Taipei Veterans General Hospital Practices Guidelines Oncology

Head and Neck Cancers

Cancer of Nasopharynx

Version 2012.V1

VGH Survival Data as of 2009/12/31

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Table of Content

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Principles for Guideline Revision

- **This guideline will be conformed to evidence-based medicine and/or complied with the currently consented practices.**
- **This guideline will be systemically reviewed in an annual guideline revision meeting within the NPC multidisciplinary conference.**
- **This guideline is based on consensus of the authors regarding the current evidence for appropriate approaches to workup and treatment.**
- **Any physician consulting this guideline is expected to use independent medical judgment of individual clinical circumstances to determine and apply optimal customized treatment for the cancer patient.**

Summary of Guidelines Updates

- **Adoption of the 7th TNM Staging system from 2010/1/1**
- **Supplemental definition of T3 for pterygopalatine fossa invasion**
- **Modification of Taipei VGH NPC Risk Group Classification**
  - Redefinition of Bulky T1 / T2
  - Reclassification of Group E to include T4N3M0 or T1-3N3 with superior mediastinal lymphadenopathy
- **Revision of management of locoregional recurrence**
- **Update of the survival data of non-metastatic NPC patients treated at Taipei VGH to substantiate the validity of the NPC practice guidelines.**
- **Discussion of radiation therapy in the manuscript**

Multidisciplinary Team

- **Radiation Oncology**
  - Radiation Oncologist; Radiation Physicist; Radiation Technologist
- **Medical Oncology**
- **Surgical Oncology specialized in Head and Neck Cancers**
  - Otorhinolaryngology (ENT)
- **Pathology**
- **Diagnostic Radiology**
- **Nuclear Medicine**
- **Specialized Nursing Care**
  - Case manager 簡伶怡
- **Dentistry/Prosthodontics**
- **Clinical Pharmacology**
- **Social Workers**
- **Nutritional Support**

Pathology

This practice guideline is applicable only for keratinizing and non-keratinizing carcinoma of nasopharynx as specified in the WHO classification. Other uncommon malignant tumor should be managed according to their histopathological diagnosis. The pathological specimen is preferably obtained from biopsy of nasopharynx.

- **Pathology: WHO 2005 classification (1991)**
  - Type I: Keratinizing Carcinoma
    - ICD-O3 Morphological code: M8071/3, Grade I or II
  - Type II: Non-Keratinizing Carcinoma
    - II-a: Differentiated (WHO 1987 classification non-keratinizing carcinoma) ICD-O3 Morphological code: M8072/3, Grade III
    - II-b: Undifferentiated (WHO 1987 classification undifferentiated carcinoma) ICD-O3 Morphological code: M8020/3, Grade IV
- **Other uncommon malignant tumors of nasopharynx**
  - Adenoid cystic carcinoma: pay special attention to peri-neural spreading in target volume delineation during radiation therapy planning..
  - Lymphoma: see practice guidelines of Non-Hodgkin's Lymphoma and Hodgkin's Disease.
  - Plasmacytoma: see practice guidelines of multiple myeloma.

Pretreatment Workup

- General medical history and physical examination

Serum Tests

- CBC
- Serum IgA levels of EB virus capsule antigen (VCA)
- Serum levels of early antigen (EA) and cDNA of (optional)
- Complete serum metabolite analyses, including liver/renal function test and LDH
- Hepatitis B and C markers, and CCr if chemotherapy is indicated
- Baseline thyroid function (optional)
- Baseline pituitary function if unavoidable high radiation dose to pituitary gland in T4 case. (optional)

Imaging Studies

- Tomographical medical imaging studies: MRI with or without contrast enhanced CT of nasopharynx.
- PET scan, optional
- Chest X-rays
- Liver sonogram
- Bone scan for stage II-IV, optional for stage I; optional if PET-CT performed
- Sonography for equivocal neck lymphadenopathy

Special Exams

- Audiometry
- Ophthalmologic exams if at high risk of radiation injury to optic nerve
- Baseline salivary function test or salivary scintigraphy
- Pre-radiotherapy dental care
- Olfactory test

MRI Protocol for Nasopharyngeal Cancer

- **Five series:**
  - Spin-Echo Axial T1
  - Spin-Echo Axial T2
  - Spin-Echo Axial T1 + Contrast + Fat Saturation
  - Spin-Echo Coronal T1 + Contrast + Fat Saturation
  - Spin-Echo Sagittal T1 + Contrast
- **Volume:**
  - From frontal sinus down to supraclavicular fossa
  - 3-5 mm slide thickness

TNM Staging System: UICC/AJCC 2010 7th Edition

T Stage

Tx: Primary tumor cannot be assessed

T0: No evidence of primary tumor

T1: Tumor confined to the nasopharynx; or extending to oropharynx and/or nasal cavities without parapharyngeal extension

T2: Tumor with posterolateral parapharyngeal extension (*beyond the pharyngobasilar fascia*)

T3: Tumor invading bony structure of skull base and/or paranasal sinuses

T4: Tumor with intra-cranial extension and/or involvement of cranial nerves, orbit, infra-temporal fossa, masticator space or hypopharynx

- Parapharyngeal space (PPS) - a triangular space:
  - Anterior to the styloid process (prestyloid space)
  - From the skull base to the level of the mandibular angle
  - Lateral to the pharynx and medial to the masticator / parotid spaces
- Masticator space
  - Medial and lateral pterygoid muscle; messator muscle, temporalis muscle.

N Stage

Nx: Regional lymph nodes cannot be assessed

N0: No regional lymph node metastasis

N1: Unilateral metastasis in neck node(s); and / or unilateral / bilateral retropharyngeal nodes; all ≤6 cm

N2: Bilateral metastases in neck node(s), ≤6 cm

N3: Metastasis in a node(s)

N3a: neck nodes >6 cm

N3b: extension to the supraclavicular fossa and superior mediastinum (above innominatge vein)

* Midline nodes are considered ipsilateral nodes.

**Supraclavicular is defined by three points: (1) the superior margin of the sternal end of the clavicle, (2) the superior margin of the lateral end of the clavicle, (3) the point where the neck meets the shoulder. Note that this would include caudal portions of Levels IV and VB. All cases with lymph nodes (whole or part) in the fossa are considered N3b.

