Draft

Chemoradiotherapy for Advanced Nasopharyngeal Cancer (NPC)

Phase I/II study

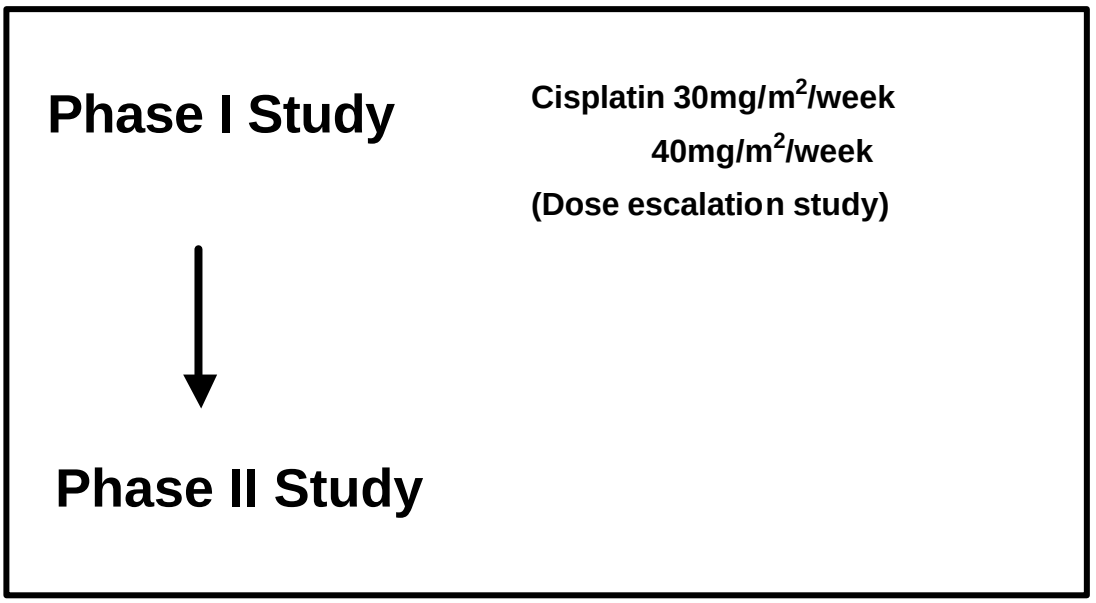
Forum for Nuclear Cooperation in Asia

(FNCA)

Application of Radioisotopes and

Radiation for Medical Use

Outline of the study



Phase I Study

1. Design of the study

Prospective phase I study

2. Objectives

1 . Evaluate the acute toxicity of concurrent chemoradiotherapy using two dose levels of cisplatin (30mg/m^2/week or 40mg/m^2/week) in patients with advanced nasopharyngeal cancer (NPC).

2 . Determine the clinically recommended dose (RD) of cisplatin.

3.Eligibility Criteria

Eligible for inclusion

1) Histologically confirmed WHO type 2 or 3, carcinoma of nasopharynx

2) Stage III, IVA, and IVB (UICC-TNM 2002, 6th edition)

3) Age: 20-70 years

4) PS: WHO 0-2

5) Adequate bone marrow, hepatic, and renal functions:

WBC≥3000/mm3

Hb≥10g/dl

Platelet≥100,000/mm3

Total bilirubin≤1.5mg/dl

AST/ALT≤2 times upper limit of normal

Serum creatinine≤1.5mg/dl

6) Written informed consent

Ineligible for inclusion

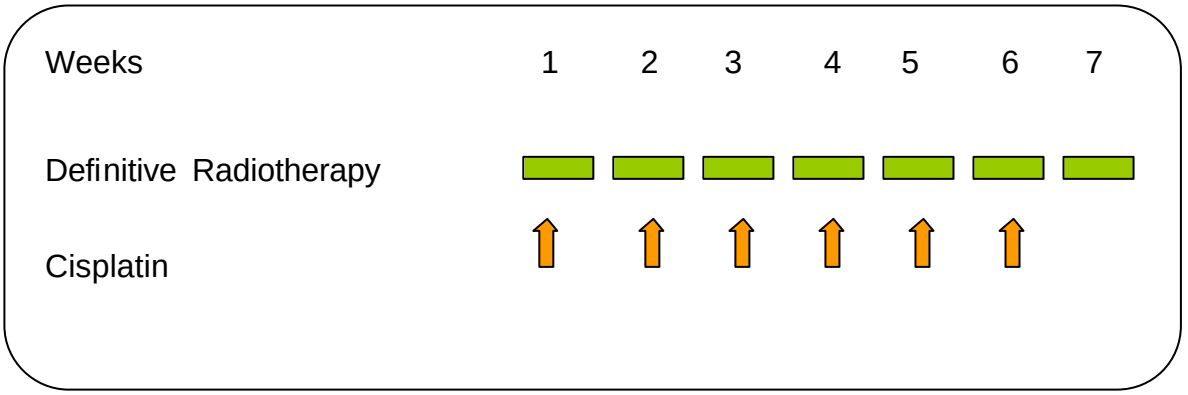
1) WHO type 1 carcinoma of nasopharynx
2) Stage IVC (UICC-TNM 2002, 6th edition)
3) Severe concomitant illness

e.g. uncontrolled cardiovascular disease, uncontrolled DM, uncontrolled psychological disorders, active infection active double cancer

