lymph node metastasis [1]. Clinically, some scattered small lymph nodes with the largest cross-sectional minor axis  $< 1$  cm, intact capsule, and absence of central necrosis are often found in imaging examinations of some of the patients. These lymph nodes are considered to be positive lymph nodes, but they fail to justify the diagnostic criteria [2, 3] and are associated with prog-

nosis. Radiotherapy dose for this type of lymph nodes is still inconclusive; relatively few domestic and foreign relevant reports are available and there is a lack of comparative study. In this study, 96 patients, with suspicious positive cervical lymph nodes, who initially receiving treatment for NO NPC were randomized into experiment group (64 Gy radiotherapy dose for suspicious positive lymph nodes) and control group (68-70 Gy radiotherapy dose for suspicious positive lymph nodes). Patients in both groups were given concomitant chemo-radiotherapy [intensity modulated radiotherapy (IMRT) + Cisplatin] and were followed up for 28-44 months. To explore an appropriate radiotherapy dose for suspicious positive cervical lymph nodes, efficacy and toxic and side-effects were compared between the two groups.

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### Materials and methods

#### General information

N0 NPC patients, with suspicious positive cervical lymph nodes, were selected from The First Affiliated Hospital of Guangxi Medical University between February and December, 2011 for the study.

Inclusion criteria were as follows: (1) Aged 18-70 years old; (2) Met with WHO diagnostic criteria; (3) Pathologically diagnosed with non-keratinizing squamous cell carcinoma; (4) Imaging diagnosed as stage N0; (5) Had no distant metastasis; (6) Demonstrated normal results of the blood routine, electrolytes, as well as liver and kidney functions; (7) Suffered from suspicious positive lymph nodes; and (8) Signed written informed consent.

Exclusion criteria were as follows: (1) Pregnant or lactating women; (2) Had undergone lymph node biopsy; (3) Were combined with other malignant tumors; and (4) Received radiotherapy or chemotherapy prior to the treatment.

According to the preliminary experiments, 96 cases were selected and assigned to the experiment group (48 cases) and control group (48 cases), using a random number table.

Diagnostic criteria for suspicious positive lymph nodes below the standard were referred to the criteria for metastatic lymph nodes, which specified the lymph nodes with the largest cross-sectional minor axis  $\geq 0.5$  cm, but  $< 1$  cm, intact capsule and absence of central necrosis.

#### Treatment protocol

*Instruments:* Stimulation was performed using a Brilliance 16-sliced CT (Philips, Dutch), and patients were radiated using a linear accelerator (IX model, Varian Inc., USA).

*CT simulation scanning:* Computed tomography (CT) scanning was performed before radiotherapy on all the patients from both the groups. Patients were kept in supine position and fixed with a head-neck-shoulder mask. The scanning ranged from calvarium to 2 cm below the clavicle, with a layer pitch 3 mm and thickness 3 mm was used. The scanning images were imported to a radiotherapy treatment planning system for analyses.

*Sketching target areas and organs at risk:* Principles described in ICRU50 and ICRU62 documents were adopted to sketch the target areas in patients from both the groups, where gross tumor volume of nasopharynx (GTVnx), suspicious positive cervical lymph nodes (GTV-nd<sub>suspicious positive</sub>), clinical target volume 1 (CTV1: high-risk area), clinical target volume 2 (CTV2: low-risk area), and normal risk organs, including spinal cord, brain stem, parotid, temporal lobe, eye ball, and crystal were sketched in the CT images referring to the MRI images.

