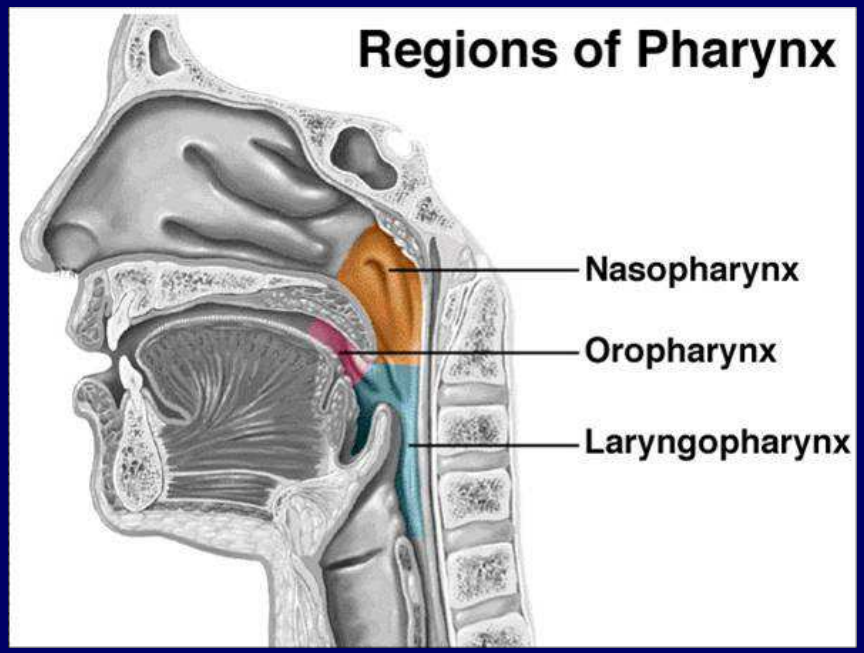
# Evidence Based Management of Nasopharyngeal cancer

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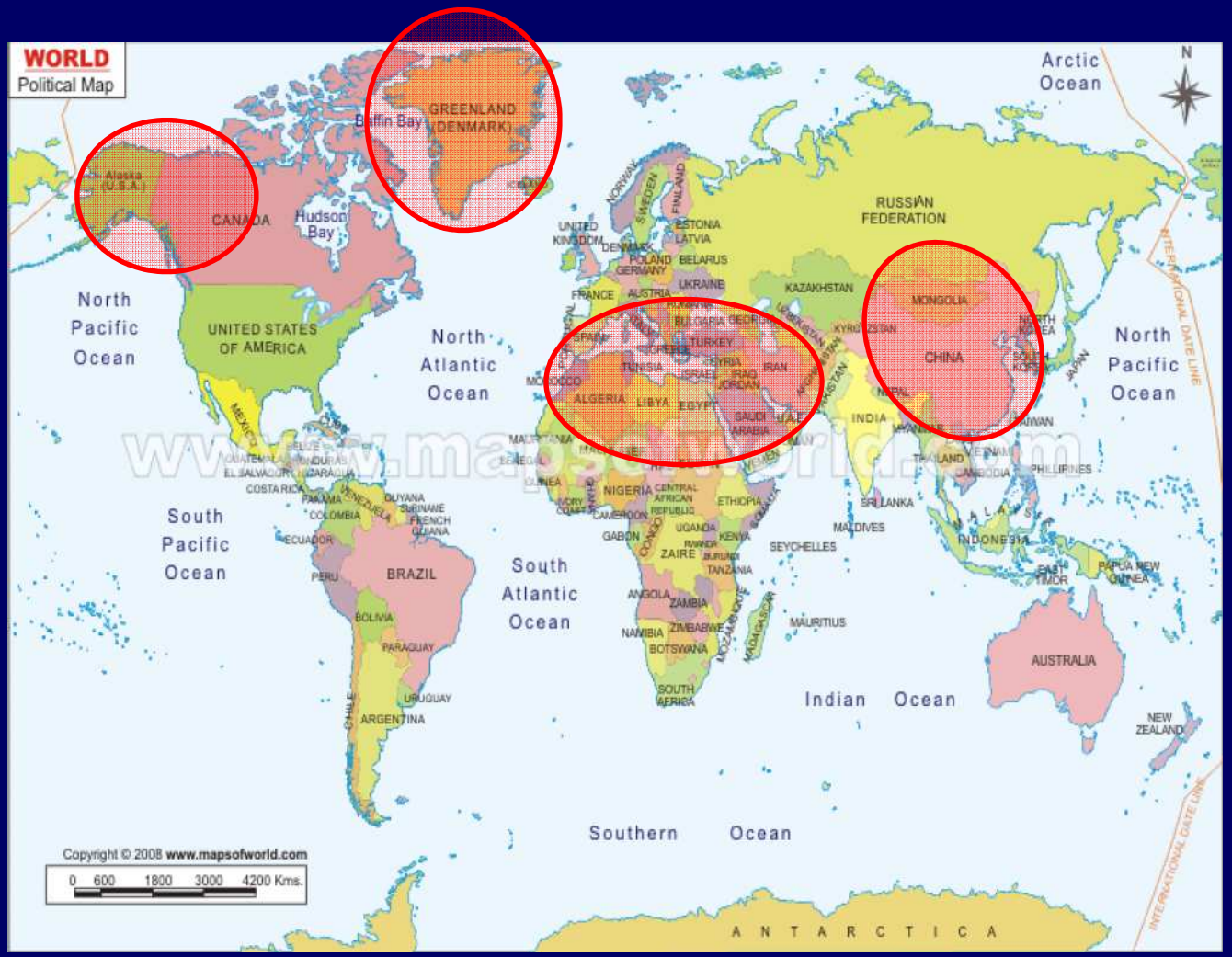
# NPC vis-à-vis other HNC

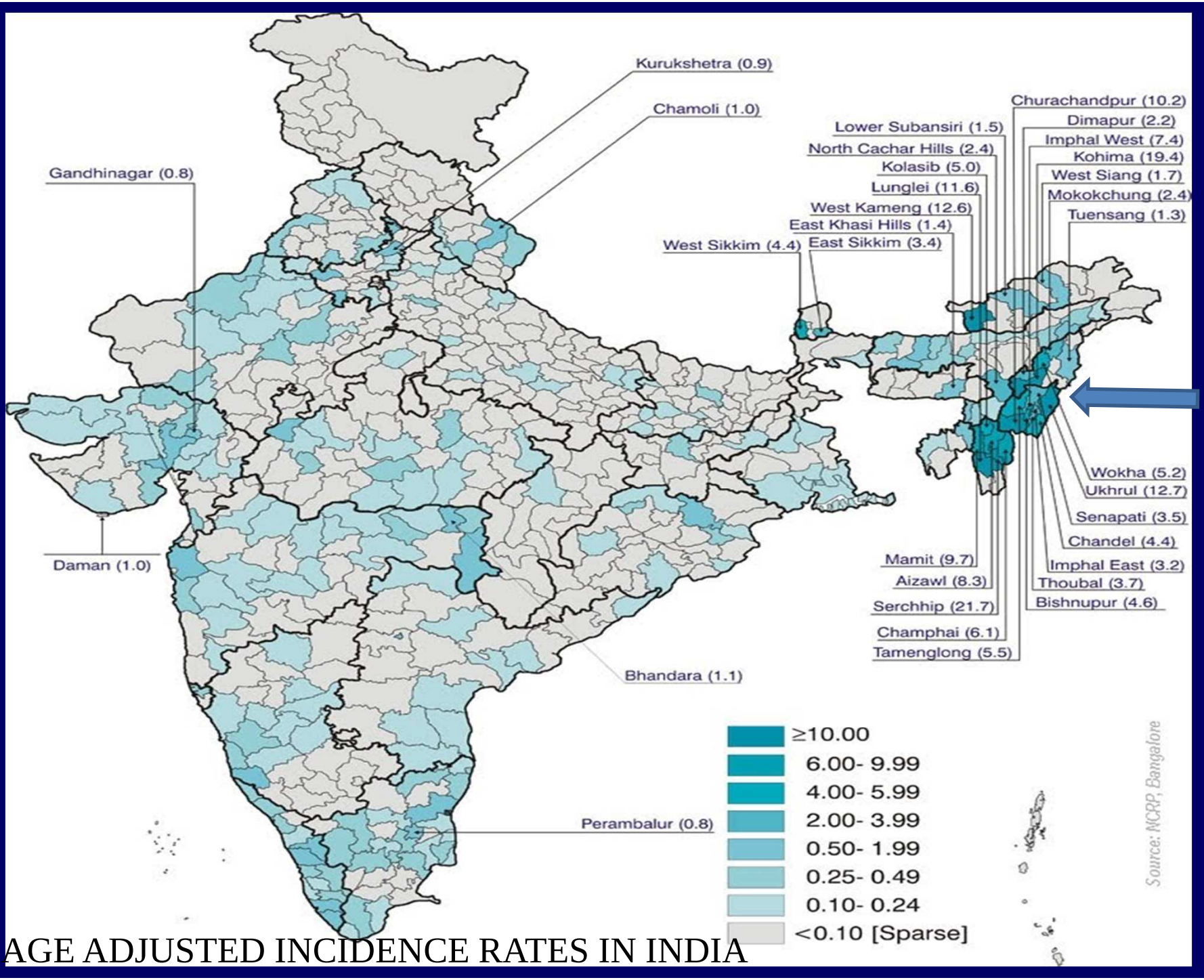
- Rare yet common form of cancer in a few well-defined populations.
- Bimodal age distribution (15-25 yrs. then 50 – 59 yrs.)
- Causation is multifactorial involving environmental, **genetic and familial** and **viral** factors.
- Majority present in advanced stages due to paucity of symptoms.
- Early lymphatic spread and notorious predilection for distant metastases
- Anatomical proximity to critical structures further adds to treatment difficulty, makes surgical extirpation difficult without morbidity. **(THANKFULLY RADIOSENSITIVE!!!!)**

# Endemic Trends

Political map of the world showing areas of high and moderate incidences in the world



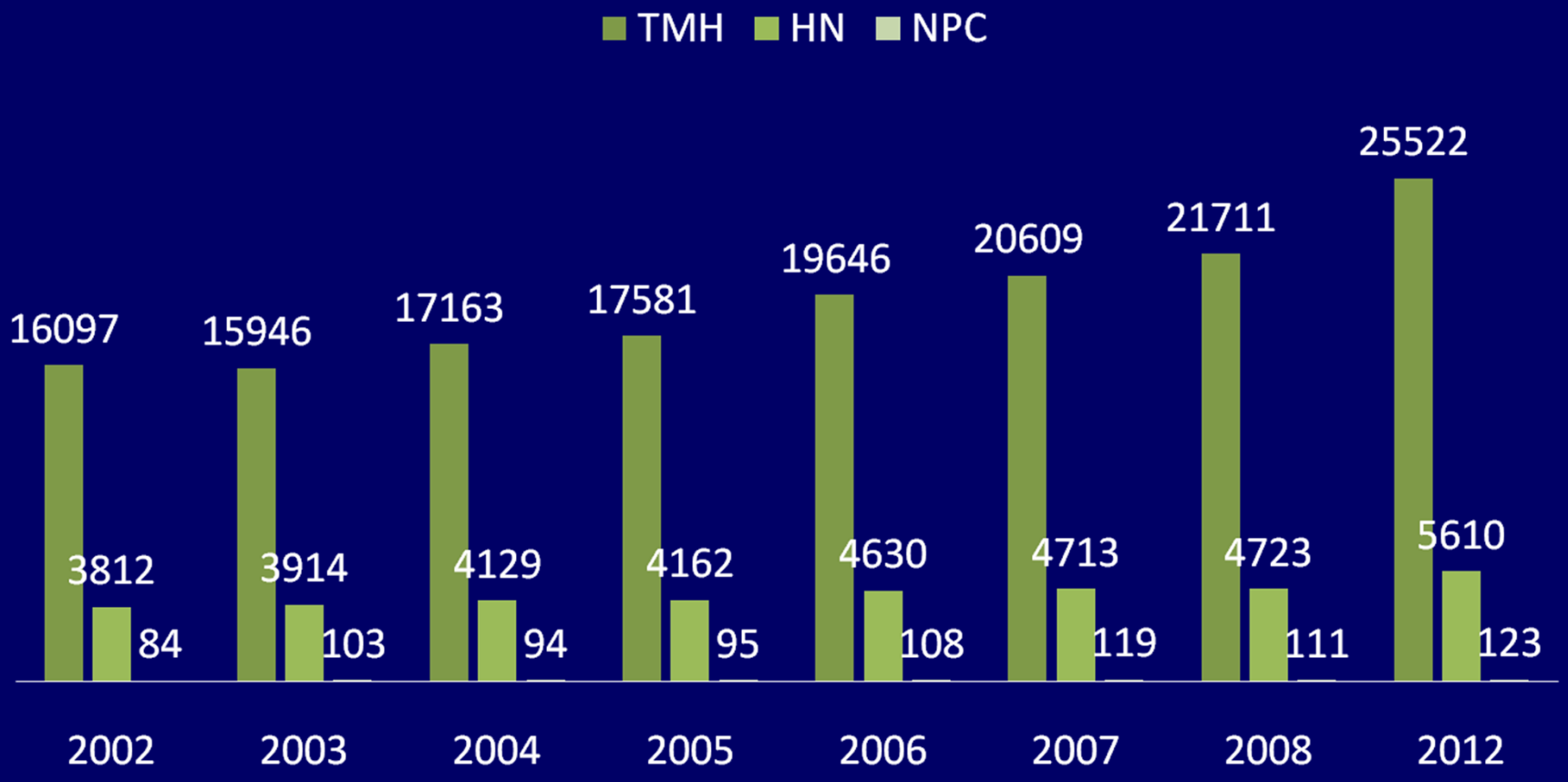

*Mimi C. Yu∗ and Jian-Min Yuan.* **Epidemiology of nasopharyngeal carcinoma.** *Seminars in* ***Cancer Biology, Vol. 12, 2002: pp. 421–429***




AGE ADJUSTED INCIDENCE RATES IN INDIA

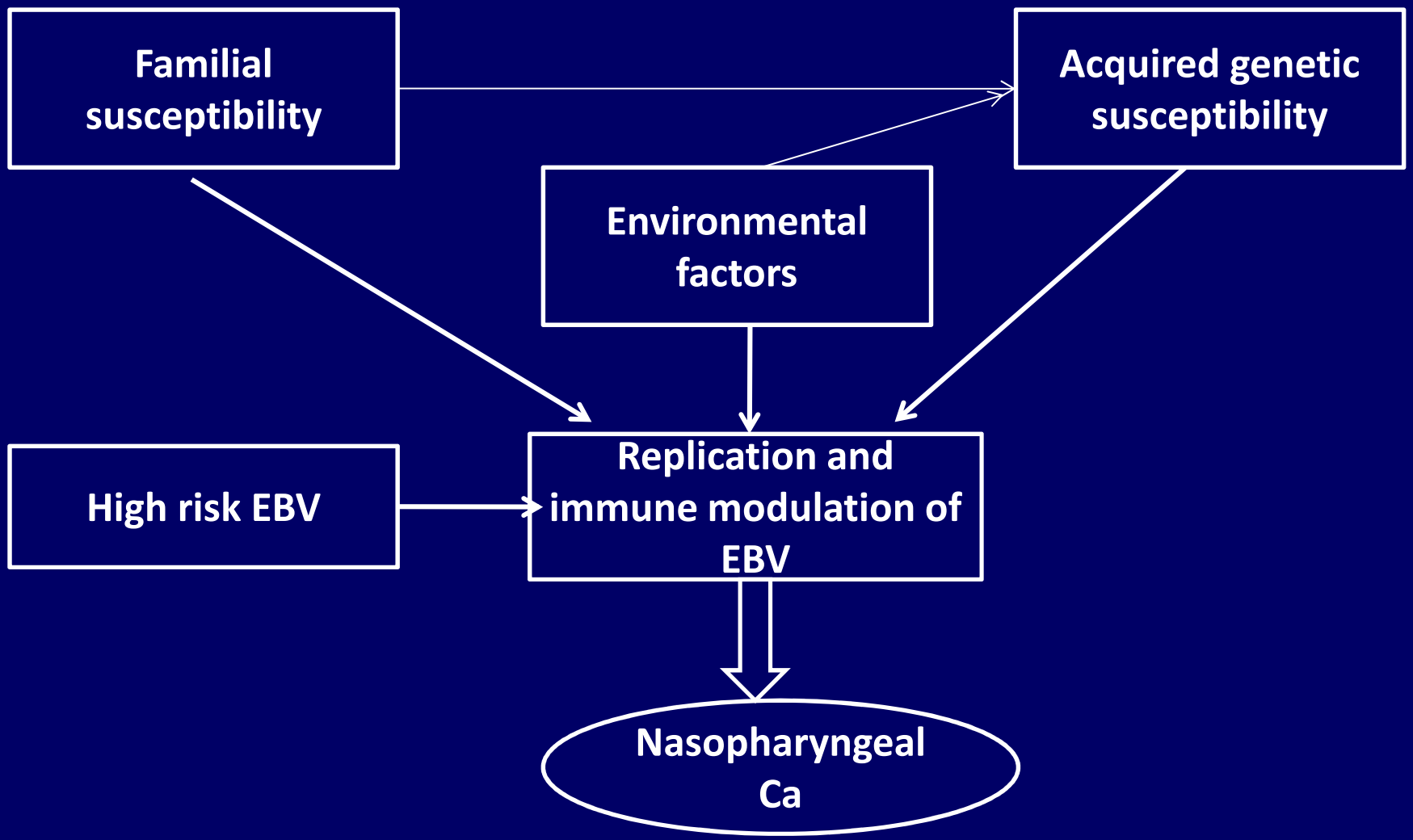
# TMH Statistics

Bar Graph showing the case load of Nasopharyngeal Ca compared to the Head and Neck Ca and total patients at TMH between 2002 – 2012