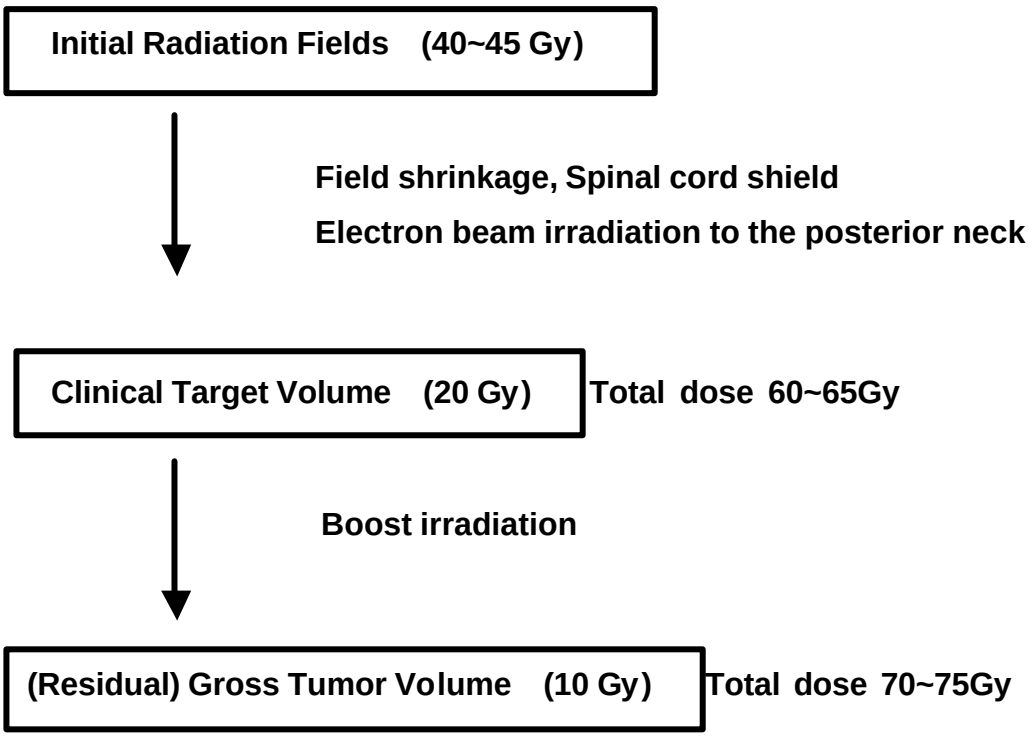
4) Prior radiotherapy or chemotherapy
5) History of other malignancies within the past 5 years except BCC and SCC in-situ of the skin and cervical cancer in-situ
6) Patients who are pregnant or lactating

4.Treatment schedule

Cisplatin is administered weekly, concurrently with definitive radiotherapy as shown.



5. Definitive Radiotherapy



6. Chemotherapy

Two dose levels of cisplatin (Level 1: 30mg/m^2/week or Level 2: 40mg/m^2/week) are investigated in dose escalation study. Cisplatin is administered weekly from week 1 for 6 consecutive weeks during the course of external beam radiotherapy.

Dose limiting toxicities (DLTs):

1. Grade 4 hematological toxicities
2. Grade 4 toxicities in skin, mucosa and salivary grand
3. Grade 3 non-hematological toxicities except 2
4. Interruption of radiotherapy $\geq$ 2 weeks
5. Interruption of chemotherapy $\geq$ 3 cycles

Clinically recommended dose (RD) is determined as follows:

Dose escalation schedule:

1. 3~6 patients / country / dose level

2. Level 1: overall incidence of DLT ≥ 1/3
   → Level 1 is judged unacceptable
3. Level 1: overall incidence of DLT < 1/3
   → Level 1 is judged acceptable → Dose escalation to Level 2
4. Level2: overall incidence of DLT ≥ 1/3
   → Level 2 is judged unacceptable → Level 1 is determined the RD
5. Level 2: overall incidence of DLT < 1/3
   → Level 2 is judged acceptable → Level 2 is determined the RD

7. Sample size

3(~6) patients / country / each dose level

8. Period of patient accrual

2 years (2003.4.1.－2005.3.31.)

