# CURRENT TREATMENT OF NASOPHARYNGEAL CARCINOMA

Oleh,
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(WEBINAR TGL 29 AGUSTUS 2020)

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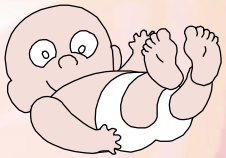

6 Februari 1950, Jember

Dokter Umum, FK UNAIR, 1977

Spesialis THT, 1982

Doktor (S3), 2001

Guru Besar, 2004

Ketua Kodi Onkologi Bedah Kepala & Leher Perhati-KL 2007-2013

Ketua I Kolegium Ilmu Kes. THT- KL Indonesia 2016-2019

Ketua Departemen / SMF Ilmu Kes. THT-KL FK UNAIR / RSUD Dr. Soetomo 2010-2016


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# INTRODUCTION

- **NPC** → malignant tumors arising from the epithelial cells lining the nasopharyngeal space
- NPC prevalence is 0.6% of all cancers worldwide and 87.000 new cases annually, with male predominant
- NPC → the most common cancer in Head & Neck region
- Mongoloid race >
- NPC are malignant tumors on the top and lateral walls of the nasopharynx, highly diversified from region to region.

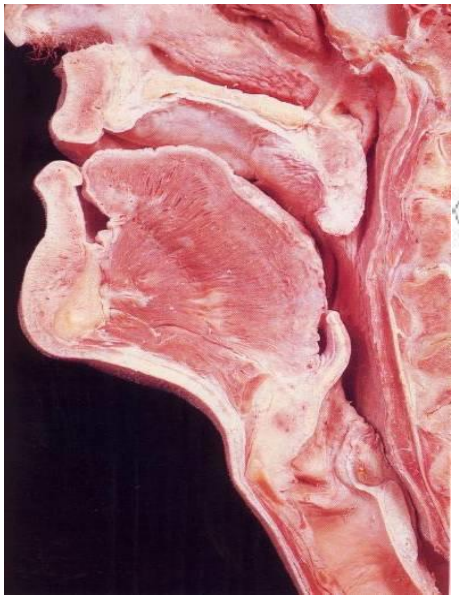
Mott EF, Sacks LR, 2018; Zhang Y, Du K,*et.al.*2019

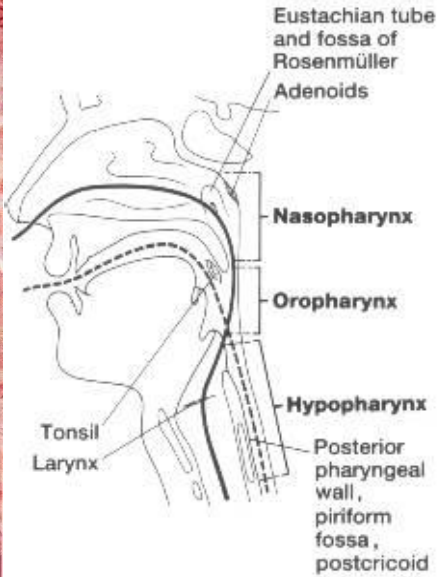
- Risk factor: Epstein Barr Virus (EBV) infection,carcinogen environment, and genetics
- Histo PA → WHO type 2 & 3 : 75% - 95%
  → radioresponsive tumors
- Rare case of early stage (5%)
- Loco-regional advanced stage 70% - 95%
- Neck lymph enlargement : 50% - 70%
  → bilateral : 80%
- Distant metastasis : 15% - 57%
- 3 serial autopsy results → **distant metastasis 87%**
  Vert Th-L bones (78%), lung (46%),liver(38%)
  **NPC → sistemic disease !!!** (Tan, et al., 1997)

- Most NPC experience toxic sensitivity to radiotherapy.
- Radiotherapy is primarily preferred in the treatment
- 5-year survival rates of early NPC patients: after radiotherapy alone are about 60% to 80%, but after chemoradiotherapy (chemosensitizer) combinations it may reach 90%.
- 3 year overall survival for advanced loco-regional NPC with radiotherapy alone : 5% - 40%, but chemoradiotherapy combinations : **89,5%**

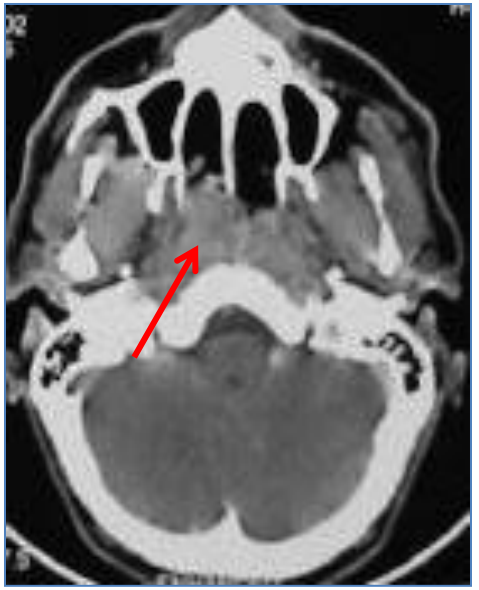
Mott EF, Sacks LR, 2018; Zhang Y, Du K,*et.al.*2019

