RESEARCH ARTICLE

Preliminary Results of a Phase I/II Study of Simultaneous Boost Irradiation Radiotherapy for Locally Advanced Nasopharyngeal Carcinoma

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Abstract

Background: The purpose of this article is to present preliminary results of simultaneous boost irradiation radiotherapy for locally advanced nasopharyngeal carcinoma (NPC). Methods: Fifty-eight patients who underwent simultaneous boost irradiation radiotherapy for NPC in Cancer Center of Sun Yat-sen University between September 2004 and December 2009 were eligible. Acute and late toxicities were scored weekly according to the Radiation Therapy Oncology Group (RTOG) acute and late radiation morbidity scoring schemes. An especial focus was on evidence of post-radiation brain injury. Also quality of life was analysed according to the EORTC (European Organisation for Research and Treatment of Cancer) recommendations. Discrete variables were compared by χ^2 test. The Kaplan-Meier method was used to calculate the survival rates and generate survival curves. Results: A total of 58 patients with a mean follow-up time of 36 months completed clinical trials.Fifty-seven patients (98.3) achieved complete remission in the primary sites and cervical lymph nodes, with only one patient (1.7%) showing partial remission.The most frequently observed acute toxicities during the concurrent chemoradiotherapy were mucositis and leucopenia. Four patients (6.9%) had RTOG grade 3 mucositis, whereas four patients (6.9%) had grade 3 leucopenia. No patient had grade 4 acute toxicity. Three (5.17%) of the patients exhibited injury to the brain on routine MRI examination, with a median observation of 32 months (range, 25-42months). All of them were RTOG grade 0. The 3-year overall, regional-free and distant metastasis-free survival rates were 85%, 94% and 91%, respectively. Conclusion: Simultaneous boost irradiation radiotherapy is feasible in patients with locally advanced nasopharyngeal carcinoma. The results showed excellent local control and overall survival, with no significant increase the incidence of radiation brain injury or the extent of damage. A larger population of patients and a longer follow-up period are needed to evaluate ultimate tumor control and late toxicity.

Keywords: Locally advanced nasopharyngeal carcinoma - simultaneous boost irradiation radiotherapy

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Introduction

Nasopharyngeal carcinoma (NPC) is highly prevalent in southern China, especially in Guang Dong and Hong Kong, due to its insidious location of tumorigenesis and various clinical symptoms, most patients has been in locally advanced stage before diagnosed (Lu et al., 2009). Main causes of failure in treatment of high T staged nasopharyngeal carcinoma are residual or recurrence (Dimery et al., 1993; Johnson et al., 2005).

Base of skull and poststyloid space are frequent locations where treatment of nasopharyngeal carcinoma fails (Cmelak et al., 2009). When there are extensive invasions of nasopharyngeal carcinoma in base of skull and posterior cranial fossa, in order to avoid excessive radiation dose in brain stem and spinal cord, conventional radiotherapy will reduce field to avoid brain stem and spinal cord after it increases to an OAR tolerated dose, a consequent miss of irradiation of partial tumor volume will occur inevitably (Chau et al., 2009). Clinical researches indicate that local control rate of nasopharyngeal carcinoma is of positive correlation with irradiation dose of target volume (Hara et al., 2003; Le et al., 2003).

Cui et al. (1992) analyze 214 cases of recurrence patients and consider recurrence of primary location to be of close relationship with miss of irradiation of target volume during the first course treatment.

Therefore, for locally advanced staged patients, traditional radiotherapy uses small skull base field boost, or retroauricular field boost when separated if the dosage of the nasopharyngeal part was 70 Gy. However, irradiation delayed may result in failure in treatment due

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Table 1. Patient Characteristics

Characteristic	NO.	
Genger		
Male	39	67.2
Female	19	32.8
Age (ya)	46 (16-68)	
Follow-up time (ma)	36 (19-75)	
Pathologic		
WHOII	10	17.2
WHOIII	48	83.8
T classificationb		
T3	29	50
T4	29	50
N classificationb		
N0	7	12.1
N1	20	34.5
N2	28	48.3
N3	3	5.1
Clinical stageb		
III	28	48.3
IVa	27	46.6
IVb	3	5.1
Boost target volume		
Area (cm2)a	16 (9-45)	
Dose (Gy)a	74 (69.6-81.1)	
BED10 (Gy)a	82.5 (75.9-94.9)	

a, Median (range); b, Determined according to the 6th International Union against Cancer staging system; WHO, World Health Organization; BED10, biologically equivalent dose (α/β is 10 Gy for early-responding tissue)

to accelerated proliferation of tumor cells.