9. Follow-up period

2 years after registration

Phase II Study

1.Design of the study

Prospective phase II study

2.Objectives

1. Determine the efficacy of concurrent chemoradiotherapy using recommended dose of cisplatin in patients with advanced nasopharyngeal cancer (NPC).
2. Determine the acute and late toxicities of this regimen.

Primary endpoint: 3-year overall survival rate

Secondary endpoint: 3-year progression-free survival rate
3-year loco-regional control rate
Acute and late toxicities

3.Eligibility Criteria

Eligible for inclusion

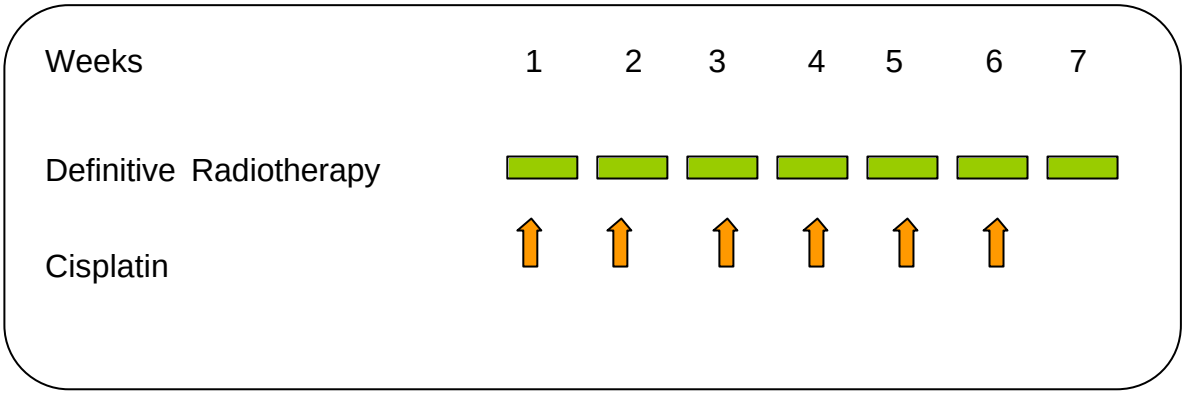
5) Histologically confirmed WHO type 2 or 3, carcinoma of nasopharynx
6) Stage III, IVA, and IVB (UICC-TNM 2002, 6th edition)
7) Age: 20-70 years
8) PS: WHO 0-2
5) Adequate bone marrow, hepatic, and renal functions:
WBC≥3000/mm3
Hb≥10g/dl
Platelet≥100,000/mm3
Total bilirubin≤1.5mg/dl
AST/ALT≤2 times upper limit of normal
Serum creatinine≤1.5mg/dl
6) Written informed consent

Ineligible for inclusion

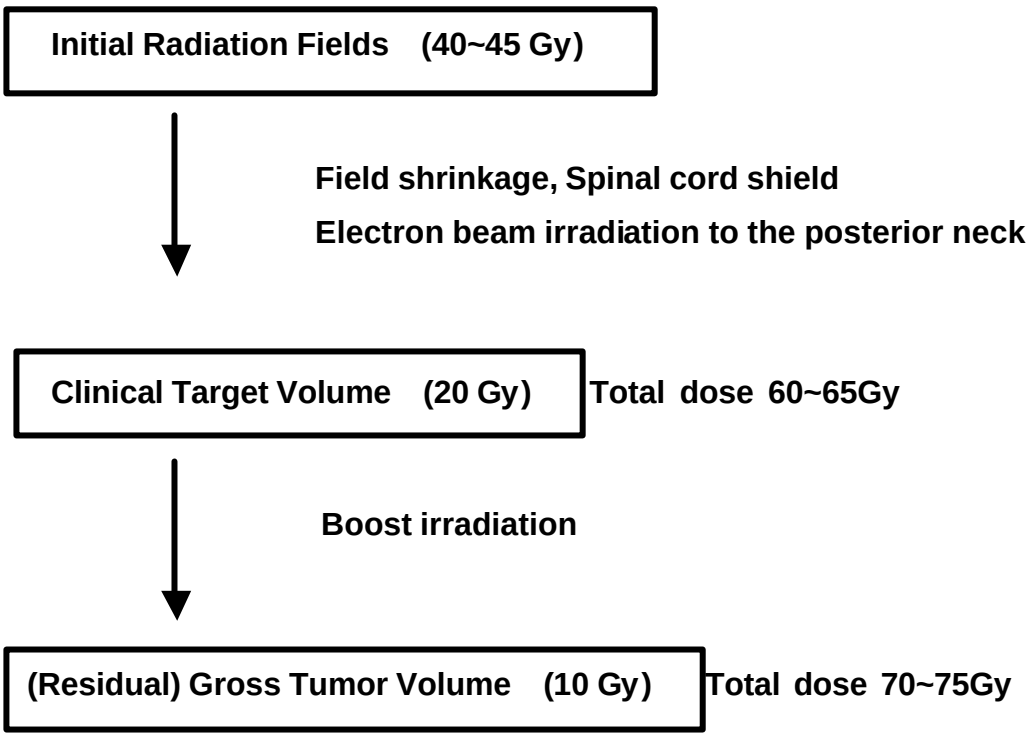
2) WHO type 1 carcinoma of nasopharynx
2) Stage IVC (UICC-TNM 2002, 6th edition)
4) Severe concomitant illness
e.g. uncontrolled cardiovascular disease, uncontrolled DM,
uncontrolled psychological disorders, active infection
active double cancer
4) Prior radiotherapy or chemotherapy
5) History of other malignancies within the past 5 years except
BCC and SCC in-situ of the skin and cervical cancer in-situ
6) Patients who are pregnant or lactating