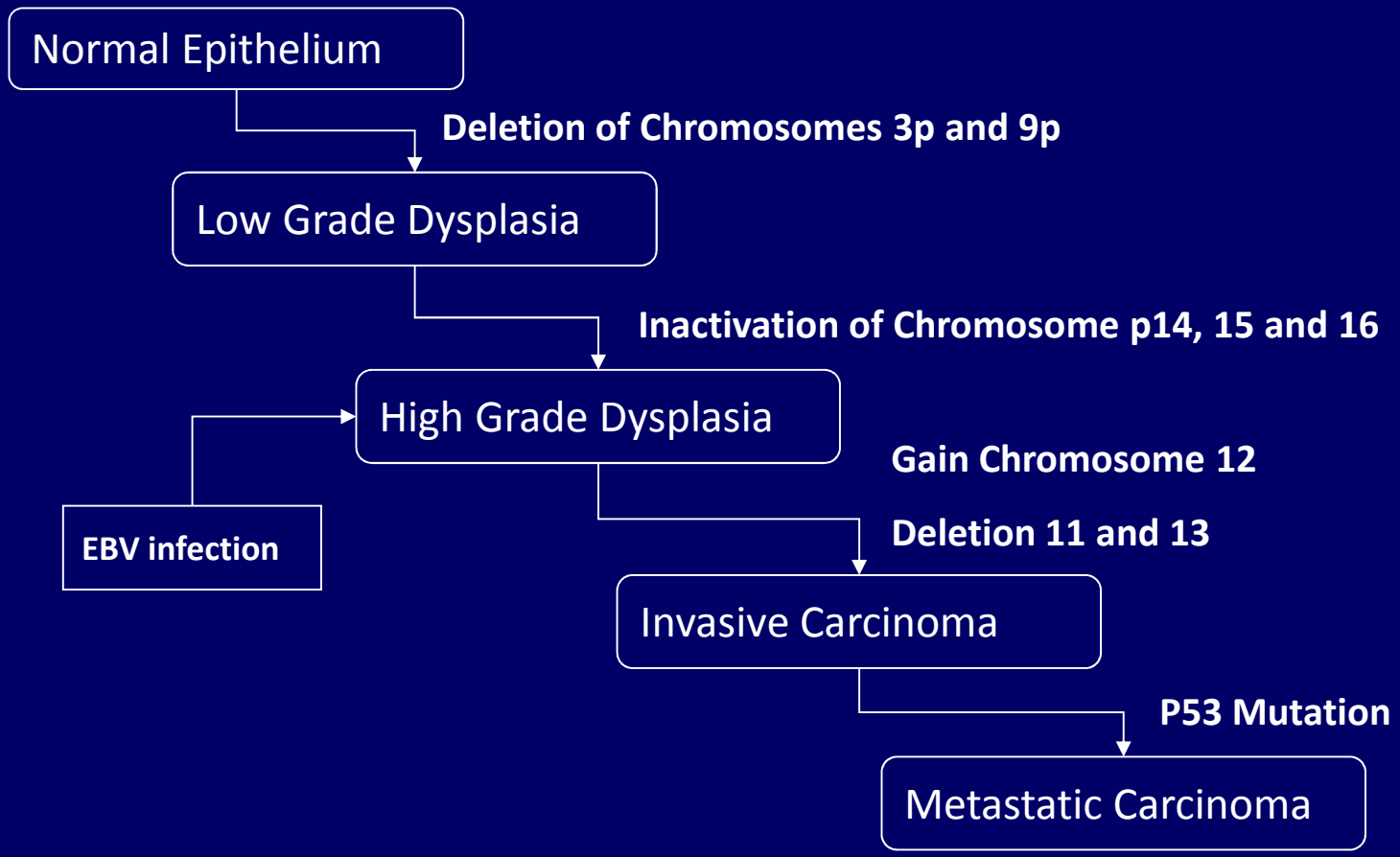



**Unpublished**

# Etiology


Familial susceptibility
Acquired genetic susceptibility
Environmental factors
High risk EBV
Replication and immune modulation of EBV
Nasopharyngeal Ca

# Etiology


Normal Epithelium
Deletion of Chromosomes 3p and 9p
Low Grade Dysplasia
Inactivation of Chromosome p14, 15 and 16
High Grade Dysplasia
EBV infection
Gain Chromosome 12
Deletion 11 and 13
Invasive Carcinoma
P53 Mutation
Metastatic Carcinoma

# EBV

- Premalignant lesions NPx - increased level of EBV – may influence early stage tumorigenesis.
- Tumorigenic potential is due to a set of latent genes: latent membrane proteins (LMP1, LMP2A, and LMP2B) and EBV-determined nuclear antigens (EBNA1 and EBNA2)
- LMP1 is the principal oncogene-mitogen-activated protein kinases, phosphoionositol-3-kinase, nuclear factor *κ*-B, and epidermal growth factor receptor (EGFR)
- LMP1 is also required for cell immortalization and is present in 80% to 90% of NPC tumors.

Brooks L, Yao QY, Rickinson AB, et al *J Virol* 1992;66(5):2689–2697.
Kung CP, Meckes DG Jr, Raab-Traub N *Virol*2011;85(9):4399–4408

- EBV linked to development of NPC through EBV DNA, RNA, and/or gene products in tumor cells of virtually all cases, regardless of geographic origin

- EBV detection in type I NPC has not always been consistent

Table 2. *Analysis of NPC by EBER ISH and LMP-1 Immunostaining*

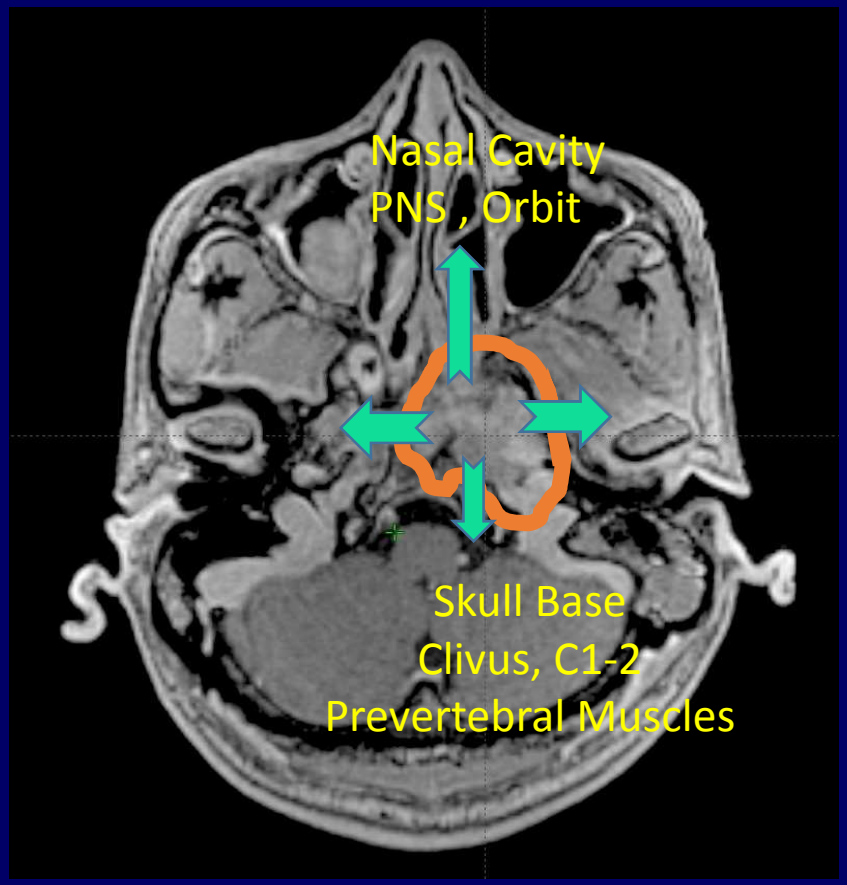
| WHO type | EBER | | LMP-1 | |
|---|---|---|---|---|
| | Number | % | Number | % |
| 1 (well differentiated) | 4/4 | 100 | 2/4 | 50 |
| 1 (moderately differentiated) | 20/20 | 100 | 3/4 | 75 |
| 1 (poorly differentiated) | 7/7 | 100 | 1/1 | 100 |
| 1 (total) | 31/31 | 100 | 6/9 | 67 |
| 2 and 3 | 89/89 | 100 | 30/41 | 73 |
| Total | 120/120 | 100 | 36/50 | 72 |

Pathmanathan R, Prasad U, Chandrika G, Sadler R, Flynn K, Raab-Traub N.: Undifferentiated, nonkeratinizing, and squamous cell carcinoma of the nasopharynx. Variants of Epstein-Barr virus-infected neoplasia. Am J Pathol 1995;146:1355 – 67.

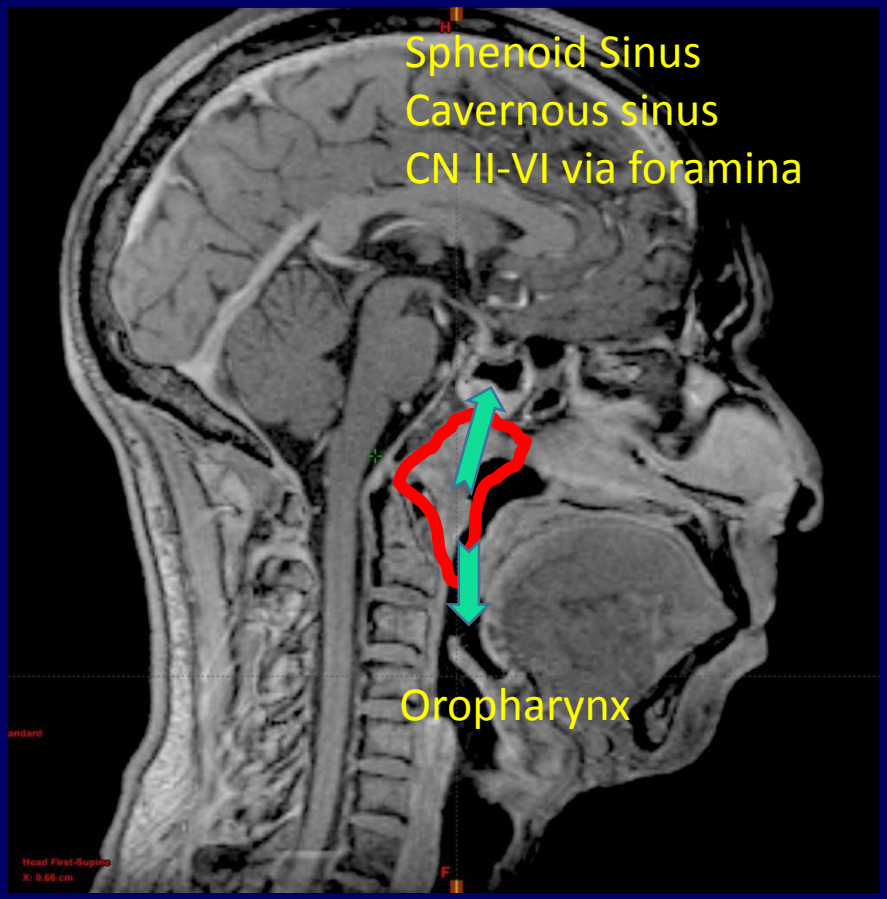
# Patterns of Spread

- Local
- Nodal
- Distant

Sinus of Morgagni →
ParaPharyngeal Space

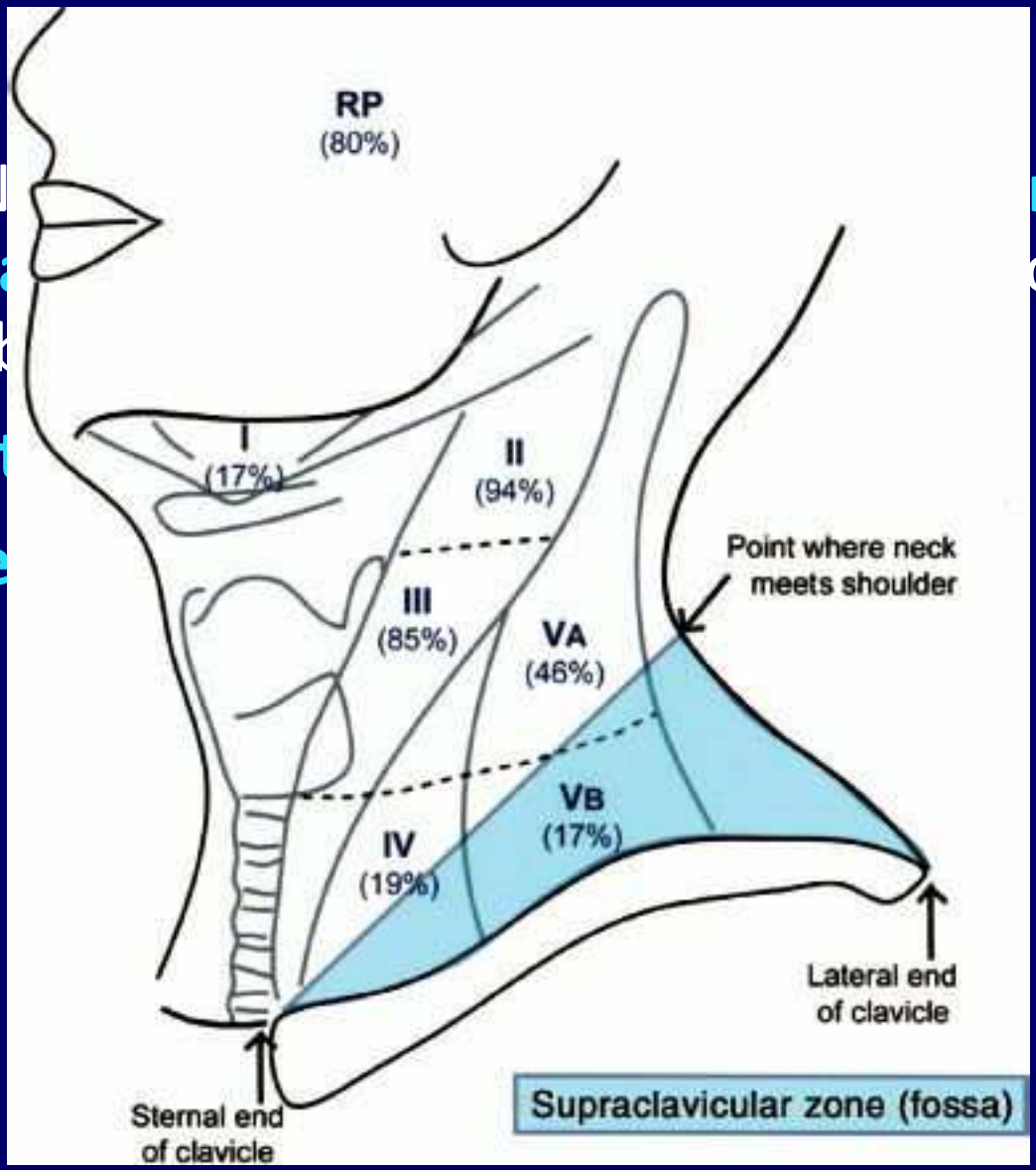



ICA, Pterygoid ms
Middle ear
CN IX-XII


Sphenoid Sinus
Cavernous sinus
CN II-VI via foramina
Oropharynx

# Lymphatic Spread

- The N… **r lymph capilla…** …ous memb…
- **Ipsilat…**
- **Bilate…**



# Hematogenous Dissemination

- Distant metastasis at presentation -3% to 6%
- 18% to 50% of cases during the disease course.
- The rate of distant metastasis is highest
- Advanced neck node metastasis, especially with low-neck involvement.
- Bone > lungs >liver.
- Lung metastasis being associated with better prognosis than other sites (Hui EP, Leung SF, Au JS, et al *Cancer* 2004;101(2):300–306.)

# Clinical Presentation

- Nasopharyngeal carcinoma presents in patients with symptoms in one or more of the following three categories
- (i) neck masses, usually appearing in the upper neck.
- (ii) presence of tumor mass in the nasopharynx (epistaxis, nasal obstruction and discharge).
- (iii) skull-base erosion and palsy of cranial nerves V and VI due to tumor extension superiorly (headache, diplopia, facial pain and numbness).

| Symptom/Sign | Chao and Perez[355] (n = 164) (%) | Lee et al[29] (n = 4768) (%) |
|---|---|---|
| Neck mass | 66 | 76 |
| Enlarged neck node(s) | | 75 |
| Nasal (discharge, bleeding, obstruction) | >37 | 73 |
| Aural (tinnitus, hearing impairment) | 41 | 62 |
| Headache | 40 | 35 |
| Cranial nerve palsy | 23 | 20 |
| Neurologic symptoms | | |
| Ophthalmic (diplopia, squint) | | 11 |
| Facial numbness | | 8 |
| Slurring of speech | | 2 |
| Sore throat | 16 | |
| Weight loss | | 7 |
| Trismus | | 3 |
| Distant metastases | | 3 |
| Dermatomyositis | | 1 |

Incidence Of Cranial Nerve Involvement By Nasopharyngeal Carcinoma At Diagnosis

| Cranial Nerve | Chao and Perez[355] (n = 164) (%) | Chan et al[82] (n = 722) (%) |
|---|---|---|
| I | – | – |
| II | 1.3 | 0.8 |
| III | 3.5 | 1.3 |
| IV | 2.4 | 0.6 |
| V | 7.8 | $V_1$ 3.5; $V_2$, 5.8; $V_3$, 3.9 |
| VI | 13.3 | 5.1 |
| VII | 3.6 | 0.1 |
| VIII | 4.8 | – |
| IX–XII | IX, 2; X, 5.4; XI, 1.3; XII, 4.8 | 2.4 |

# Staging Workup

**Staging Workup**

- Endoscopic examination& biopsy
- MRI face, neck with PNS
- **PET- CT**

or

- Chest X-Ray
- **CT scan / MRI** face, neck, including PNS
- USG abdomen
- Bone scan especially in WHO type IIb

**Other Workup**

- **EBV Titres**
- Dental prophylaxis
- Audiometry & visual field testing
- Nutritional counselling
- Thyroid function

# Pathological Classification

## WHO Classification, 2005

**Carcinoma**

- Type 1 : Keratinizing Squamous cell carcinoma
- Type 2 : Nonkeratinizing carcinoma
  - Type 2.1 : Differentiated subtype
  - Type 2.2 : Undifferentiated subtype
    Lympho-epithelioma (morphological variant)
- Type 3 : Basaloid Squamous cell carcinoma

**Other malignant tumors**

- Papillary Adeno CA
- Plasmacytoma
- Minor salivary gland tumors
- Melanoma
- Rhabdomyosarcoma
- Chordoma
- Lymphoma (NHL, DLBCL)

# Radiographic Studies

MRI better sensitivity than CT

Detection rates of MRI and CT Scan compared

- **IC Extension** 57 % vs. 36 %
- **Skull base involvement** 60 % vs. 40 %
- **Retropharyngeal node** 58 % vs. 21 %
- Prevertebral muscle infiltration 51 % vs. 22 %
- MRI detected bone erosion in all cases, as seen on CT
- **Upstage of T stage in 22%, downstage in 4 %**

Ng, et al. Neuroradiology, 1997

# Radiographic Studies

| Site | Sensitivity (MRI) | Sensitivity (CT) |
|---|---|---|
| Skull base | 60% | 40% |
| Intracranial involvement | 57% | 36% |
| Retropharyngeal node | 58% | 21% |
| Tumor infiltration of prevertebral muscles | 51% | 22% |

The study found a significantly higher sensitivity of MRI compare to CT scan.

T-staging was modified in 27% of patients, with 22% being upstaged and 4% being downstaged.