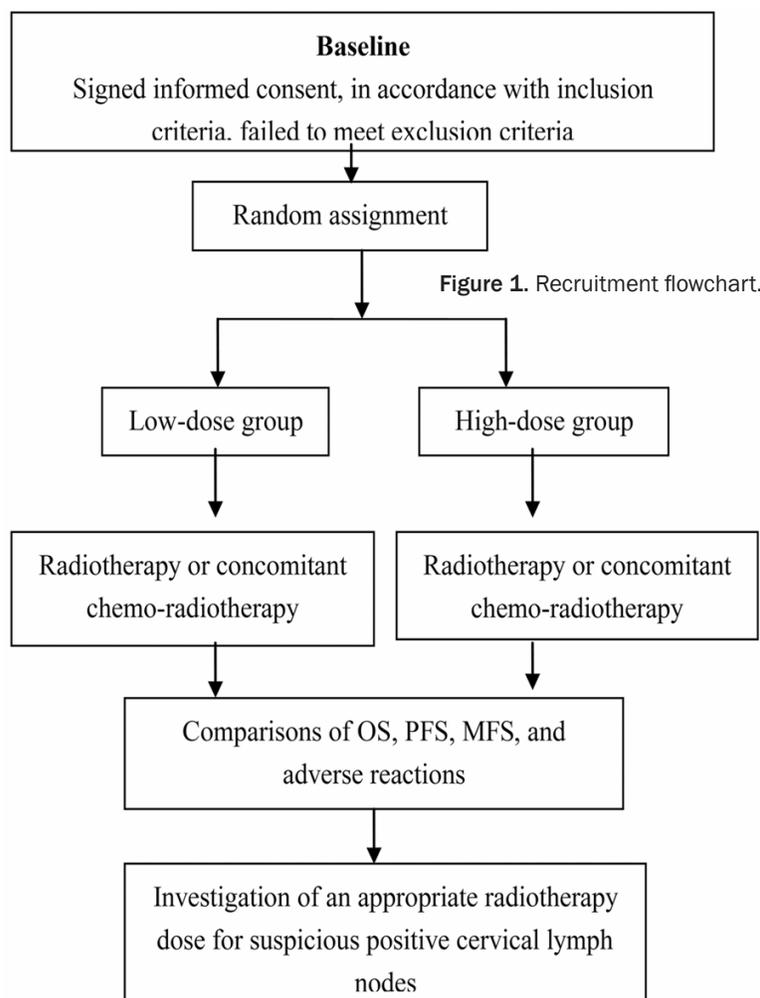
*Prescribed dose:* Patients in both the groups received a course of radical radiotherapy, where prescribed doses with statistical insignificance were applied to GTVnx, CTV1, and CTV2 (GTVnx DT 70~74 Gy, CTV1 DT 60~64 Gy, CTV2 DT 50 Gy~54 Gy), while a different prescription dose was applied to GTV-nd<sub>suspicious positive</sub> (DT 64 Gy in experiment group, and DT68~70 Gy in control group). The limiting dose for involved organs were determined according to the Radiation Therapy Oncology Group Protocol 02-25: 40~50 Gy for brain stem, 35~40 Gy for spinal cord, 45~50 Gy for optic nerve, optic chiasm, and pituitary gland, 40~55 Gy for temporal lobe, 3~5 Gy for crystal, 24~30 Gy for parotid, 30~50 Gy for temporo-mandibular joint, and 40~50 Gy for inferior maxillary bone.

*Irradiation method:* Patients in both the groups were exposed to IMRT, with 7 coplanar conformal fields. Patients from both the groups were exposed to preventive irradiation in the upper neck region. After planned optimization, lateral intensity data was obtained from each field, and dose for each area was verified, followed by 6 MV high-intensity X-ray irradiation with a linear accelerator.

*Radiotherapy:* T3/T4-stage patients in both the groups were given concurrent chemotherapy, with a single-agent Cisplatin (80~100 mg/m<sup>2</sup>) from the first day of radiotherapy, and all of them successfully received two cycles (21 days for one cycle) of concurrent chemotherapy. On the other hand, T1/T2-stage patients received only radiotherapy.

*Observation and follow-up:* During the treatment, primary lesion and regression of cervical lymph nodes were closely monitored. In addition, the radiotherapy toxicity according to the

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were examined: blood routine, biochemistry, chest film, abdominal B-ultrasound, fiberoptic pharyngoscopy, and MRI examination of head and neck. Patients with suspicious distant metastasis underwent chest and abdomen CT or bone ECT, or even PET-CT, if appropriate.

### Statistical analysis

Primary outcomes included OS, recurrence-free survival (RFS), and metastasis-free survival (MFS). Statistical analyses were performed using SPSS17.0 software, wherein the K-M method and log-rank test were adopted, and a difference with  $P < 0.05$  was considered statistically significant.

### Results

#### Recruitment flowchart

Recruitment flowchart (see **Figure 1**).

#### Baseline data (**Table 1**)

**Table 1.** Comparisons of 96 NO NPC patients with suspicious positive cervical lymph nodes in different radiotherapy dose groups

|                  | Low-dose group | High-dose group | P      |
|------------------|----------------|-----------------|--------|
| Sex (number)     |                |                 |        |
| Male             | 35             | 36              | > 0.05 |
| Female           | 13             | 12              | > 0.05 |
| Age (years)      | 47.2           | 48.1            | > 0.05 |
| T stage (number) |                |                 |        |
| T1               | 4              | 5               | > 0.05 |
| T2               | 13             | 16              | > 0.05 |
| T3               | 25             | 21              | > 0.05 |
| T4               | 6              | 6               | > 0.05 |
| Nodes (number)*  | 71             | 90              | > 0.05 |

\*Nodes = Suspicious positive lymph nodes.