M Stage

M0: No distant metastasis

M1: Distant metastasis

Summary of Changes: 7Th TNM System

- **The T2a stage of the 6th TNM stage, invasion to soft tissues of oropharynx and/or nasal cavity only without parapharyngeal space extension, is designated as T1 in the 7Th TNM stage. Therefore, the 6th TNM Stage IIA (T2aN0M0) and Stage IIB (T2bN0M0) will now be Stage I and Stage II, respectively, in the 7th TNM Stage,**
- **Retropharyngeal lymph node(s), regardless of unilateral and bilateral, is staged as N1 in the 7th TNM stage.**
  - Combined retropharyngeal lymphadenopathy and unilateral neck lymphadenopathy is classified as N1.
- **There is no clinical Mx classification (cMx) and no pathological M0 classification (pM0).**
  - The only evaluation necessary to classify as clinically M0 is history and physical examination.
  - Negative biopsy of a suspected lesion does not completely rule out missed biopsy or other elsewhere occult distant metastases.

TNM Staging System: UICC/AJCC 2010 7th Edition
Taipei VGH Supplement

T Stage

- **Cavernous sinus and/or dura invasion should be classified as T4.**
- **Lateral Pterygoid muscle invasion is classified as infra-temporal fossa invasion, and hence T4.**
- **Pterygopalatine fossa invasion should be classified as T3.**

- **There is a big jump of T stage from T1 for oropharyngeal invasion to T4 of hypopharyngeal invasion.**
- **There is also a jump of T stage from T2 of parapharyngeal invasion to T4 of lateral pterygoid invasion.**
- **T1/T2 with *T>6cm* should be documented for risk grouping.**
- **T3 with anterior ethmoid extension between eyeballs should be documented for risk grouping.**

Imaging Criteria for Lymphadenopathy (LAP)

- **Pathological features**
  - Central necrosis
  - Extracapsular extension (ECE) or Extranodal spread (ENS)
- **Size (maximum diameter)**
  - Level I and IIa (jugulodigastric node) >1.5cm
  - Retropharyngeal LAP > 5mm
  - Other regions (including IIb) > 1cm
- **Imaging features favoring pathological LAP**
  - Group of 3 contiguous lymph nodes with diameter ≥8mm.
  - Long-Short Axis Ratio <2
- **Imaging features favoring benign/reactive lymph node**
  - Intact hilum
  - Long-Short Axis Ratio ≥2

N Stage

- **The N staging method should include at least CT and/or MRI.**
- **The size of lymphadenopathy (LAP) should be measured by CT and/or MRI, and not by palpation/inspection.**
- **The diameter of LAP should be the sum of multiple contiguous confluent LAP.**
- **The size of the largest individual LAP should be documented for risk grouping.**
- **The level of LAP should be documented for risk grouping.**
- **Level 4/5b LAP at T1 transverse process or below or below the transverse vein of neck should be classified as supraclavicular LAP.**
- **Level Ib and pre-auricular/peri-parotid LAP should be documented for risk grouping.**

TNM Staging System: UICC/AJCC 2010 7th Edition
Stage Grouping of M0 Disease (M1 disease as Stage IVc)

	T1	T2	T3	T4
N0	I	II	III	IVa
N1	II	II	III	IVa
N2	III	III	III	IVa
N3	IVb	IVb	IVb	IVb

Taipei VGH Risk Group for Nasopharyngeal Cancer
T and N Modification

T Stage Modification

- **Bulky T1 +/- RP LAP and/or T2 with diameter > 6cm should be treated as T3.**
- **Bulky T3 with anterior ethmoidal extension between eyeballs should be treated as T4.**
- **Invasion of parotid gland should be treated as T4.**

N Stage Modification

- **Bulky N1 with the following features should be treated as N2.**
  - Level I-b LAP
  - Pre-auricular or peri-parotid LAP
  - Level III/Va LAP
  - Any individual LAP > 3cm

Taipei VGH Risk Group Mapping Table for NPC

M0	Non-Bulky T1 ≤ 6 cm	Non-Bulky T2 ≤ 6 cm	Non-Bulky T3 or Bulky T1-2 >6cm	T4 or Bulky T3 (anterior ethmoid extension)
N0	A	A	B	C
Non-Bulky N1 (level II and all LAP ≤ 3cm)	B	B	B	C
N2 or Bulky N1 (level Ib, or III/Va, or preauricular, or single LAP > 3cm)	D_1	D_1	D_1	D_1
N3 without Superior Mediastinal LAP	D_2	D_2	D_2	E
N3 with Superior Mediastinal LAP	E	E	E	E

Localized NPC: Low Risk Groups

Risk Group A

- **Definition**
  - Non-bulky T1/T2 (T<6cm) N0 M0
- **Treatment of Choice**
  - Radical radiation therapy alone
- **Alternative Treatment**
  - CCRT only

Risk Group B

- **Definition**
  - T1 or T2, and Non-bulky N1
  - Non-bulky T3, N0 or Non-bulky N1
- **Treatment of Choice**
  - CCRT only
- **Alternative Treatment**
  - Induction chemotherapy + CCRT
  - Radical radiotherapy alone

See T and N Modification for definition of bulky T and bulky N

Localized NPC: High Risk Groups

Risk Group C

- **Definition**
  - Bulky T3 or T4, N0 or Non-bulky N1
- **Treatment of Choice**
  - Induction chemotherapy + CCRT
- **Alternative Treatment**
  - Induction chemotherapy + CCRT + adjuvant chemotherapy
  - CCRT only

Risk Group D and E

- **Definition**
  - T1-4, N2 or Bulky N1 (D_1)
  - T1-3, N3 (D_2)
  - T4N3 Or TxN3 with superior mediastinal LAP (E)
- **Treatment of Choice**
  - Induction chemotherapy + CCRT + adjuvant chemotherapy
- **Alternative Treatment**
  - Induction chemotherapy + CCRT
  - CCRT only
- **Clinical Trial/Research Protocol**
  - Enrollment to clinical trial, especially for stage IV (D_2) patients