And around tumor tissues, such adjacent organs which are sensitive to irradiation as parotid gland, brain stem, spinal cord, temporal lobe and optic nerves, three dimensional conformal radiation therapy has no advantage in skull base or posterior skull base boost by using en bloc by 2 lateral faciocervical photon beams above their maximal dose limit of the brain stem and spinal cord.

IMRT featured by its dosiology advantages with high modulated intensity almost solves the contradiction between insufficient dose in irregular target volume and restricted dose in normal tissues, which brings a groundbreaking progress in increasing local control rate (Lee et al., 2002; Kam et al., 2004; Wolden et al., 2006), however, because of its complicated technique and limited resources, Spread of IMRT is restricted in underdeveloped area.

So on the premise that there are effective protection of normal tissues and no prolonged time of treatment, how to promote dose in insufficient dose areas like base of skull has been the hot spot in research.

Huang et al. (2008) consult principles of IMRT and Simultaneous Boost Irradiation Radiotherapy, use split-filling and simultaneous boost irradiation for locally advanced nasopharyngeal carcinoma patients with extensive C-type invasions in base of skull and posterior cranial fossa and retro-styloid, and compare it with traditional retroauricular field boost and 3D conformal boost techniques by dosimetry, they consider that Simultaneous Boost Irradiation Radiotherapy improves dose unif in target volume and offers simultaneous high dose irradiation in insufficient dose areas like base of skull when treated by conventional radiotherapy, and better reduces irradiation in Organs at Risk (OARs) like brain stem.

So we assume that it could increase local control rate and reduces irradiation dose in OARs like brain stem to use split-filling and simultaneous boost irradiation radiotherapy for locally advanced nasopharyngeal carcinoma patients so that occurrence of radiaton damage reduces or becomes less severe, and long-term quality of life of patients improves.

This text expounds preliminary clinical results of treatment in locally advanced nasopharyngeal carcinoma by split-filling and simultaneous boost irradiation radiotherapy, including acute toxic reaction, long-term complications, especially for brain damage; and long-term survival rate and quality of life are analyzed.

Materials and Methods

General data of patients

Nasopharyngeal carcinoma patients with initial treatment which have been confirmed by pathological diagnosis between Dec. 2004 and Mar. 2009.Medical examinations should be performed before treatment such as: complete history data, a general physical examination, hematological indices (blood routine, blood biochemistry, hepatitis, EB virus antibody, blood type), nasopharyngeal fiberscope, chest X-ray, ultrasound of abdomen, MRI of nasopharynx and cervical part, whole body bone scan, ECG. Oral scaling is required before treatment for all patients.

Eligible conditions: (1) nasopharyngeal carcinoma confirmed by pathological diagnosis (2) stageT3-4 (3) without receiving radiotherapy or chemotherapy ever before (4) age<80y (5) KPS score≥70 points (6) without hematological disorders (7) WBC≥4.0×10^9/L, PLT≥10×10^9/L (8) serum creatinine concentration<94 umol/L, transaminase is less than 2.5 times the upper limitation of normal value.

Exclusion criteria: (1) with other malignant tumors confirmed before or accompanied by a second primary tumor (2) pregnance or lactation (3) a known matastasis.

All patients should sign informed consent. Staging refers to sixth edition in 2002 of UICC (Fleming et al., 2002; Sobin et al., 2002). 58 patients was enroled in the group (male 39 cases, female 19 cases), median age was 46 years of age (16y-68y). Pathological classification of WHO: 10 cases of type II; 48 cases of type III (Table 1).

Chemotherapy regimen

All enroled patients receive simultaneous chemo and radiation, Nedaplatin 80 mg/m^2 was added in 500ml normal saline and administered intravenously no less than 2 hours for Day 1, 5-fu 500 mg/m^2 was administered by micropump for 96 hours, Day 2- Day 5, the chemo cycle is 28 days.