RTOG irradiation reaction criteria was assessed. During the follow-up, the following items

Among the participants, 71 were men and 25 women, with age in the range of 18-63 years (median age 45 years), and castigliano score of  $\geq 80$ . All the patients underwent plain and enhanced MRI on the nasopharynx and neck before the treatment to determine T and N stages of the carcinoma. In terms of T-staging according to the AJCC Cancer Staging Manual 7<sup>th</sup> ed. [4], there were 9 cases of T1 stage, 29 cases of T2 stage, 46 cases of T3 stage, and 12 cases of T4 stage. In the participants, a total of 161 suspicious positive lymph nodes were observed, including 85 suspicious positive lymph nodes in unilateral neck of 60 patients, and 76 suspicious positive lymph nodes in bilateral necks of 36 patients. Moreover, among the observed nodes, 12 lymph nodes were observed in Ib region, 45 in IIa region, 51 in IIb region, 38 in III region, 6 in IV region, and 9 in V region. In total, 71 and 90 suspicious positive lymph nodes were observ-

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**Table 2.** Dose and volume of risk organs

| OAR           | Volume            | Average dose (Gy) |                 |
|---------------|-------------------|-------------------|-----------------|
|               |                   | Low-dose group    | High-dose group |
| Brain stem    | 5%                | 41.38             | 42.62           |
| Spinal cord   | 1 cm <sup>3</sup> | 39.68             | 40.96           |
| Temporal lobe | 33%               |                   |                 |
| Left          |                   | 20.05             | 18.87           |
| Right         |                   | 19.72             | 19.53           |
| Parotid       | 33%               |                   |                 |
| Left          |                   | 43.88             | 52.24           |
| Right         |                   | 42.91             | 51.15           |
| Pituitary     | 5%                | 24.60             | 23.81           |
| Optic nerve   | 5%                |                   |                 |
| Left          |                   | 10.94             | 10.11           |
| Right         |                   | 12.31             | 10.37           |
| Optic chiasm  | 5%                | 28.56             | 27.93           |

\*OAR = organ at risk.

**Table 3.** Prognosis of 96 NO NPC patients in different radiotherapy dose groups

|                     | Low-dose group | High-dose group |
|---------------------|----------------|-----------------|
| Recurrence (number) | 2              | 4               |
| Metastasis (number) | 2              | 2               |
| Death (number)      | 3              | 5               |

ed in the experiment and control groups, respectively.

Follow-up ranged from the date of diagnosis to December 30, 2014. There were 4 lost cases, with a 1-year follow-up rate of 100% and 3-year follow-up rate of 95.8%. Patients were rechecked once every 3 months within 2 years after the treatment, and once every 6 months afterwards.

*Prognosis: therapeutic results, recurrence, and metastasis (Tables 2, 3)*

In all of the patients, the 3-year OS and TFS scores were 91.6% and 84.4%, respectively. There were 8 death cases (3 cases in experiment group and 5 cases in control group), with a survival range of 16-38 months. Three cases died of local recurrence (2 cases in experiment group and 1 case in control group), 4 due to distant metastasis (1 case in experiment group and 3 cases in control group), and 1 death was caused to non-tumor reasons. Three cases suf-

fered from local recurrence (1 case in experiment group and 2 cases in control group), 1 case from cervical recurrence (Ib region) (control group), with a recurrence rate of cervical lymph nodes of 1.0%, and 3 cases suffered from distant metastasis, including 2 cases of bone metastasis (1 case in experiment and control groups separately), and 1 case of lung metastasis (experiment group).

### *Comparison of short-term efficacy and adverse reactions*

At the end of radiotherapy, regression of the cervical lymph nodes was observed. Among the 71 suspicious positive lymph nodes in the experiment group, 59 cases of CR, 5 cases of PR, and 7 cases with no changes, with an efficiency of 90.1%, were observed. Among the 90 suspicious positive lymph nodes in the control group, 75 cases of CR, 9 cases of PR, and 6 cases of no changes, with an efficiency of 93.3%, were observed. No significant difference was observed in terms of efficiency between the groups. In terms of cervical mucocutaneous reactions, 4 cases from experiment group and 2 cases from control group suffered from dry dermatitis (skin with dryness and desquamation) and moist dermatitis (skin with ulceration and exudation), respectively, with an incidence of 12.5%. In the control group, 11 cases suffered from dry dermatitis and 5 cases suffered from moist dermatitis, with an incidence of 33.3%, thereby showing significant difference as compared to the experiment group ( $P < 0.05$ ).