# ANATOMY



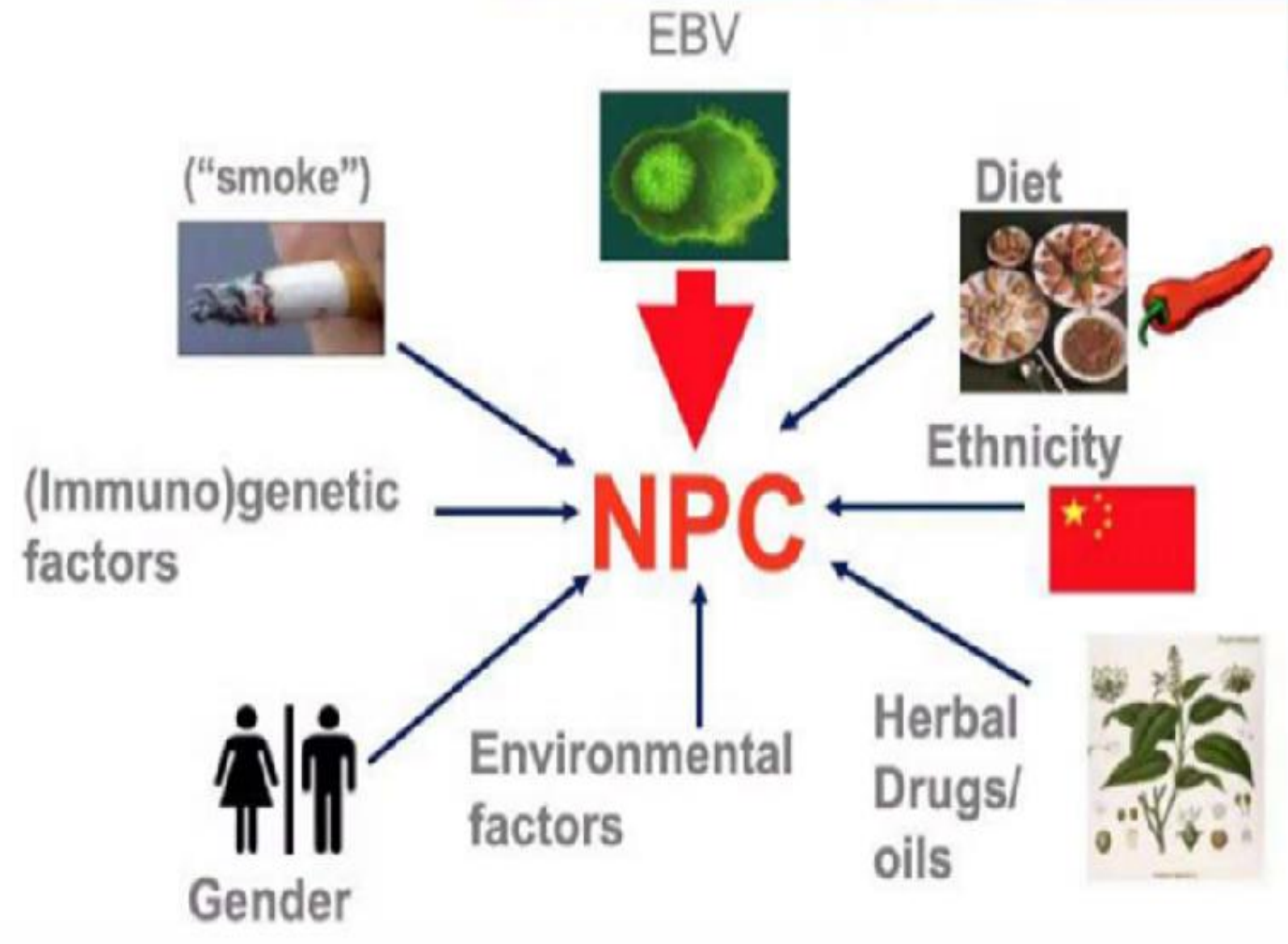



NPC Patient

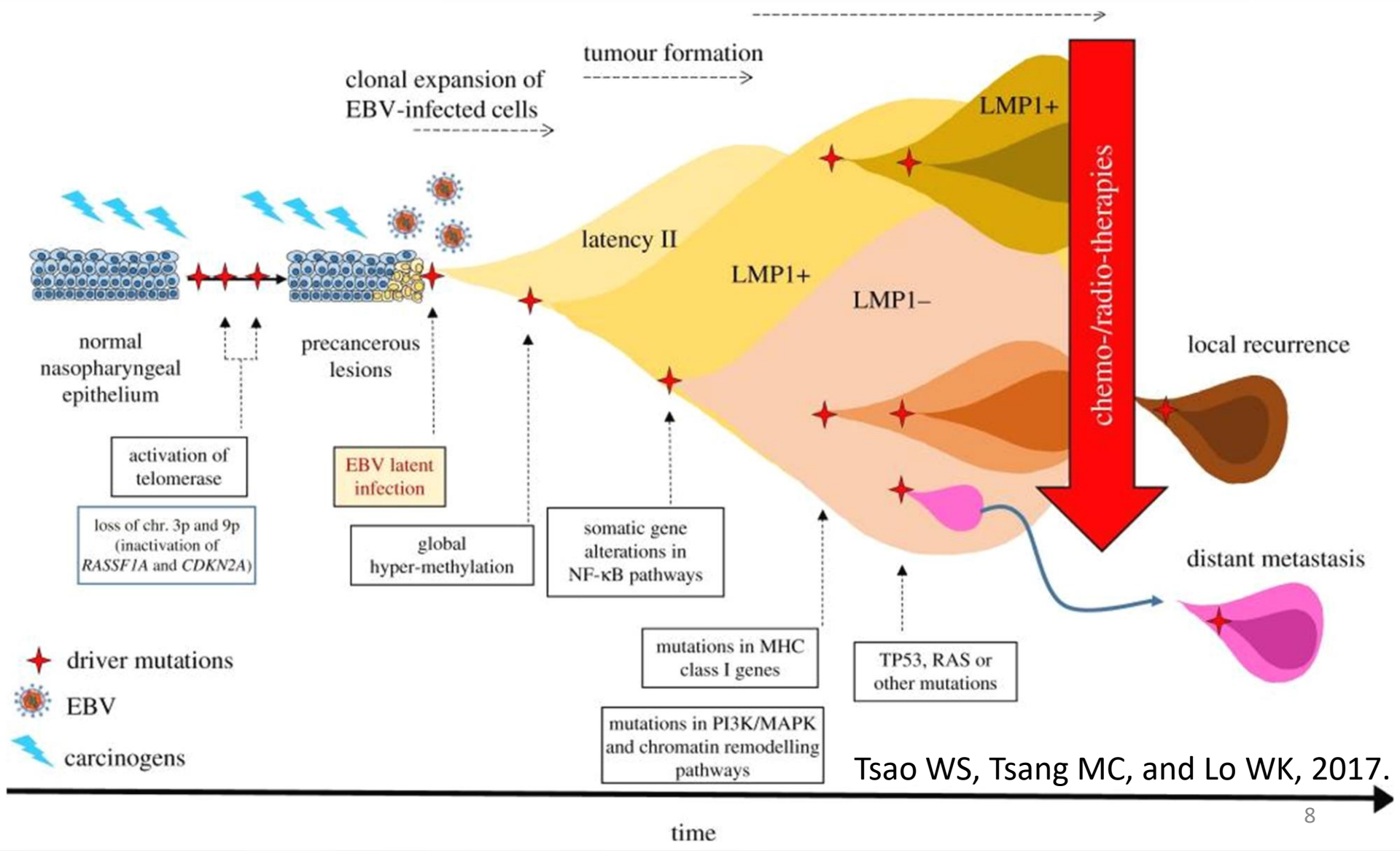


CT scan

# ETIOLOGY& RISK FACTORS



# Pathogenesis




Tsao WS, Tsang MC, and Lo WK, 2017.