Radiotherapy plan

Positioning immobility: patients laid in supine position, and head bent hypsokinesis to make mandible be perpendicular to surface of treatment couch, which was

fixed by appropriative headframe and thermoplastic mask. Patients undergo lamellar contrast CT localization scan by Siemens P l u s 4 -C T simulated locator, scanning scope was from the top of the head downwards to the up of clavicle, slice thickness was 3mm, data were inported to EXOMIO1.0 CT sim planning system, drawing target volume and OARs, one of patients' image (stageT4N2M0, pathological changes involved sphenoidal sinus, base of skull and hibateral lymph nodes) was chosen to inported to 3DRTP system of Pinnacle3-6.2b-AdacLaboratories, according to requirement of CT-sim target region, target volume and OARs were drawn, three-dimensional image reconstruction was then carried out.

Target volume: G T V n x displayed by MRI image was the regions where primary nasopharyngeal carcinoma was and invasions were, and a treatment dose of over 68 Gy was required; C T V1 including G T V n x and 0.5~1.0 cm outside G T V n x (the whole nasopharyngeal mucous layers and 0.5~ 1.0 cm outside the layers should be included and extention distances were corrected properly according to adjacent anatomic structure of sub-clinical area), required a treatment dose of over 60 Gy; C T V 2 including C T V l and the potential adjacent anatomic structure of sub-clinical area invaded by tumor, such as entire nasopharynx, together with the parapharyngeal space, posterior third of the nasal cavity, skull base, posterior ethmoid sinus, sphenoid sinus, pterygospinosus, pterygopalatine fossae, cavernous sinus, et al.And an extention of adjacent l ~ 2 negtive lymph node draining regions which required a treatment dose of over 50 Gy.

PTV was planned target volume, P T V n x, P TV 1, P TV 2 were respectively G T V n x, CTV1, and C T V2 with an extention of a certain safety margin, generally an extention of 0.5 cm each forwards, upwards, downwards, leftwards and rightwards, and backwards for 0.2~0.3 cm, and was corrected properly according to adjacent tissues' characteristics, for example extention margin was reduced properly when closing to brain stem.

OARs included brain stem, temporal lobe, spinal cord of cervical segments, middle ear and temporomandibular joint and so on.

Design methods High-energy photon beam of 8MV and electron-ray of 8-12MeV were used for irradiation.It was carried out by four phases according to conventional radiotherapy plan: PhaseA hibateral encompassed en bloc by 2 lateral faciocervical photon beams and the lower cervical lymphatics is treated separately by an anterior photon portal with a total irradiation dose of 34 to 36Gy for 17 to 18 fractions; PhaseB hibateral the shrinking facito-cervical fields (avoid spinal cord)+ the posterior cervical β beam fields (8-1 2 M e V) +the lower anterior cervical agential fields with a total irradiation dose of 14 to 16 Gy for 7 to 8 fractions. PhaseC treatment plan aimed directly at P T V n x and P T V l were designed bilateral lateral fields avoid brain stem, meanwhile including as much PT V n x as possible with a total irradiation dose of 10Gy for 5 fractions.PhaseD aimed directly at PTVnx, with a total irradiation dose of 6-10 Gy for 3-5 fractions. Boost irradiation of sclerotin of base of skull and soft tissues surrouned by were set as simultaneous complementary boost target volume (BTV), namely on a conventional irradiation of 2 Gy/F basis with a simultenous boost irradiation of 0.3 Gy/F, to avoid brain stem and reduce irradiation margin of temporal lobe as far as possible.

CT scan was rechecked after an irradiation of every 20Gy, 40Gy and 60Gy during treatment, in order to formulate individualized therapy plan according to treatment response and correct treatment plan in time.
Conversion of bed-biological equralent dose applied a BED formula which is equivalently of a fractionated radiation of 2Gy: D meant the total dose (Gy), d meant the dose of fractionated radiation (Gy): $BED=D\times[1+d/(\alpha/\beta)]$, α/β value of the early reacting tissues is 10.

Dosiology evaluating indicators.

Target region: They were mainly the Dmax, Dmin and Dmean doses of BTV (sclerotin of base of skull and mass of tissues surrounded by), the 95% prescription dose containing 95% of target volume; the 70Gy and 80Gy containing volume percentage V70, V80.

OARs: It was mainly the Dmean of brain stem, repectively 50Gy and 60Gy containing volume percentage V50, V60, the Dmax of 33% of volume was D33.

Others included Dmean, V60 and D50 of homolateral temporal lobe.

Curative effect and prognostic indicators.