4.Treatment schedule

Cisplatin is administered weekly, concurrently with definitive radiotherapy as shown.



5.Definitive radiotherapy



6.Chemotherapy

Cisplatin is administered at the recommended dose weekly from week 1 for 6 consecutive weeks during the course of external beam radiotherapy.

7.Sample size

50 patients

8. Period of patient accrual

1 years (2004.4.1.－2005.3.31.)

9. Follow-up period

5 years after registration

1. Background

Nasopharyngeal carcinoma (NPC) is more common among Southeast Asian, North African, and Eskimo populations. Because of anatomic limitations and a high degree of radiosensitivity, NPC has traditionally been treated by radiotherapy rather than surgery. Although early stage NPC is highly cured by radiotherapy alone, however, in locoregionally advanced disease, despite good initial response to irradiation, local failures and distant metastases highly occur, resulting in a 5-year survival rate of around 50 %. Since NPC is also more sensitive to chemotherapy than head and neck cancers at other sites, the use of combination of chemotherapy and radiotherapy has been investigated.

Theoretically, chemotherapy and radiotherapy have a synergistic effect. Many chemotherapeutic agents including cisplatin have demonstrated to have the effect of radiation potentiator in vivo. The possible mechanisms for enhanced radiation effects are: hypoxic cell sensitization with the increased hydroxyl radical yield, inhibition of repair of sub-lethal radiation damage, synchronization of cells to a radiosensitive phase of the cell cycle, and toxic ligand release.

Recent clinical phase III trials have shown the encouraging data on concurrent cisplatin-based chemotherapy and radiotherapy in patients with advanced NPC. However, different staging systems, prognostic factors, drugs, and schedules have been used, the optimal drug, timing of delivery, dosage, and duration of therapy remain controversial. To evaluate the toxicity and efficacy by adding chemotherapy, we conducted the phase I / II study.

[References]

1. Garden AS, The Nasopharynx, mosby, Radiation Oncology 8th edition, 2003
2. Douple EB, et al. Int J Radiat Oncol Biol Phys1979; 5:1335
3. Bachaud JM, et al. . Int J Radiat Oncol Biol Phys1996; 36:999-1004
4. Chan AT, et al. J Clin Oncol 2002;20:2038-44
5. Al-Sarraf M, et al. J Clin Oncol 1998;16:1310-17
6.Lin JC, et al. J Clin Oncol 2003;21:631-7

2.Study Type

Prospective phase I and II study

2. Objectives

Phase I Study:

1.Evaluate the acute toxicity of concurrent chemoradiotherapy using two dose levels of cisplatin (30mg/m^2/week or 40mg/m^2/week) in patients with advanced nasopharyngeal cancer (NPC).

2.Determine the clinically recommended dose (RD) of cisplatin.

Phase II Study:

3.Determine the efficacy of concurrent chemoradiotherapy using RD of cisplatin in patients with advanced nasopharyngeal cancer (NPC).

4.Determine the acute and late toxicities of this regimen.