# HISTOPATHOLOGY

## Latest WHO Classification (2017)

**Table 5.2** International/WHO nasopharyngeal carcinoma (NPC) pathological classifications.

| Year | Description | Changes |
|---|---|---|
| Ewing (1929) | NPC can be histopathologically divided into five types:<br>a. Squamous cell carcinoma (SCC)<br>b. Transitional cell carcinoma<br>c. Lymphoepithelial carcinoma<br>d. Malignant adenoma<br>e. Cystic adenoid basal cell carcinoma | |
| UICC (Union for International Cancer Control) NPC Symposium (1967) | NPC can be histopathology divided into seven major types:<br>a. Typical (or classic) epidermoid carcinoma<br>b. Clear cell carcinoma<br>c. Spindle cell carcinoma<br>d. Transitional cell carcinoma<br>e. Lymphoepithelial carcinoma<br>f. Pleomorphic carcinoma<br>g. Mixed-cell carcinoma subtypes | |
| First Edition WHO NPC histopathological classification (1978) | NPC can be histopathology divided into three major types:<br>a. Type 1 (SCC)<br>b. Type 2 [nonkeratinizing carcinoma (NKC)]<br>c. Type 3 (Undifferentiated carcinoma) | WHO defined NPC is nasopharyngeal cancer with evidence of squamous differentiation by light microscopy (adenocarcinoma and salivary gland tumors were not included) |

Sharif TES, *et.al.* 2020

# Latest WHO Classification.....

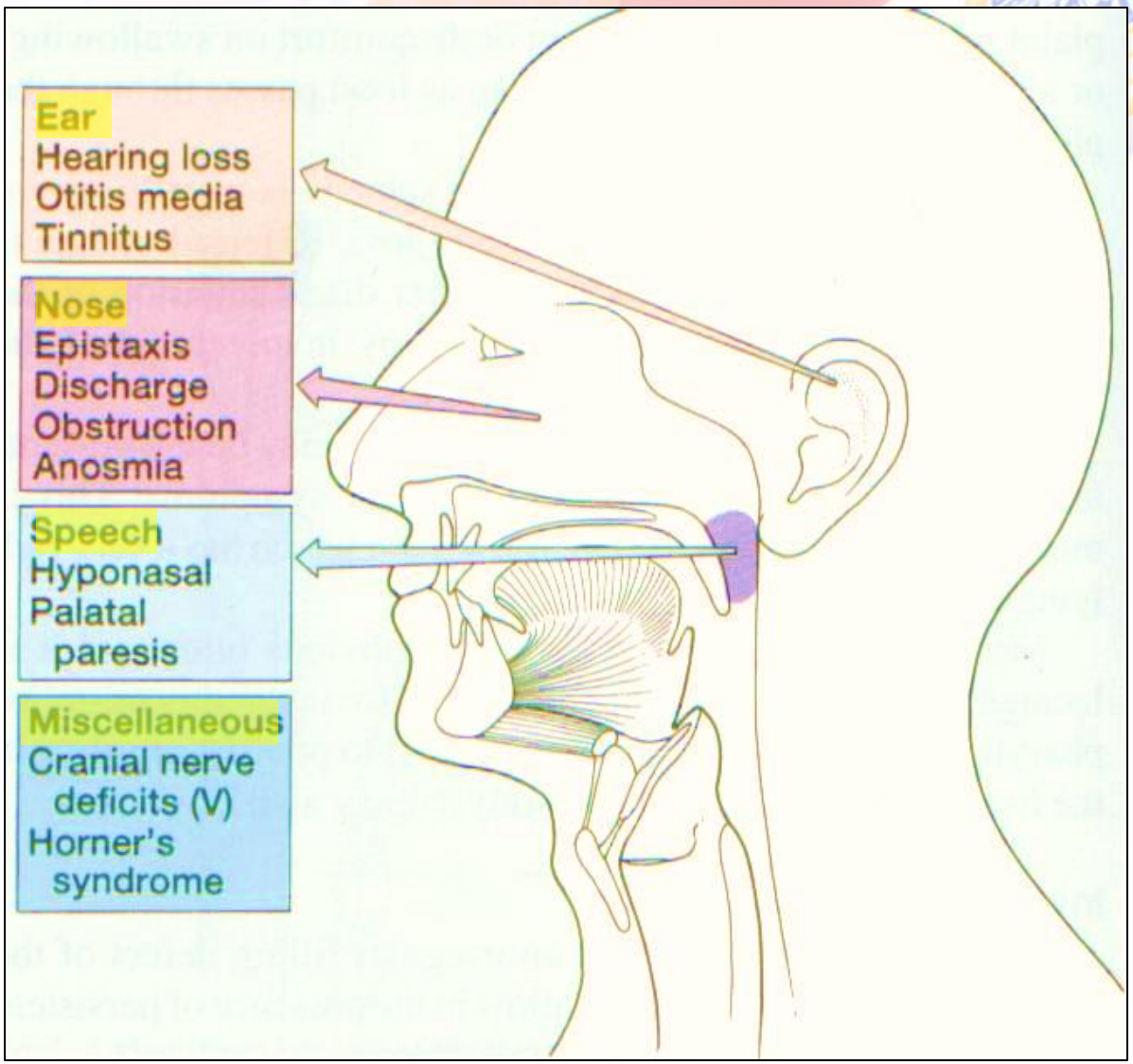
| | | |
|---|---|---|
| Second Edition WHO NPC histopathological classification (1991) | NPC histopathological classification can be divided into two major types:<br>a. Keratinizing squamous cell carcinoma (KSCC) (two subtypes)<br>i. Well and moderately differentiated<br>ii. Poorly differentiated<br>b. NKC (two subtypes)<br>i. Differentiated<br>ii. Undifferentiated | The use of numerical designation of WHO types 1, 2, and 3 was eliminated |
| Third Edition WHO NPC histopathological classification, (2005) | NPC histopathological classification can be divided into three types:<br>a. KSCC<br>b. NKC<br>i. Undifferentiated<br>ii. Differentiated<br>c. Basaloid squamous cell carcinoma (BSCC) | BSCC was introduced as independent category |

**Table 5.3** Classification of nasopharyngeal carcinoma (NPC) WHO fourth edition (2017).

| ***Nasopharyngeal carcinoma*** | |
|---|---|
| Nonkeratinizing squamous cell carcinoma | 8072/3 |
| Keratinizing squamous cell carcinoma | 8071/3 |
| Basaloid squamous cell carcinoma | 8083/3 |

Sharif TES, *et.al.* 2020

# SIGN AND SYMPTOMS



# Secondary Examination

- Radiology
  1. Skull X-ray (AP, lateral, skull base, Water's)
  2. CT scan / MRI with contrast agent
  3. Thorax x-ray (PA) → lung metastasis?
  4. Abdominal sonography → liver metastasis?
  5. *Bone scintigraphy* → bone metastasis?

# TNM System of NPC (UICC 8th Edition, 2018)

**T categories**

**T1** Unchanged

**T2** Tumour with extension to parapharyngeal space and/or infiltration of the medial pterygoid, lateral pterygoid, and/or prevertebral muscles

**T3** Tumour invades bony structures of skull base cervical vertebra, pterygoid structures, and/or paranasal sinuses

**T4** Tumour with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, parotid gland and/or infiltration beyond the lateral surface of the lateral pterygoid muscle

**N Categories**

**N1** Unilateral metastasis, in cervical lymph node(s), and/or unilateral or bilateral metastasis in retropharyn-geal lymph nodes, 6 cm or less ,above the caudal border of cricoid cartilage

**N2** Bilateral metastasis in cervical lymph node(s), 6 cm or less above the caudal border of cricoid cartilage

**N3** Metastasis in cervical lymph node(s) greater than 6 cm in dimension and/or extension below the caudal border of cricoid cartilage