### *Comparison of long-term efficacy and adverse reactions*

Until the end of the follow-up (December 30, 2014), there were 4 lost cases (2 cases in each of the groups), with a follow-up rate of 95.8%. There were 8 death cases with a survival range of 16-38 months (3 cases in experiment group and 5 cases in control group), of which 3 cases died of local recurrence, 4 cases died of distant metastasis, and 1 case died due to non-tumor reasons. One case from the control group suffered from regional lymph node recurrence. The 3-year OS scores were 93.5% and 89.1%, RFSs were 87.0% and 80.4%, and MFSs were 89.6% and 85.4% for experiment and control groups, respectively. These values indicated that the differences were not statisti-

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cally significant between the two groups ( $P > 0.05$ ). However, 1 case (2.2%) from the experiment group and 4 cases (8.7%) from the control group suffered from severe fibrosis of cervical soft tissues. The difference between the groups was statistically significant ( $P < 0.05$ ).

### *Effects of irradiation dose on cervical recurrence*

In the experiment group, none of the cases was found to suffer from cervical recurrence; however, in the control group, 1 case suffered cervical recurrence in Ib region, with a recurrence rate of cervical lymph nodes of 2.1%. The difference between the two groups was statistically insignificant ( $P > 0.05$ ).

### **Discussion**

NPC is a malignant tumor, with a very high rate of incidence in Southern China. NO NPC accounts for 4-35.9% of all NPC patients [1, 5-7]. So far, 50 Gy~54 Gy was used as the preventive cervical irradiation dose for NO NPC; however, the irradiation dose for suspicious positive lymph nodes below the standard has not been clarified in the guidelines. Although a dose of 64 Gy has been recommended by the expert consensus, it lacks the sufficient clinical evidence for its application.

Treatment efficiency of NPC is closely related to the local irradiation dose. Teo et al. [8, 9] reported that the increase of dose is closely associated with tumor control following irradiation with a conventional radical dose. In outlining the NPC target area, CTV1 was found to be the high-risk area, which refers to possible invasive areas adjacent to the primary tumors or metastatic lymph nodes. Normally, the radiotherapy dose for high-risk area is about 64 Gy. Since suspicious positive lymph nodes are closely met with the diagnostic criteria of the positive lymph nodes, it is unlikely to exclude the possibility of malignancy only by MRI, especially when the pathological diagnosis is unavailable. Therefore, we believe it is reasonable to classify suspicious positive lymph nodes as high-risk regions, and to irradiate the suspicious positive lymph nodes with a dose of 64 Gy. Previous studies have reported cases suffering from recurrence of cervical lymph nodes following radiotherapy treatment for NO

NPC. Chen SY et al. [10] reported a 23.2% recurrence rate of cervical lymph nodes in NO NPC patients after irradiation with a preventive dose, thereby suggesting that a preventive dose of 50-54 Gy is likely to induce higher regional recurrence rate for suspicious positive lymph nodes of NPC. It may be attributed to the tumor metastasis that might have occurred in lymph nodes, with normal size and morphology. The same can be confirmed by imaging and pathological studies of the cervical lymph nodes. Thus, it is necessary to increase the irradiation dose for suspicious positive cervical lymph nodes.

Studies by Ma DY et al. [11] reported that size of lymph nodes was the most significant factor affecting the residual cervical lymph nodes; larger lymph nodes might lead to a poorer blood supply to tumor center and a higher proportion of hypoxic cells, thereby resulting in a stronger resistance to irradiation and more difficult dissipation. Since the size of suspicious positive lymph nodes is even smaller, they should theoretically present an even higher sensitivity to irradiation than positive lymph nodes, thereby providing a biological basis for a lower dose of 64 Gy compared to the radical dose. For these lymph nodes, a dose of greater than 66 Gy, referring to the radical treatment of positive lymph nodes, tend to achieve the curative treatment, but at the same time is prone to aggravate the cervical radio-dermatitis, soft-tissue fibrosis, and other severe adverse reactions. Therefore, in this study, we selected a dose of 64 Gy, between the doses of radical and preventive radiotherapy. As compared to the preventive dose of 50~54 Gy, a dose of 64 Gy could ensure a sufficient dose for suspicious positive lymph nodes, thereby reducing the recurrence of local lymph nodes, whereas a radical radiotherapy dose of greater than 66 Gy could alleviate the radioactive adverse reactions with good tolerance. These findings were consistent with our earlier results [12].