See T and N Modification for definition of bulky T and bulky N

Management of Metastatic NPC

- **Enrollment to clinical trial is encouraged.**
- **Systemic chemotherapy is the mainstay of treatment.**
  - At least 4-6 courses of systemic chemotherapy.
  - Response evaluation should be done after the 2nd or 3rd courses of systemic chemotherapy.
  - Targeted therapy, such as Cetuximab, as second line therapy.
- **Palliative RT**
  - Early administration of palliative RT for symptomatic weight-bearing bone metastases, brain metastasis, and metastatic lesions causing spinal cord compression, obstructive jaundice/obstructive pneumonitis.
  - Delayed administration of palliative RT for asymptomatic metastatic lesions
  - See Principles of Palliative RT
- **RT for locoregional disease of M1 NPC**
  - If radiotherapy is to be given to the locoreginal disease, it could be performed after the 4th course of systemic chemotherapy.
  - See Principles of RT for M1 NPC

Treatment Alternatives by Taipei VGH Risk Groups for NPC
Summary Table

	A	B	C	D	E /M1
RT Only 放射治療	1	3	*	*	*
CCRT only 同步藥物放射治療	2	1	2	3	*
Induction + CCRT 導引藥物治療 + 同步藥物放射治療	-	2	1	2	*
Induction + CCRT + Adjuvant 導引藥物治療 + 同步藥物放射治療 + 輔助藥物治療	-	-	3	1	*
Systemic chemotherapy 藥物治療為主 ± CCRT or RT	-	-	-	-	1

The numbers in the table represent the priority of treatment alternatives for each risk group with 1 being the treatment of choice. For patient with age > 70 or low performance status (KPS < 70 or ECOG 3), the treatment intensity should be reduced at the discretion of attending physician.

Management of Residual Tumors/Lymphadenopathy

- At the discretion of radiation oncologist, a boost dose, 10Gy in 5 fraction or less, can be given to residual tumor / lymphadenopathy found at the end of standard dose 70Gy.
- Biopsy of residual primary tumor and/or lymphadenopathy should be done after an observation period of 12 weeks after full-course of RT.
- Once residual disease is confirmed, PET scan and MRI should be done for planning of salvage treatment.
- Salvage operation could be considered for operable residual disease.
- Radical neck dissection is the preferred salvage treatment for residual lymphadenopathy
- Re-irradiation of residual disease is indicated when surgical margin is positive or salvage surgery is not feasible.

Management of Locoregional Recurrence

- **Tissue proof of locoregional recurrence should be obtained.**
- **Once locoregional recurrence is confirmed, PET scan and MRI should be done for planning of salvage treatment.**
- **For in-infield recurrent NPC**
  - Salvage endoscopic nasopharyngectomy would be feasible for recurrent NPC in nasopharynx, paranasopharyngeal space, parapharyngeal space, paranasal sinuses, infratemporal fossa without intracranial extension to the cavernous sinus.
  - Re-irradiation is indicated when surgical margin is positive or salvage surgery is not feasible.
  - Post-operative chemotherapy may be indicated.
- **For recurrent NPC in anterior marginal miss**
  - Surgery is the treatment of choice if the tumor can be completely removed without the need of post-operative irradiation.
  - Re-irradiation would be the treatment of choice for radiosensitive tumor.
  - Surgery with or without post-operative radiotherapy is feasible for radioresistant tumor.
- **Selective neck dissection is the preferred salvage treatment for recurrent neck lymphadenopathy.**

Principles of Radiation Therapy

See Practice Guidelines of Radiation Therapy for general standard operating procedures, tolerance dose of critical normal structures, quality assurance, DVH criteria for plan approval, and etc.

- **Radiation therapy for newly diagnosed non-metastatic NPC**
- **Radiation Therapy for M1/Group E disease**
- **Re-irradiation of recurrent primary tumor and/or lymphadenopathy**

Principles of Radiation Therapy for Newly Diagnosed Non-Metastatic NPC

- **Delineation of Gross Target Volume**
  - Image fusion with MRI (See NPC MRI Protocol) and optional PET-CT for precise delineation of GTV, as defined in ICRU report 50 and 62)
- **Delineation Clinical Target Volume**
  - CTV_H: GTV of primary tumor and neck lymphadenopathy
  - CTV_M:

    Primary Tumor
    - Inclusion of whole nasopharynx:
      Superior skull base: 1cm above foramen lacerum, Foramen ovale
      Parapharyngel /retropharyngeal space and prevertebral muscle down to C1-2 junction, Pterygopalatine fossa, posterior wall of maxillary sinus
    - 2- (near critical structures) to 5-mm margins around GTV for T2-T4 lesions
    - Inclusion of bilateral tonsils
    - Inclusion of whole clivus in case of clivus invasion

    Lymphatic region
    - Inclusion of level II for all N stages
    - Inclusion of one level below GTV of neck node
    - Level I-b irradiation can be excluded but should be included with gross level I-b lymphadenopathy and be considered to be included in the presence of large II-a (>3cm) lymphadenopathy.
    - Exclusion of non-invaded surrounding muscle
  - CTV_L:
    - Lymphatic region one level away from GTV of neck lymphadenopathy
- **Margins for Planning Target Volume**
  - 3 mm around primary tumor
  - 5 mm around neck lymphadenopathy
- **Radiation Dose**
  - CTV_H: **69.3-74 Gy in 33~37 fractions**
    Optional 66Gy/30 fractions for stage I & II disease with T1/non-bulky T2 and N0/non-bulky N1
  - CTV_M: 57Gy-63Gy in 30-35 fractions
  - CTV_L: 45-54Gy/25-30 fractions or 56Gy/35 fractions
  - Boost dose, up to a maximal total dose of 80Gy, to residual tumor / lymphadenopathy at the discretion of radiation oncologist.
  - CTV of unplanned neck lymph node biopsy / dissection with negative margin: 59.4Gy-63Gy in 30-35 fractions
  - CTV of unplanned neck lymph node biopsy / dissection with positive margin: 65 Gy at least
- **Radiation Technique**
  - Intensity Modulated Radiation Therapy (IMRT) with simultaneous integrated boost (SIB)
- **Timing of Radiation Therapy**

  Radiotherapy alone:
  Within 2 weeks after the completion of staging procedures or as soon as healing of the teeth extraction wound.