**M categories**

M0 No dis

M1 Distant metastasis

# Staging of NPC
# (UICC 8th Edition, 2018)

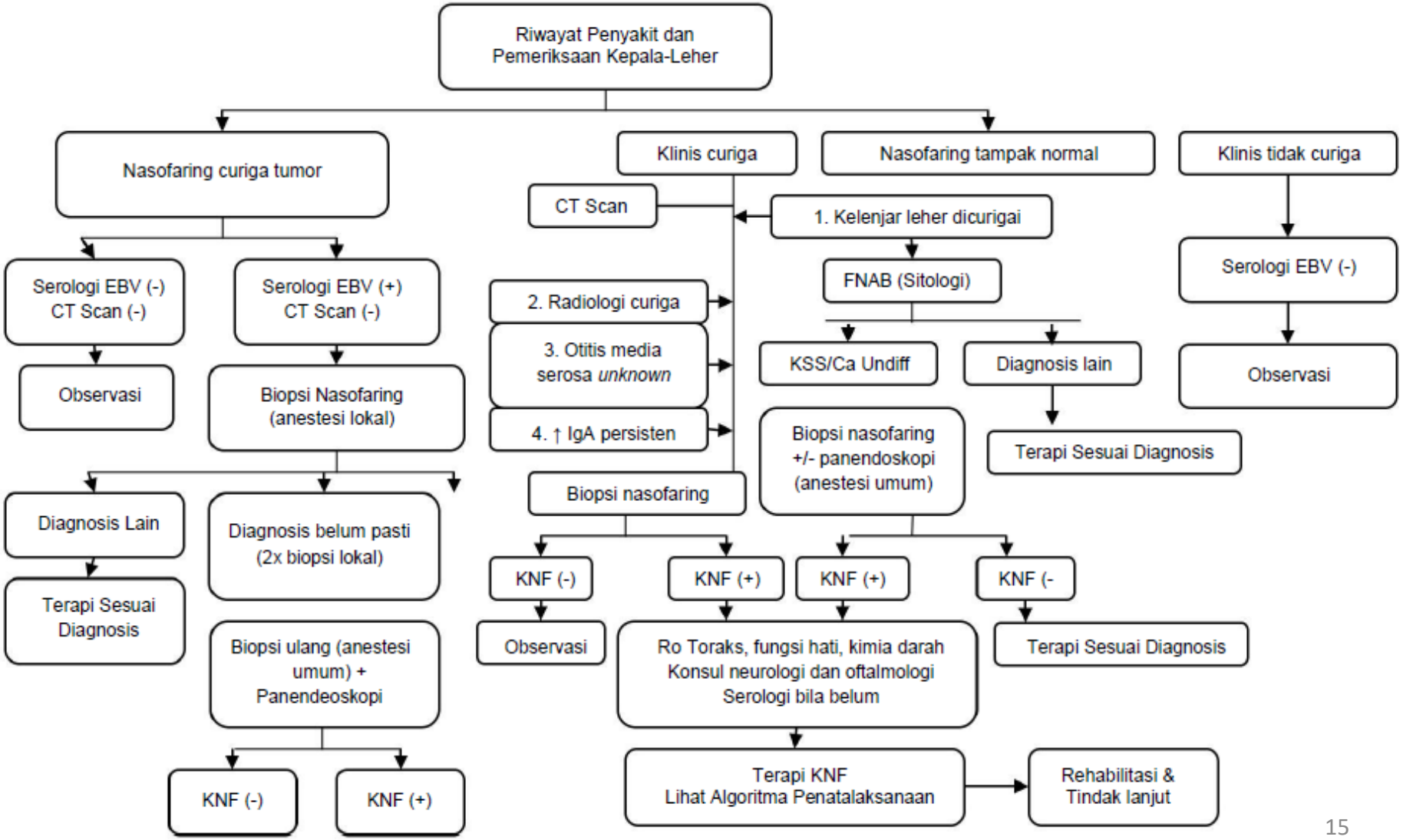
**Stage Groups**

| | | | |
|---|---|---|---|
| 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 IVA | T4 | N0, N1, N2 | M0 |
| | Any T | N3 | M0 |
| Stage IVB | Any T | Any N | M1 |

Stage IV compressed previous stage IVB now IVA

# Diagnostic Algorithm of NPC

Panduan Penatalaksanaan Karsinoma nasofaring, **KEMENKES-RI, 2015**.



# THERAPY

## Treatment of choice for NPC :

## External beam radiation

→ dose 6600 – 7000/7500 cGy

- primary, upper cervical nodes, positive lower nodes (involved neck)

Consider 5000 – 6000 cGy prophylactic therapy of clinically negative lower neck (un involved neck)

# Development of Nasopharyngeal Carcinoma Management

* **Radiology/radiotherapy technology**

**1950** . Telecobalt 60

. New radiotherapy equipment & technique

* Proton, Neutron, Phimeson

. LINAC → 2 DRT

**1980** **. 3 DRT**

* Hyperfractionated (bid, tid)

* **Chemotherapy→ Chemoradiotherapy (3 DRT)**

. New cytostatic combination

**1995** * **IMRT**, IGRT → **Chemoradiotherapy (IMRT)**

**2000** * **Targeted therapy**

. Anti EGFR monoclonal antibodies

**2010** * **Surgery**

- maxillary swing,
- neck dissection,
- nasopharyngectomy endoscopic

# How to improved local control of NPC ?

1. Improved fractionation such as accelerated fractionation
2. Combined use of radiotherapy with chemotherapy
3. Dose escalation by means such as intracavitary brachytherapy boost and stereotactic boost
4. Combined use with Targeted therapy
5. Surgery (open or endoscopic nasopharyngectomy)

# NPC Treatment

1. 3 D Conformal Radiation Therapy (3 D CRT)
   Hyperfractionated RT (bid, tid)
   IMRT
2. Combined chemotherapy and radiotherapy (induction, concurrent and / or adjuvant)
3. Salvage surgery for recurrent small tumour +/- post chemo-radiotherapy

# Treatment Highlight

1. Good outcomes
2. Reduce or minimal distant failure
3. Quality of life
4. New treatment strategies

# Current treatment modalities in NPC

**Novel targeted agents offer the promise of better treatment options**

- eg. Cetuximab, Nimotuzumab

**Four modalities therapy**

| | | | |
|---|---|---|---|
| **Radiotherapy** | **Chemotherapy** | **Targeted therapy** | **Surgery** |

Each treatment modality has its own advantages and limitations

# 3 Dimensional Conformal Radioterapy (3 DCRT)

- ***Treatment planning system*** **technology (3 DRT)**

→ local control more effective than 2 DRT

- Followed by **accelerated fractionated radiotherapy, brachytherapy intracaviter,** etc