Ng et al. compared MRI and CT in assessing extent of disease

# Role of PET-CT

- Diagnostic: Local spread of disease

  Regional extent of disease
- Response evaluation
- Prognostic importance
- Treatment intensification

# Metastatic Work-up- Role of PET

PET is a sensitive technique to detect occult mets.

N= 300

**TABLE 2**

Number of Patients by Metastatic Regions and by Scoring of $^{18}$F-FDG PET and CWU

| Metastatic region | No. | Scoring of PET | | | Scoring of CWU | | |
|---|---|---|---|---|---|---|---|
| | | 2 | 1 | 0 | 2 | 1 | 0 |
| Skeleton (+) | 48 | 37 | 9 | 2 | 14 | 2 | 32 |
| Skeleton (−) | 252 | 4 | 65 | 183 | 3 | 4 | 245 |
| Chest (+) | 27 | 22 | 2 | 3 | 6 | 5 | 16 |
| Chest (−) | 273 | 5 | 20 | 248 | 5 | 30 | 238 |
| Liver (+) | 23 | 11 | 1 | 11 | 6 | 2 | 15 |
| Liver (−) | 277 | 0 | 4 | 273 | 1 | 22 | 254 |
| Other (+) | 15 | 10 | 0 | 5 | — | — | — |
| Other (−) | 285 | 0 | 5 | 280 | — | — | — |

Diagnostic Efficacies, Sensitivities, Specificities, and Accuracies of $^{18}$F-FDG PET, CWU, and Their Combination

| Analysis | AUC | Sensitivity (%) | Specificity (%) | Accuracy (%) |
|---|---|---|---|---|
| Patient-based | | | | |
| PET | 0.941 | 82.0 | 97.1 | 94.0 |
| CWU | 0.657 | 32.8 | 96.7 | 83.7 |
| PET + CWU | 0.917 | 83.6 | 93.7 | 91.7 |
| Region-based | | | | |
| Skeleton | | | | |
| PET | 0.940 | 77.1 | 98.4 | 95.0 |
| SS | 0.655 | 29.2 | 98.8 | 87.7 |
| PET + SS | 0.936 | 79.2 | 97.2 | 94.3 |
| Chest | | | | |
| PET | 0.928 | 81.5 | 98.2 | 96.7 |
| CXR | 0.650 | 22.2 | 98.2 | 91.3 |
| PET + CXR | 0.911 | 81.5 | 96.3 | 95.0 |
| Liver | | | | |
| PET | 0.757 | 47.8 | 100 | 96.0 |
| US | 0.643 | 26.1 | 99.6 | 94.0 |
| PET + US | 0.757 | 47.8 | 99.6 | 95.7 |

SS = skeletal scintigraphy; CXR = chest radiography; US = abdominal ultrasonography.

- As distant metastasis is more common in pts with node positive disease it is a standard workup investigation for these patients.
- 13% pt had an impact on management.

Liu et al. PET Can Replace Conv work-up in Met Staging Of NPC: The Journal of Nuclear Medicine; Vol. 48 ; No. 10;October 2007

# Metastatic Work-up- Role of PET

- PET best for metastatic work-up, more so if combined with CT
- 95 patients (85 primary, 10 recurrent CA)
- FDG-PET used in addition to conventional work-up
- Conventional work-up detected metastases in 4 patients, PET detected them in 14

| **Sensitivity** | **100%** |
|---|---|
| Specificity | 90.1% |
| Positive Predictive Value | 63.6% |
| Negative Predictive Value | 100% |

Chang, et al. IJROBP, 2005

# FLUORINE-18 FLUORODEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY/COMPUTED TOMOGRAPHY IMAGING IN PATIENTS WITH CARCINOMA OF THE NASOPHARYNX: DIAGNOSTIC ACCURACY AND IMPACT ON CLINICAL MANAGEMENT

ARIE GORDIN, M.D.,* AVISHAY GOLZ, M.D.,* MARCELLO DAITZCHMAN, M.D.,†
ZOHAR KEIDAR, M.D., PH.D.,‡ RACHEL BAR-SHALOM, M.D.,‡ ABRAHAM KUTEN, M.D.,§
AND ORA ISRAEL, M.D.‡

**Conclusions:** In cancer of the nasopharynx, the diagnostic performance of PET/CT is better than that of stand-alone PET or CI. Positron emission tomography/computed tomography had a major impact on further clinical management in 57% of patients. 

Table 2. Diagnostic accuracy of CT, PET, and PET/CT: Study-based analysis*

| | CT/MRI | PET | PET/CT | *p* |
|---|---|---|---|---|
| Sensitivity (%) | 92 | 92 | 92 | ns |
| Specificity (%) | 15 | 65 | 90 | 0.02, PET vs. CT<br><0.01, CT vs. PET/CT<br>0.06, PET vs. PET/CT |
| PPV (%) | 60 | 76 | 90 | <0.01, CT vs. PET/CT<br>0.06, PET vs. PET/CT |
| NPV (%) | 60 | 86 | 90 | 0.03, PET vs. CT<br>0.02, CT vs. PET/CT |
| Accuracy (%) | 60 | 80 | 91 | 0.02, PET vs. CT<br><0.01, CT vs. PET/CT<br>0.06, PET vs. PET/CT |

*Abbreviations:* CT = computed tomography; PET = positron emission tomography; MRI = magnetic resonance imaging; ns = nonsignificant; PPV = positive predictive value; NPV = negative predictive value.

IJROBP 2007 Jun 1;68(2):370-6. Epub 2007 Feb 26

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Review

# Comparison of (18)F-FDG PET/CT, MRI and SPECT in the diagnosis of local residual/recurrent nasopharyngeal carcinoma: A meta-analysis ☆

Junbao Wei, Su Pei, Xiaodong Zhu *

## SUMMARY

The objective of this study was to assess the overall diagnostic value of MRI, SPECT and (18)F-FDG PET/CT in detecting local NPC residual/recurrence with a meta-analysis. We performed a systematic review with meta-analyses to compare the diagnostic performance of nuclear magnetic resonance Imaging (MRI), single photon emission computed tomography (SPECT) and 18-fluoro-2-deoxyglucose positron emission tomography ((18)F-FDG PET/CT) as imaging modalities for the detection of local residual or recurrent nasopharyngeal carcinoma (NPC). MEDLINE, EMBASE and publisher databases were searched in December 2014. Methodological quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool. Pooled estimation and subgroup analysis data were obtained by statistical analysis. Seventeen studies were included in the meta-analysis. The pooled sensitivity estimates for (18)F-FDG PET/CT (90%) and SPECT (85%) were not significantly higher than MRI (77%) ($p = 0.096$ and 0.164, respectively). The pooled specificity estimates for (18)F-FDG PET/CT (93%) and SPECT (81%) were significantly higher than MRI (76%) ($p = 0.033$ and 0.042, respectively). The pooled DOR (Diagnostic odds ratio) estimates for (18)F-FDG PET/CT (73.27) were significantly higher than MRI (12.09) ($p = 0.019$) while the pooled DOR estimates for SPECT (78.69) were not significantly higher than MRI (12.09) ($p = 0.872$). For (18)F-FDG PET/CT, there were no significant differences between PET–CT and PET on all of the variables including sensitivity, specificity, PLR (Positive likelihood ratio), NLR (Negative likelihood ratio) and DOR ($P > 0.05$). For SPECT, there were no significant differences between 201Tl-SPECT and MIBI-SPECT on all of the variables including sensitivity, specificity, PLR, NLR and DOR ($P > 0.05$). Both (18)F-FDG PET/CT and SPECT are very accurate for the detection of local residual or recurrent NPC, they are superior to MRI in distinguishing recurrent NPC from fibrosis or scar tissue after RT in irradiated fields with distortion of normal architecture. For (18)F-FDG PET/CT, the diagnostic accuracy PET/CT was not significantly different than that of PET alone. For SPECT, 201Tl-SPECT and MIBI-SPECT have the same diagnostic accuracy.

Diagnostic performance for PET/PET–CT, SPET and MRI.

| Subgroup | Summary sensitivity (95% confidence interval) | Summary specificity (95% confidence interval) | Summary LR+ (95% confidence interval) | Summary LR− (95% confidence interval) | DOR (95% confidence interval) |
|---|---|---|---|---|---|
| *SPECT* | | | | | |
| Overall | 0.85(0.77–0.92) | 0.81(0.85–0.95) | 7.21(3.88–13.41) | 0.22(0.14–0.34) | 78.69(29.27–211.55) |
| Thallium-201 | 0.84(0.71–0.93) | 0.89(0.78–0.96) | 7.16(2.54–20.24) | 0.19(0.08–0.47) | 74.42(17.98–308.13) |
| Tc-99 m | 0.87(0.73–0.95) | 0.93(0.84–0.98) | 8.43(3.39–20.97) | 0.19(0.10–0.36) | 82.92(20.91–328.77) |
| *P* | 0.956 | 0.149 | 0.155 | 0.941 | 0.233 |
| *FDG PET/PET–CT* | | | | | |
| Overall | 0.90(0.85–0.94) | 0.93(0.90–0.95) | 8.90(5.75–13.75) | 0.15(0.10–0.21) | 73.27(39.84–134.76) |
| PET | 0.93(0.87–0.97) | 0.92(0.89–0.95) | 8.79(5.36–14.41) | 0.12(0.07–0.21) | 90.12(38.69–209.93) |
| PETCT | 0.85(0.74–0.92) | 0.93(0.89–0.96) | 8.40(2.88–24.54) | 0.17(0.10–0.30) | 53.70(16.16–178.45) |
| *P* | 0.262 | 0.850 | 0.523 | 0.250 | 0.175 |
| *MRI* | | | | | |
| Overall | 0.77(0.70–0.83) | 0.76(0.73–0.79) | – | – | 12.09(2.26–64.60) |
| *P*(MRI *vs.* SPECT) | 0.164 | 0.042 | – | – | 0.872 |
| *P*(MRI *vs.* FDG PET/PET–CT) | 0.096 | 0.033 | – | – | 0.019 |
| *P* (SPECT vs. FDG PET/CT) | 0.554 | 0.789 | – | – | 0.098 |

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Review

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# EBV

- Known fact that high Anti EBV antibodies are expressed in NPC (1970).
- IgA correlates with tumor burden, remission and recurrence.
- Precedes tumor by several years hence forms the basis of screening test in high risk populations.
- EBV is present in the cells of almost all primary & metastatic NPC, regardless of tumor histology, stage of disease, or patient geographic location.
- Plasma EBV DNA quantification has been recommended to follow patients & predict outcome of treatment.
- Independent biomarker to predict survival.

# TNM Staging (AJCC 7th Edition)

| | | | |
|---|---|---|---|
| **Nasopharynx (T)** | | | |
| T1 | Tumour confined to nasopharynx, with or without extension to oropharyngx, nasal cavity but without parapharyngeal extension | | |
| T2 | Tumour with parapharyngeal extension | | |
| T2a | Tumour extends to oropharyngx and/or nasal cavity without parapharyngeal extension | | |
| T2b | Tumour with parapharyngeal extension | | |
| T3 | Tumour invades bony structures of skull and/or paranasal sinuses | | |
| T4 | Tumour with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, orbit or masticator space | | |
| **Regional lymph node (N)** | | | |
| N1 | Unilateral cervical, unilateral or bilateral retropharyngeal lymph node(s), 6_cm or less in greatest dimension, above supraclavicular fossa | | |
| N2 | Bilateral cervica lymph nodes, ≤6 cm in greatest dimension, above supraclavicular fossa | | |
| N3 | Metastasis in lymph node(s), >6 cm in dimension (N3a) or in the supraclavicular fossa (N3b) | | |
| **Distant metastasis (M)** | | | |
| M0 | No distant metastasis | | |
| M1 | Distant metastasis | | |
| **Stage grouping** | | | |
| Stage 0 | T *in situ* | N0 | M0 |
| Stage I | T1 | N0 | M0 |
| Stage II | T1 | N1 | M0 |
| | T2 | N0, N1 | M0 |
| Stage III | T1,T2 | N2 | M0 |
| | T3 | N0, N1, N2 | M0 |
| Stage VIA | T4 | N0, N1, N2 | M0 |
| Stage IVB | Any T | N3 | M0 |
| Stage IVC | Any T | Any N | M1 |

Changes from 6th edition

T2a lesions moved to T1. T2b moved to T2.
Stage IIB was moved to II and Stage IIA merged with Stage I
New designation for retropharyngeal lymph nodes (all are N1 nodes)

**Notes**
More advanced N-stages into lower stage groupings — N1 is stage II instead of III, N2 is III instead of IV

# Prognostic Factors

**Patient**

- Age (Younger age better prognosis)
- Sex (Females better prognosis)

**Tumor**

- Histology subtype
- T stage - Local control and survival
- N stage - Distant metastasis and survival
- Tumour volume
- Imaging: **PET-CT**: pre & post treatment, SUV, MTV, TLG

**Other parameters**

- EBV titres
- EGFR overexpression
- VEGF exp, LDH etc.

**Risk stratification: Individualising treatment, optimising cure, acceptable toxicities**

# Prognostication - Role of PET-CT

# THE ROLE OF PRETREATMENT FDG-PET IN NASOPHARYNGEAL CARCINOMA TREATED WITH INTENSITY-MODULATED RADIOTHERAPY

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**Conclusion: SUVmax is a potential independent prognostic predictor of clinical outcomes in patients with nasopharyngeal carcinoma treated with IMRT alone or with CCRT. A high $^{18}$F-FDG uptake (SUVmax >5) indicates poor outcome in patients with NPC.**

Table 3. Multivariate analysis of clinical and therapeutic variables

| | 5-year LFFS | | 5-year DFS | | 5-year OS | |
|---|---|---|---|---|---|---|
| Variable | HR (95% CI) | *p* value | HR (95% CI) | *p* value | HR (95% CI) | *p* value |
| Sex (M/F) | 1.1 (0.18–7.2) | 0.882 | 0.5 (0.09–2.5) | 0.381 | 1.2 (0.13–12.3) | 0.829 |
| Age, years (≤50/>50) | 1.8 (0.25–12.9) | 0.558 | 5.7 (0.94–34.7) | 0.059 | 1.8 (0.12–27.9) | 0.663 |
| T category (T1–2/T3–4) | 0.9 (0.00–9.9) | 0.966 | 0.2 (0.01–4.3) | 0.320 | 0.6 (0.02–14.8) | 0.753 |
| N category (N0–1/N2–3) | 1.6 (0.00–16.7) | 0.638 | 1.4 (0.03–15.1) | 0.274 | 1.5 (0.01–17.1) | 0.377 |
| Stage (I–II/III–IV) | 0.0 (0.0–39.2) | 0.963 | 1.5 (0.05–47.2) | 0.827 | 0.5 (0.01–34.2) | 0.756 |
| SUVmax category (≤5/>5) | 16.9 (1.6–172) | 0.017 | 268 (13.3–5434) | 0.000 | 10.3 (0.866–122.4) | 0.065 |
| Treatment strategy (RT/CCRT) | 2.1 (0.2–20.9) | 0.520 | 15.3 (0.86–270.9) | 0.063 | 0.0 (0.00–) | 0.977 |

*Abbreviations:* CCRT = concurrent chemotherapy and radiation therapy; CI = confidence interval; DFS = disease-free survival; HR = hazard ratio; LFFS = local failure-free survival; OS = overall survival; RT = radiotherapy; SUVmax = maximum maximum standardized uptake value.

# FDG-PET in Carcinoma Nasopharynx - Can we predict outcomes and tailor therapy based on post radiotherapy FDG-PET?

G. Baijal, S. G. Laskar, V. Rangarajan, S. Shah, M. Sengar, T. Gupta, A. Budrukkar, V. Murthy, P. S. Pai, J. P. Agarwal, *Tata Memorial Centre, Mumbai, India*

**Methods:**

- Patients were classified as Responders (Group A) if there was complete response on PET CT or as Non-Responders (Group B) if there was any uptake above the background activity.

**Results:**

- The DFS at 3 years was 87.3% and 19.7% for Group A and B, respectively ($p < .001$).
- Multivariate analysis revealed Groups to be the only significant factor predicting Disease Free Survival (p-value 0.002 and <0.001 respectively).
- In Group B the commonest site of disease failure was distant.

**Conclusions:**

- PET-CT can be used as a method to evaluate response and , prognosticate in patients with NPC.
- Further to this it may also be used as a tool to select patients for adjuvant therapy.

# FDG-PET in Carcinoma Nasopharynx - Can we predict outcomes and tailor therapy based on post radiotherapy FDG-PET?

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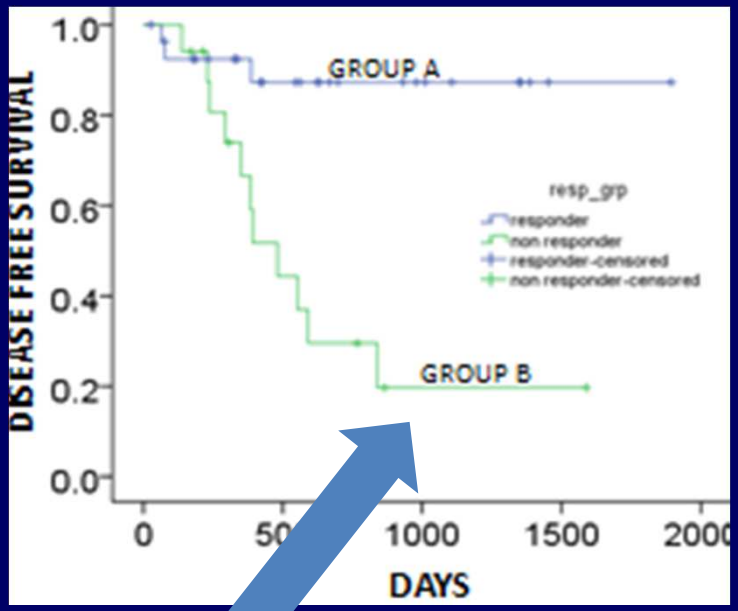
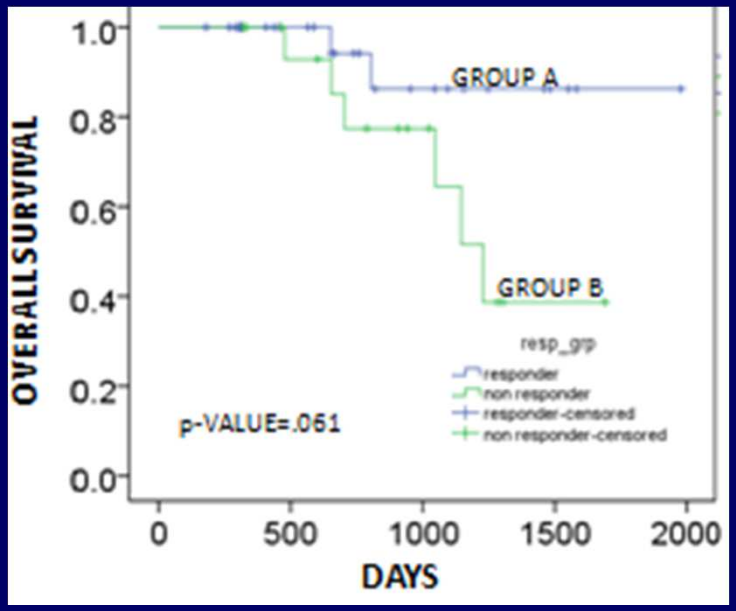



**Do these patients need more treatment?**

G Baijal, S G Laskar, V Rangarajan et al.
FDG-PET in Carcinoma Nasopharynx-Role in Response Evaluation."
Abstract. In proceedings of Cancer Imaging & Radiation Therapy;
2011 April 29-30; Atlanta (GA) USA: CIRT; 2011; p 58; abstr no. 183.