### **Conclusion**

A basic goal of radiotherapy is to improve the therapeutic gain ratio, which refers to maximizing the killing of tumor cells, and simultaneously reduce unnecessary irradiation to surrounding normal organs and tissues, decrease the extent of side effects, and improve the quality of life of patients. In this study, we used an irra-

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diation dose of 64 Gy for the treatment of suspicious positive cervical lymph nodes in NPC patients, and achieved a 3-year OS rate of 93.5% and a TFS rate of 87.0%, which were comparable to the results in literature [13, 14]. An irradiation dose of 64 Gy was able to achieve good short-term and long-term efficacies, with small adverse reactions and good tolerance, thereby providing a feasible therapeutic choice for suspicious positive cervical lymph nodes in NPC patients.

### Limitations

Limitations include small sample size and lack of multi-center randomized controlled study. Therefore, further studies are required to investigate the long-term efficacy and adverse reactions.

### Disclosure of conflict of interest

None.

**Address correspondence to:** Jun Lv, Department of Radiation Oncology, First Affiliated Hospital of Guangxi Medical University, Guangxi Province, Nanning 530021, China. Tel: +86-13481095127; Fax: +86-21-64085875; E-mail: 87800197@qq.com

### References

- [1] Tang L, Mao Y, Liu L, Liang S, Chen Y, Sun Y, Liao X, Lin A, Liu M, Li L and Ma J. The volume to be irradiated during selective neck irradiation in nasopharyngeal carcinoma: analysis of the spread patterns in lymph nodes by magnetic resonance imaging. *Cancer* 2009; 115: 680-688.
- [2] van den Brekel MW, Stel HV, Castelijns JA, Nauta JJ, van der Waal I, Valk J, Meyer CJ and Snow GB. Cervical lymph node metastasis: assessment of radiologic criteria. *Radiology* 1990; 177: 379-384.
- [3] staging CCoNc. 2010 Consensus of target and dose in intensity modulated radiotherapy for Nasopharyngeal Carcinoma. *Chinese Journal of Radiation Oncology* 2011; 20: 267-269.
- [4] (AJCC) Ajcoc. Cancer staging manual. New York: Springer; 2009.
- [5] Ng WT, Lee AW, Kan WK, Chan J, Pang ES, Yau TK and Lau KY. N-staging by magnetic resonance imaging for patients with nasopharyngeal carcinoma: pattern of nodal involvement by radiological levels. *Radiother Oncol* 2007; 82: 70-75.
- [6] Wang XS, Hu CS, Ying HM, Zhou ZR, Ding JH and Feng Y. Patterns of retropharyngeal node metastasis in nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2009; 73: 194-201.
- [7] Chen QS, Lin SJ and JJ P. Cervical lymph node metastasis in 779 patients with nasopharyngeal carcinoma. *China Oncology* 2010; 20: 50-54.
- [8] Teo PM, Leung SF, Tung SY, Zee B, Sham JS, Lee AW, Lau WH, Kwan WH, Leung TW, Chua D, Sze WM, Au JS, Yu KH, O SK, Kwong D, Yau TK, Law SC, Sze WK, Au G and Chan AT. Dose-response relationship of nasopharyngeal carcinoma above conventional tumoricidal level: a study by the Hong Kong nasopharyngeal carcinoma study group (HKNPCSG). *Radiother Oncol* 2006; 79: 27-33.
- [9] Teo PM, Leung SF, Lee WY and Zee B. Intracavitary brachytherapy significantly enhances local control of early T-stage nasopharyngeal carcinoma: the existence of a dose-tumor-control relationship above conventional tumoricidal dose. *Int J Radiat Oncol Biol Phys* 2000; 46: 445-458.
- [10] Zhang MQ and Chen MZ. [Analysis of 174 cases with cervical cancer in women under 35 years old]. *Zhonghua Fu Chan Ke Za Zhi* 2003; 38: 689-693.
- [11] Ma DY, Wang RS and Z QG. Logistic regression analysis of the factors influencing residual cervical lymphatic metastasis in NPC after radiotherapy. *Chinese Journal of Clinical Oncology* 2007; 34: 278-281.
- [12] Shi Y, Wang R and Lv J. Research of radiotherapy dose on suspicious positive lymph nodes in neck negative nasopharyngeal carcinoma patients. *Cancer Search on Prevention and Treatment* 2013; 40: 608-612.
- [13] Xie FY, Peng M, Hu WH, Han F, Wang X and Xu HM. [Prophylactic irradiation of cervical lymph nodes for Stage-NO nasopharyngeal carcinoma]. *Chin J Cancer* 2010; 29: 106-110.
- [14] Gao Y, Zhu G, Lu J, Ying H, Kong L, Wu Y and Hu C. Is elective irradiation to the lower neck necessary for NO nasopharyngeal carcinoma? *Int J Radiat Oncol Biol Phys* 2010; 77: 1397-1402.