PILOT STUDY OF CONCURRENT CHEMO-RADIOTHERAPY FOR ADVANCED NASOPHARYNGEAL CARCINOMA

(Forum for Nuclear Cooperation in Asia)

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LEAD AGENCY:

FORUM FOR NUCLEAR COOPERATION IN ASIA

PROJECT BRIEF DESCRIPTION

- **Non-randomized phase I-II trial.**
- **Concurrent chemo-radiotherapy**
  - **standard radiotherapy**
  - **weekly chemotherapy.**
- **chemotherapy may act or give synergistic effect w/ RT by sensitizing tumor cells.**

OBJECTIVES:

- **GENERAL:**

  Evaluate the acute & late toxicity of patients w/ NPC treated w/ standard RT concurrent w/ weekly chemotherapy.

- **SPECIFIC:**

  Determine the efficacy of the treatment regimen as to response rate, duration of response & time-to-tumor progression or recurrence.

SIGNIFICANCE OF THE STUDY:

- 6th most common cancer among Filipinos.
- With improved RT techniques, local control has also improved.
- With chemotherapy, 3 year survival has improved from 46% to 76%.
- Incidence of distant failure reduced from 35% to 13%.

BRIEF LITERATURE REVIEW:

- NPC is both radio & chemo sensitive.
- RADIOTHERAPY:
  - used as single modality for cure.
  - highly curable in early stage.
  - poor outcome in advance stages.
  - good local control.

BRIEF LITERATURE REVIEW:

CHEMOTHERAPY:

- undefined role.
- taken as experimental.
- adjuvant & neo adjuvant chemo is not conclusive to benefit the patient.

BRIEF LITERATURE REVIEW:

COMBINED CHEMORADIOTHERAPY:

- concurrent chemoradiotherapy improves survival in advance NPC.
- too toxic if given in large amount.
- some chemotherapeutic regimen are too toxic & has unacceptable morbidity.

BRIEF LITERATURE REVIEW:

- Improved survival in cervical cancer is an attractive proposition in NPC.
- Weekly chemotherapy potentially cause continued enhancement of RT effect to tumor cells.
- Easier to increase or adjust in presence of acute complications.
- This regimen is a common practice in cervix cancer management.

BRIEF LITERATURE REVIEW:

Why concurrent chemoradiotherapy?

- acts synergistically with radiation by sensitizing cell to RT.

- chemotherapy synchronizes cells into a more radiation sensitive phase and potentiate the effect of RT.

RESEARCH METHODOLOGY

- **Non-randomized phase I/II trial in Asia and Southeast Asian multi-center study:**
- **Participating countries:**

Vietnam (2 centers)
Malaysia(2 centers)

Indonesia	**China**
Philippines	**Thailand**
Korea	**Japan**

RESEARCH METHODOLOGY

Conduct of study:

This study will be conducted according to Good Clinical Practice guidelines and Declaration of Helsinki.

RESEARCH METHODOLOGY

- Evaluation before treatment:
- Medical history & PE
- ENT evaluation
- Biopsy/histopathology report
- CXR, CT scan of post-nasal space up to thoracic inlet. (MRI & bone scan optional.)
- Nutritional & dental assessment
- Blood chemistries

RESEARCH METHODOLOGY

- **Treatment protocol:**

  Concurrent chemoradiotherapy

- **RT: Standard fractionation (1.8 to 2 Gy/day for 6.5 to 7.5 weeks).**
- **Chemotherapy: weekly cisplatinum at 30 mg/m^2, IV infusion.**

RESEARCH METHODOLOGY

- **Prophylactic medications:**
- **Radiotherapy = dental clearance & oral fluoride prophylaxis.**
- **Chemotherapy = dexamethasone p.o. given 2 days prior to start of chemo, routine hydration and anti-emetics.**

RESEARCH METHODOLOGY

Target population:

ONLY THREE PATIENTS IN THE PHILIPPINES

RESEARCH METHODOLOGY

INCLUSION CRITERIA:

- **Age range (20 - 70 y.o.)**
- **Biopsy proven WHO type 2 or 3, NPC**
- **Stage III, IVA & IVB (TNM 1997)**
- **No distant metastases**
- **No previous history of cancer except stage 0 carcinoma of cervix or basal cell carcinoma.**

RESEARCH METHODOLOGY

INCLUSION CRITERIA:

- **WHO performance status 0-2**
- **WBC > 3,500/L**
- **Platelet count > 100,000/L**
- **Hemoglobin > 10 gm/dL**
- **Crea clearance > 6ml/min**
- **Patients should be accessible to follow-up.**

RESEARCH METHODOLOGY

EXCLUSION CRITERIA:

- **WHO type I NPC**
- **Stage IV C**
- **WHO performance status > 3**
- **History of cancer within 5 years except for skin cancer & CIS of cervix.**
- **Previous RT to head and neck.**

RESEARCH METHODOLOGY

EXCLUSION CRITERIA:

- **severe concomitant medical illness like uncontrolled diabetes or hypertension.**
- **Concurrent chemotherapy or investigational therapy.**
- **pregnancy and/or lactation**
- **patients who are unlikely to follow-up.**

PATIENT ASSESSMENT

During treatment:

- **weekly assessment for toxicity.**
- **toxicity grading according to standard NCICTC/WHO criteria.**
- **toxicity evaluation shall include the skin, mucosa, nausea, vomiting and weight loss.**

Stopping rule:

WBC	< 3,000/mm^3
Platelet count	<75,000/mm^3
Fever	> 38 ^{0} C
Performance status:	3-4
Grade 3 nausea	

Stopping rule:

When patients develop grade 3-4 non-hematological toxicities (mucositis), chemotherapy or radiotherapy should be interrupted according to institutional policy.

CRITERIA FOR DISCONTINUATION OF TREATMENT

- Progressive disease (PD)
- Very serious acute toxicities:
  - grade 4 non-hematological toxicities.
  - septic shock due to hematologic toxicities.
  - treatment related death.
- denial or withdrawal of the protocol treatment.

CRITERIA FOR DISCONTINUATION OF TREATMENT

- **Interruption of radiotherapy more than 3 weeks.**
- **Cases that are judged to be difficult to continue the protocol treatment by the responsible physician.**

PATIENTS' PROFILE

- 3 patients enrolled in the study.
- Age ranged from 46 – 62 years old.
- All are males.
- Filipino

CASE 1:

- I. C. , 46 years old.
- Chief complaint - blurring of vision.
  - bilateral rectus muscle palsy.
- Biopsy of the nasopharyngeal mass:
  - poorly differentiated squamous cell CA.