4.Eligibility Criteria

Inclusion criteria

1) Histologically confirmed WHO type 2 or 3, carcinoma of nasopharynx
2) Stage III, IVA, and IVB (UICC-TNM 2002, 6th edition)
3) Age: 20-70 years
4) PS: WHO 0-2
5) Adequate bone marrow, hepatic, and renal functions:

WBC≥3000/mm3

Hb≥10g/dl

Platelet≥100,000/mm3

Total bilirubin≤1.5mg/dl

AST/ALT≤2 times upper limit of normal

Serum creatinine≤1.5mg/dl

6) Written informed consent

Exclusion criteria

1) WHO type 1 carcinoma of nasopharynx
2) Stage IVC (UICC-TNM 2002, 6th edition)

3) Severe concomitant illness

e.g. uncontrolled cardiovascular disease, uncontrolled DM, uncontrolled psychological disorders, active infection active double cancer

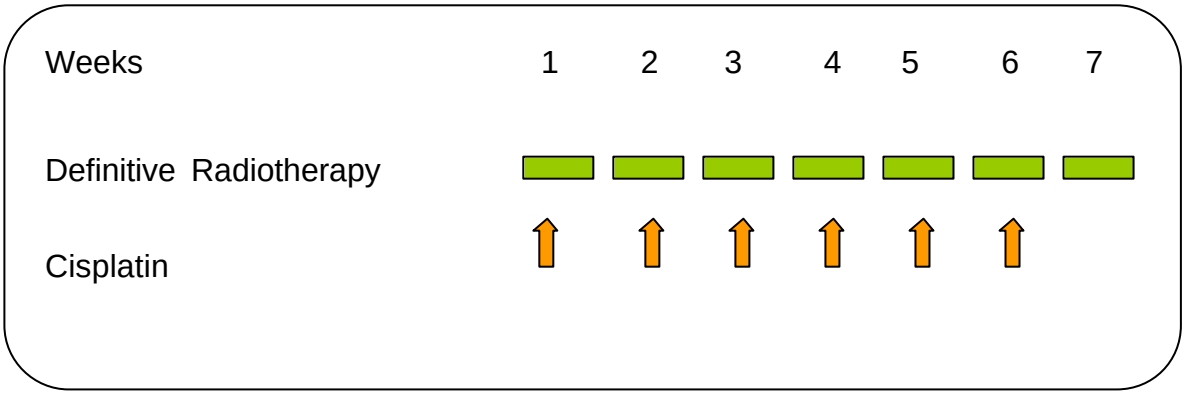
4) Prior radiotherapy or chemotherapy

5) History of other malignancies within the past 5 years except BCC and SCC in-situ of the skin and cervical cancer in-situ

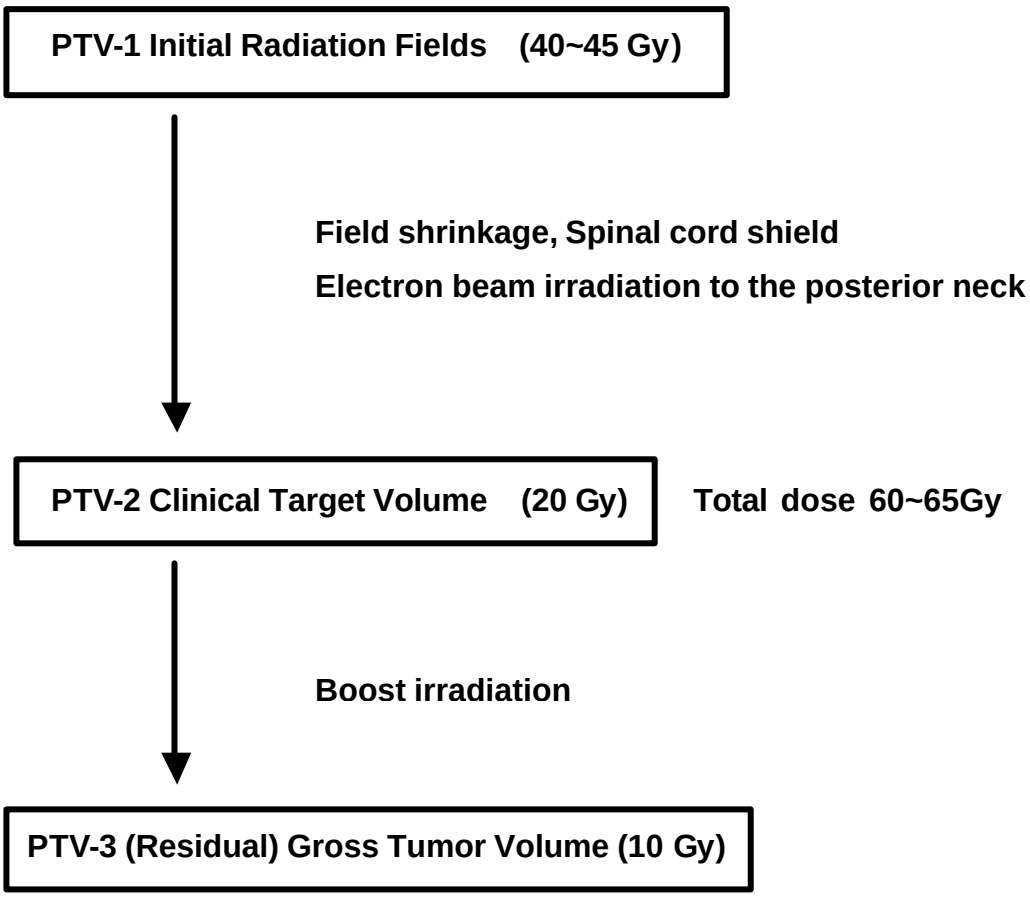
6) Patients who are pregnant or lactating