Early NPC → Tx 3 DCRT : 5 ysr 80% -

**Stereotactic radiotherapy/surgery** → LCR : 72%-86%

for T1 of NPC → response rate : 96%

**2000 : Gamma knife** → state of the art SRT equipment

Chan, 2003;Teo, 2003

# 3 DRT...

Post radiotherapy **(3 DRT) → survival rate**

early NPC → 5 ysr : 68% - 85%

advanced NPC → 5 ysr : 5% - 40%

**Average Survival Sate**

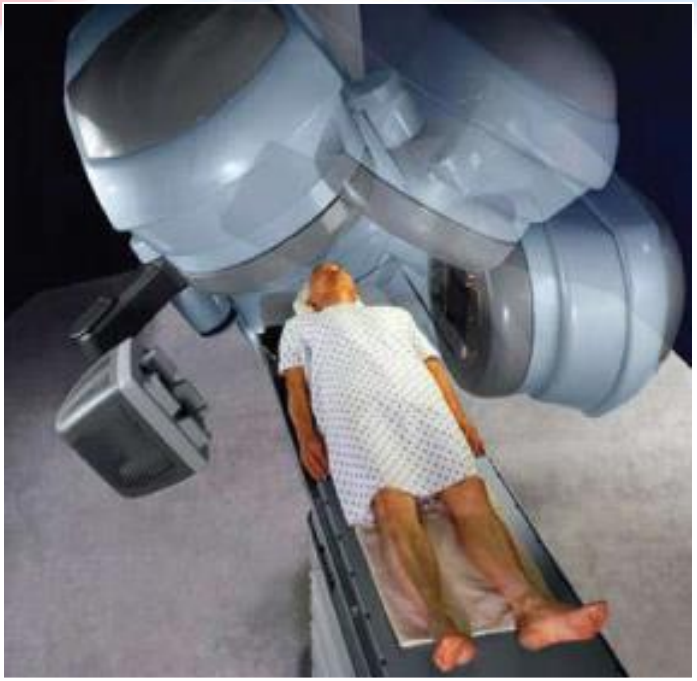
1 year : 82,7%

2 year : 67,4%

5 year : 47,8%

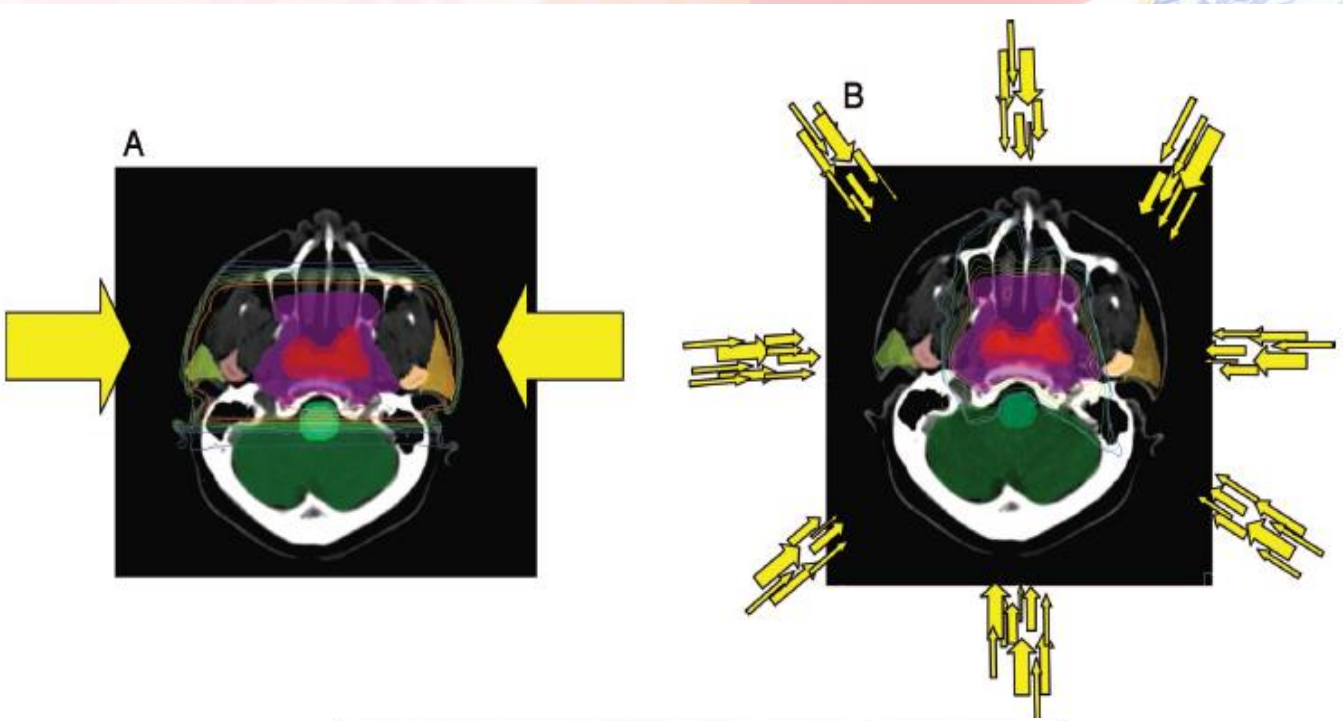
10 year : 39,8%

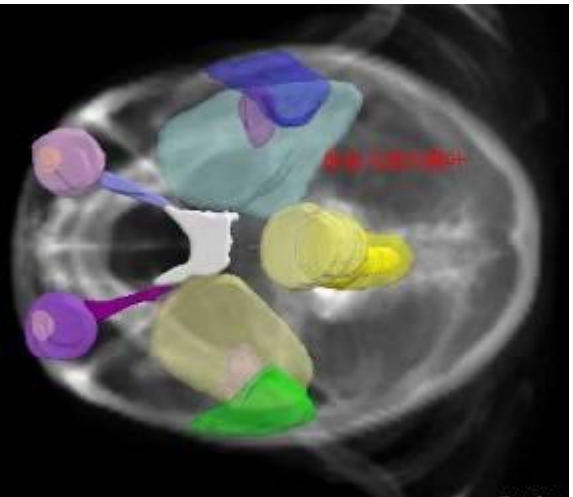
# IMRT
## (Intensity Modulated Radiotherapy)
### New radiation technique