CASE 1:

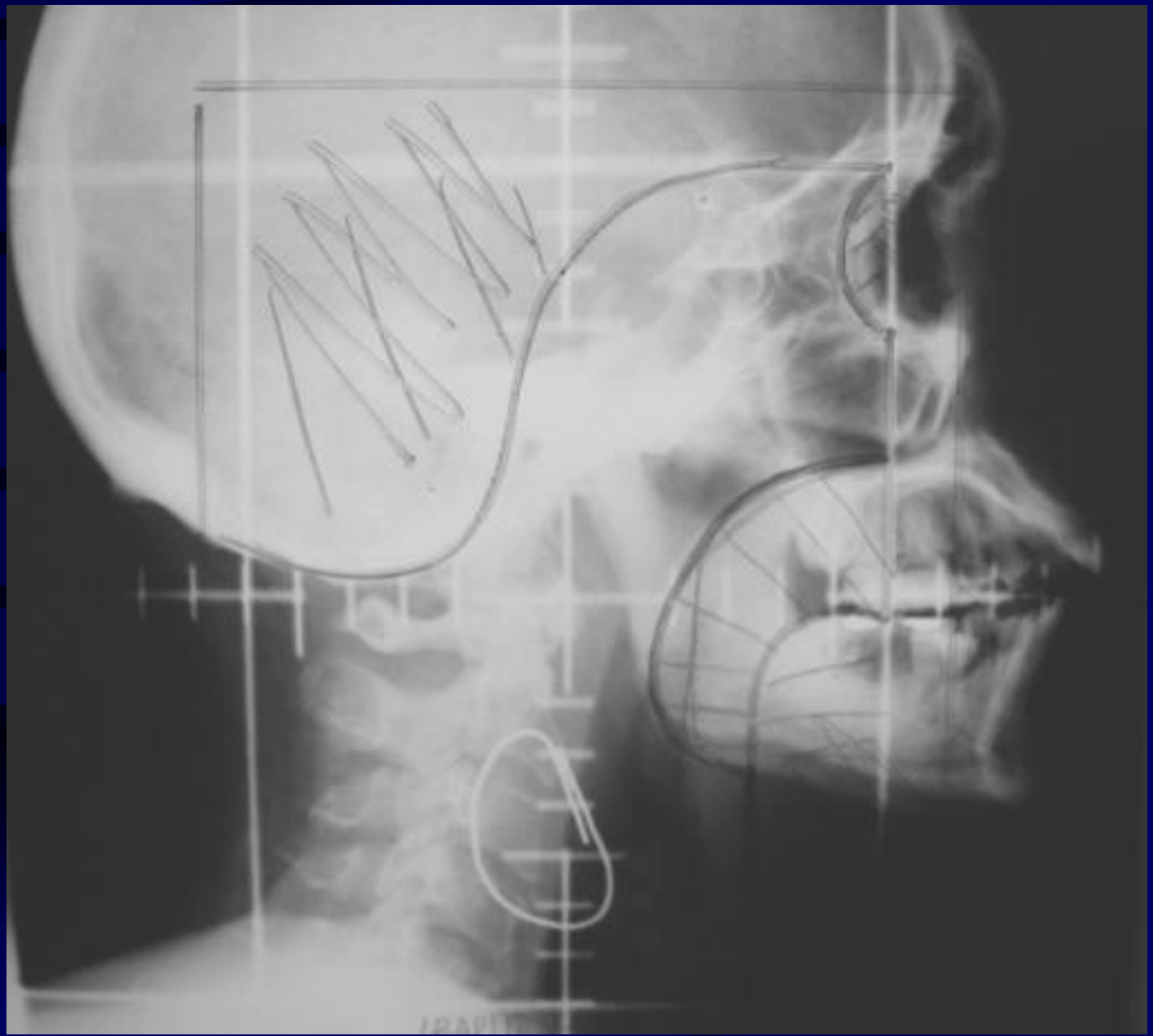
- CT scan of the nasopharynx:
  - soft tissue fullness in the left side of nasopharynx with blunting of the torus tobarius.
  - Fossa of Rossenmuller obliterated.
- CT scan of the brain and orbit:
  - negative

CASE 1:

- **Metastatic work-up : all are negative.**
- **Clinical and radiologic diagnosis/ staging:**

  poorly differentiated NPCA stage 1VA (T4N1Mx).


XHATRON



CASE 2:

R. F. , 62 years old.

Chief complaint - bilateral neck mass.

Biopsy of the right supraclavicular mass:

large cell undifferentiated CA

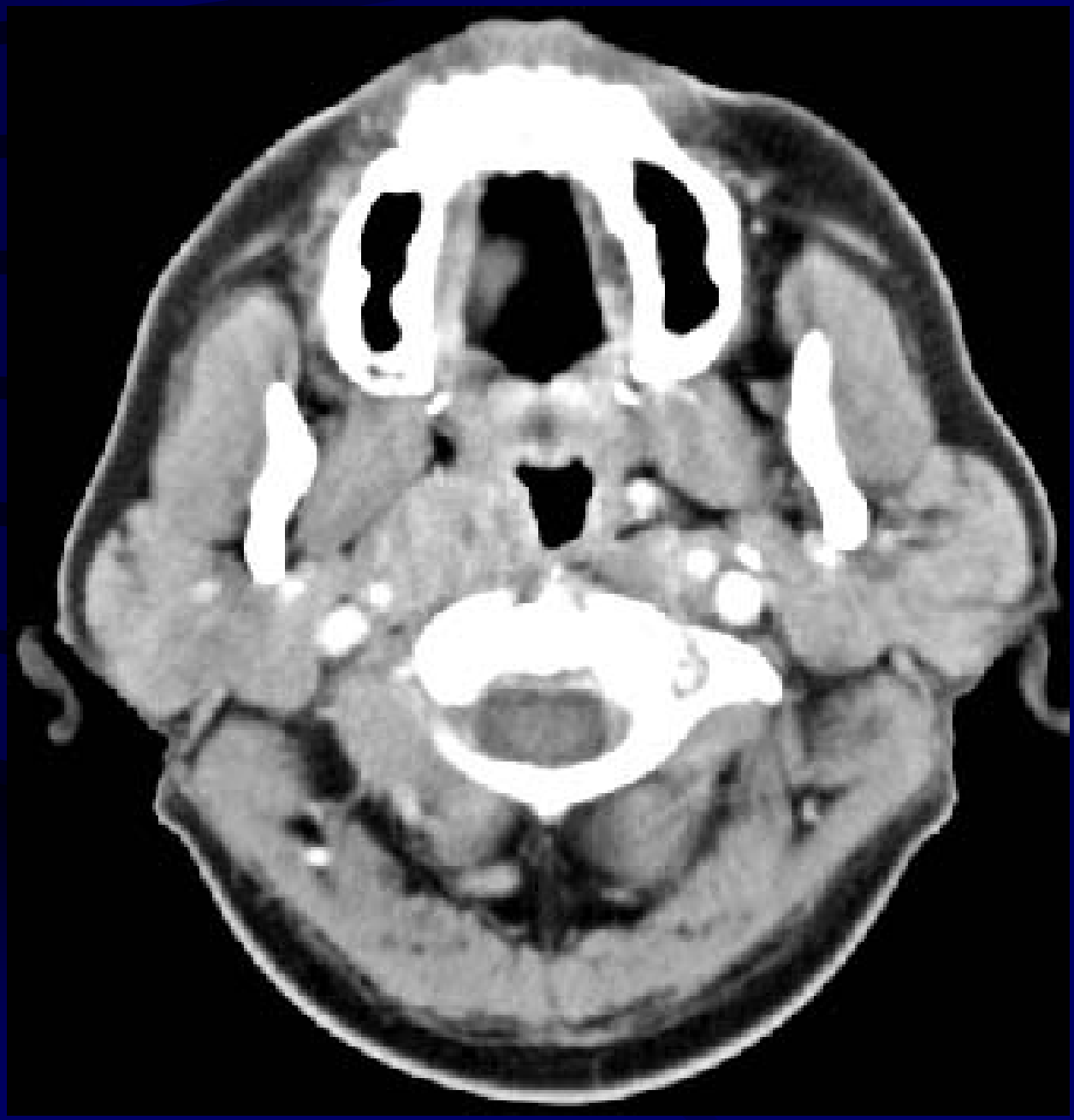
LCA (-), Cytokeratin (+)