5.Treatment schedule

Cisplatin is administered weekly, concurrently with definitive radiotherapy as shown.



6.Radiation Therapy



6-1.Radiation Therapy technique

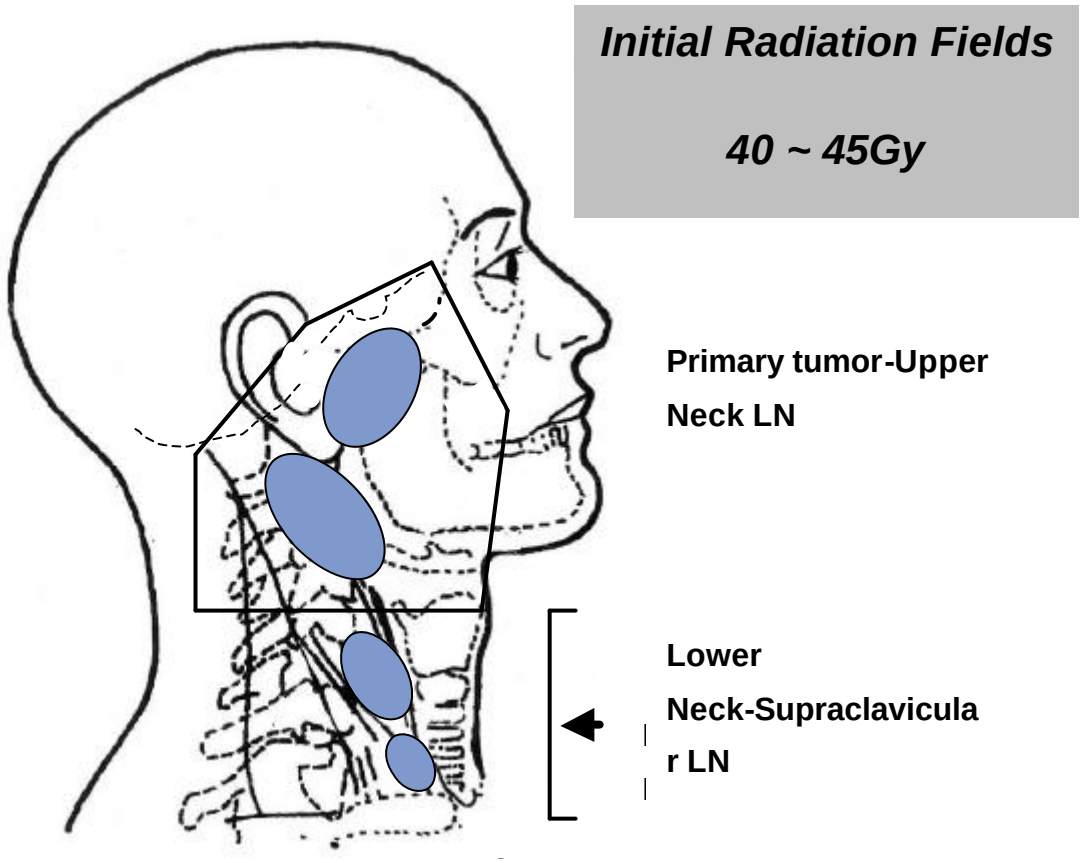
Initial Radiation Fields

Initial radiation fields consists of a three-field technique: lateral opposed fields for the primary tumor-upper neck and a matching anterior lower neck-supraclavicular portal.