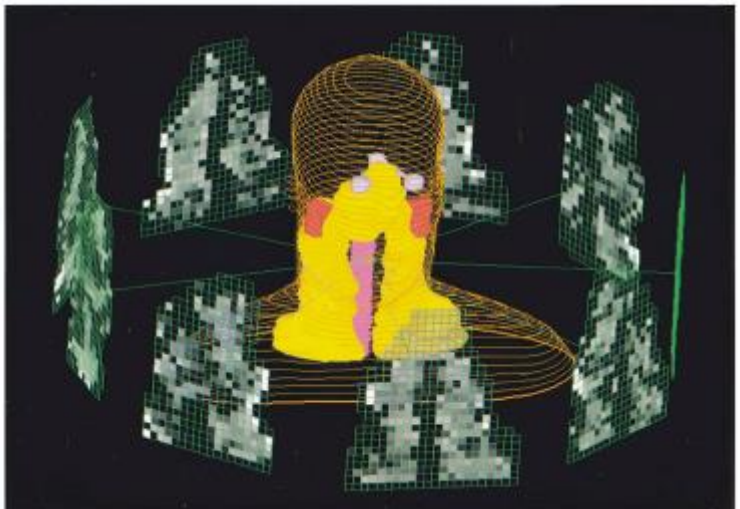


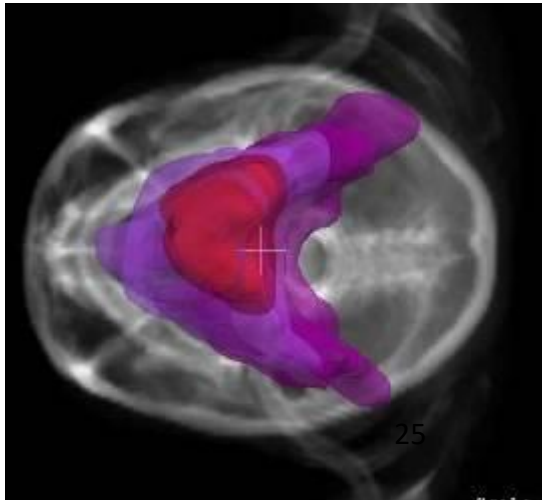
- **Preserved Parotid Function**
- **Improved LRC**

# Advanced Technique → IMRT



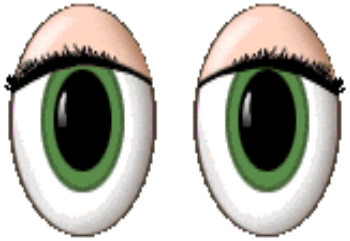







## Intensity Modulated Radiation Therapy (IMRT)

- "A cutting edge radiation technique"
  → **highly effective**



Goal :

- Reduce local failure (improve local-regional control) by improve target volume localisation, and dose adjustment
- Reduce toxicity (protect normal tissue) by improving dose distributions to OAR (safe increase of tumor dose)

  Site : oropharynx, parotid gland sparing

**Novel techniques !!!** (Nutting C, 2008)

# Research of IMRT in NPC

- Study at Cancer Center of Sun Yat Sen University (SYSU), Guangzhou China (2001-2006)

**400 NPC patients** → T1 : 43 patients, T2 : 153 patients, T3 : 141 patients, dan T4 : 63 patients

177 pts → **IMRT alone,** 233 pts → **IMRT+ Chemotx**

- Local failure : 11 patients. Regional failure :9 patients
- **Local control** : 1 yr : 98,46%
  2 yr : 97,74%
  3 yr : 93,90%
- **Regional control** :
  1 yr : 98,97%
  2 yr : 97,42%
  3 yr : 95,92%

**OS**:1-yr 97.91%
3-yr 90.15%
5-yr 86.88%

Conclusion : **IMRT → high locoregional control**

Tai Xiang Lu, 2012

# Chemotherapy in NPC

(FDA recommendation)

- **Chemotherapy** → **Single**

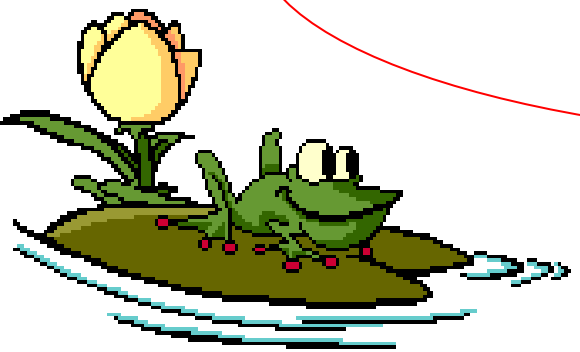
  Cisplatin, Carboplatin, 5-FU, MTx, Bleomycin, Mitomycin C, Doxorubicin, Cyclophosphamide, Docetacel, Vincristine, Paclitaxel

**Combination**

Cisplatin/5-FU, Carboplatin/5FU,

Cisplatin/Paclitaxel, Cisplatin/Docetaxel

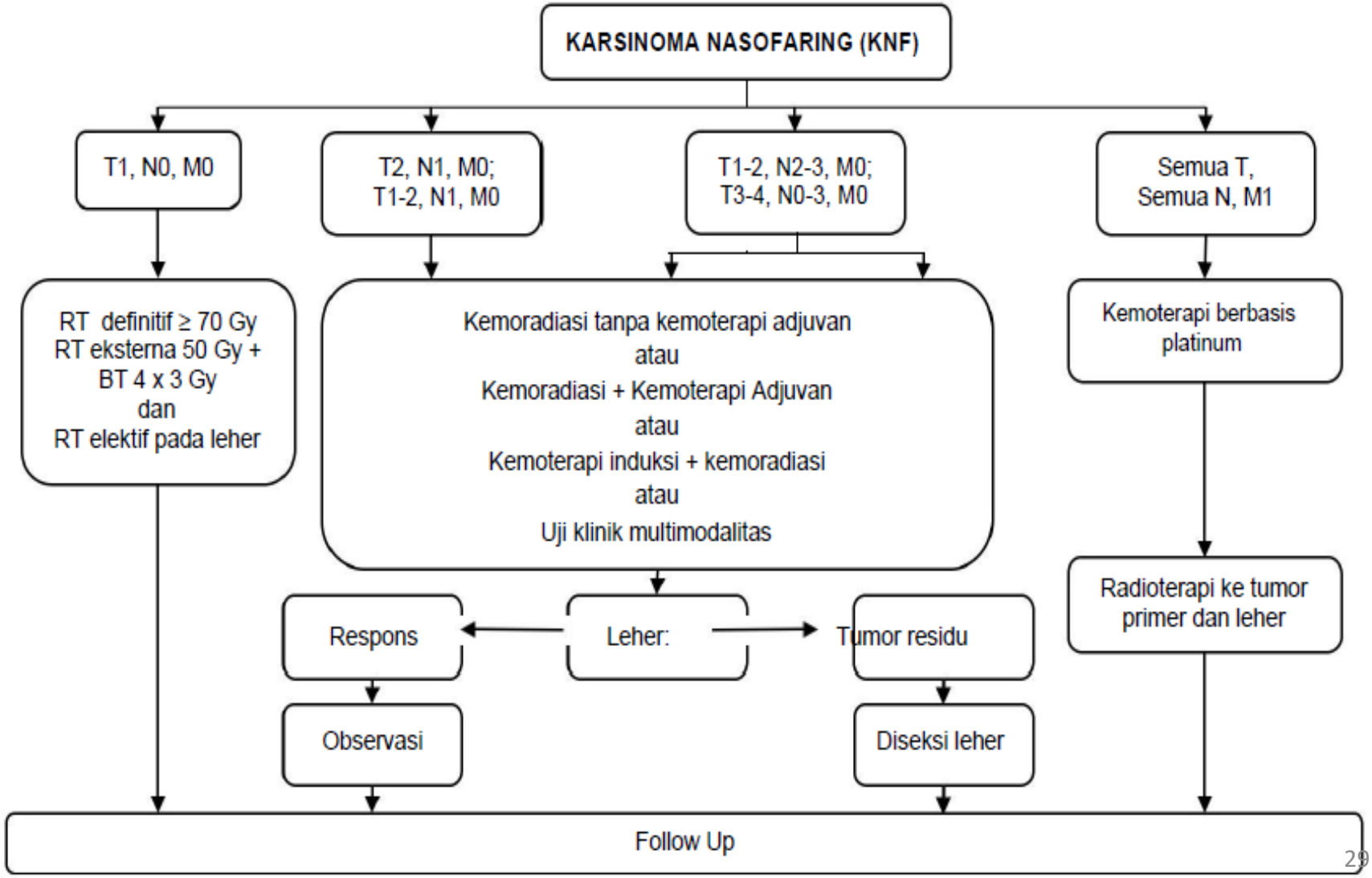
Cisplatin/ gemcitabine



**Induction (neoadjuvant), concurrent and / or adjuvant**

# TREATMENT ALGORITHM OF NPC

Panduan Penatalaksanaan Karsinoma nasofaring, KEMENKES-RI, 2015.