Current curative effect is evaluated according to WHO RECIST, it is considerd to be uncontrollable that the residual is of no remission yet after 3-month radiotherapy. Prognostic indicators include overall survival (OS), recurrence free survival (RFS), distant metastasis free survival (DMFS). Calculation of Follow-up time of the experiment dates from the time patients is treated.

Treatment-related toxicity, evaluation of quality of life and requirement of follow-up.Acute and long-term adverse reactions are evaluated according to RTOG/ EORTC (Cox et al., 1995). Routine tests of hematology are underwent each week during treatment period.Scoring of patients' quality of life refers to European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30) (Aaronson et al., 1993).

Way of follow-up includes telephone, letter visit and outpatient recheck. During the process of follow-up, any of the suspicious recurrence or metastasis should be proved by CT, MRI, bone scanning and nasopharyngo-fiberoscope.

Statistical methods

To use SPSS18.0 statistical package for statistical analysis, study endpoint includes overall survival (OS), recurrence free survival (RFS), distant metastasis free survival (DMFS) and long-term adverse reactions.

Categorical data is analyzed by chi-square test, univariate survival analysis uses Kaplan-Meier (Kaplan et al., 1958), and survival curve is drawn as well.

Results

Follow-up

The deadline of follow-up is Mar. of 2011, median

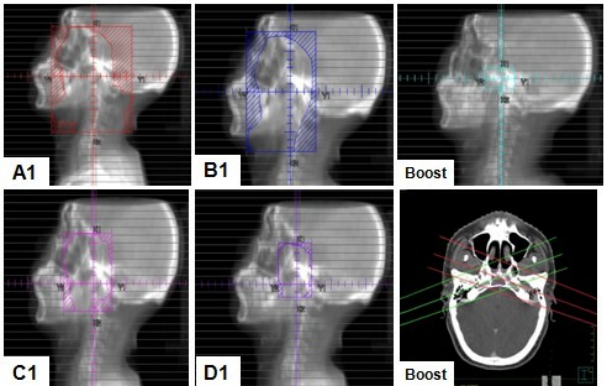

Figure 1. Design the Facio-cerrical Fields Aimed to PTV2 (A1) and the Shrinking Facito-cervical Fields Avoid Spinal Cord (B1). Lateral fields boost 60Gy aimed to PTV1 (C1). boost 70Gy according to PTVnx, (D1). a pair of boost filed from B which total dose is 0.3Gy/F according to BTV

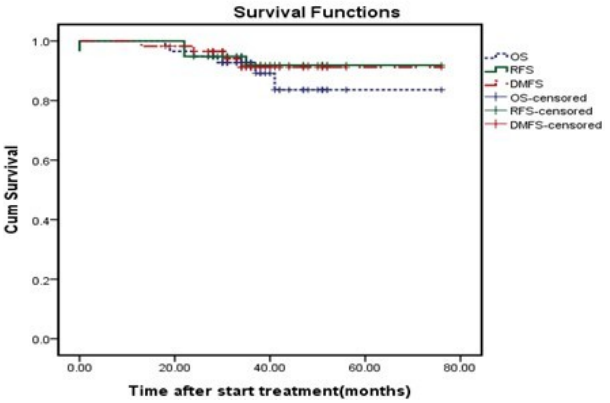

Figure 3. The 3-years Overall Survival (OS) Rate was 85.0% (blue line); the Relapse-free Survival (RFS) Rate was 94.0% (green line) and the Distant Metastasis-free Survival (DMFS) Rate was 91.0% (red line)