# Clinical impact of metabolic and anatomic imaging in nasopharyngeal carcinoma treated with chemo-radiotherapy

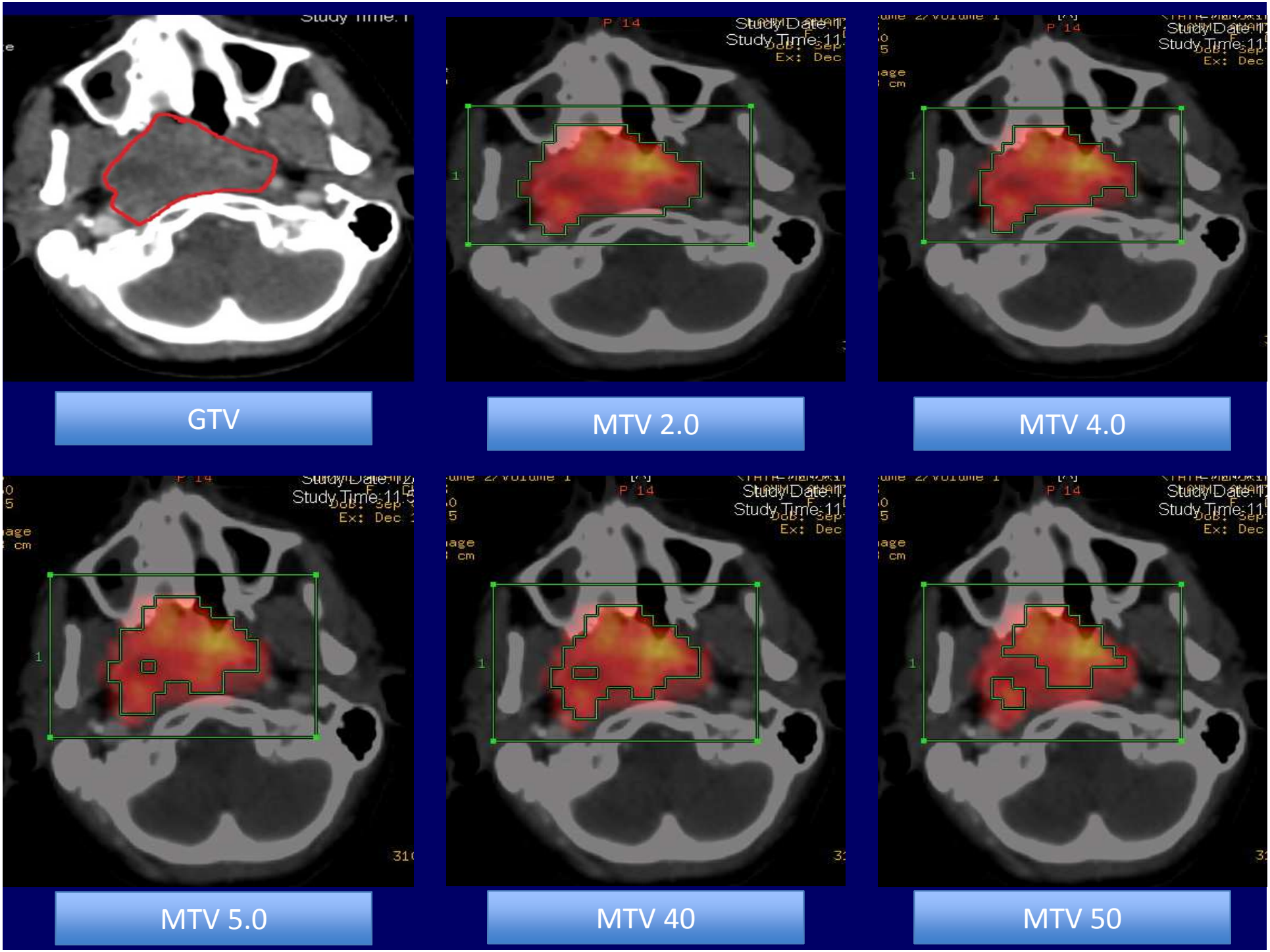
S. Ghosh Laskar[1], A. Pilar[1], N. Purandare[2], V. Rangarajan[2], A. Budrukkar[1], T. Gupta[1], V. Murthy[1]

**Purpose:**

- To correlate anatomic tumour volumes (gross tumour volumes), metabolic tumour volume (MTV) and total lesional glycolysis (TLG) with loco regional control (LRC),disease-free survival (DFS), distant metastases free survival (DMFS) and overall survival (OS).

**Methods:**

- GTV, MTV, and TLG were generated on pre-treatment PET CT. Metabolic response was assessed with post treatment PET CT. Outcome data was collected from hospital records.
- Multiple MTV's were generated using various SUV thresholds.


GTV
MTV 2.0
MTV 4.0
MTV 5.0
MTV 40
MTV 50

Radiotherapy and Oncology
Volume 114, Supplement 1, February 2015, Pages 59
5th ICHNO International conference on innovative approaches in head and neck oncology, 12-14 February 2015, Nice, France

Poster: Imaging

PO-120: Clinical impact of metabolic and anatomic imaging in nasopharyngeal carcinoma treated with chemo-radiotherapy

S. Ghosh Laskar, A. Pilar, N. Purandare, V. Rangarajan, A. Budrukkar, T. Gupta, V. Murthy

doi:10.1016/S0167-8140(15)34880-5

**Results:**

- Nodal GTV, total GTV were significant predictors of DFS, DMFS and OS (hazard ratio range 1.15- 1.20, p value < 0.03).
- **Conclusions:** Nodal volume and GTV significantly impact DFS, DMFS and OS. Total MTV has an impact on DMFS. PMR results in poor local and regional control. There is significant association between total MTV and MR, patients with PMR having higher MTV.
- Post treatment metabolic response (MR) had no impact on DFS, DMFS and OS .
- Patients with partial MR (PMR) had a significantly poorer local control (91% vs. 67% p=0.042) and regional control (96% vs. 71% p=0.016) compared to patients with complete MR (CMR).

# Treatment

- Surgery difficult ; only role in:
  - Biopsy for pathologic diagnosis
  - Salvage for persistent / recurrent disease

- Standard of care is Radical RT ± CT
  - Stage I – II : Radical RT alone
  - Stage IIB – IV : Radical RT + CT

**5 yr OS rates ~ 75 % are attainable now**

- RT dose of 70Gy using conventional fractionation recommended.
- IMRT to be preferred if resources allow.

- Addition of CT to RT is most beneficial in the concurrent setting
- Accelerated fractionation and use of Induction -Concurrent sequence of chemotherapy can be used for improving treatment efficacy in advanced stage tumors

# Treatment

**Staging Workup**
- Endoscopic examination& biopsy
- PET- CT

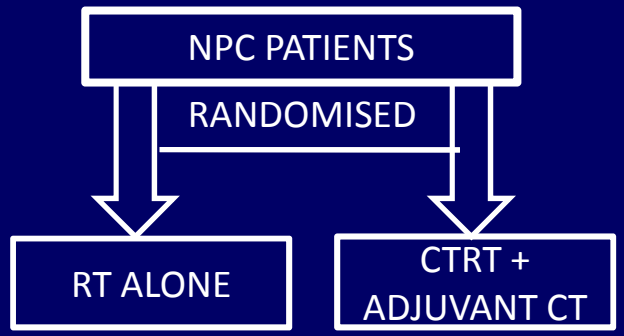
OR
- Chest X-Ray
- CT scan / MRI face, neck, including PNS.
- Bone scan especially in WHO type Iib

**Other Workup**
- EBV Titres
- Dental prophylaxis
- Audiometry & visual field testing
- Nutritional counselling
- Thyroid function

| T1N0M0 | **T2N0M0** | **T3-4N0M0/ANY T N+** | **ANY T ANY N M1** |
|---|---|---|---|
| •**Radical RT alone**<br>•**Lesions classified as T2a by previous staging – CTRT**<br>**Level 1** | •**CTRT level 1**<br>•**Neo Adjuvant CT x 2 cycles + CTRT level2** | •**Neo Adjuvant CT x 2 cycles + CTRT level2**<br>•**CTRT + Adjuvant CT level1**<br>•**CTRT** | •**Platinum based CT as 1st line**<br>•**RT or CTRT**<br>•**Palliative radiotherapy to symptomatic metastatic site or for palliation of progressive locoregional disease**<br>**Level2/3** |

# Chemoradiotherapy Versus Radiotherapy in Patients With Advanced Nasopharyngeal Cancer: Phase III Randomized Intergroup Study 0099

By Muhyi Al-Sarraf, Michael LeBlanc, P.G. Shanker Giri, Karen K. Fu, Jay Cooper, Te Vuong,




| | 5yr DFS | Overall survival |
|---|---|---|
| RT alone | 29% | 37% |
| CT +RT | 58% | 67% |
| P value | < 0.001 | 0.001 |

- Reduction in Loco regional failure &
- Distant failure

- First randomized trial to demonstrate significant survival benefit of combining chemotherapy with RT in NPC.
- Tested both concurrent and adjuvant chemotherapy schedules, however was not designed to separate the benefit from one over the other.
- Poor compliance of patients for adjuvant chemotherapy schedules was an issue.

# Current Standard of care

Chemo radiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099 by **M Al-Sarraf et al, *JCO, vol 16,1310-1317***

| Intergroup 0099 Study n = 147 | TMH Series( CTRT) n = 59 |
|---|---|
| • 3 year PFS : 69% | • 3 year PFS : 77% |
| • 3 year OAS : 78% | • 3 year OAS : 76% |
| • Toxicity: Grade III/IV hematological 12% | • Toxicity : Grade III/IV hematological 13% |
| • Loco regional failure: 12% | • Loco regional Failure: 19% |
| • Isolated Distant metastasis: 9% | • Isolated Distant metastasis:14% |

# CHEMOTHERAPY IN LOCALLY ADVANCED NASOPHARYNGEAL CARCINOMA: AN INDIVIDUAL PATIENT DATA META-ANALYSIS OF EIGHT RANDOMIZED TRIALS AND 1753 PATIENTS

BERTRAND BAUJAT, M.D.,* HÉLÈNE AUDRY, M.SC.,* JEAN BOURHIS, M.D., PH.D.*

**Purpose :** To study the effect of adding chemotherapy to radiotherapy (RT) on OS and EFS for patients with nasopharyngeal carcinoma.

**Results :**

- Absolute gain at 5 years :
  - EFS : 10 % (52 % vs. 42%)
  - OS : 6 % (62 % vs. 56 %)
  - pooled Hazard ratio of death : 0.82 ($p$ 0.006)
- A significant interaction was observed between the timing of chemotherapy and OS ($p$ 0.005), benefit resulting from concomitant chemotherapy.

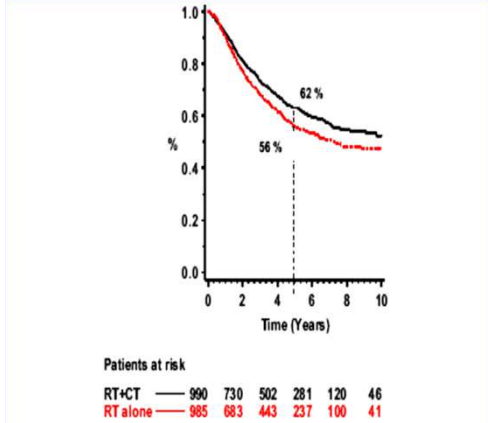



Fig. 2. Kaplan-Meier overall survival curves in radiotherapy (RT) and radiotherapy plus chemotherapy (RT+CT) groups.

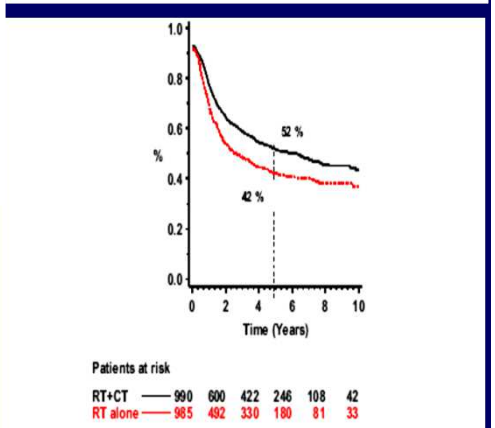
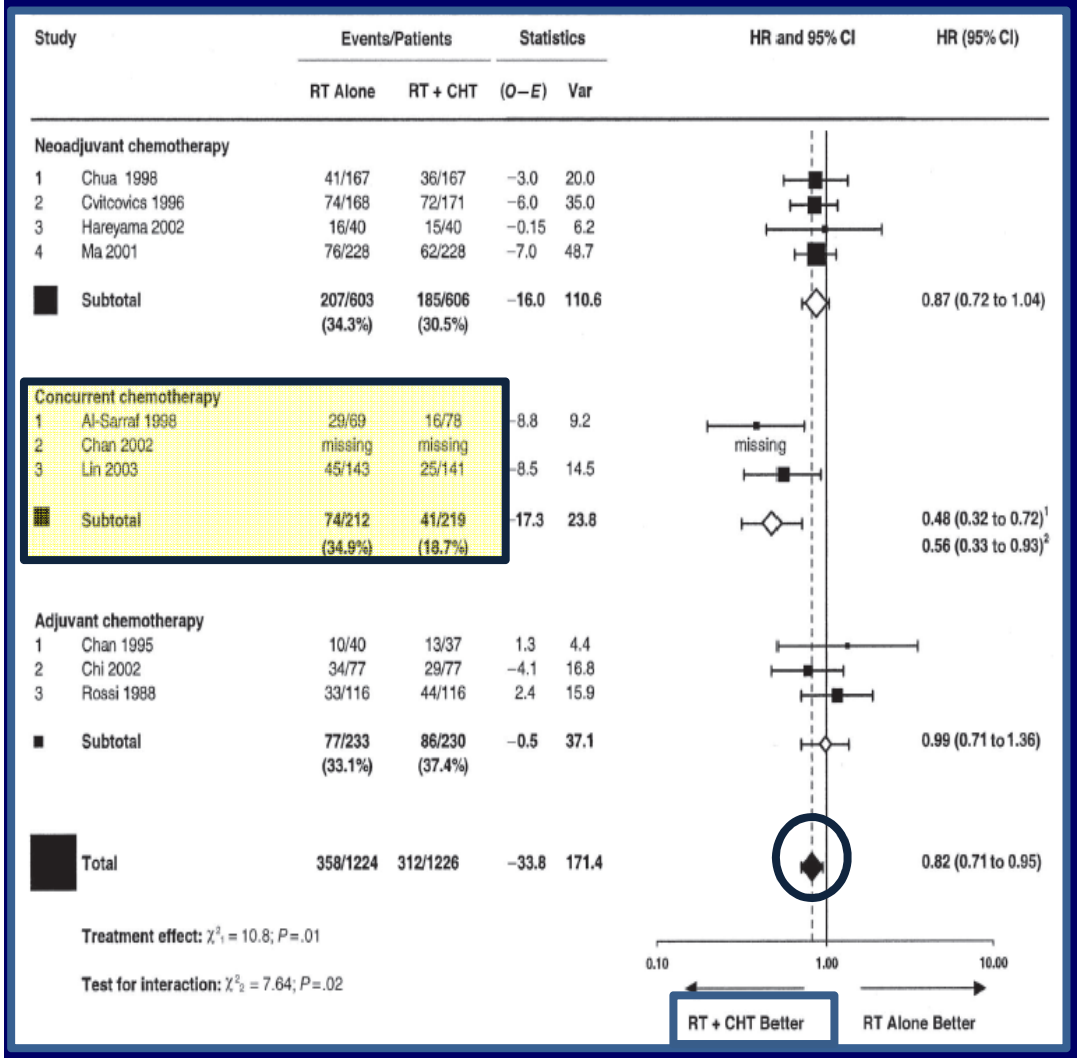



Fig. 4. Kaplan-Meier event-free survival curves in radiotherapy (RT) and radiotherapy plus chemotherapy (RT+CT) groups.

**Conclusion :**

- Chemotherapy led to a small, but significant, benefit for overall survival and event-free survival.
- This benefit was essentially observed when chemotherapy was administered concomitantly with RT.