  Following induction / neoadjuvant chemotherapy
  Within 4 weeks after the start of the last course of induction chemotherapy

Radiation Therapy for Metastatic NPC or Locoregional Recurrence

RT for Metastatic NPC

- **Locogegional irradiation for M1 disease**
  - Given after 3-4 courses of systemic chemotherapy
  - Optionally, 10% reduction from the standard dose along with concurrent chemotherapy
- **Palliative RT**
  - 30-50 Gy in 12-25 fractions to metastatic lesions, if indicated

RT for Locoregional Recurrence

**If salvage surgery is not feasible for the recurrent disease, or positive margins is found after salvage surgery,
re-irradiation could be done with the following principles:**

- **Target volume**
  - Recurrent GTV with minimal but adequate margin
- **Radiation Dose**
  - 60Gy in 5-6 weeks
- **Fractionation**
  - Hyperfractionated RT 60 Gy in 50 fractions, or
  - Conventional QD fractionation 60Gy in 30 fractions
- **Concurrent chemotherapy, if not contraindicated**

Critical Structures and Radiation Tolerance Tolerance Dose

Normal Tissue	Ideal Criteria	Acceptable Criteria
Brain Stem	<54Gy	1ml or less < 60Gy
Spinal Cord	<45Gy	1ml or less < 50Gy
Parotid Gland	mean < 26Gy	mean dose < 35Gy
Optic nerve	<50Gy	<56Gy
Lens	< 6Gy	<10Gy
Inner Ear	<50Gy; mean < 45Gy	-
Temporal Lobe	< 56Gy	1% < 63Gy

Principles of Chemotherapy

- The regimens and dose intensity are similar for systemic chemotherapy for M1 NPC, induction chemotherapy and adjuvant chemotherapy.
- The regimens and dose intensity of chemotherapy for concurrent chemotherapy is generally altered or reduced to decrease the severity of mucositis.
- Performance status and age of patient should be factored in the incorporation and administration of chemotherapy.
- Other drugs combined with cisplatin such as paclitaxel, tegafur/uracil, mitomycin, epirubicin, etc. could be considered according to the specific patients' condition with consensus reached in the combined conference
- Carboplatin should only be considered unless patient's CCr < 40 or other inevitable reasons that cisplatin cannot be used.
- Cetuximab could be added according to the physician's judgments

Induction Chemotherapy

- For T1-3 N1-3 M0 of NPC, the duration of induction chemotherapy should be limited to 6-8 weeks.
- For large T4 NPC with high risk of radiation injury to optic nerve, brain stem and/or spinal cord, 9-12 weeks of induction chemotherapy could be given to reduce tumor bulk in order to reduce the probability of radiation injury.
- Response to induction chemotherapy should be well documented.
- Following the induction chemotherapy, CCRT should be given instead of radiotherapy alone to combat possible accelerated repopulation.
- CT simulation for RT should be arranged 2 weeks in advance before the start of RT, so that the CCRT could be performed as on week 7-9 (T1-3) or week 10-13 (T4).

Adjuvant Chemotherapy

- Adjuvant chemotherapy should be performed within 8 weeks after the completion of radiation therapy.
- If less than partial response after the induction chemotherapy is observed, a change of adjuvant regimen, such as adding cetuximab targeted therapy, should be considered.
- The cycle number of adjuvant chemotherapy is usually 3 for Q3W/Q4W regimens or 6 for Q2W regimens.

Regimens of Induction/Adjuvant/Systemic Chemotherapy

- **4-day PFL (Q3W)**
  - Cisplatin 80 mg/m^2 infusion for 3 hour
  - 5-FU: 600 mg/m^2 per 24 hours as a 96 hour continuous infusion
  - Leucovorin 90 mg/m^2 per 24 hours as a 96 hour continuous infusion
- **PCF (Q3W)**
  - Paclitaxel 135 mg/m^2 infusion for 3 hours on Day 1
  - Cisplatin 75 mg/m^2 infusion for 3 hours on Day 1
  - 5-FU: 600 mg/m^2 per 24 hours as a 96-hour continuous infusion
- **TPF (Q3W)**
  - Docetaxel 60 mg/m^2 infusion for 3 hours
  - Cisplatin 75 mg/m^2 infusion for 3 hours
  - 5-FU: 850 mg/m^2 per 24 hours as a 96-hour continuous infusion
- **Cisplatin + DeGramount (Q2W)**
  - Cisplatin 50 mg/m^2 infusion for 3 hours
  - Leucovorin 200 mg/m2 infusion for 2 hours per day for 2 days
  - 5-FU 400 mg/m^2 infusion for 30 minutes per day for 2 days
  - 5-FU 600 mg/m^2 per 24 hours as a 48-hour continuous infusion
- **PMU (Q4W)**
  - Cisplatin 70 mg/m^2 infusion for 3 hours
  - Mitomycin C 7 mg/m^2 infusion for 30 min.
  - Tegafur 100mg + Uracil 224 mg, PO TID, continuous