# TREATMENT OF NPC

NPC researches in the world :

2016 : United Kingdom
2018 : India
2019 : Beijing / China
2019 : Amerika
2019 : Hubei / China

2020 : NCCN Guidelines of NPC

*The Journal of Laryngology & Otology* (2016), **130** (Suppl. S2), *S97–S103*.

GUIDELINE



doi:10.1017/S0022215116000517

# Nasopharyngeal carcinoma: United Kingdom National Multidisciplinary Guidelines

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## Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK. Although much commoner in the eastern hemisphere, with an age-standardised incidence rate of 0.39 per 100 000 population, cancers of the nasopharynx form one of the rarer subsites in the head and neck.[1] This paper provides recommendations on the work up and management of nasopharyngeal cancer based on the existing evidence base for this condition.

London / Inggris : 2016

# Nasopharyngeal carcinoma : United Kingdom National Multidisciplinary Guidelines…..

*Recommendations*

- Patients with nasopharyngeal carcinoma (NPC) should be assessed with rigid and fibre-optic nasendoscopy. (R)
- Nasopharyngeal biopsies should be preferably carried out endoscopically. (R)
- Multislice computed tomographic (CT) scan of head, neck and chest should be carried out in all patients and magnetic resonance imaging (MRI) where appropriate to optimise staging. (R)
- Radiotherapy (RT) is the mainstay for the radical treatment for NPC. (R)
- Concurrent chemoradiotherapy offers significant improvement in overall survival in stage III and IV diseases. (R)
- Surgery should only be used to obtain tissue for diagnosis and to deal with otitis media with effusion. (R)
- Radiation therapy is the treatment of choice for stage I and II disease. (R)
- Intensity modulated radiation therapy techniques should be employed. (R)
- Concurrent chemotherapy with radiation therapy is the treatment of choice for stage III and IV disease. (R)
- Patients with NPC should be followed-up and assessed with rigid and/or fibre-optic nasendoscopy. (G)
- Positron emission tomography–computed tomography (PET–CT), CT or MRI scan should be carried out at three months from completion of treatment to assess response. (R)
- Multislice CT scan of head, neck and chest should be carried out in all patients and MRI scan whenever possible and specially in advanced cases with suspected recurrence. (R)
- Surgery in form of nasopharyngectomy should be considered as a first line treatment of residual or recurrent disease at the primary site. (R)
- Neck dissection remains the treatment of choice for residual or metastatic neck disease whenever possible. (R)
- Re-irradiation should be considered as a second line of treatment in recurrent disease. (R)

Hindawi
Journal of Oncology
Volume 2018, Article ID 3725837, 7 pages
https://doi.org/10.1155/2018/3725837

*Review Article*

# Current Role of Chemotherapy in Nonmetastatic Nasopharyngeal Cancer

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Nasopharyngeal carcinoma is highly radio- and chemosensitive tumor with its unique clinical and biological behavior. Treatment of stage I disease is radical radiotherapy alone. For stage II disease treatment is radiotherapy with or without chemotherapy. The standard of care for locally advanced nasopharyngeal cancer (stages III-IVB) is concurrent chemoradiation. Optimum timing and sequence of chemotherapy are not yet well-defined. The role of adjuvant and induction chemotherapy is debatable. Here we are going to highlight the role of chemotherapy in nasopharyngeal carcinoma, its benefit, and controversies regarding timing and sequences.

Kolkata / India : 2018

Cancer Manag Res. 2019; 11: 6365–6376.
Published online 2019 Jul 10. doi: 10.2147/CMAR.S197544
PMCID: PMC6628961
PMID: 31372041

# Chinese expert consensus on diagnosis and treatment of nasopharyngeal carcinoma: evidence from current practice and future perspectives

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▸ Author information ▸ Article notes ▸ Copyright and License information Disclaimer

China : 2019

## Abstract

Go to:

Nasopharyngeal carcinoma (NPC) is a rare type of head and neck cancer, with a higher incidence reported only in Southeast Asia and Northern Africa. Owing to the rarity of NPC occurrence, no internationally accepted consensus or guideline for its diagnosis and treatment is available. Based on the current evidences and practices, the Chinese experts on multidisciplinary diagnosis and treatment of NPC were designated to develop a national consensus for the treatment strategy of NPC. In this consensus, we report the development for improving the treatment efficacy and quality of life of NPC patients in China. The consensus also describes and recommends the role of multidisciplinary management approach in the management of NPC. A multidisciplinary team should include experts from different domains who can cater to the individualized needs of patients with NPC in a much more efficient manner. In addition, the team may also play a key role in developing guiding principles for future research, contributing to the improvement in the management of NPC.

**Keywords:** Asian, Chinese, consensus, nasopharyngeal carcinoma, radiotherapy

# Chinese expert consensus on diagnosis and treatment of nasopharyngeal carcinoma: evidence from current practice and future perspectives .....

## Treatment options for stage I NPC

Radiotherapy is the main treatment for the NPC patients without distant metastasis. For stage I, a radical dose of 66–70 Gy and 56 Gy administered to the primary tumor and the upper neck, respectively, is necessary for tumor control and prevention of local recurrence, and the local control rate is over 90% for patients with stage T1N0M0.[21,22] A single-center retrospective study by Gao et al reported a 5-year OS of 85% and a local control rate of 90% in stage N0 cases without irradiating the lower cervical region. The study reported a very low failure rate of <0.2%. This evidence suggested that radiotherapy is not necessary in the lower cervical region in stage N0 cases.[23]

# Treatment recommendations in stage II NPC

**Recommendations**

(i) For conventional radical radiotherapy, a dose fraction of 2.0 Gy/fx and a total dose of 66–70 Gy/33–35fx are recommended. For IMRT, a fractioned dose of 2.12–2.25 Gy/fx and a total dose of 66–72 Gy (30–33 times) are recommended. Patients with a significant residual disease after irradiation should be administered local extended-dose irradiation or additional 6 Gy external irradiation or stereotactic radiotherapy or breech-loading intracavitary brachytherapy with an additional 6–10 Gy dose.