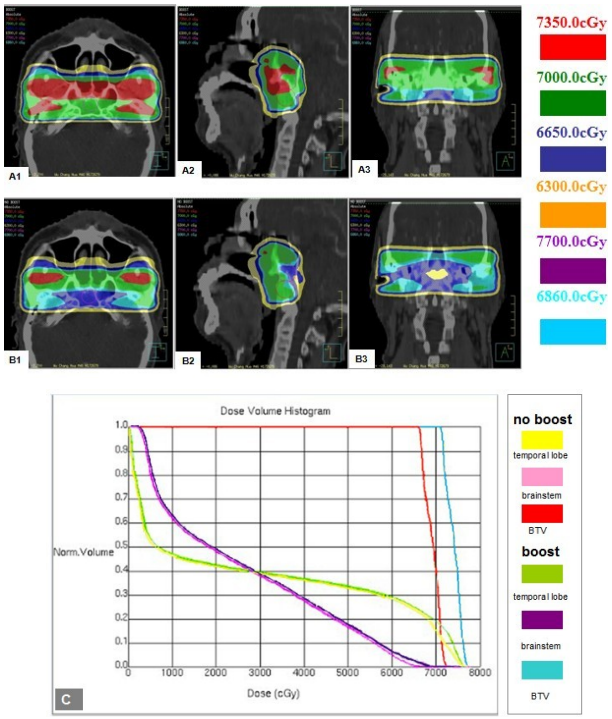

Figure 2. Simultaneous Boost Irradiation Boost in Regions Like Base of Skull by Simulative Three-dimensional Image Reconstruction in High-dose Regions. V70 achieves 100%, V80 is 0%, V95% is 100%, showed in cross section (A1), median sagittal section (A2), Coronal section (A3); High-dose spots of conventional radiotherapy do not cover invasion regions of sclerotin of base of skull, V70 achieves only 40%, V95% is 84.8%, showed in cross section (B1), median sagittal section (B2), Coronal section (B3). It shows in Table C that simultenous boost irradiation increases dose in dose-insufficient regions like base of skull without increasing irradiation dose of OARs such as brain stem and temporal lobe,etc when compaired with conventional radiotherapy

follow-up time is 36 months (18-76 months), lost of follow up for 2 cases, follow-up rate is 96.6%. Those 2 cases of lost of follow-up and 1 case of patient who dies of irrelevant disease are dealt as censored data. All survivors had been observed for more than 3 years.

Evaluation of treatment plan

To choose one case of nasopharyngeal carcinoma patients whose stage is T4N2M0 and is confirmed undifferentiated non-keratinizing carcinoma by pathological diagnosis, MRI indicates top nasopharyngeal wall, right wall of the nasopharynx, parapharyngeal space and the right side of the slope, the ministry of sphenoid and sphenoid base are invaded by tumor, treatment plan is respectively inported to 3DRTP system by conventional radiotherapy and concomitant boost radiotherapy respectively, and three-dimensional image reconstruction is performed.Conventional radiotherapy for patients is that PhaseA dose is 36Gy/18F ; PhaseB dose is 14Gy/7F; PhaseC dose is increased to 60Gy to aim directly at PTV1; PhaseD boost to 70Gy including PTVnx.

Simultenous boost irradiation aims directly at invasion region of sclerotin of base of skull and BTV surrounded by with a pair of boost fileds 0.3Gy/F on the basis of conventional radiotherapy from the start of PhaseB plan to the end of PhaseD.Angles of filed are set as 110°and 250°respectively, area of field is 13 cm^2, to avoid brain stem and reduce irradiation margin of temporal lobe as far as possible (Figure 1).

Comparison of plans between the two groups through target volume dosiology indicates that coverage rate of target volume by simultenous boost irradiation is over 98%, high-dose region is markedly formed in marginal zones like sclerotin of base of skull, Dmax and Dmin are respectively 77.5Gy and 71.0Gy, Dmean vaule is 74.0±1.69Gy.

In conventional radiotherapy, Dmax and Dmin of the skull base are respectively 73.1Gy and 66.1Gy, Dmean value is 69.1.0±1.76Gy.

Dose volume histogram (DVH) shows that after simultenous boost irradiation, base of skull V70 achieves 100%, V95% achieves 100%; while after conventional radiotherapy, V70 achieves only 40%, V95% achieves 84.8%.Both V80 are 0%.After simultenous boost irradiation, Dmean of brain stem is respectively 25.0Gy, V50 is 16.82%, V60 is 6.21%, D33 is 35Gy. Dmean of homolateral temporal lobe is 27.68Gy, V60 is 28.77%, D33 is 46.5Gy. Simultenous boost irradiation increases

Table 2. Acute Toxicity (Rtog Radiation Morbidity Scoring Criteria)

Type	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Skin	0	39	17	2	0
Mucous membrane	0	26	28	4	0
Pharynx	11	37	9	1	0
Salivary gland	11	42	5	0	0
White blood cell	13	15	26	4	0

irradiation dose of insufficient dose regions like base of skull, but meanwhile does not increase dose of OARs like brain stem and temporal lobe (Figure 2).