# Overall Survival



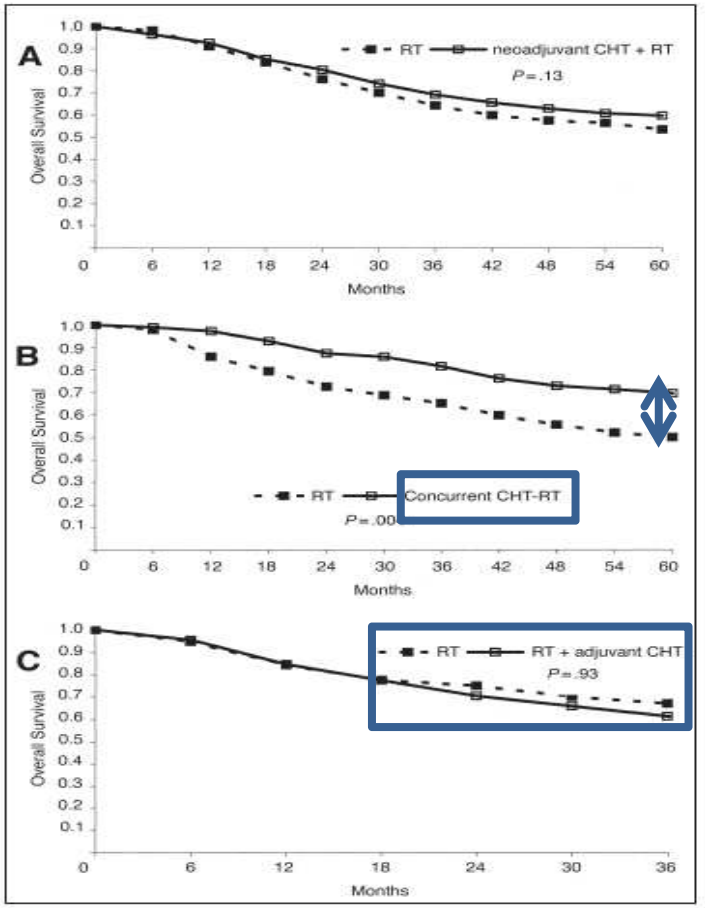
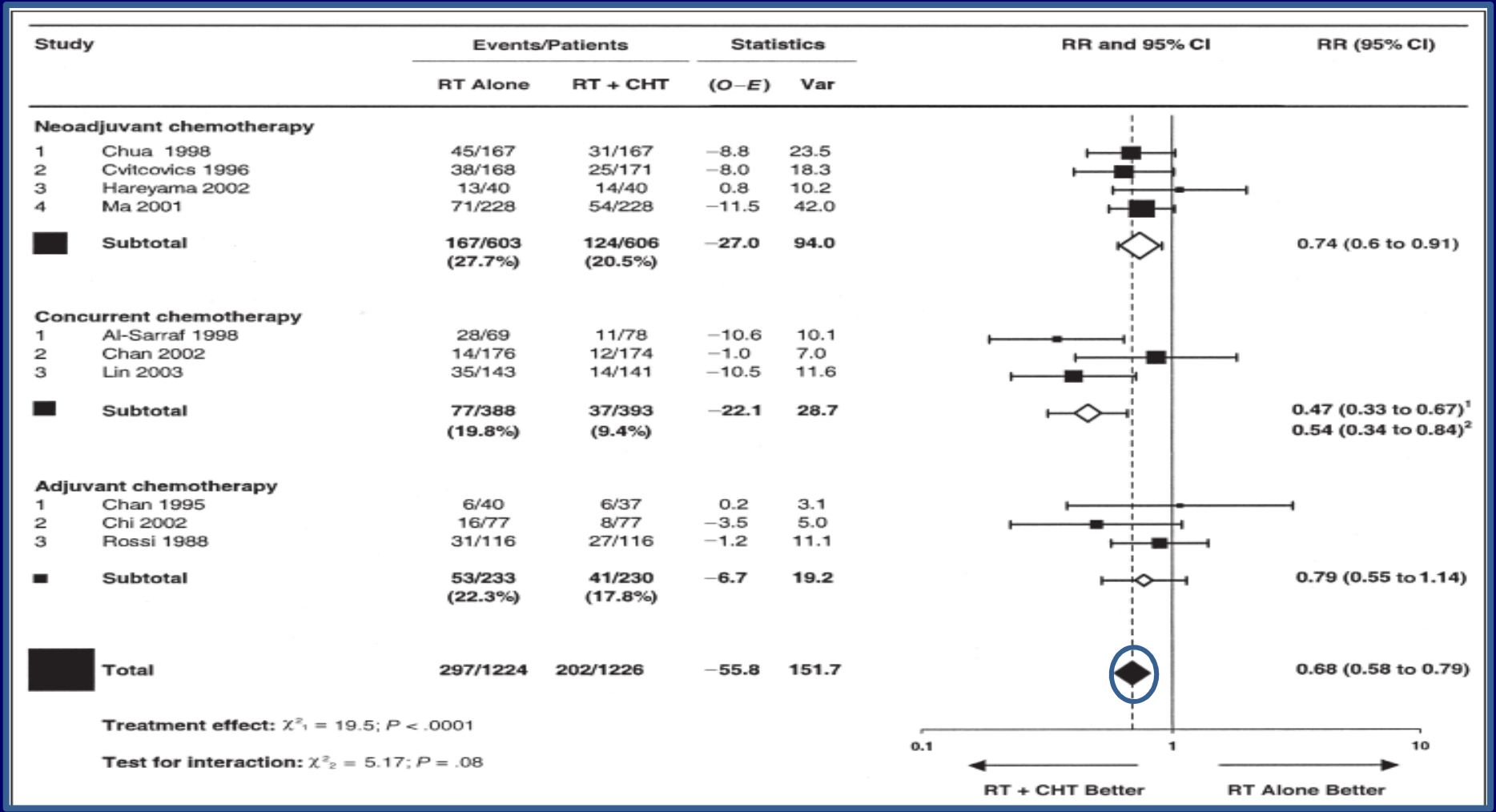
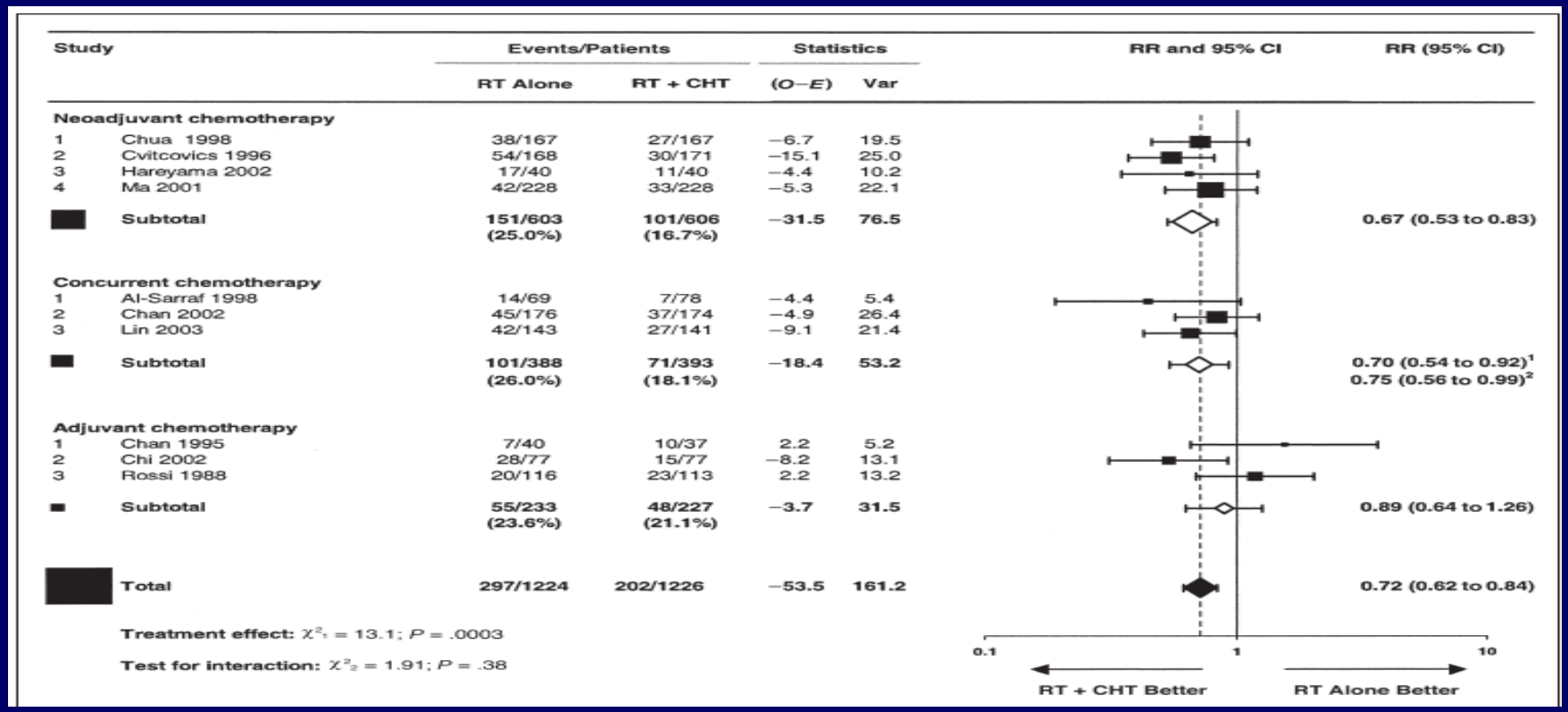




**Fig 2.** Estimated overall survival for (A) neoadjuvant, (B) concurrent, and (C) adjuvant chemotherapy. RT, radiation therapy; CHT, chemotherapy; RT, radiation therapy.

# Locoregional Recurrence



# Distant Metastases



| Study | | Events/Patients | | Statistics | | RR and 95% CI | RR (95% CI) |
|---|---|---|---|---|---|---|---|
| | | RT Alone | RT + CHT | (O−E) | Var | | |
| **Neoadjuvant chemotherapy** | | | | | | | |
| 1 | Chua 1998 | 38/167 | 27/167 | −6.7 | 19.5 | | |
| 2 | Cvitcovics 1996 | 54/168 | 30/171 | −15.1 | 25.0 | | |
| 3 | Hareyama 2002 | 17/40 | 11/40 | −4.4 | 10.2 | | |
| 4 | Ma 2001 | 42/228 | 33/228 | −5.3 | 22.1 | | |
| | **Subtotal** | **151/603 (25.0%)** | **101/606 (16.7%)** | **−31.5** | **76.5** | | **0.67 (0.53 to 0.83)** |
| **Concurrent chemotherapy** | | | | | | | |
| 1 | Al-Sarraf 1998 | 14/69 | 7/78 | −4.4 | 5.4 | | |
| 2 | Chan 2002 | 45/176 | 37/174 | −4.9 | 26.4 | | |
| 3 | Lin 2003 | 42/143 | 27/141 | −9.1 | 21.4 | | |
| | **Subtotal** | **101/388 (26.0%)** | **71/393 (18.1%)** | **−18.4** | **53.2** | | **0.70 (0.54 to 0.92)[1] 0.75 (0.56 to 0.99)[2]** |
| **Adjuvant chemotherapy** | | | | | | | |
| 1 | Chan 1995 | 7/40 | 10/37 | 2.2 | 5.2 | | |
| 2 | Chi 2002 | 28/77 | 15/77 | −8.2 | 13.1 | | |
| 3 | Rossi 1988 | 20/116 | 23/113 | 2.2 | 13.2 | | |
| | **Subtotal** | **55/233 (23.6%)** | **48/227 (21.1%)** | **−3.7** | **31.5** | | **0.89 (0.64 to 1.26)** |
| | **Total** | **297/1224** | **202/1226** | **−53.5** | **161.2** | | **0.72 (0.62 to 0.84)** |

**Treatment effect:** $\chi^2_1 = 13.1$; $P = .0003$

**Test for interaction:** $\chi^2_2 = 1.91$; $P = .38$



The study results show

- Survival benefit for concurrent chemo (absolute benefit of 20% at 3 years)
- No survival benefit for Neoadjuvant or adjuvant chemo.

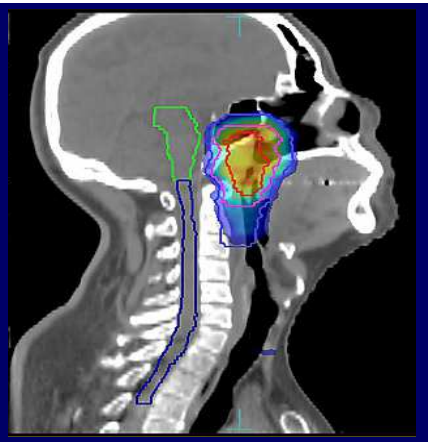
# So what did we know about addition of chemotherapy after MAC-NPC ????

**Table 8.** Randomized Trials Comparing Concurrent Chemoradiotherapy Versus Radiotherapy Alone for Nasopharyngeal Carcinoma

| Author | Al-Sarraf[3,4] | Lin[7] | Chan[24,25] | Kwong[22] | Wee[23] | Current |
|---|---|---|---|---|---|---|
| Toxicity-overall | | | | | | |
| Acute | | | | | | |
| Crude rate, % | 76 *v* 50 | NR | NR | NR | NR | 94 *v* 53 |
| *P* | .01 | | | | | < .01 |
| Late | | | | | | |
| Actuarial rate, % | NR | NR | NR | NR | NR | 28 *v* 13 |
| *P* | | | | | | .02 |

- Improved loco regional control with addition of chemotherapy (80%).
- Improved Distant control with addition of chemotherapy.
- Improved PFS and OS with addition of chemotherapy
- Poor compliance of adjuvant chemotherapy cycles.
- Increased acute and late toxicities
- Benefit was essentially due to concurrently administered CT
- But Role of ACT was left unanswered?

# Era of IMRT – Further Improvement in LRC



- Survival improvements probably do not always relate to the use of chemotherapy.
- Contemporary series enjoy a greater advantage compared with historical results because of advances in tumour imaging and radiotherapy delivery.
- There is little controversy that IMRT is preferred for NPC if resources permit.
- Together with chemotherapy, all IMRT series report excellent results, with local control exceeding 90% at 2-5 years.
- It is impossible to assess the impact of these improvements of RT on previous trial results, and it remains plausible that benefits with chemotherapy may be lesser in the current RT era..

# Modern RT Series: LRC(>90%)

| Author | Chemotherapy (%) | Time (Year) | Tumor Control | | | |
|---|---|---|---|---|---|---|
| | | | Local FFR (%) | Nodal FFR (%) | Distant FFR (%) | OS (%) |
| Lee[64] | 75 | 4 | 97 | 98 | 66 | 88 |
| Kwong[65] | 0 | 3 | 100 | 92 | 100 | 100 |
| Kam[66] | 30 | 3 | 92 | 98 | 79 | 90 |
| Wolden[67] | 93 | 3 | 91 | 93 | 78 | 83 |
| Kwong[57] | 68 | 2 | 96 | | 94 | 92 |
| Lin[68] | 90 | 3 | 95 | 98 | 90 | 90 |
| Tham[69] | 57 | 3 | 90 | — | 89 | 94 |
| Lee[70] | 84 | 2 | 93 | 91 | 85 | 80 |
| Wong[71] | 73 | 3 | 94 | 93 | 87 | 87 |
| Su[72] | 0 | 5 | 97 | 98 | 98 | — |
| Ng[73] | 84 | 2 | 95 | 96 | 90 | 92 |
| Bakst[63] | 100 | 3 | 91 | 91 | 91 | 89 |
| Xiao[74] | 100 | 5 | 95 | — | — | 75 |
| Lai[75] | 81 | 5 | 93 | 97 | 84 | — |
| Ma[76] | 100 | 2 | 93 | | 93 | 90 |

# Evolution of treatment for nasopharyngeal cancer – Success and setback in the intensity-modulated radiotherapy era

Anne W.M. Lee [a,*], Wai Tong Ng [b], Lucy L.K. Chan [b], Wai Man Hung [b], Connie C.C. Chan [b], Henry

- **Purpose :** To assess the therapeutic gains and setbacks as we evolved from the 2-dimensional radiotherapy (2DRT) to conformal 3-dimensional (3DRT) and to intensity-modulated (IMRT) era.
- **Results :**
  - The 3DRT era achieved significant improvement L-FFR,DSS and OS. Neurological damage and bone/soft tissue necrosis were significantly reduced. However, the improvement in D-FFR was insignificant.
  - IMRT era achieved significantly higher D-FFR, but L-FFR did not show further improvement.
  - 5-Year DSS increased from 78% in the 2DRT, to 81% in the 3DRT, and 85% in the IMRT era, while the corresponding neurological toxicity rate decreased from 7.4% to 3.5% and 1.8%.

**Conclusions:**

- Significant improvement in survival and reduction of serious toxicity was achieved as we evolved from 2DRT to 3DRT and IMRT era.
- L-FFR reached a plateau in the 3DRT era, and it is worrisome that the result for T4 remained unsatisfactory

| Endpoints | 5-year rate (%) | | | Comparison with 2DRT (p value) | |
|---|---|---|---|---|---|
| | 2DRT | 3DRT | IMRT | 3DRT | IMRT |
| Part A. Treatment efficacy | | | | | |
| Local failure-free Rate | | | | | |
| T1–2 | 85 | 94 | 92 | 0.005 | 0.16 |
| T3–4 | 74 | 84 | 83 | 0.002 | 0.022 |
| Distant failure-free rate | | | | | |
| Stage I–II | 92 | 93 | 94 | 0.71 | 0.74 |
| Stage III–IV | 74 | 81 | 82 | 0.17 | 0.012 |
| Disease-specific survival | | | | | |
| Stage I–II | 91 | 93 | 94 | 0.067 | 0.56 |
| Stage III–IV | 69 | 79 | 84 | 0.002 | <0.001 |
| Overall Survival | | | | | |
| Stage I–II | 87 | 88 | 91 | 0.021 | 0.75 |
| Stage III–IV | 60 | 71 | 79 | 0.001 | <0.001 |

| Endpoints | 5-year rate (%) | | | Comparison with 2DRT (p value) | |
|---|---|---|---|---|---|
| | 2DRT | 3DRT | IMRT | 3DRT | IMRT |
| Part A. Treatment efficacy | | | | | |
| Part B. Major late toxicity | | | | | |
| All neurological toxicity (any grade) | 7.4 | 3.5 | 1.8 | 0.001 | 0.001 |
| Temporal lobe necrosis | 2.5 | 1.8 | 0.2 | 0.016 | 0.081 |
| Brainstem damage | 0.5 | 0 | 0 | 0.070 | 0.15 |
| Cranial neuropathy | 4.7 | 2.1 | 1.6 | 0.020 | 0.010 |
| Soft tissue/bone necrosis (grade $\geqslant$ 3) | 2.6 | 0.6 | 0.5 | 0.007 | 0.017 |
| Hearing impairment (grade $\geqslant$ 3) | 10.1 | 19.2 | 17.2 | <0.001 | 0.004 |
| Massive bleeding (grade $\geqslant$ 3) | 0 | 0.3 | 0.2 | 0.74 | 0.42 |

- The improvement in tumour control is attributed not merely to changing RT technique and dose, but also improving accuracy in delineation of tumour extent with advances in imaging technology, increasing use of more potent chemotherapy in patients with advanced disease.