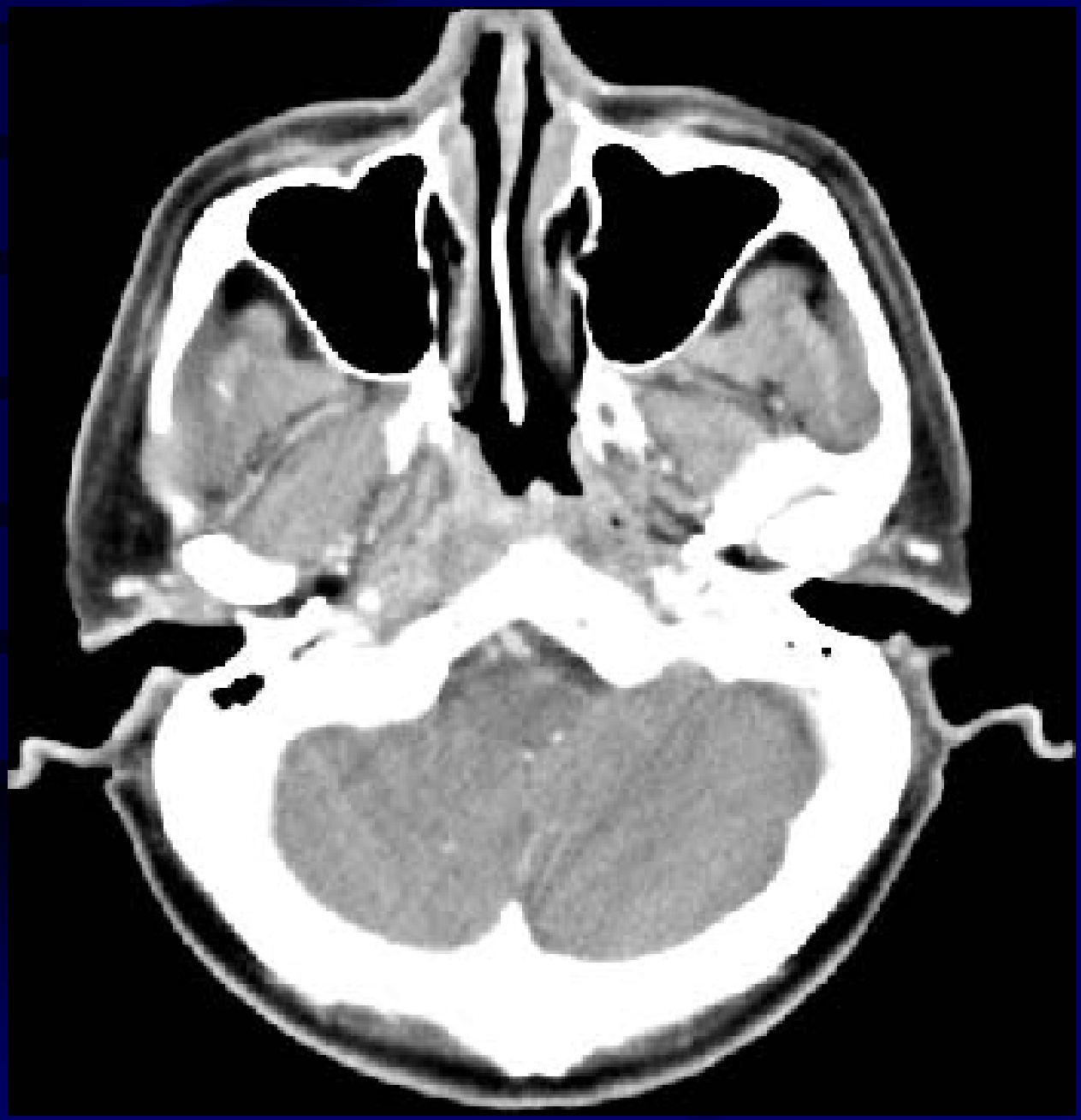
CASE 2:

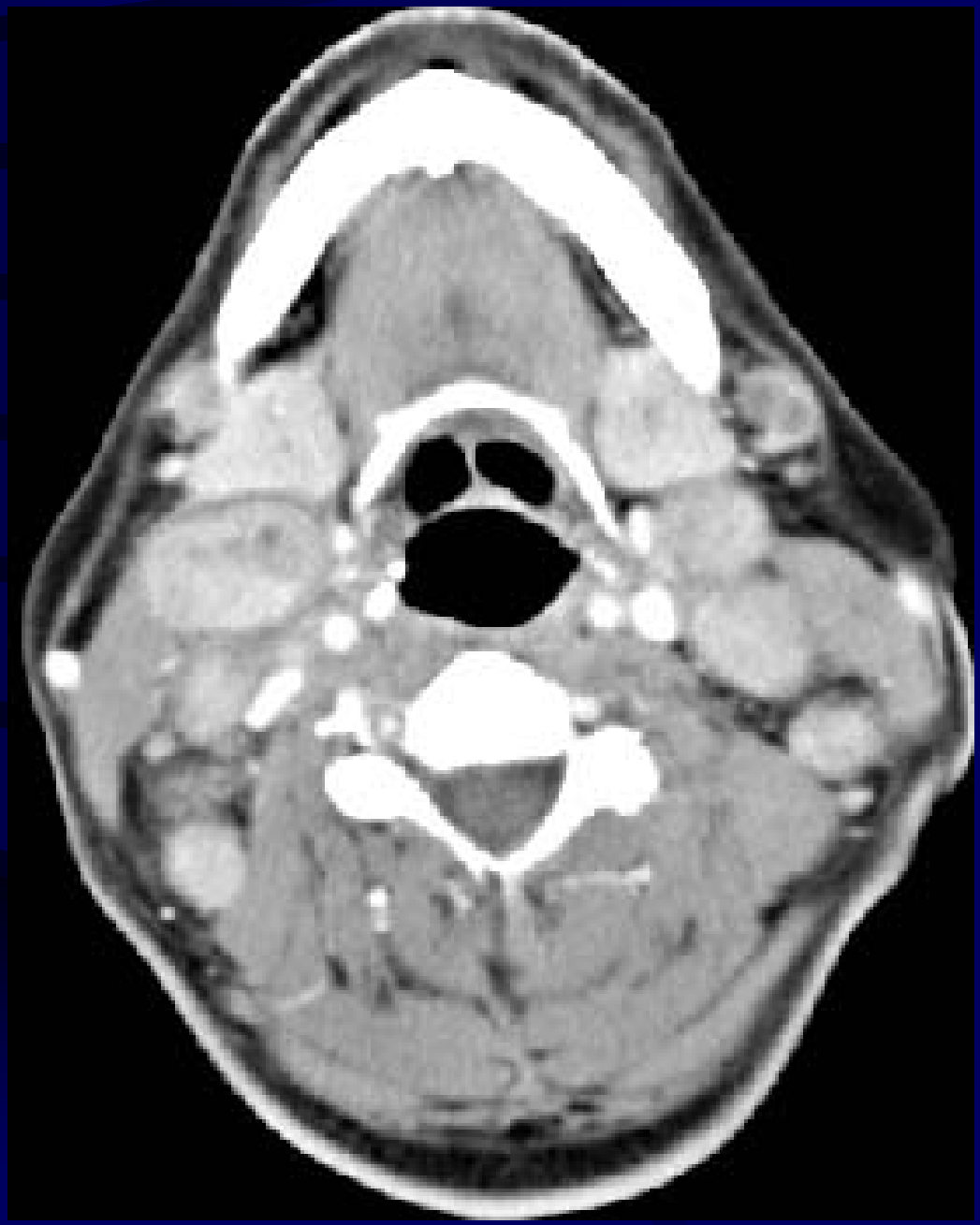
CT Scan of the nasopharynx / neck:

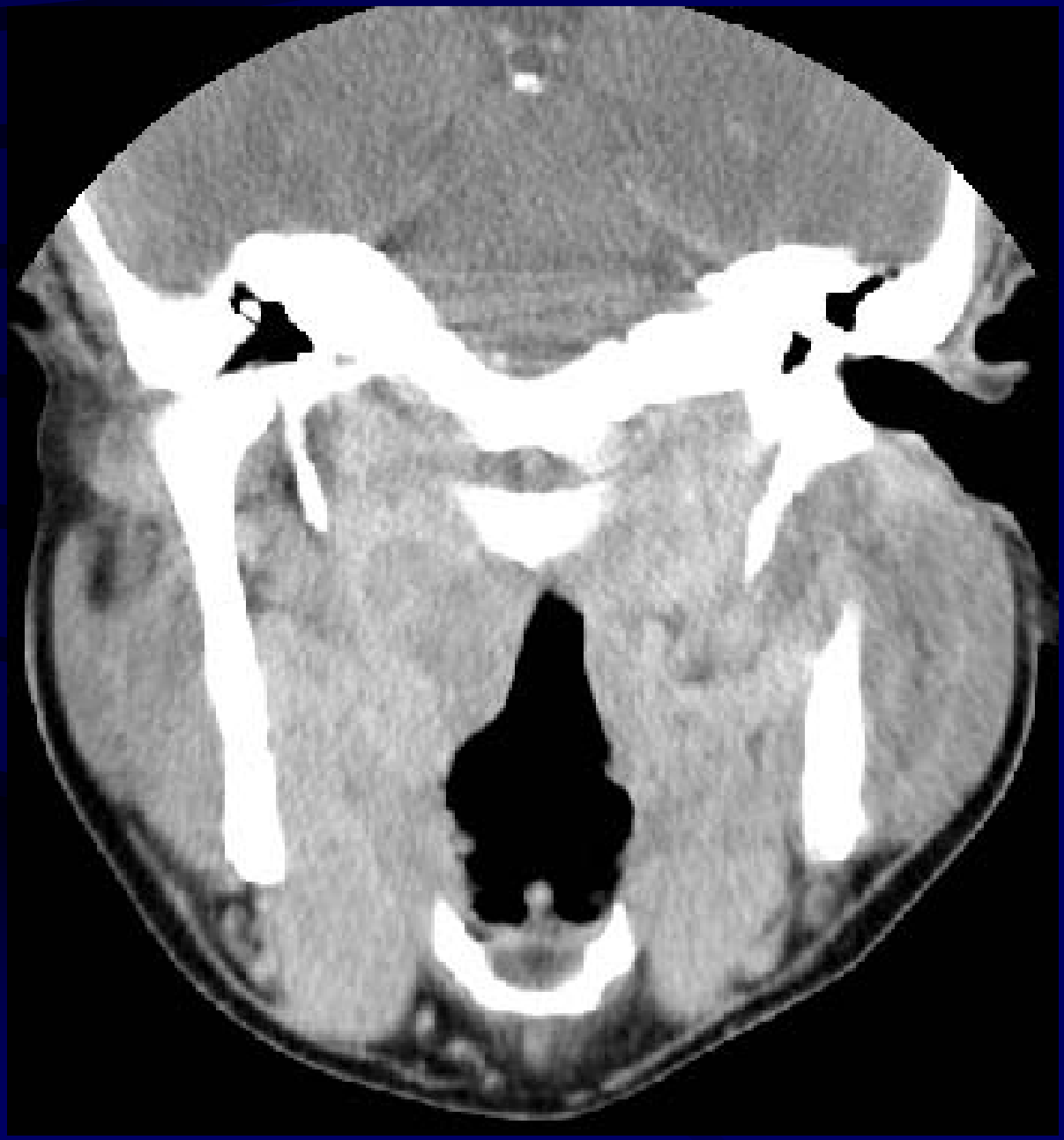
- soft tissue fullness on the right side of nasopharynx extending to the oropharynx with attenuation of ipsilateral parapharyngeal space.