Chemotherapy Regimen for Concurrent Chemoradiotherapy

- **4-day PFL with reduced 5FU dose**
  - Cisplatin 80 mg/m^2 infusion for 3 hour
  - 5-FU: 400 mg/m^2 per 24 hours as a 96 hour continuous infusion
  - Leucovorin 90 mg/m^2 per 24 hours as a 96 hour continuous infusion
  - Total 2 cycles during RT, 4 weeks apart
- **PMU (PMuFur)**
  - Cisplatin: 70 mg/m^2 infusion for 3 hours
  - Mitomycin C: 7 mg/m^2 IV > 3-5 min
    - Total 2 courses, 4 weeks apart
  - Tegafur 100mg + Uracil 224 mg, PO TID, through out RT
- **CFHX (Q3W) x 2 cycles**
  - Cisplatin 20mg/m^2 infusion for 4 hours
  - 5-FU 600mg/m^2 per 24 hours as a 96-hour continuous infusion
  - Hydroxyurea 500mg po stat and bid x11 doses
- **PT**
  - Cisplatin:60 mg/m^2 IV infusion for 3 hours, D2
  - Taxol:135 mg/m^2 IV infusion for 3 hours, D1
  - Total 2 courses, 4 weeks apart
- **Weekly Cisplatin**
  - Cisplatin 30 mg/m^2 infusion for 3 hour QW Week 1 through Week 7 during RT
- **Weekly Cisplatin + Cetuximab (QW) x 7 cycles**
  - Cisplatin 30-35 mg/m^2 infusion for 3 hours
  - Cetuximab 400 mg/m^2 infusion for 2 hours at first cycle
  - Cetuximab 250 mg/m^2 infusion for 2 hours from 2nd cycle
- **Q3W Cisplatin**
  - Cisplatin 100 mg/m^2 infusion for 3 hour
  - Week 1, 4 and 7 during RT
- **Cetuximab (QW) x 7 cycles**
  - Reserved for patients unsuitable for cisplatin-based chemotherapy (?)
  - Cetuximab 400 mg/m^2 infusion for 2 hours at first cycle
  - Cetuximab 250 mg/m^2 infusion for 2 hours from 2nd cycle

Timing

- **The concurrent chemotherapy should start before the 6th fraction of radiotherapy.**

Follow-Up

- **If the patient develops of symptoms and signs for recurrent disease during the follow-up, the following studies may be arranged ahead of the fixed follow-up schedule.**
- **Physical examination and endoscopy**
  - During treatment: weekly
  - 1st year: monthly
  - 2nd year: every 2 months
  - 3rd year: every 3 months
  - 4th year and thereafter: every 6 months
- **Timing of biopsy for residual disease**
  - 12 weeks after the completion of RT
- **MRI of nasopharynx**
  - 12 weeks after the completion of radiotherapy
  - 1 years after the start of treatment
  - Every 6 months for the 2nd & 3rd years
  - Once a year thereafter
- **CXR**
  - Every 6 months in the first 3 years
  - Once a year thereafter
- **Liver Sonography**
  - Every 6 months in the first 3 years
  - Once a year thereafter
- **Bone scan**
  - Once a year for N3 disease
- **Serum metabolite analysis for liver and renal function**
  - Every 3 months in the first 2 years
  - Every 6 months thereafter up to 5 years
- **Thyroid function test**
  - Once a year
- **Audiometry**
  - Once a year for 5 year
- **Dental care**
  - Every 6 months
- **Swallowing function**
  - Optional VFSS in the 5th year after radiotherapy
- **Salivary function**
  - Optional salivary function test at 1 year, 3 year and 5 year from start of radiotherapy
- **Quality of life**
  - Optional QOL survey at 1 year, 3 year and 5 year from start of treatment

Acronym

- **3D-CRT: 3D Conformal Radiation Therapy**
- **CCRT: Concurrent chemoradiotherapy**
- **CTV: Clinical Target Volume**
- **GTV: Gross Tumor Volume**
- **IMRT: Intensity Modulated Radiation Therapy**
- **MRI: Magnetic Resonance Image**
- **NPC: Nasopharyngeal Cancer**
- **PET: Positron Emission Tomography**
- **PTV: Planning Target Volume**
- **RT: Radiation Therapy**
- **WHO: World Health Organization**

Manuscript

Multidisciplinary team

The management of nasopharyngeal cancer is a joined effort of a specialized multidisciplinary oncological team (NPC multidisciplinary team), consisting of radiation oncologist, medical oncologist, head and neck surgical oncologist, pathologist, radiologist, radiation physicist, radiation technologist, dentist, oncological nurse and social workers.

Diagnosis, Tissue Proof and Histopathology

Definitive diagnosis of nasopharyngeal cancer (NPC) is made by endoscopic biopsy of the primary nasopharyngeal tumor, even though occasionally a NPC patient has incisional biopsy of neck lymphadenopathy prior to biopsy of the primary tumor. This practice guidelines are applicable only for keratinizing (WHO type I) and non-keratinizing (WHO type II) carcinoma. Other malignant tumors of nasopharynx, such as adenoid cystic carcinoma, lymphoma and plasmacytoma, should refer to respective guidelines for optimal management. In Taiwan and other Asian country, keratinizing carcinoma accounts for less than 2% of all NPC. The non-keratinizing carcinoma could be further classified into 2 subtypes: differentiated (II-a) and undifferentiated (II-b). The differentiation/histology grades for WHO type I, II-a and II-b are moderately differentiated (grade 2), poorly differentiated (grade 3) and undifferentiated (grade 4), respectively. The outcome of WHO type II-a and II-b are similar. The radiosensitivity and outcome of WHO type I is believed to be somewhat inferior to that of WHO type II. The management of NPC, however, is basically the same for all these 3 subtypes.

TNM Stage and Taipei VGH Risk Group

The UICC/AJCC TNM staging system, 7th edition of 2010 is used in order to report and compare the results. There are some ambiguous definition or gray area of the 6th TNM that may incur different interpretation and hence inconsistent staging. Supplemental definitions are thus defined by the panel member for consistent staging for NPC (See Taipei VGH Supplement for TNM system of NPC). Of the Taipei VGH supplement to NPC TNM staging, there are 4 major amendments: 1) Measurement of size of lymphadenopathy by MR and/or CT, not by physical examination. 2) Measurement of confluent lymphadenopathy for reporting size of lymphadenopathy. 3) Definition of lymphadenopathy at T1 or below the transverse vein as supraclavicular lymphadenopathy (N3b).

Management by Taipei VGH Risk Group

Most institutes use TNM stage grouping for treatment planning. There are some minor deficiencies of the 7th TNM system, which may not reflect the true prognosis of an individual patients. The deficiencies of the existing TNM include: 1) No T2-3 definition between T1 oropharyngeal invasion and T4 for hypopharyngeal invasion. 2) A jump from N1 to N3 for unilateral lymphadenopathy at cut-off lymph node size of 6cm. 3) No definition of T stage for parotid invasion. 4) No definition of N stage for pre-auricular and peri-parotid lymphadenopathy. And 5) Suboptimal stage grouping for reflecting prognosis. For optimal management, the NPC panel members use additional criteria to define Taipei VGH NPC Risk Groups for decision making.