Primary tumor-Upper Neck LN

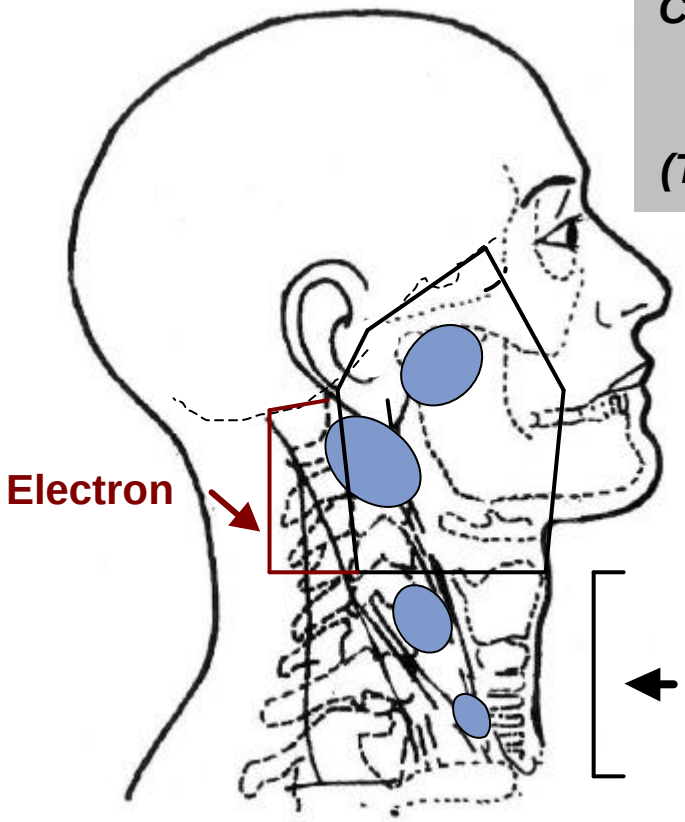
Superior: 2cm beyond visible tumor (CT, MRI),
including base of skull, and sphenoid sinus
Anterior: Posterior ethomoid cells, or
Posterior 1/3rd of maxillary antrum,
or at least 1.5 cm beyond visible tumor
Posterior: At least 1.5 cm beyond palpable node(s)
Inferior: Thyroid notch

Lower Neck-Supraclavicular LN



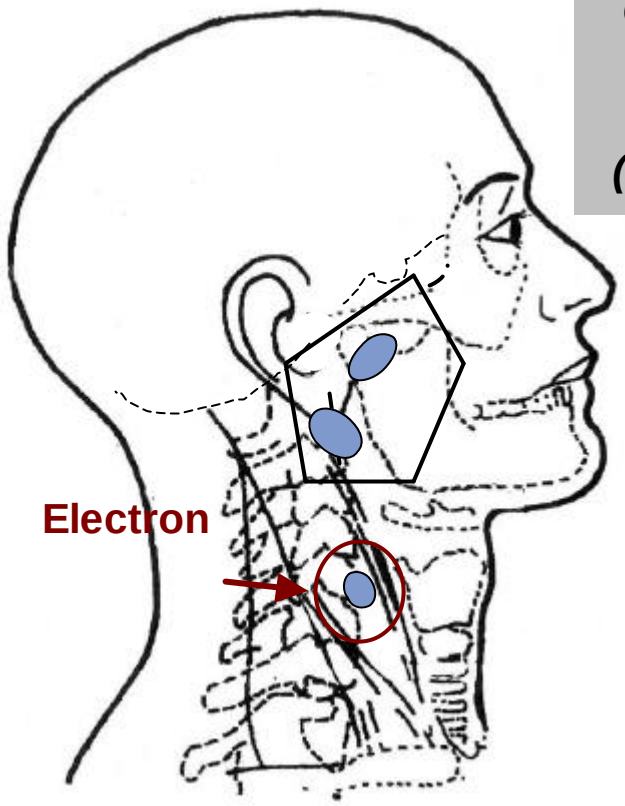
Clinical Target Volume
20Gy

(Total dose 60 ~ 65Gy)



(Residual)
Gross Tumor Volume
10Gy

(Total dose 70 ~ 75Gy)



6-2. Total Dose to Primary Tumor & Neck Nodes

Primary tumor	T1-2 :	65-70 Gy (Brachytherapy can be used)
	T3 :	66-70 Gy
	T4 :	66-75 Gy
Neck nodes	N0 :	40-50 Gy
	N1 :	65-70 Gy (Electron boost can be used)
	N2 :	
	N3 :	
(Spinal cord)		≤ 40-45 Gy

6-3. Interruption of radiotherapy

When the patients develop grade 3 non-hematological toxicities (e.g. mucositis), radiotherapy can be interrupted according to the each institutional policy.

7.Chemotherapy

7-1. Dose of Cisplatin

Phase I study: 30 → 40 mg/m2/wks (dose escalation study)

Phase II study: (____) mg/m2/wks (recommended dose)

7-2. Administration of Cisplatin

Cisplatin is administered weekly starting from week 1 for 6 consecutive weeks during the course of external beam radiotherapy.

Patients receive cisplatin intravenously over about 1.5 hours followed by external beam radiotherapy after administration of cisplatin. Radiotherapy should be given within 2 -2.5 hours following cisplatin.