-enlarged lypmh nodes both internal jugular, supraclavicular, posterior cervical, submandibular.









CASE 2:

- **Metastatic work-up : negative**
- **Clinical and radiologic staging:**

  undifferentiated NPCA stage 1VB

  (T2bN3bMx)

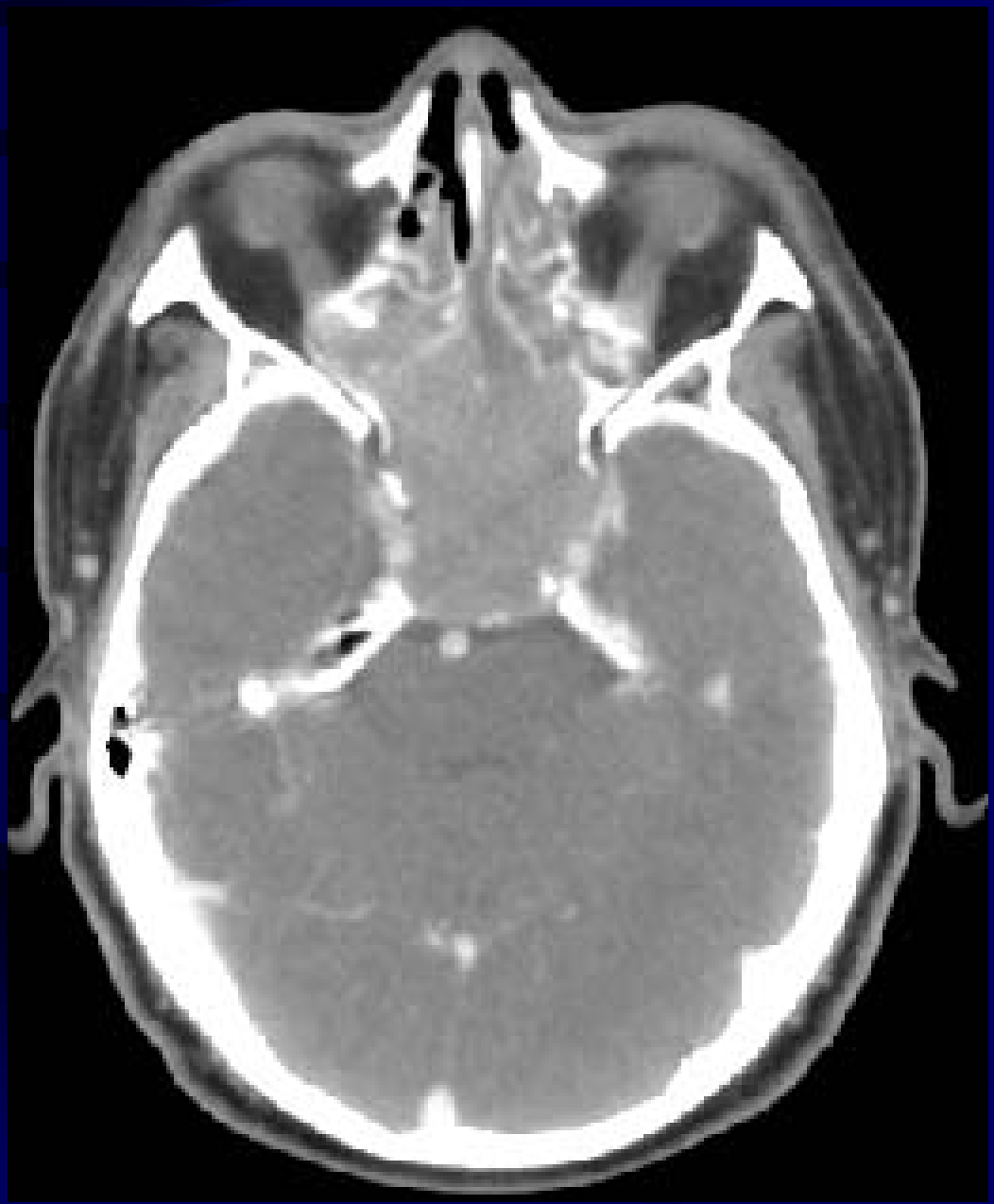
CASE 3:

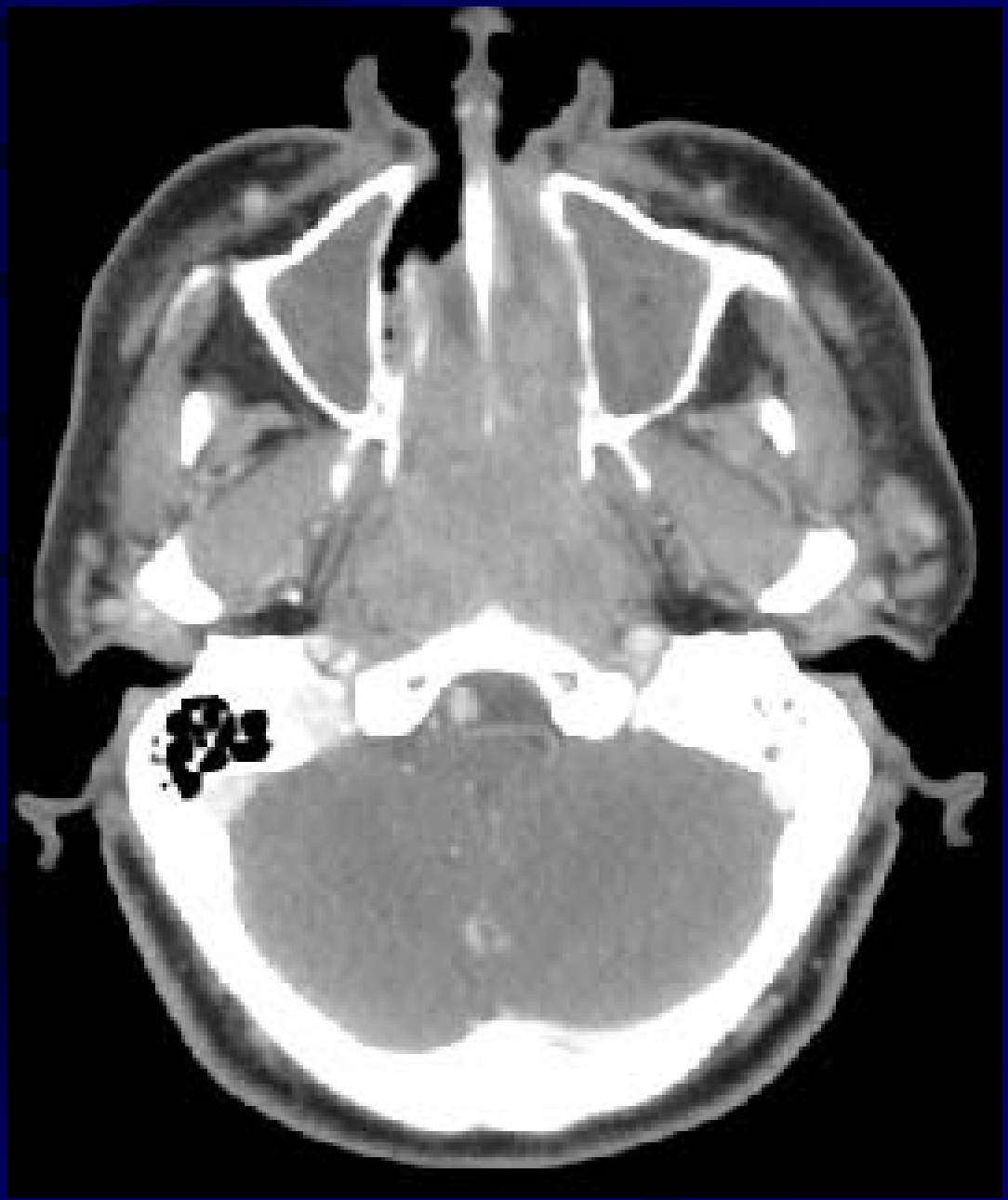
- H.R., 56 year old male
- Chief complaint - bilateral neck mass
  - bilateral rectus muscle palsy
- Biopsy of the neck mass:
  - Undifferentiated CA
  - Cytokeratin(-), LCA (+)