- The independent impact of chemotherapy is particularly difficult to assess, since most patients with advanced disease in the IMRT era received chemotherapy

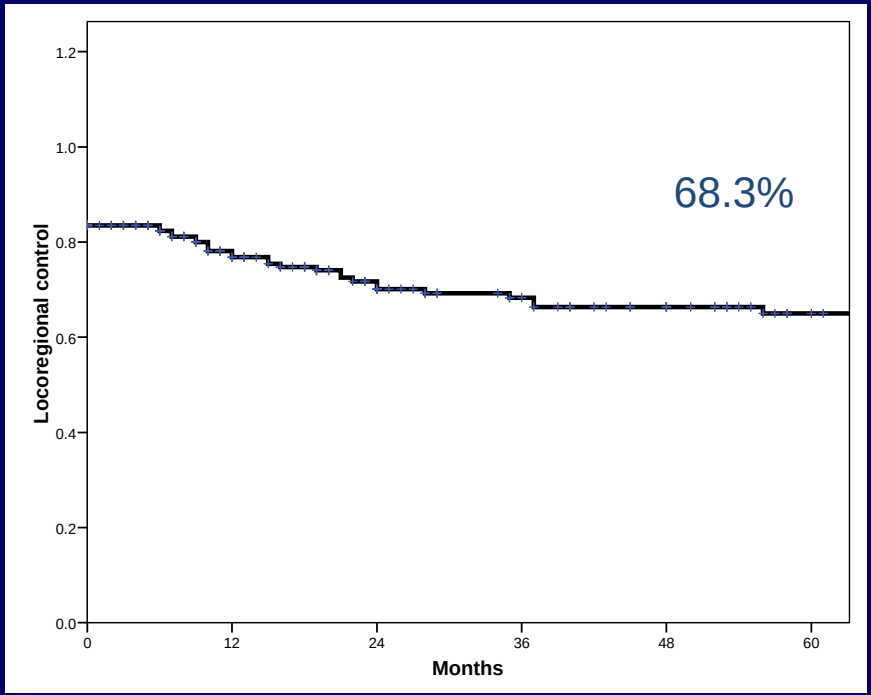
# TMH IMRT-Series (113pts)

- Median age: 46years (range 18-85yrs).
- MC histology: Undifferentiated carcinoma(95%).
- Median follow up: **27months** (range 6-78months).
- 101 patients alive at last follow up.
- 3 year estimated loco regional control **(LRC): 86%**
- 3 year estimated distant metastases free survival **(DMFS): 81%**
- 3 year estimated overall survival **(OS): 87%**

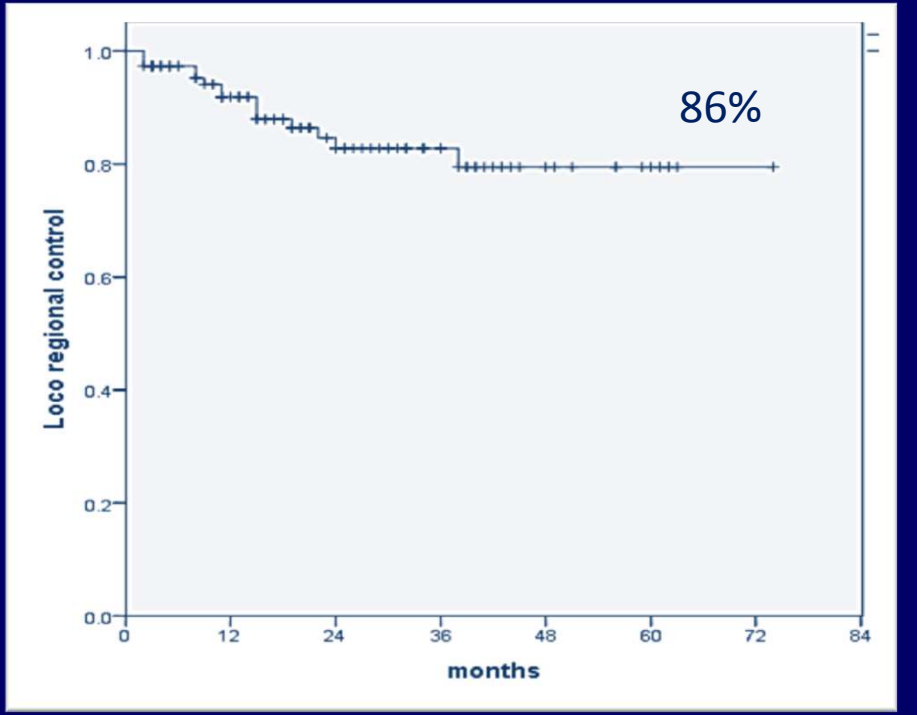
Unpublished

# TMH- 2D Era vs. IMRT

3- year Loco regional control - 2DRT

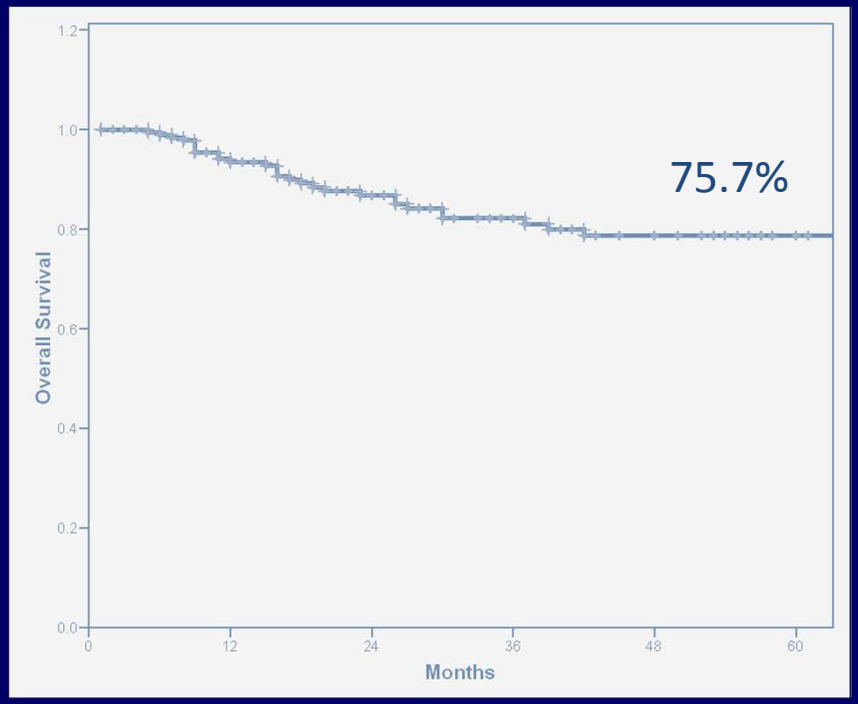



3- year Loco regional control- IMRT

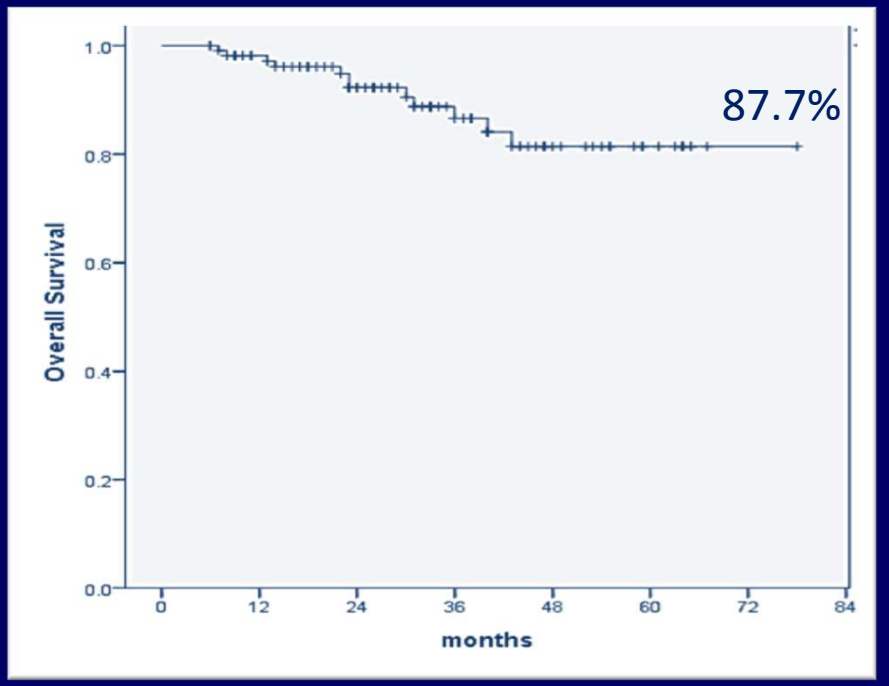


# TMH- 2D era vs. IMRT

3- year Overall Survival- 2DRT




3- year Overall Survival- IMRT



# Rationale For Brachytherapy In Nasopharynx

- Good local control is achieved with Radiotherapy or RT+ Chemotherapy.
- Higher the dose higher the local control. [Good Dose Response Relation]

[ Vikram et al, Marks et al ]

- Brachytherapy → Steep dose fall off → Particular interest in NPC because of proximity to critical dose limiting structures
- Several techniques have been tried-
    - Trans palatal interstitial implantation
    - Several endocavitory applicator based tech.
- NPx is secluded, midline surrounded by bones, vessels and nerves

- hence endocavitory procedure most suitable.

# Role of Brachytherapy

- Most studies showed that local control upto 90 – 95 % could be achieved for T1-T2 tumours with acceptable late toxicities

- However, problems with brachytherapy include :
  - Dose delivered through brachytherapy is adequate only for superficial non-bulky tumours
  - Outcome depends on accurate placement of the catheters, which largely depends on patient anatomy and clinician's skill

## Indications

1. Boost for persistent disease after radiotherapy or chemo- radiotherapy
    - T1, T2a tumors
    - T2b tumors with good response
2. Recurrent cases

## Suitable Candidate

1. Tumors restricted to Nasopharynx
    - with no involvement of nasal cavity or oropharynx
2. Thickness of CTV <10 mm -
    - superficial tumors/ tumors that have shrunk significantly
    - well circumscribed, superficial local recurrences.

# Literature Review of studies using ILBT as BOOST

| Author [Ref] | T- Stage | Dose (Gy) | | Chemo-therapy | 5-yr local control | 5-yr survival |
|---|---|---|---|---|---|---|
| | | EBRT | Brachytherapy | | | |
| Chang [20] 1996 | T1-2 (133) | 64.8-68.4 Gy | HDR: 5-16.5 Gy/ 1-3 # @ 2 cm off axis | Nil | < 72.5 Gy : 73%<br>72.5-75Gy: 94%<br>> 75 Gy : 79% | 72%<br>92%<br>77% |
| Slevin [22] 1997 | T1 = 1, T2 = 4 T3 = 3 | 45-60 Gy | HDR: 5-7.5Gy/ 1# | Nil | 87% (3y) | 37% (3y DFS) 75% (3y OS) |
| Levendag [7] 1998 | T1 = 3, T2 = 9 T3 = 17, T4 = 13 | T1-3 = 60 Gy T4 = 70 Gy | T1-3: 18Gy/6 # T4: 16Gy/4 # @ 1 cm off-axis | 1 (2.5%) | 86% (3y) | 71% (3y DFS) |
| Syed [12] 2000 | T1 = 1, T2 = 4 T3 = 6, T4 = 4 | 50-60 Gy | HDR Implant: 33-37 Gy | 5 (33%) | 59% | 74% (5y DFS) 61% (5y OS) |
| Teo [18] 2000 | T1 = 74 T2 = 89 | 60 Gy | HDR:18-24 Gy / 3# @ 1cm off-axis | 10 (6%) | 93% | 88% (5y DFS) |
| De Nittis [23] 2002 | T1-T3 = 11 | 64-70 Gy (66 Gy median) | HDR: 6-15 Gy / 1-2 # @ 0.5 cm | 11 (100%) | 100% (3y) | 100% (3y OS) |
| Lee [19] 2002 | T1 = 21, T2 = 18 T3 = 4 | 54-72 Gy | HDR 5-7Gy/1-2 # LDR: 10-54 Gy. | 17 (40%) | 89% | 75% (5y DFS) 86% (5y OS) |
| Levendag [17] 2002 | T1 = 7, T2 = 39 T3 = 11, T4 = 14 | 60-70 Gy | HDR: 11-18 Gy / 4-6 # @ 1 cm off axis | 20 (41%) | I-IIB: 100% (2y) III-IVB: 86% (2y) | I-IIB: 90% (2y DFS) 61% (2y OS) III-IVB:74% (2y DFS) 66% (2y OS) |
| Ozyar [21] 2002 | T1 = 45, T2 = 32 T3 = 13, T4 = 16 | 58-71 Gy (65.4 Gy median) | HDR: 12 Gy/3 # @ 1 cm off-axis | 55 (51%) | 86% (3y) | 76% (3y CSS) 67% (3y DFS) |
| Lu [26] 2004 | T1 = 22 T = 11 | 70 Gy | HDR: 10 Gy/2 # @ 1 cm off axis | 33 (100%) | 93.6% (2y) | 74% (2y DFS) 82% (2 y OS) |
| TMH Present study | T1-2 = 6 T3-4 = 4 | 60-70 Gy | HDR: 5-14 Gy / 1-4 # @ 1 cm off axis | 8 (80%) | 90% (3y) | 60% (3y DFS) |

Malde et al Bull Cancer2005

# Tata Memorial Hospital Experience

## High dose rate brachytherapy boost for primary nasopharyngeal carcinoma: preliminary results of an ongoing prospective study

1998-2003, 10 patients of primary NPC

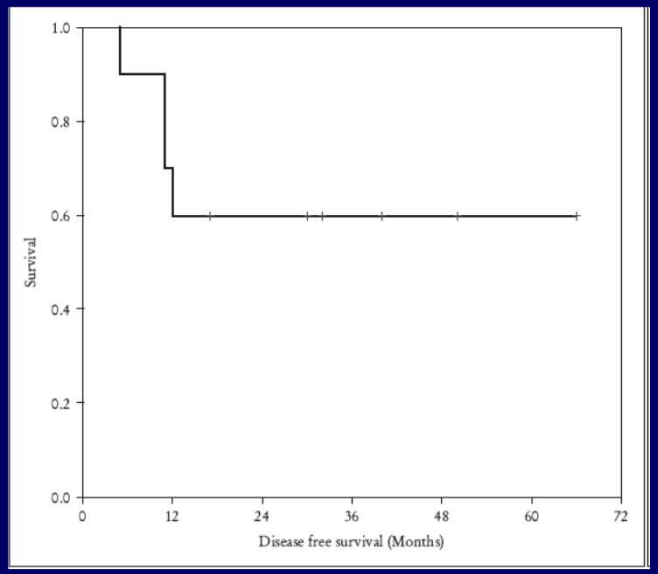
Median EBRT dose-66Gy

Median HDR- Brachy Boost dose-12Gy/1-4#

Rotterdam Silicone Nasopharyngeal applicator

| Patient characteristics | | Patients (nb) |
|---|---|---|
| Age (years) | ≤ 50 years | 6 |
| | > 50 years | 4 |
| Sex | Male | 7 |
| | Female | 3 |
| Tumor Status | T1-2 | 6 |
| | T3-4 | 4 |
| Nodal Status | Node positive | 8 |
| | Node negative | 2 |

Results: Local control- 90%(3yrs)




Toxicity

No patient had significant late toxicities except

Mild Xerostomia-8/10

Persistent crust formation- 1/10

R Malde et al Bull Cancer 2005

# Is Additional Chemotherapy Needed Beyond Concurrent Setting??

- The role of ACT, which was used by Al- Saraff and many other studies after that, was unanswered by the previous MAC-NPC.
- In the Modern RT era, NPC enjoys over 90% LRC, but 22% of the NPC patients still **fail at distant sites** ( constituting over 60% of the failures) – Blanchard et.al 2015
- Still a huge scope for improvement….

# But is ACT the best way to give additional chemotherapy???

Induction-concurrent sequence
-Compliance
- Efficacy
-Toxicities

# Why the Neoadjuvant approach ?

**Table 2.** Compliance with Radiotherapy and Chemotherapy

| Study | No. of Patients | Compliance (%) | | | |
|---|---|---|---|---|---|
| | | RT | indCHT | conCHT | adjCHT |
| Chua et al,[12] 1998 | 334 | 98 *v* 98 | 92 | — | — |
| Cvitkovics et al,[13] 1996 | 339 | 93 *v* 92 | 95 | — | — |
| Hareyama et al,[14] 2002 | 80 | 98 *v* 98 | 88 | — | — |
| Ma et al,[16] 2001 | 456 | 98 *v* 98 | 68/32* | | |
| Al-Sarraf et al,[3] 1998 | 147 | 91 *v* 73 | — | 63 | 55 |
| Chan et al,[9] 2002 | 350 | nm | — | 44 | — |
| Lin et al,[15] 2003 | 284 | 98 *v* 99 | — | 87 | — |
| Chan et al,[10] 1995 | 82 | 100 *v* 100 | 100 | — | 54 |
| Chi et al,[11] 2002 | 157 | nm | — | — | 52 |
| Rossi et al,[17] 1988 | 229 | nm | — | — | 80 |
| Weighted average compliance | | | 94 | 63 | 66 |

Abbreviations: RT, radiotherapy; indCHT, induction chemotherapy; conCHT, concomitant chemotherapy; adjCHT, adjuvant chemotherapy; nm, not mentioned.
*Compliance for two and three cycles of chemotherapy, respectively.

Better compliance

# Randomized Phase II Trial of Concurrent Cisplatin-Radiotherapy With or Without Neoadjuvant Docetaxel and Cisplatin in Advanced Nasopharyngeal Carcinoma

*Edwin P. Hui, Brigette B. Ma, Sing F. Leung, Ann D. King, Frankie Mo, Michael K. Kam, Brian K. Yu,*

- **PURPOSE:** To compare the toxicities, tumor control, survival, and quality of life of NPC patients treated with sequential NACT followed by CTRT or CTRT alone.
- **Methods :** 65 eligible patients were randomly assigned to NACT followed by CTRT (n 34) or CTRT alone (n 31).
- **RESULTS :**
  - The 3-year PFS for NACT versus control arm was 88.2% and 59.5% (hazard ratio 0.49; *P* .12).
  - The 3-year OS for NACT versus control arm was 94.1% and 67.7% (hazard ratio 0.24 *P* .012).
  - Dose intensities of concurrent cisplatin, late RT toxicities and quality of life scores were comparable in both arms.

Conclusion:

- Neoadjuvant docetaxel-cisplatin followed by CRT was well tolerated with a manageable toxicity profile that allowed subsequent delivery of full-dose CRT.
- Preliminary results suggested a positive impact on survival.

# Survival benefit of induction chemotherapy in treatment for locally advanced nasopharyngeal carcinoma – A time-to-event meta-analysis

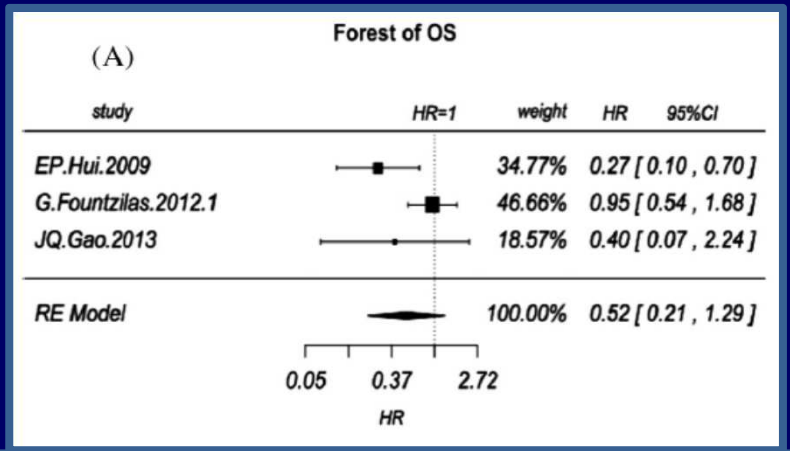
Yaqi Song [*,1], Wanwei Wang [1], Guangzhou Tao [1], Xilie Zhou

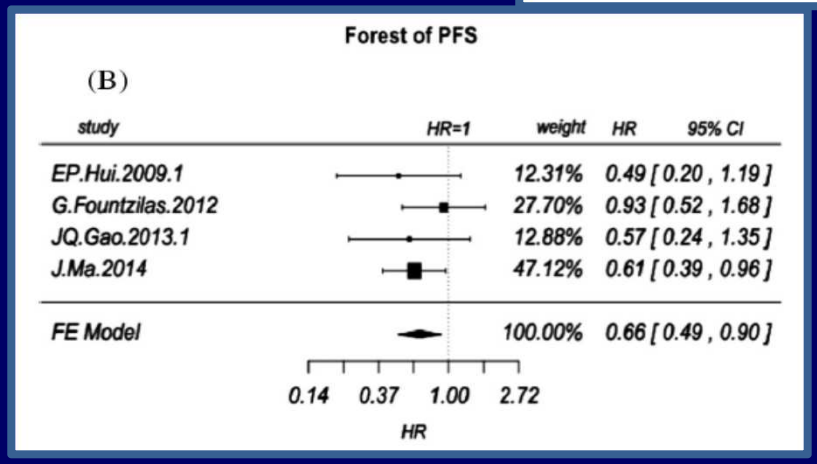
- **Purpose** : compare the long time efficacy of induction chemotherapy followed by CTRT (IC + CTRT) and CTRT alone in locally advanced nasopharyngeal carcinoma (LANPC).