Manuscript (II)

In this practice guidelines, the NPC panel members recommend treatment of choice based on Taipei VGH risk group. Because TNM stage and Taipei VGH Risk Group are classified by pre-defined cut-off values, there is inevitably variation of prognosis within a stage group or risk group. As a result, the NPC panel members also provide alternative treatment plans for each risk group. The NPC panel members strongly recommend that the treatment of choice for risk group be performed whenever feasible. The alternative treatments could be offered to the patient only when the treatment of choice is refused by the patient, or when NPC team member, by their own independent medical judgment to the context of individual patient's clinical circumstance and sub-TNM grouping, to perform a customized care.

In addition, cancer patients are encouraged to participate in a clinical trial for the best management care.

Radiation therapy is the mainstay of the treatment for localized nasopharyngeal cancer with 7th TNM stage I to IV-B.

Combined radiation therapy and chemotherapy are indicated for medically-fit NPC patients of stage T1-2N1M0, stage III, and stage IV-A and IV-B disease. Radiotherapy alone is indicated for patients who are not medically fit for aggressive combined chemotherapy.

Patients with distant metastases at presentation, i.e. stage IV-C, should receive chemotherapy first, followed by radiotherapy with standard or reduced dose to the primary tumor and draining lymphatic regions.

There is no so-called standard chemotherapy regimen for NPC. Most regimens for NPC are Cisplatin-based with or without 5FU.

Target therapy with anti-EGF Cetuximab can be considered in patients with poor renal function or intolerance to Cisplatin-based chemotherapy.

The treatment results in terms of overall survival for NPC patients treated at Taipei VGH are graphed in the page 34. As clearly shown in the Fig 1 (right upper), the overall survival rates of NPC has been greatly improved through out the 4 era: 1) 1971-1985 Cobalt-SSD; 2) 1986-1995 2D-Linac-SAD; 3) 1996-2002 3D Conformal Radiotherapy. and 4) IMRT and CCRT.

The 5-year overall survival (5-Y OS) rates of each era are tabulated in the next page. The 5-Y OS rates are 100%, 96.3%, 85.2% and 59.4% for stage I, II, III and IVa-b, respectively. In the IMRT-CCRT era.

The improved and good survival data in the IMRT-CCRT era at Taipei VGH validates the effectiveness of this guideline.

Manuscript – Principles of Radiation Therapy (I)

Treatment Preparation

All patients should have pre-radiation therapy dental evaluation and dietitian consultation. The patient is set up for simulation and RT in a supine position with head extended and immobilized by a customized thermoplastic mask Special attention and measures should be made to ensure the preproduction of shoulder and neck position through out the course of RT.

CT Simulation

CT image provides electron density for tissue heterogeneity correction of radiation dose computation. CT simulation with 3-5 mm slide thickness should be taken prior to 3D-CRT or IMRT planning. For optimal digital reconstructed radiograph (DRR) rendering, a 3mm slide thickness of CT simulation is preferred.

Target Delineation

MRI is the imaging modality of choice for diagnostic workup of NPC for its high tissue contrast. (Chong 1996, Gong 1991, Ng 1997). The pulse sequence of MRI should include pre-contrast T1 without fat saturation series and post-contrast with fat saturation series. Ng et al. reported a significantly higher detection rate by MRI versus CT for intracranial extension (57% vs. 36%), skull base involvement (60% vs. 40%), retropharyngeal node (58% vs. 21%), and prevertebral muscle infiltration (51% vs. 22%)3. To exploit the superior sensitivity, image fusion of diagnostic MR to simulation CT is recommended for precise gross target volume (GTV) delineation and optimal treatment planning (Emami 2003). If image fusion with diagnostic MRI and/or PET is not available for RT planning, both non-contrast and contrast CT simulation should be performed for optimal target delineation.

The common radiologic criteria for defining a lymph node as metastatic include the presence of central necrosis or extracapsular spread, shortest axial diameter $\geq$10 mm (11 mm for jugulodigastric node and 5 mm for retropharyngeal node), or group of three of more contiguous lymph nodes that are borderline in size (Van den Brekel 1990).

NPC is both radiosensitive and chemosensitive. The gross tumor volume could have dramatically shrinkage during the course of radiation therapy. The body surface contour could also be changed by tumor shrinkage and weight loss secondary to toxicity. These could potentially affect the tumor control rate and increase complication. It is thus recommended that a second CT simulation be taken for adaptive re-planning of the last 20-30Gy RT.

Target Volume

The report and documentation of various target volumes, such as Gross Tumor Volume (GTV), Clinical Target Volume (CTV), and Planning Target Volume (PTV) should follow the definitions in report 50 and report 62 from the International Commission of Radiation Units and Measurement (ICRU). The practice guideline, “Basic Common Items of Radiation Therapy Summary Report Version 2009”, of Taiwan Society for Therapeutic Radiology and Oncology (TASTR0) recommends to report external beam radiotherapy by dose levels: CTV_H, CTV_M and CTV_L for high, mid and low dose levels, respectively, corresponding to the tumor burden. The description and naming of neck lymphatic station included in the various CTVs should follow the consensus of the intergoup guideline (Gregoire 2003)

The external beam radiotherapy for NPC is usually given to two or three dose-level of CTVs. Different centers may have different philosophies in defining the CTV_H, CTV_M, and CTV_L in NPC. There is no level I evidence in regard to the delineation of optimal treatment volume. The following recommendations are consensus-based:

The CTV_H consists at least GTV of both primary tumor and lymphadenopathy. Some center may include a margin of 5mm around the GTV and/or the whole nasopharynx in CTV_H. Any identifiable extracapular spread around gross lymphadenopathy should be included in CTV_H.