Therapeutic evaluation

Complete the treatment there are 57 cases of complete remission (98.3%), one case of partial remission (1.7%); 57cases of cervical lymph node complete remission (98.3%), one case of partial remission (98.3%). During follow-up process, one case of partial remission patients never achieves complete remission.There are two cases of complete remission patients who suffer nasopharyngeal recurrence 19 months and 35 months respectively after treatment. There are totally four cases of distant metastasis, including one case of hepatic metastasis, one case of pulmonary metastasis, two cases of osseous metastasis. Five cases of death, including one case of incontollable primary tumor, three cases of tumor metastasis, one case of death of accident.The three-year overall survival rate is 85%, relapse-free rate is 95% and DMFS rate is 91% (Figure 2). Acute adverse reactions.

It counts for much that mucosa reaction and leukopenia among acute adverse reactions observed during chemo and radiation therapy, including four cases of 3-degree mucositis of RTOG, four cases of 3-degree leukopenia, and no toxic 4-degree reactions or above are observed (Table 2).

Radiation brain injury

Diagnosis of radiation brain injury is made according to history, clinical manifestation and diagnosis of imaging text.Imaging text is the main criterion of diagnosis.

During follow-up process, there is no case of 1-degreee radiation brain injury or above, according to late stage radiation injury criterion of RTOG.There are three cases of radiation brain injury discovered by routine recheck of MRI of pharynx nasalis, the median time is 32 months (25-42 months), without symptoms like cerebralgia, drowsiness, memory decay or signs of nervous system.

The median irradiated area is 16 cm^2 (9-45 cm^2) for 58 cases of patients, all three cases of radiation brain injury occur with a BTV area over 16 cm^2. Incidence rate of radiation brain injury between groups with irradiated area over 16 cm^2 and less than 16 cm^2 is considered to be of statistical significance by chi-square test ($P<0.05$).

Factors like irradiation dose, age which may affect occurrence of radiation brain injury are of no statistical significance by univariate analysis (Table 3). COX regression analysis of multiple factor is not performed due to few cases of radiation brain injury.

Quality of life

Among all the enrolled patients, five cases of death and two cases of lost of follow-up are removed, the surplus 51 cases of patients receive (EORTC QLQ-C30) questionnaire survey at the last time of follow-up.

Standardized score for every field is 0~100 points. The higher scores in function field and general health status field the better the functional status and quality of life, and the higher scores in symptom field the more symptoms or problems (the poorer quality of life).

Discussion

Radiotherapy is still the main radical treatment for nasopharyngeal carcinoma without distant metastasis, experiences of Tai Wan indicates that the 5-year overall survival rate, local control rate and disease free survival rate of nasopharyngeal carcinoma are respectively 59%, 78% and 52% by the treatment of conventional radiotherapy, while the 5-year overall survival rate is only 41-47% for staged T3-4 patients, and disease free survival rate drops to 30-39% (Yeh et al., 2005), local control of nasopharyngeal carcinoma is of close relationship with irradiation dose and the overall treatment time (Kwong et al., 1997; Teo et al., 2006), local control rate could be increased to 90%by late-course three dimensional conformal radiotherapy boost ever (Chen et al., 2006; Hara et al., 2008), or treatment effect could be promoted by means of the accelerated fractionation to change cancer biological effect (Lee et al., 2001; Wolden et al., 2001), but some researches believe that it pays for increase of late toxicity (Teo et al., 2000). It is still challengeable to increase local control rate for staged T3-4 patients (Yu et al., 2005), in recent years, along with the application of intensity modulated radiation therapy technique, local control rate of nasopharyngeal carcinoma is increased further without increasing late irradiation-related complications due to its best coverage advantage (Lu et al., 2008; Kim et al., 2009; Lin et al., 2009).

IMRT is a radiation treatment technique with multiple beams incident from different directions in which at least some of the beams are intensity-modulated so that each beam intentionally delivers a non-uniform dose to the target.The desired dose distribution in the target is

Table 3. Single Factor Impact on Radiation Brain Injury

Radiation brain injury (n)	BTV area (cm^2)		*p*	BTV dose (Gy)		*p*	Age (y)		*p*
	>16	≤16		>74	≤74		>46	≤46	
Yes	3	0	0.048	1	2	0.553	2	1	0.513
No	23	32		28	27		26	29	

BTV, Boost Target Valume

achieved after superimposing such beams. The additional degrees of freedom to adjust intensities of individual rays are utilized to achieve a better target dose conformality and/or better sparing of critical structures.