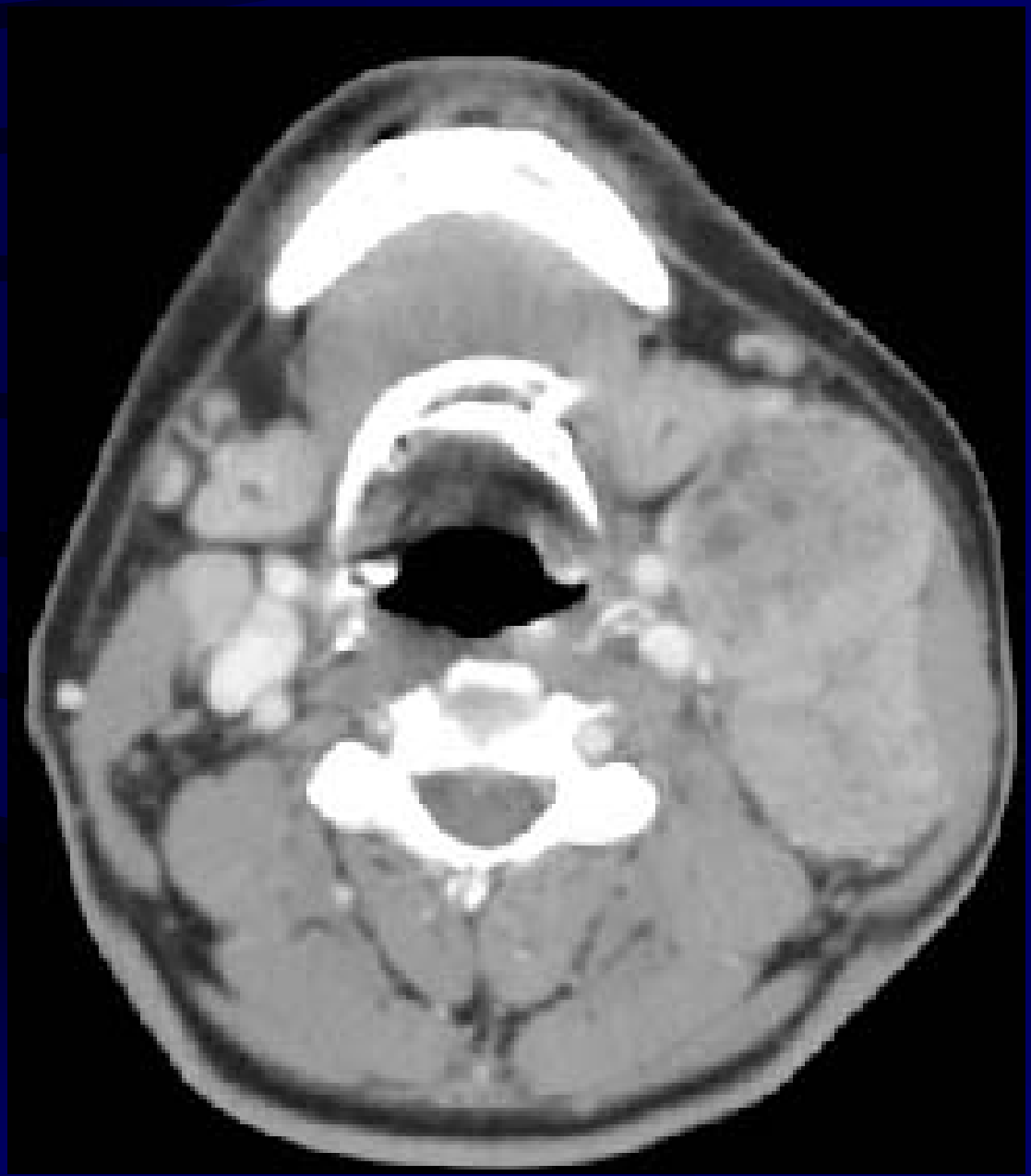
CASE 3

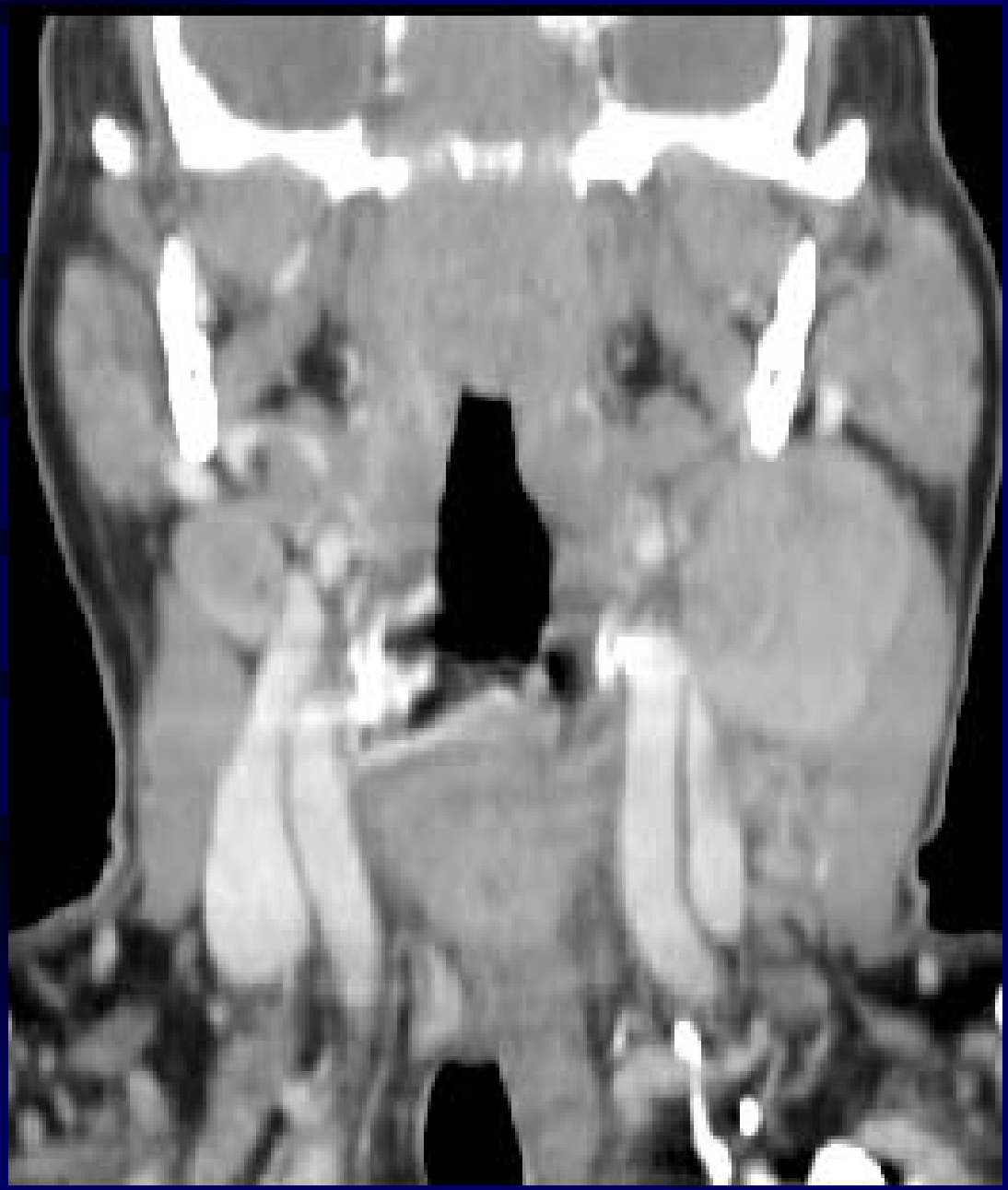
CT Scan of the Nasopharynx/ Neck/ Head

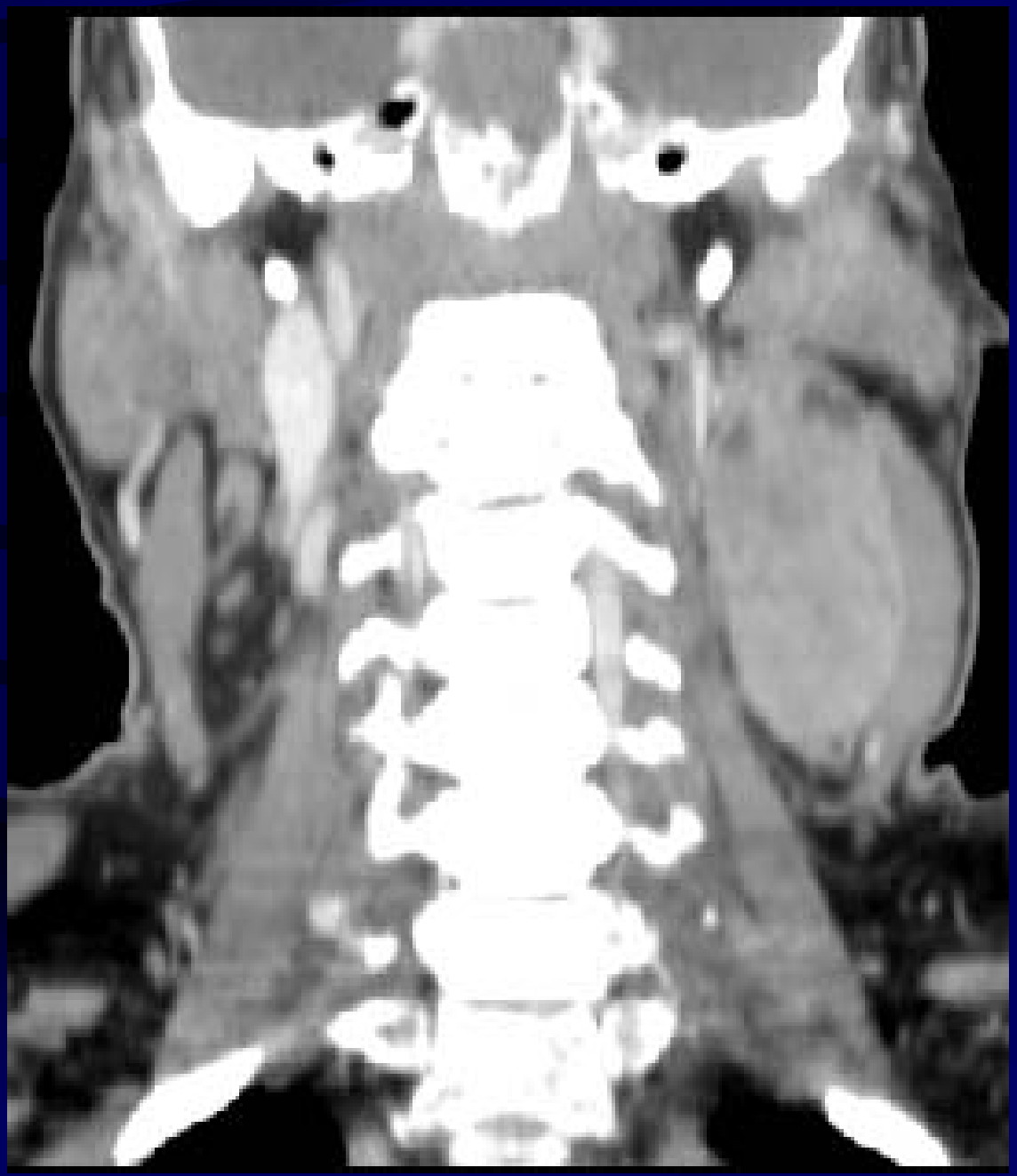
- **Soft tissue fullness obliterating the NP extending to posterior nasal cavity , sphenoid, ethmoid, clivus, prepontine cisterns.**
- **Enlarged lymph nodes in the internal jugular chain, posterior cervical spaces.**











CASE 3:

- **Metastatic work-up: negative**
- **Clinical and radiologic diagnosis:**
  undifferentiated NPCA stage 1VB
  (T4N3bMx).