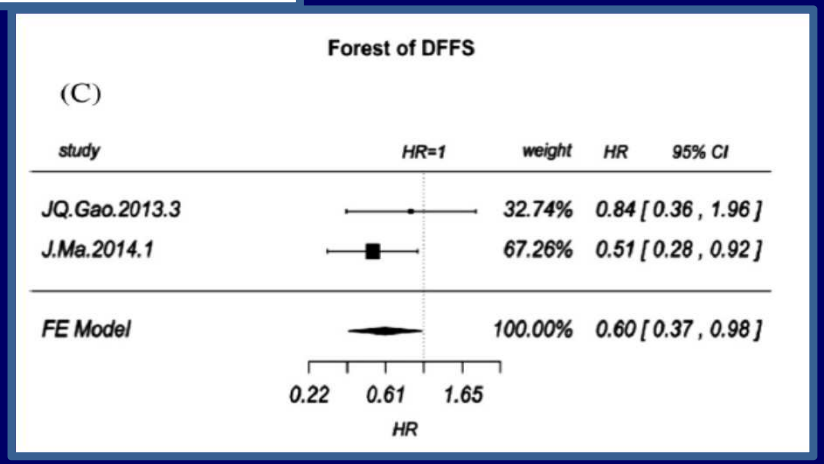
- **Results :** Compared with CCRT alone, IC+CCRT gave an→
  - HR for OS- 0.52 (0.21–1.29)
  - HR for PFS- 0.66 (0.49–0.90)
  - HR for DFFS- 0.60 (0.39–0.98)
  - HR for LFFS- 0.66 (0.16–2.65).

- **Conclusions :** Induction chemotherapy could significantly reduce the hazard of progression and distant metastasis in LANPC on the basis of concurrent CTRT, but do less with the hazard of overall death and loco-regional failure.

# IC+CCRT VS. CTRT



## Preliminary Results of Trial NPC-0501 Evaluating the Therapeutic Gain by Changing From Concurrent-Adjuvant to Induction-Concurrent Chemoradiotherapy, Changing From Fluorouracil to Capecitabine, and Changing From Conventional to Accelerated Radiotherapy Fractionation in Patients With Locoregionally Advanced Nasopharyngeal Carcinoma

Anne W.M. Lee, MD[1]; Roger K.C. Ngan, FRCR[2]; Stewart Y. Tung, FRCR[3]; Ashley Cheng, FRCR[4]; Dora L.W. Kwong, MD[5];

- **Purpose :** potential therapeutic benefit from changing to an induction-concurrent chemotherapy sequence, replacing fluorouracil with oral capecitabine, and/or using accelerated rather than conventional radiotherapy fractionation.
- **Methods :** 6 Arm Randomised controlled trial, 706 pts.
- **Results :**
  - Comparisons of induction PF versus adjuvant PF did not indicate a significant improvement.
  - Unadjusted comparisons of induction sequences versus adjuvant sequences did not reach statistical significance, but adjusted comparisons indicated favorable improvements by induction sequence.

**TABLE 4.** Multivariate Analyses of the Independent Significance of the Experimental Intervention on Tumor Control: Hazard Ratios, 95% Confidence Intervals, and *P* Values

| Analysis[a] | PFS | | OS | |
|---|---|---|---|---|
| | HR (95% CI) | *P* | HR (95% CI) | *P* |
| Regimen group and fractionation in patients randomized to all 6 arms, n = 706 | | | | |
| Regimen group | | .009 | | .003 |
| Induction PF vs adjuvant PF | 0.82 (0.57-1.19) | .29 | 0.76 (0.48-1.19) | .23 |
| Induction PX vs adjuvant PF | 0.54 (0.36-0.80) | .002 | 0.42 (0.25-0.70) | .001 |
| Fractionation: Acceleration vs conventional | 1.13 (0.82-1.54) | .46 | 1.11 (0.75-1.62) | .61 |
| Chemotherapy sequence and fractionation in patients randomized to all 6 arms, n = 706 | | | | |
| Sequence: Induction vs adjuvant | 0.67 (0.48-0.93) | .016 | 0.57 (0.39-0.86) | .006 |
| Fractionation: Acceleration vs conventional | 1.14 (0.83-1.56) | .41 | 1.12 (0.76-1.64) | .57 |
| Regimen and fractionation in patients randomized to induction arms, n = 473 | | | | |
| Regimen: Induction PX vs induction PF | 0.67 (0.44-1.02) | .059 | 0.57 (0.34-0.97) | .038 |
| Fractionation: Acceleration vs conventional | 1.34 (0.90-2.01) | .16 | 1.31 (0.80-2.18) | .30 |

**TABLE 2.** Tolerance to Chemotherapy

| Chemotherapy | Percentage of Patients | | | | | |
|---|---|---|---|---|---|---|
| | Conventional Fractionation | | | Accelerated Fractionation | | |
| | Adjuvant PF (Arm 1A) | Induction PF (Arm 2A) | Induction PX (Arm 3A) | Adjuvant PF (Arm 1B) | Induction PF (Arm 2B) | Induction PX (Arm 3B) |
| Concurrent | | | | | | |
| None | 3 | 7 | 5 | 0 | 3 | 5 |
| 1 Cycle | 3 | 3 | 4 | 3 | 6 | 7 |
| 2 Cycles | 40 | 49 | 58 | 75 | 85 | 83 |
| 3 Cycles | 55 | 40 | 33 | 22 | 6 | 5 |
| Nonconcurrent | | | | | | |
| None | 19 | 1 | 1 | 17 | 1 | 0 |
| 1 Cycle | 8 | 6 | 7 | 12 | 8 | 3 |
| 2 Cycles | 8 | 4 | 7 | 8 | 0 | 9 |
| 3 Cycles | 65 | 89 | 85 | 63 | 91 | 88 |

# Toxicities

**TABLE 5.** Safety: Major Toxicity (Grade ≥3)

| Toxicity | Sequence: Induction vs Adjuvant |
|---|---|
| Any acute toxicity | 50[a] vs 19 |
| Late toxicity (grade ≥3): Actuarial rate at 3 y, % | |
| Central nervous system[c] | 0.9 vs 0.8 |
| Ear toxicity[c] | 7 vs 8 |
| Soft tissue/bone damage necrosis | 0.8 vs 1.7 |
| Others | 0.9 vs 2.0 |
| Any late toxicity | 9 vs 12 |

Therefore NACT appears to be more efficacious and provides better compliance with manageable toxicity profile…..

SO IS THE FINAL VERDICT OUT YET???……

# What is the best treatment in nasopharyngeal carcinoma? An individual patient data network meta-analysis

P. Blanchard[1], A. Lee[2], J. Leclercq[3], J. Ma[4], A.T.C. Chan[5],

- **Methods :** Network analysis performed on the recently updated IPD meta-analysis.

- **Results :**
  - CRT-AC ranked the best treatment regarding OS with a probability of 94%. HR of OS for CRT-AC was 0.64 compared to RT alone and 0.82 compared to CRT.
  - The probability that either CRT-AC or IC-CRT (i.e. CRT + CT given at another timing) is the best treatment was 97%, 96%, 81% and 93% for OS, PFS, LRFFS and DMFS respectively.

**Conclusion :**

- Addition of AC or IC to CRT may improve further the tumour control probability and patient survival over CRT alone.

# Role of Accelerated Fractionated RT + CT (Concurrent + Adjuvant)

| Author | Pts | Stage IV (%) | RT | CT Concurrent | CT Adjuvant | F / U (yrs) | tumor Control (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | OS | EFS | LR-FFR | D-FFS |
| Wolden et al | 50 | 44 | 70 Gy / 6 wks | Cisplatin | Cisplatin + 5-FU | 3 | 84 | 66 | 89 | 79 |
| Jian et al | 48 | 77 | 74 Gy / 7 wks | Cisplatin | Cisplatin + 5-FU | 3 | 72 | 71 | 91 | NR |
| Lin et al | 63 | NR | 72 – 74 Gy / 6 wks | Cisplatin + 5-FU | Cisplatin ± 5-FU | 3 | 74 | 64 | 89 | 74 |

# Role of Accelerated Fractionated RT + CT (Concurrent + Adjuvant)

- NPC-9902 Randomized Trial
- 189 patients in total
- Patients with T3-T4, N0-N1, M0 disease
- Comparison between 2Gy/# x 5 days (CF) and 2Gy/# x 6 days
- Significantly better Event Free Survival in RT using AF + Concurrent CT than in RT using AF alone (94 % vs 70 %) at 3 yrs, $p < 0.01$

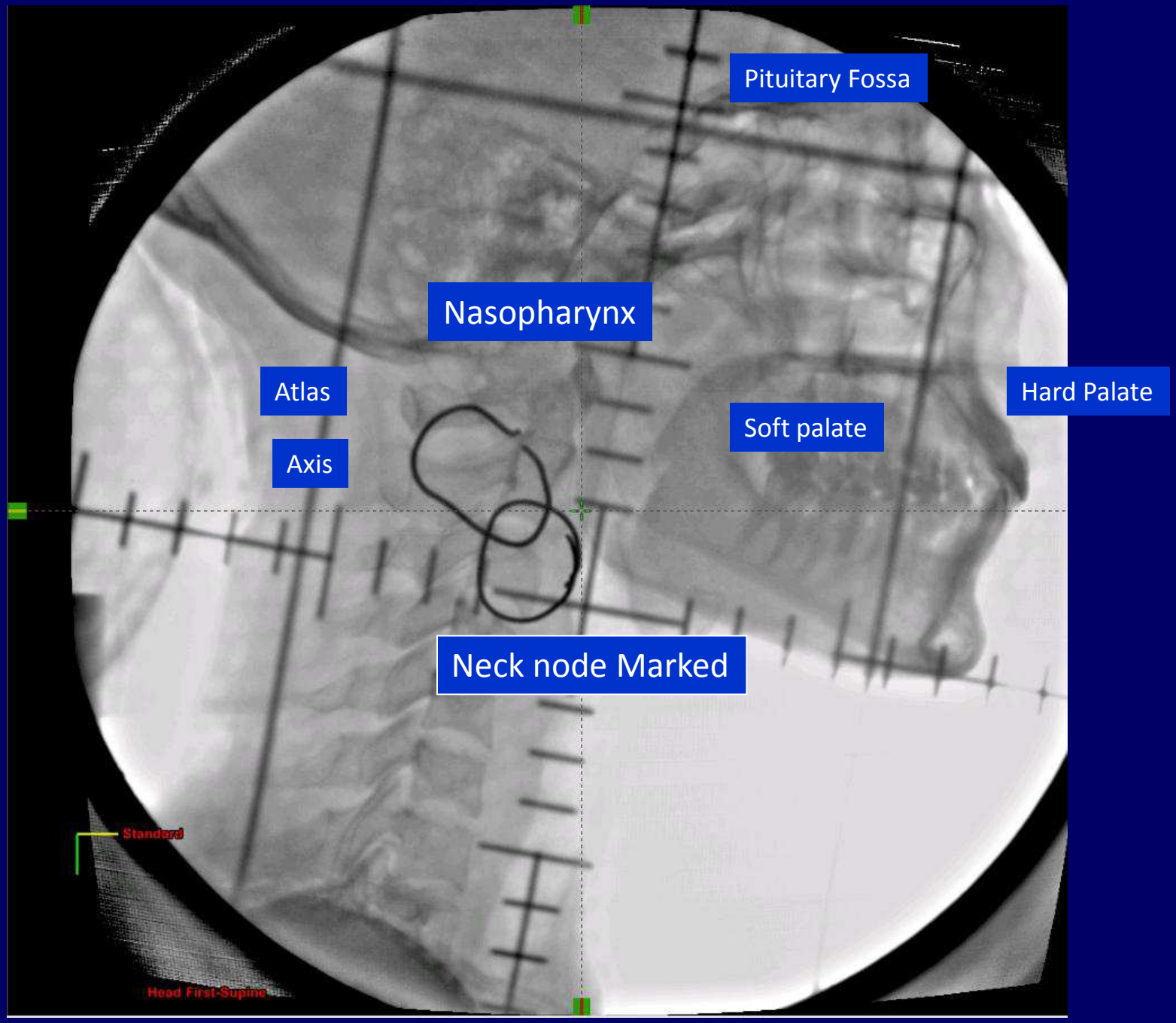
# Toxicities

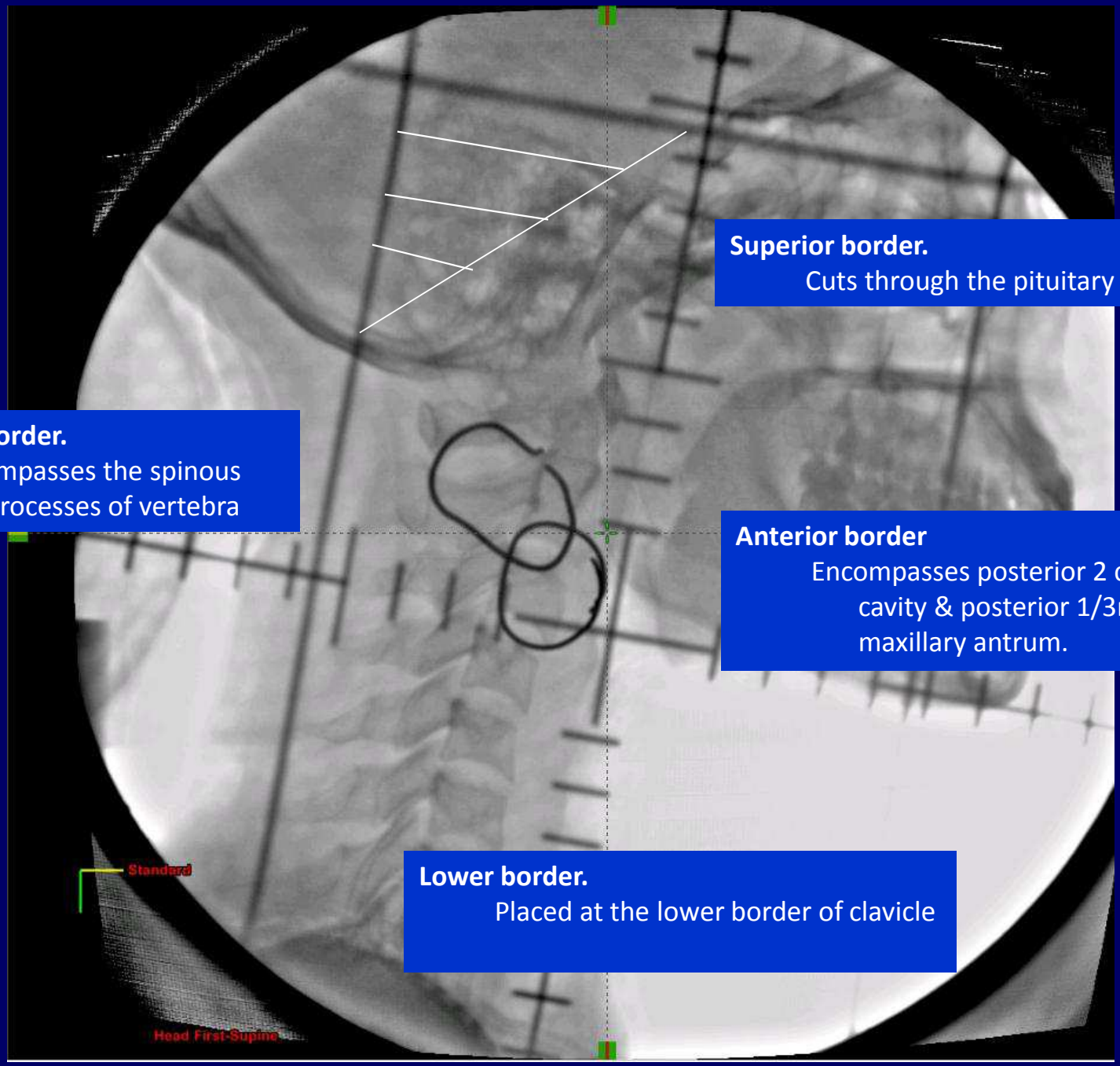
| | NPC 9901 Trial | | NPC 9902 Trial | | | |
|---|---|---|---|---|---|---|
| **No. of patients** | 348 | | 189 | | | |
| **Treatment period** | 1999 - 2004 | | 1999 - 2004 | | | |
| **Median F / U (yrs)** | 2.3 | | 2.9 | | | |
| | CF Arm | CF+C Arm | CF Arm | AF Arm | CF+C Arm | AF+C Arm |
| **Acute Toxicities** | **53** | **84** | | | | |
| **Total radiation dose (mean) (Gy)** | 68 | 69 | 69 | 69 | 68 | 69 |
| **Types of Late Complication** | | | | | | |
| Temporal lobe neuropathy | 0 | 0 | 2.4 | 0 | 0 | 0 |
| Cranial neuropathy | 1.1 | 0.6 | 2.4 | 0 | 3.9 | 0 |
| Endocrine dysfunction | 0.6 | 3.5 | 2.4 | 1.9 | 2 | 4.5 |
| Hearing loss / Otitis | 8 | 14.1 | 9.5 | 15.4 | 15.7 | 22.7 |
| Soft tissue damage | 1.7 | 3.6 | 0 | 3.8 | 2 | 11.4 |
| Eyeball damage | 0 | 0 | 2.4 | 0 | 2 | 0 |
| Others | 0.6 | 0.6 | 4.8 | 5.8 | 3.9 | 13.6 |
| **Overall Incidence of Late Toxicities** | | | | | | |
| Cumulative | **11.4** | **19.8** | **16.7** | **21.2** | **27.5** | **31.8** |
| 3 year actuarial rate | **13** | **28** | **14** | **22** | **31** | **34** |
| Comparisons with CF | - | p = 0.24 | - | p = 0.37 | p = 0.13 | p = 0.05 |
| **Mortality** | 0 | 0.6 | 0 | 0 | 0 | 0 |

Lee, et al, NPC-9901, JCO, 2005 Lee, et al, NPC-9902, IJROBP, 2006

# Regions covered in Conventional EBRT

- Whole of nasopharynx.
- Adjacent structures
  - Sphenoid sinus.
  - Posterior ethmoid cells.
  - Floor of middle cranial fossa.
  - Base of skull.
  - Posterior nasal cavity.
  - Posterior 1/3rd of maxillary sinus.
  - Lateral & posterior pharyngeal wall to the lower pole of tonsil.
  - Retropharyngeal nodes.
- Cervical lymph nodes.