Some studies found that in local control of tumor the technical of IMRT was not over three-dimensional conformal radiation therapy (3D-CRT) or two-dimensional radiation therapy (2D-RT), ramarkabley, and the only advantage of IMRT was to reduce the occurrence of xerostomia (Rades et al., 2007).

Some scholars believe that IMRT benefits remarkably for early stage nasopharyngeal carcinoma, while with no such remarkable advantage for advanced nasopharyngeal carcinoma by a retrospective study of treatment effect between IMRT and conventional two-dimensional radiation therapy (Lai et al., 2010). And as for national conditions of develpoing countries like ours, conventional radiotherapy will still play an important role in the treatment of nasopharyngeal carcinoma for a period of time in the future (Yin et al., 2008).

Chau et al. (2001) believe two-dimensional radiation therapy could not achieve satisfactory coverage dose for pathological changes of invaded areas like base of skull and parapharyngeal space.Therefore, how to increase local control for advanced nasopharyngeal carcinoma without increasing late toxic reactions by conventional radiotherapy is a burning difficult problem. Due to the extensive invasion of advanced nasopharyngeal carcinoma, the relatively large tumor-volume load results in radioresistance because of local hypoxia (Li et al., 2006).

Researches on 3-d dosiology by some scholars indicate that there is usual attenuation of dose in sclerotin of base of skull treated by irradiation of 60Co or X-ray beams of MV degree linear accelerator, because this region locates at the edge of field, dose in the base of skull is 7%-15% less than that in the center, so it could be controlled in a high dose (Chau et al., 2001).

Wolden et al. (2006) suggest an increase of irradiation dose in the tumor target volume to improve local control rate after the analysis of reasons for local failure.But there are many adjacent OARs with low-tolerated dose, single beam direction of conventioanal radiotherapy could not increase target volume dose and simultaneously reduce irradiation dose in normal tissues.

Kam et al. (2003) compare nasopharyngeal carcinoma IMRT and treatment plan of conventional radiotherapy, The dose of IMRT was that V95% of target volume is 68Gy, 57.5Gy for the conventional, so with a lower dose in dose-insufficient area of base of skull.

Some scholars (Lu et al., 2001) believe that invasion of sclerotin of base of skull is of remarkable correlation with local control and survival and prognosis, the lower actual irradiation dose in sclerotin of base of skull of invaded areas than radical dose in center field is the main reason for the increase of local recurrence rate, and suggest a supplementary irradiation dose in base of skull or a change of the fractionation irradiate plan in order to increase local control rate.

So for advanced nasopharyngeal carcinoma with an extensive invasions of base of skull, retro-styloid, conventional radiotherapy usually uses retroauricular field boost after lateral fields to avoid brain stem. However, because of non-exposed part of GTV of posterior fossa and poststyloid district in lateral fields radiotherapy and using retroauricular field boost after break of 2 weeks, which cause fractional irradiation and increase the accelerating reproliferation chance of tumor cell, finally, lead to irradiation failure and metastasis. In addition, the dosage of retroauricular field has poor homogeneity, which form a sensible high dose area, finally increase the risk of necrosis of Nasopharyngeal soft tissue and skull base (Huang et al., 2008).

For locally advanced patients, some scholars use the skull base boost technique to supplement the insufficient irradiation dose, but there are still risks that the overall treatment time is prolonged and tumor is of accelerated repopulation which result in reduce of local control rate.

The skull base boost technique may both increase the irradiation dose in normal tissues of brain and the incidence rate of radiation brain injury. Xie et al. (2005) find that the incidence rate of radiation brain injury in the group of the skull base boost and in contorl group without skull base boost is 7.4% and 4.3%, respectively, by a retrospective analysis.

Kwong et al. (2006) treat advanced nasopharyngeal carcinoma by simultanenous boost irradiation through intensity-modulated radiotherapy technique, namely to use different fractionation irradiate for different target volume in order to increase bed biologically effective dose in primary tumor and reduce irradiation of sensitive organs to the largest degree.

This study refer to the principle of IMRT and simultaneous boost irradiation of skull base, using PTVnx2Gy/F conventional radiotherapy and boost field 0.3Gy/F boost radiotherapy in edge region of skull base which owe doasage. This kind of treatment finally increase irradiate dose and equivalent biological effect.