RESULTS:

All of the 3 patients completed the prescribe dose of chemoradiotx EXCEPT for the 3rd patient with interruption on the *6th* week for *1* week because of grade 3 mucositis.

TOXICITY INTRA-CHEMORT

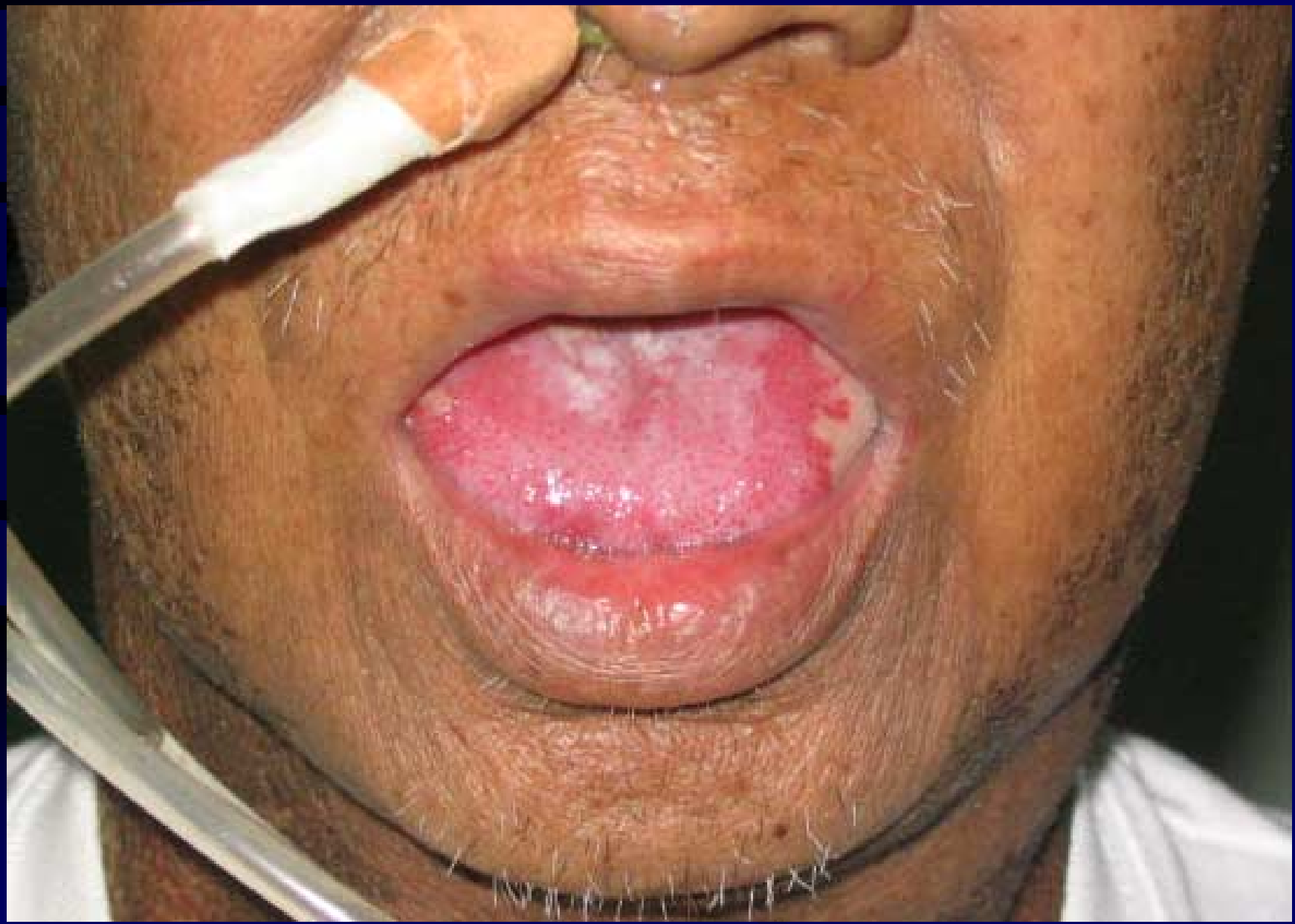
PATIENT 1	WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5	WEEK 6	WEEK 7	WEEK 8
SKIN	0	0	2	2	2	2	3	3
MUCOSITIS	0	0	1	2	2	2	2	2
NAUSEA	0	0	0	0	0	0	0	0
VOMITING	0	0	0	0	0	0	0	0
WEIGHT LOSS	0	0	0	0	0	0	0	0
HEMATOLOGC	0	0	0	0	0	0	0	0

TOXICITY INTRA-CHEMORT

PATIENT 2	WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5	WEEK 6	WEEK 7	WEEK 8
SKIN	0	1	2	3	3	3	3	3
MUCOSITIS	0	0	2	2	2	2	2	2
NAUSEA	0	0	0	0	0	0	0	0
VOMITING	0	0	0	0	0	0	0	0
WEIGHT LOSS	0	0	0	0	0	0	0	0
HEMATOLOGIC	0	0	0	0	0	0	0	0

TOXICITY INTRA CHEMORT

PATIENT 3	WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5	WEEK 6	WEEK 7	WEEK 8
SKIN	0	0	1	2	2	3	2	2
MUCOSITIS	0	1	2	2	2	3	2	3
NAUSEA	0	0	0	0	0	1	0	1
VOMITING	0	0	0	0	0	1	0	1
WEIGHT LOSS	0	0	0	0	0	0	0	0
HEMATOLOGIC	0	0	0	0	0	0	0	0



FOLLOW-UP:

CT Scan due for: Case 1 - Dec. 2003

Case 2- Jan. 2004

Case 3 - Mar. 2004

MARAMING SALAMAT PO!