Pituitary Fossa
Nasopharynx
Atlas
Axis
Hard Palate
Soft palate
Neck node Marked
Standard
Head First-Supine




**Superior border.**
Cuts through the pituitary fossa.

**Posterior border.**
Encompasses the spinous processes of vertebra

**Anterior border**
Encompasses posterior 2 cm of nasal cavity & posterior 1/3rd of maxillary antrum.

**Lower border.**
Placed at the lower border of clavicle

# RT : Treatment Volume: Neck

- Elective irradiation of B/L cervical LNs is recommended in all N0 patients
- Patients with clinically –ve necks undergoing elective neck irradiation have significantly lesser nodal relapse rates than untreated ones (40 % vs. 11 %)
- Patients with nodal relapse, even after salvage treatment, have a significantly higher incidence of distant metastasis than those without relapse (21 % vs. 6 %)

Anne Lee, et al. IJROBP 1992

JOURNAL OF NASOPHARYNGEAL CARCINOMA

# N0-N1 Nasopharyngeal Carcinoma: Can the uninvolved neck be spared?

Sarbani Ghosh Laskar[1], G Lavanya [1], Jai Prakash Agarwal[1]

## Can The Lower Neck Be Spared In N0 Neck Or Be Given Lower Doses In The Presence Of Small Volume Disease In The Upper Neck (N1)?

A systematic review was carried out to evaluate the available evidence addressing the issue of sparing the low risk neck regions in patients with N0 and N1 stage.

Available literature reveals that even in the N0 neck, bilateral retropharyngeal group and level II lymph nodes should be considered at risk and cannot be omitted from the radiation portals. The lower neck region is usually at much lower risk of developing metastases in the absence of level II LN involvement and maybe spared.

In the N1 patient, contralateral lower neck is at minimal risk of developing disease, and there is a possibility of not treating these regions. Such a practice warrants a stringent follow-up protocol.

2014, 1(12): e12. doi:10.15383/jnpc.12.

# CTV Delineation for Conformal Planning

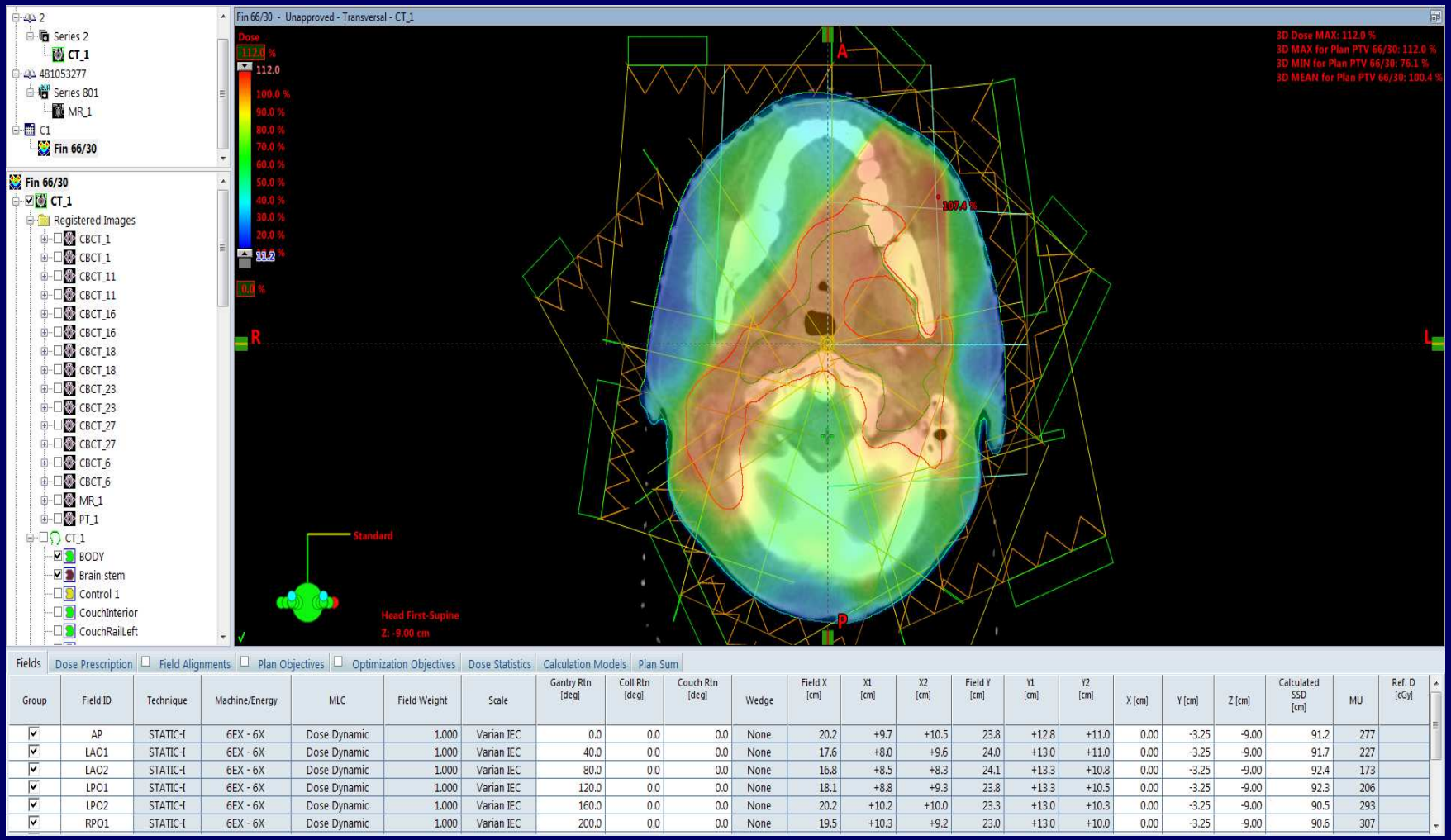
| HIGH RISK CTV | Gross disease with adequate margins (Primary + nodes) |
|---|---|
| INTERMEDIATE RISK CTV | High-risk subclinical region- entire nasopharynx, retropharyngeal nodes, skull base, clivus, pterygoid fossae, PPS, sphenoid sinus, posterior 1/3 nasal cavity & maxillary sinuses to include the pterygopalatine fossae |
| LOW RISK CTV | Uninvolved nodal levels B/L level II-V<br>(Level I may not be treated if uninvolved) |

- Tumor delineation done on contrast enhanced CT images
- MRI and FDG PET-CT information should be used whenever available

RTOG 0615

# CTV Delineation

| | RTOG 0615 | Reduced Volume [Lee 2002] |
|---|---|---|
| Sphenoid Sinus | Inferior Part<br>[Entire SS in T3,T4] | Inferior Part<br>[Entire SS, if involved] |
| Ethmoid Sinus | Not included | Posterior |
| Nasal Cavity | Posterior ¼ to 1/3 | 5 mm anterior to Choana |
| Maxillary Sinus | Posterior ¼ to 1/3 | 5 mm anterior to Maxillary Mucosa |
| Clivus | Anterior ½ to 2/3 | Anterior 1/3 |
| Retropharyngeal LN | Skull Base to Cranial edge of Hyoid | Skull Base to Cranial edge of C2 |
| RetroStyloid space | Included | Not included unless involved |
| Level Ib | Included in Node + pt | Not included unless involved |




Fields | Dose Prescription | Field Alignments | Plan Objectives | Optimization Objectives | Dose Statistics | Calculation Models | Plan Sum

| Group | Field ID | Technique | Machine/Energy | MLC | Field Weight | Scale | Gantry Rtn [deg] | Coll Rtn [deg] | Couch Rtn [deg] | Wedge | Field X [cm] | X1 [cm] | X2 [cm] | Field Y [cm] | Y1 [cm] | Y2 [cm] | X [cm] | Y [cm] | Z [cm] | Calculated SSD [cm] | MU | Ref. D [cGy] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ☑ | AP | STATIC-I | 6EX - 6X | Dose Dynamic | 1.000 | Varian IEC | 0.0 | 0.0 | 0.0 | None | 20.2 | +9.7 | +10.5 | 23.8 | +12.8 | +11.0 | 0.00 | -3.25 | -9.00 | 91.2 | 277 | |
| ☑ | LAO1 | STATIC-I | 6EX - 6X | Dose Dynamic | 1.000 | Varian IEC | 40.0 | 0.0 | 0.0 | None | 17.6 | +8.0 | +9.6 | 24.0 | +13.0 | +11.0 | 0.00 | -3.25 | -9.00 | 91.7 | 227 | |
| ☑ | LAO2 | STATIC-I | 6EX - 6X | Dose Dynamic | 1.000 | Varian IEC | 80.0 | 0.0 | 0.0 | None | 16.8 | +8.5 | +8.3 | 24.1 | +13.3 | +10.8 | 0.00 | -3.25 | -9.00 | 92.4 | 173 | |
| ☑ | LPO1 | STATIC-I | 6EX - 6X | Dose Dynamic | 1.000 | Varian IEC | 120.0 | 0.0 | 0.0 | None | 18.1 | +8.8 | +9.3 | 23.8 | +13.3 | +10.5 | 0.00 | -3.25 | -9.00 | 92.3 | 206 | |
| ☑ | LPO2 | STATIC-I | 6EX - 6X | Dose Dynamic | 1.000 | Varian IEC | 160.0 | 0.0 | 0.0 | None | 20.2 | +10.2 | +10.0 | 23.3 | +13.0 | +10.3 | 0.00 | -3.25 | -9.00 | 90.5 | 293 | |
| ☑ | RPO1 | STATIC-I | 6EX - 6X | Dose Dynamic | 1.000 | Varian IEC | 200.0 | 0.0 | 0.0 | None | 19.5 | +10.3 | +9.2 | 23.0 | +13.0 | +10.0 | 0.00 | -3.25 | -9.00 | 90.6 | 307 | |

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Phase III randomised trial

# A prospective, randomized study comparing outcomes and toxicities of intensity-modulated radiotherapy vs. conventional two-dimensional radiotherapy for the treatment of nasopharyngeal carcinoma

Gang Peng, Tao Wang, Kun-yu Yang, Sheng Zhang, Tao Zhang, Qin Li, Jun Han, Gang Wu *

*Results:* The 2 groups were comparable with respect to all parameters of demographics and disease characteristics (all, $p > 0.05$). Median follow-up was 42 months (range, 1–83 months). The 5-year actuarial local control rate was 90.5% in the IMRT group and 84.7% in the 2D-CRT group. The local control rates were 91% for stage T3 and 81.5% for stage T4 disease in the IMRT group and 80% and 62.2% in the 2D-CRT group, respectively. The 5-year actuarial nodal relapse-free survival (NRFS) rate was 92.4% in the IMRT and 92.9% in the 2D-CRT group ($p > 0.05$). The NRFS was 93.9% for N2 disease in the IMRT group and 91.4% in the 2D-CRT group ($p = 0.02$). The 5-year overall survival (OS) rate was 79.6% for the IMRT group and 67.1% for the 2D-CRT group ($p = 0.001$). When stratified for stage, a significant difference was only noted for stage III disease. In terms of radiation-induced toxicities, patients in IMRT group had significantly lower radiation-induced toxicities than those in 2D-CRT group.

*Conclusion:* IMRT provides improved local-recurrence free survival, especially in late-stage NPC patients and is associated with a lower incidence of toxicities.

| Study Author | RT Technique | Assessment technique | Proportion of Grade ≥ 2 Xerostomia at 1-year follow-up | Proportion of Grade ≥ 2 Xerostomia 2-year follow-up |
|---|---|---|---|---|
| Pow et al. (2006) | Conventional vs IMRT<br>n = 51 | Subjective (EORTC) | 50% vs 4.8% (p= - 46% | N.A |
| Kam et al. (2007) | Conventional vs IMRT<br>n = 60 | Subjective (EORTC/RTOG Score) | 82% vs 39% (p=0.001) – 43% | N.A |

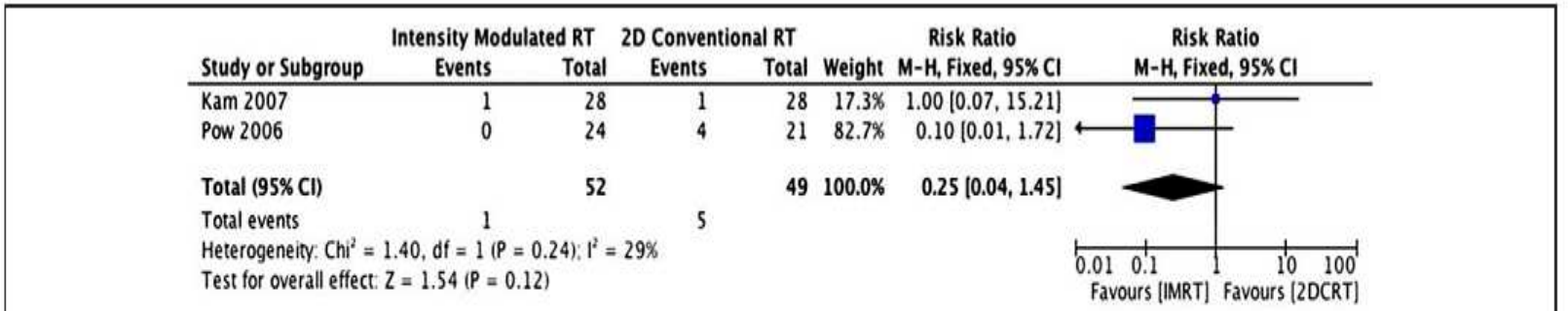


FIGURE 2. Intensity-modulated radiation therapy (IMRT) versus 2D conventional radiotherapy (RT), outcome: local failure at 1-year follow-up. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com]

TABLE 3. Recommendations based on National Health and Medical Research Council additional levels and grades for recommendations for developers of guidelines.

| Components | Grade | Comments |
|---|---|---|
| Evidence base | | |
| Local control | B | 2 RCTs (Peng et al[25], Kam et al[24]). Peng et al[25] sufficiently powered. Kam et al[24] reported on oncologic outcomes but is not large to detect the size and direction of any effects. |
| Regional control | B | 2 RCTs (Peng et al[25], Kam et al[24]). Peng et al[25] sufficiently powered. Kam et al[24] reported on oncologic outcomes, but was not large enough to detect the size and direction of any effects. |
| Overall survival | B | 1 RCT (Peng et al[25]) |

CLINICAL REVIEW

David W. Eisele, MD, *Section Editor*

# Evidence on effectiveness of intensity-modulated radiotherapy versus 2-dimensional radiotherapy in the treatment of nasopharyngeal carcinoma: Meta-analysis and a systematic review of the literature

Jayson Co, MD,* Michael Benedict Mejia, MD, Janine Margarita Dizon, PhD

# Prescription of Dose

**Dose Principles**

- Gross Disease – 70 Gy
- High Risk – 55-60Gy
- Low Risk – 45-50Gy

- **<u>BUT</u> Dose Tolerance Issues for normal organs**

**Early stage T1-2N0**

– Phase I – 46 Gy / 23 # to Primary + Full neck

– Phase II – 14 Gy/7# off cord

– Phase III – 10 Gy / 5 # Boost to Primary tumor with margins

**Advanced stage T3-4 / N+**

– Phase I – as above

– Phase II – as above WITH Posterior electron boost if LN +ve

– Phase III- as above

# RT Dose

- For T1 – T3 tumours, 100 % local control rates for patients given > 70 Gy; 80 % for those given 66 – 70 Gy
- For T4 tumours, control rates ~ 55 % attained with doses > 70 Gy
- Conclusion :
  - Total dose is the most important radiation factor affecting local control.
  - Doses of 70 Gy & above are needed to attain appreciable control rates in

- Dose per fraction does not affect local control, but it does affect late tissue toxicities (temporal lobe necrosis). Risk increases with use of fraction size > 2 Gy

*Anne Lee, et al. IJROBP 1998 & 2002*

- Retrospective analysis
- 1008 pts of Nonkeratinizing SqCa Nasopharynx stage T1N0-3M0
- Treated with RT alone using 4.5 – 6 MV using 3-field technique
- Total dose 45.6 - 60 Gy; Fraction size 2.5 - 4.2 Gy **(BED : 63 – 75 Gy)**
- Hazard of local failure decreased by 9 % per additional Gy of radiation dose added

# Dose Escalation

- Improvement in local tumor control rates reported by giving escalated doses
- External Beam RT

  (Conventional / 3DCRT / IMRT / SMART)
- Brachytherapy boost
- Stereotactic RT boost

# RT Parameters

**RT Volumes**: Elective nodal Irradiation recommended **(level 2/3)**

**RT Dose:** Doses ≥ 70Gy **(level 2)**

**Dose/ #: not> 2.1Gy/ # (level2)**

**Altered fractionation: SIB/ Accelerated (level1)**

**Type of RT: Conformal (IMRT) (Level 1)**

# Conclusions

- Surgery difficult ; only role in :
  - Biopsy for pathologic diagnosis
  - Salvage for persistent / recurrent disease

- Standard of care is Radical RT ± CT
  - Stage I – II : Radical RT alone
  - Stage IIB – IV : Radical RT + CT

**5 yr OS rates**
**> 75 %**

- IMRT to be preferred if resources allow

- Addition of CT to RT is most beneficial in the concurrent setting for the locally advanced cancers

- Neoadjuvant Vs concurrent Vs adjuvant chemotherapy The battle continues…

- Accelerated fractionation & use of Induction -Concurrent sequence of chemotherapy can be used for improving treatment efficacy in advanced stage tumours

- Treatment intensification comes at the cost of increased toxicity

## Further Reading

Original article

# Evolution of treatment for nasopharyngeal cancer – Success and setback in the intensity-modulated radiotherapy era

Anne W.M. Lee [a,*], Wai Tong Ng [b], Lucy L.K. Chan [b], Wai Man Hung [b], Connie C.C. Chan [b], Henry C.K. Sze [a], Oscar S.H. Chan [b], Amy T.Y. Chang [b], Rebecca M.W. Yeung [b]

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# Unanswered Questions????