The CTV_M usually consists of the following structures: 1) CTV_H plus 3-mm to 5-mm margins (2-mm or less margin near the critical structures such as brain stem); 2) Whole nasopharynx; 3) Parpharyngeal space and retropharyngeal lymph nodes: 4) pterygopalatine fossa, 5) posterior wall of maxillary sinus; 6) the adjacent skull base and foramen; 7) bilateral level II lymph node stations; and 8) the lymph node station of the gross metastatic lymphadenopathy. Paravertebral muscles, sternocleidomastoid muscles and inferior lateral portion of the medial pterygoid muscle without gross tumor invasion and/or infiltration can be excluded from CTV_M.

The CTV_L usually consists of distant neck lymphatic station, down to bilateral level IV, without gross metastatic lymphadenopathy. Level Ib without gross lymphadenopathy can usually be spared. In case of association with large >3cm level IIA lymphadenopathy, level IB could be electively included in either CTV_M or CTV_L.

The PTV covers the CTV with additional uncertainty margin needed for systemic and random setup variations. Individual centers may have different uncertainty margin for PTV in their actual practice. With proper immobilization and meticulous care in setup, an expansion margin of 3 mm is usually adequate for the primary tumor region. The uncertainty margin for neck lymphatic region is 3-5mm or even more. With the introduction of image guided radiation therapy delivery (IIGRT or IGRTD), the uncertainty margin may be reduced to 2mm. Per recommendation of ICRU report 62, the margin near critical structures can be reduced to avoid late complication.

Manuscript – Principles of Radiation Therapy (II)

Dose, Fractionation and Time

Based on the retrospective 2D-RT data, the most common prescribed total dose of external beam RT to gross tumor (CTV_H) of NPC is 66 to 72 Gy given in 1.8Gy to 2 Gy per fraction, 5 fractions per week, over a period of 6 to 8 weeks. The recommended total doses for elective treatment of subclinical disease (CTV_M and CTV_L) is around 50-60Gy.

A total dose of 70Gy in 7 weeks in the 2D-RT era could adequately control T1-T2 tumor. The control rate of T3-T4 with 70Gy or more given by 2D-RT is less than 55% (Perez 1992). The control rate of T3-T4 has been dramatically improved to >90% by 70Gy of IMRT with or without concurrent chemotherapy.

Before the era of IMRT, the dose per fraction for gross tumor (CTV_H) and subclinical disease (CTV_M and/or CTV_L) were the same and the whole course of RT was usually given in 2 phases: Phase 1 with initial large fields to cover both the gross tumor and the subclinical disease up to 45 to 54Gy, followed by Phase 2 with coned down fields to boost the gross tumor up to the 66Gy~70Gy or more.

In the era of IMRT, simultaneous integrated boost (SIB) becomes technically feasible and gains popularity with its potential radiobiological benefit: 1) Increased tumor cell killing with high-dose 2 to 2.4Gy per fraction for CTV_H, and 1) Reduced normal tissue side effects with low-dose 1.6 to 1.9Gy per fraction for CTV_M and CTV_L. Different centers have various schemes of dose per fraction for SIB-IMRT. The consensus of this panel is to include the GTV only in the CTV_H in case of applying extra high-dose 2.1Gy-2.4Gy per fraction in SIB-IMRT. It is also a consensus to avoid dose per fraction below 1.7Gy to treat CTV_M and/or below 1.6Gy to treat CTV_L in SIB-IMRT.

For large residual lymphadenopathy presented at the end of the 70Gy, a focal boost dose of fractionated 4-10Gy can be given at the discretion of radiation oncologist, as an alternative to neck dissection.

For large T4 intracranial invasion, hyperfractionated RT with 1.2Gy per fraction and 2 fractions per day up to a total dose of 72Gy to 75.6Gy can be applied to decrease the risk of late complication (Wolden 2003).

Various accelerated fractions schemes were tested in non-randomized studies in 2D-RT era. The rate of temporal necrosis was found to increased with 1.6Gy per fractions, 2 fractions per day (Leung 1992, Jen 2001)

External Beam Treatment Planning and Irradiation Technique

Compared to 2D RT, 3D conformal RT improves tumor coverage (Leibel), increases local control rate and reduces xerostomia (Yen). Dosimetry studies in various centers have concluded that the conformity of radiation dose distribution to target volume of NPC can be further improved by Intensity modulated radiation therapy (IMRT) (Hunt, Kam, Xia). IMRT is thus the radiation technique of choice for NPC. There are various forms of IMRT, including step-and-shoot, sliding windows, intensity modulated arc therapy (IMAT), and tomotherapy. There is no prospective study to compare locoregional tumor control rate among these IMRT techniques.

Plan approval and normal tissue dose constraint

Dose volume histogram (DVH) is the basic and most important tool for plan assessment and approval. There is no level I evidence in regard to plan approval criteria for PTV and CTV. The ideal approval criteria for CTV and its associated PTV is 1) 100% of CTV and 95% PTV receiving at least the corresponding prescribed dose level, and 2) 100% of PTV receiving at least 95% of the corresponding prescribed dose level. By discretion of radiation oncologist, the approval criteria could be loosen in case of PTV overlapping with critical structures or PTV flushing outside body for superficial large lymphadenopathy. For CTV_H and PTV_H, the maximum dose should be kept below 115% of the prescribed isodose and less than 10% of PTV_H receiving 110% or more of the prescribed dose.

The common dose constraints to critical structures are listed as the followings:

Normal Tissue	**Ideal Criteria**	**Acceptable Criteria**
Brain Stem	*<54Gy*	*1ml or less < 60Gy*
Spinal Cord	*<45Gy*	*1ml or less < 50Gy*
Parotid Gland	*mean < 26Gy*	*mean dose < 35Gy*
Lens	*< 6Gy*	*<10Gy*
Optic nerve	*<50Gy*	*<56Gy*
Temporal Lobe	*< 56Gy*	*1% < 63Gy*