Patients should be hydrated with more than 2000 ml of normal saline in total. Anti-emetics, such as 5-hydroxytryptamane 3 receptor (5-HT3) antagonists and dexamethasone should be given with chemotherapy. G-CSF can be used according to the indication.

7-3. Dose modification or Delay of Chemotherapy

No dose modifications are allowed.

Administration of cisplatin should be discontinued according to the criteria described below.

1. Grade 2 hematological toxicities: WBC<3000/mm3 or Platelet<75000/mm3
2. Fever >38.0 ^{o}C
3. PS 3-4
4. Grade 2 renal dysfunction
5. Grade 4 toxicities in skin, mucosa and salivary grand
6. Grade 3 non-hematological toxicities except 4
   (e.g. nausea, vomiting, weight loss, fatigue)

Administration of cisplatin is resumed when the hematological toxicities are recovered to WBC $\geq$3000/mm3 and Platelet $\geq$75000/mm3.
Administration of cisplatin is resumed when the non-hematological toxicities are recovered to grade 1.

8. Criteria for discontinuance of the protocol treatment

Protocol treatment should be discontinued according to the criteria described below.

1. Disease status: PD
2. Interruption of radiotherapy for longer than 2 weeks due to toxicities
3. Denial or withdrawal of the protocol treatment
4. Cases that are judged to be difficult to continue the protocol treatment by the responsible physician

Patients in the criteria should be excluded from the evaluation for treatment

efficacy, but included in the evaluation for toxicity.

9. Additional therapy

When patients show any obvious clinical evidence of recurrence or relapse, they can receive any kind of treatment.

Adjuvant therapy can be allowed according to the each institutional policy.

(need discussion)

When the response of the protocol treatment is SD or PD, patients can receive any adjuvant therapy.

10. Assessment of toxicity and efficacy

10-1. Acute toxicities

Acute toxicities for each patient are serially monitored during and after treatment (within 90 days from the beginning of treatment).

Acute hematological toxicities (WBC, Neutrophiles, Hb, Platelets)

Acute non-hematological toxicities (skin, mucositis, pain due to radiation, salivary gland, nausea, vomiting, weight loss, fatigue)

Acute hematological and non-hematological toxicities are assessed according to the NCI/CTC version 2.0, 1999.

10-1. Late toxicities

Late toxicities for each patient are periodically monitored after treatment.

1. Subcutaneus
2. Mucosa
3. Skin
4. Salivary Gland
5. Others

Late toxicities are assessed according to the RTOG/EORTC late radiation morbidity scoring scheme.

10-2. Tumor response

Tumor response is evaluated according to the WHO standard response criteria

WHO standard response criteria

RESPONSE	CODE	DESCRIPTION
Complete response	CR	Complete disappearance of all known measurable and evaluable disease determined by 2 measurements not less than 4 weeks apart.
Partial Response	PR	50% or greater decrease in the sum of the products of the greatest lengths and perpendicular width of the largest measurement of all measurable lesions for at least 4 weeks with no appearance of new lesions No increase in evaluable disease during this period.
Stable disease	SD	Any change in tumour size. Or lack of thereof, for a period of at least 8 weeks, which is less than partial response yet does not indicate tumour progression
Progression	PD	Greater than 25% increase in the sum of the products of measurable disease, reappearance of measurable disease, clear worsening of evaluable disease, appearance of any new lesions including brain metastases even if there is response outside of the brain or significant worsening of conditions presumed to be related to malignancy.

11. Endpoints

Phase II study:

Primary end point:

3-year overall survival rate

Secondary end point:

3-year progression free survival rate

3-year locoregional control rate

Acute and late toxicities

12. Sample size

Phase I study:

3~(6) patients / country / each dose level

Phase II study:

50 patients.

13. Period of patient accrual

Phase I study: 2 years (2003.4.1.—2005.3.31.)

Phase II study: 1 years (2004.4.1.—2005.3.31.)

14.Follow-up period

Phase I study: 2 years after registration

Phase II study: 5 years after registration

15. Informed consent

Written informed consent is mandatory to enter this study. This informed consent form should be translated in each native language.

16.Registration and Follow-up of patients

The National Institute of Radiological Sciences in Japan plays a role of the data

center.

The registration sheets (No. 1- 5) are filled in and sent to the data center by fax or e-mail as soon as possible after the completion of assessment for acute reaction.

The follow-up sheet is filled in and sent to the data center once a year after treatment.

The Data Center:

Tatsuya OHNO, M.D., Ph.D.
Research Center Hospital for Charged Particle Therapy
National Institute of Radiological Sciences in Japan
4-9-1 Anagawa, Inage-ku, Chiba, 263-8555, Japan
Fax: +81-43-256-6507
e-mail: y_machid @ nirs.go.jp