Treatment plan shows after three-dimensional image reconstruction that in conventional irradiation, dose-insufficient areas like base of skull change to high-dose areas which could increase local control rate. And irradiation dose in OARs is not increased.

Li et al. (2006) propose that radiosensibility could be divided into two biological behaviour types as the radiosensitive and the radioresistant.So during the process of treatment, to adjust total irradiation dose in time according to margins of pathological changes and sensitivity to treatment in order to avoid over-irradiation for sensitive patients and insufficient irradiation for resistant patients.This promises a stronger possibility and feasibility for increasing local control rate and general curative effect by further adjusting fraction dose and total dose of individualized treatment of irradiation.

Xiao et al. (2010) report that locally advanced nasopharyngeal carcinoma is treated by intensity modulated radiation therapy and simultaneous chemo and radiotherapy, the 3-year overall survival rate is 87.7%, local control rate is 94.9%, an retrospective analysis of simultaneous chemo and radiotherapy of cis-platinum complexes combined with IMRT for staged T3-4 nasopharyngeal carcinoma patients by Frank (Wong et

al., 2010) shows that the 3-year DFSR is 91.8% for staged T3-4 patients, and the overall survival rate for staged III-IVb patients is 64.2-87.4%.

In this research, the 3-year overall survival rate is 85%, the 3-year relapse-free rate is 94% and DMFS rate is 91%. There are three cases are of radiation brain injury by MRI check, median time is 32 months after radiotherapy (25-42 months), these three patients has no obvious symptoms and signs of nervous system, symptom degree of RTOG is zero.

To survey patients' quality of life by EORTC QLQ-C30 score, score of patients' physical function is 93.5±9.6 points, general health status scores 78.9±18 points, cognitive function scores 78.3±22.6 points, in symptom field score of insomnia is 21.5±24.5 points, affection of financial status scores 22.2±29.5 points, scores of the survey of this research is close to score of quality of life of head and neck cancer patients, after treatment of IMRT by the survey of scholars abroad, while factors like regional and cultural differences should be considered (Graff et al., 2007).

We achieve invigorative result which is of similar or even better curative effect to intensity modulated radiation therapy, and with no obvious increase of incidence rate of radiation brain injury and aggravation of its severity, which requires long-time follow-up to prove.

Lee et al. (2005) believe that with rapid technologic advances (in imaging methods, computerized planning systems, and radiation therapy facilities) and accumulation of radiobiological knowledge (on optimization of time, dose, and fractionation), better results might be achievable by aggressive radiation therapy in the modern era. Furthermore, with the major changes in the staging system, treatment results for corresponding stages will inevitably be different. All of these may result in bias in the comparison of curative effect in different times.

Thanks to the booming development of imaing techniques like MRI, PET/CT, margin of tumor target volume could be defined more precisely, so whether increase of imaing techniques or improvement of radiotherapy that contributes to the remarkable advantage of increasing local control rate of nasopharyngeal carcinoma by intensity modulated radiation therapy requires a large number of cases for contemporaneity matched pair study to ensure the equilibrium distribution of factors of therapeutic outcome and prognosis.

Because of few cases of brain injury, in this research, reasons for radiation brain injury are not analyzed by multiplicity analysis, population should be further enlarged and follow-up time be increased to study relationship between BTV irradiation area and radiation brain injury.

But in view of univariate analysis that comparison of incidence of radiation brain injury between area over 16 cm^2 and area less than 16 cm^2 is of statistical significance, we suggest BTV volume be controlled within 16 cm^2 and avoid tried to limit the radiation volume while omit hypoxia area by introduing Biological Target Volume and combining functional image like PET (Wu et al., 2011) to make simultaneous boost irradiation of BTV portal contain hypermetabolism oxygen-deficient region, and irradiate tumor with high dose and at the time reduce range of irradiation of OARs surrounded by.

In conclusion, there is of certain value for this research that it indicates simultaneous boost irradiation could increase overall survival rate and recurrence free survival rate for locally advanced nasopharyngeal carcinoma and does not increase the incidence rate of radiation brain injury and its aggravation of severity which promises a stronger possibility and feasibility for increasing general curative effect and improving quality of life of patients.

The current result is a preliminary clinical report, which requires randomised control trial with intensity modulated radiation therapy and prolonging follow-up time to renew its treatment effect and long-term adverse reactions.

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