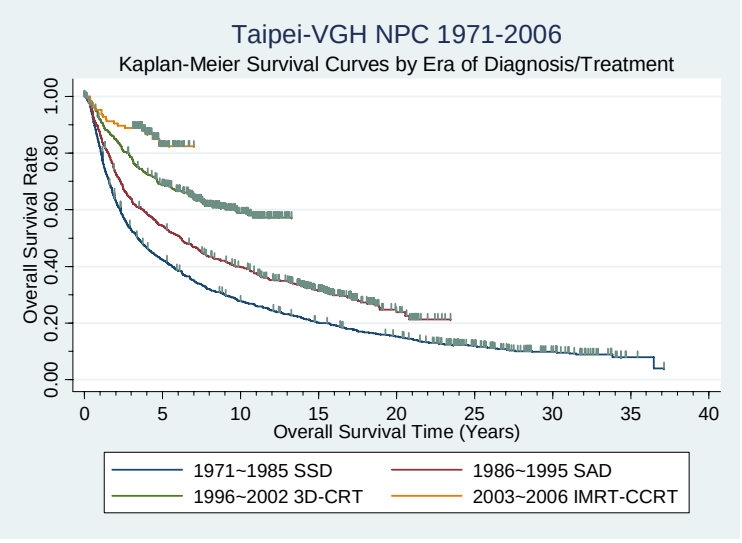
Brachytherapy

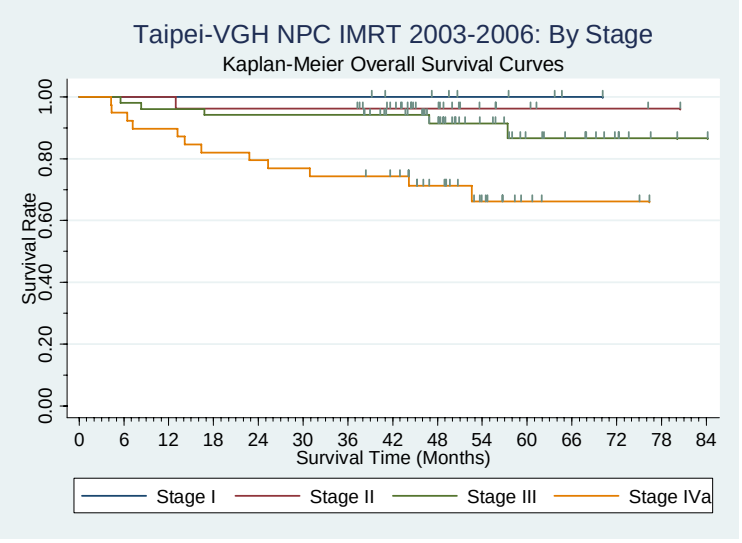
Several retrospective studies showed that intra-cavity brachytherapy boost improved primary tumor control rate for T1-T2 NPC for 2D external beam RT (Wang 1991, Teo 2000). Its benefit in the era of IMRT and concurrent chemotherapy is unknown.

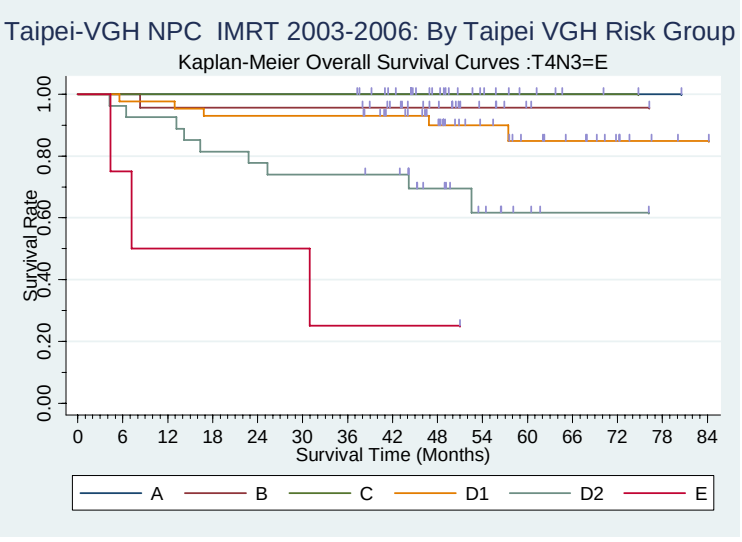
5-Year Overall Survival Rate and Median Survival Time of Non-Metastatic NPC at Taipei VGH by Different Treatment Era

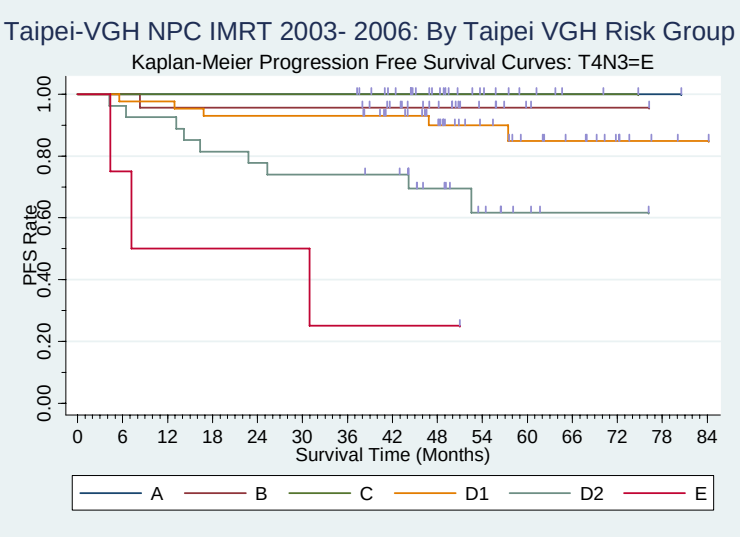
TNM Stage	1971~1985 SSD Cobalt	1986~1995 SAD Linac	1996~2002 3D-CRT	2003~2006 IMRT-CCRT
I	83.7% / 12.9Y	78.1% / 14.1Y	88.7% / -	100% / -
II	55.6% / 6.9Y	61.7% / 9.4Y	78.3% / -	96.3% / -
III	35.4% / 2.8Y	53.9% / 6.9Y	66.6% / -	85.2% / -
IVa-b	27.7% / 2.0Y	38.7% / 2.7%	52.1% / 5.9Y	59.4% / -
All	42.2% / 3.5Y	54.2% / 6.1Y	68.6% / -	80.1% / -

Taipei VGH NPC Survival Curves: M0









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