(ii) Patients with parapharyngeal obvious invasion/enlarged neck lymph nodes or retropharyngeal lymph nodes (diameter ≥2.0 cm) are recommended cisplatin monotherapy 35–40 mg/m$^2$/week or 80–100 mg/m$^2$/3 weeks.

# Treatment recommendations for locally advanced NPC

**Recommendations**

**1.Chemotherapy regimen (specific therapeutic dose) and radiotherapy dose**

For patients undergoing radical radiotherapy with two dimensional technique, a fractioned dose of 2.0 Gy/fx and a total dose of 66–70 Gy/33–35 fx are recommended. For IMRT, a fractioned dose of 2.12–2.25 Gy/fx and a total dose of 66–72 Gy (30–33 times of fractioned dose) are recommended. Patients with a significant residual disease after radiation therapy should be administered local extended-dose irradiation or an additional external irradiation dose of 6 Gy or stereotactic radiotherapy with an additional dose of 6–10 Gy. Patients without contraindications to chemotherapy are recommended to be prescribed with concurrent chemotherapy, with cisplatin monotherapy 35–40 mg/m$^2$/week or 80–100 mg/m$^2$ ETW as the mainstay.

**2. Adjuvant chemotherapy recommendations**

(i) Cisplatin + Fluorouracil (PF regimen):[2,34–36,45] 5-fluorouracil (5-FU) 1000 mg/m$^2$/day for 4 days [96 hr continuous intravenous (IV) infusion] or 5-FU 800 mg/m$^2$/day IV infusion for 5 days [120 hrs IV infusion]; Cisplatin (DDP) 80 mg/m$^2$ IV on day 1 or DDP 20 mg/m$^2$/day IV infusion on days 1–4; repeat the cycle every 28 days for 2–4 courses.

(ii) Fluorouracil + Carboplatin (FC regimen)[38] 5-FU 1000 mg/m$^2$, 96 hr continuous IV infusion; carboplatin AUC 5 IV on day 1; repeat the cycle every 21 days for 2–4 courses,

## 3. Induction chemotherapy (neoadjuvant chemotherapy) recommendations

(i) Docetaxel, cisplatin, fluorouracil (TPF regimen): Docetaxel 70 mg/m$^2$ IV on day 1; DDP 75 mg/m$^2$ IV on day 1; 5-FU 1000 mg/m$^2$ 96 hr continuous infusion; repeat the cycle every 28 days for 2–4 courses[71] or docetaxel 60 mg/m$^2$ IV on day 1; DDP 60 mg/m$^2$, IV on day 1; 5-FU 600 mg/m$^2$, 120 hr continuous infusion; repeat the cycle every 3 weeks for three cycles before CCRT.[72]

(ii) Gemcitabine + Carboplatin (GC regimen)[48] Gemcitabine 1000 mg/m$^2$ IV on days 1 and 8; carboplatin AUC 5 IV on day 1; repeat the cycle every 21 days for 2–4 courses

(iii) Docetaxel + Cisplatin (DP regimen)[49] Docetaxel 75 mg/m$^2$ IV and DDP 75 mg/m$^2$ IV on day 1; repeat the cycle every 21 days for 2–4 courses

(iv) Cisplatin + Fluorouracil (PF regimen)[73] DDP 100 mg/m$^2$ IV on day 1; 5-FU 1000 mg/m$^2$ 96 hr continuous infusion; repeat the cycle every 3 weeks for 3 cycles.

(v) EGFR monoclonal antibody combined with CRT/RT[61] Cetuximab IV at a starting dose of 400 mg/m$^2$ on day 1 about 7–10 days before starting CRT/RT; further weekly infusion at a maintenance dose of 250 mg/m$^2$ used with CRT/RT.

# Treatment recommendations for recurrent or metastatic NPC

**Recommendations**

**Locally recurrent disease**

(i) The total dose of radiotherapy administered in patients with locally recurrent nasopharyngeal carcinoma (NPC) should be recalculated after considering the patient's condition, the extent of tumor invasion, and tumor volume. At present, there is no consensus on the best dose fraction and total doses. Generally, larger dose fractions and the total dose lead to a higher local control rate, but also more toxicities. The local control rate of total dose ≥60 Gy with regular dose fractions is significantly better than <60 Gy.

# CHEMOTHERAPY REGIMEN RECOMMENDATIONS

**Recommendations**(a) **Patients with Locally recurrent and metastatic nasopharyngeal carcinoma (NPC) who are not suitable for radiotherapy/ Surgery**

1. GP regimen: Gemcitabine 1250 mg/m$^2$ IV on days 1 and 8; DDP 75 mg/m$^2$ IV on day 1; repeat the cycle every 21 days for 6 courses[77] or gemcitabine 1000 mg/m$^2$ IV on days 1 and 8; DDP 80 mg/m$^2$ IV on day 1; repeat the cycle every 21 days for 6 courses.[78]
2. Docetaxel + Carboplatin [DC regimen][:79] Docetaxel 65 mg/m$^2$ IV on day 1; carboplatin AUC 6 IV on day 1; repeat the cycle every 21 days for 6 courses.
3. TC regimen[:80] Paclitaxel 175 mg/m$^2$ IV on day 1; carboplatin AUC 6 IV on day 1; repeat the cycle every 21 days for 6 courses
4. TPF regimen[:82] Paclitaxel 135 mg/m$^2$ IV on day 1; DDP 25 mg/m$^2$ IV on days 1 to day 3; 5-FU 600–1000 mg/m$^2$/day 120 hr continuous infusion; repeat the cycle every three weeks for 6 courses
5. CC regimen[:85] Capecitabine 1000 mg/m$^2$ PO BID on days 1–14 and DDP 80 mg/m$^2$ IV on day 1; repeat the cycle every 21 days for 6 courses
6. Gemox regimen[:86] Gemcitabine 1000 mg/m$^2$ continuous IV infusion at a constant rate of 10 mg/m$^2$·min on day 1; oxaliplatin 100 mg/m$^2$ IV on day 2; repeat the cycle every 14 days for 12 courses

# Regimen for resistant platinum-based chemotherapy

1. Gemcitabine regimen[:88] Gemcitabine 1000 mg/m$^2$ IV on days 1, 8, and 15; repeat the cycle every 28 days for 6 courses
2. GN regimen[:87] Gemcitabine 1000 mg/m$^2$ IV on days 1 and 8; vinorelbine 25 mg/m$^2$ IV on days 1 and 8; repeat the cycle every 21 days for 6 courses
3. Capecitabine regimen[:89] Capecitabine 1250 mg/m$^2$ PO BID on days 1–14, repeat the cycle every 21 days
4. Docetaxel regimen[:90] Docetaxel 30 mg/m$^2$ IV on days 1, 8, and 15, followed by 1 week rest; repeat the cycle every 28 days for 6 courses
5. Cetuximab + Carboplatin regimen[:91] Cetuximab, IV at a starting dose of 400 mg/m$^2$ on day 1; further weekly infusion at a maintenance dose of 250 mg/m$^2$; carboplatin AUC 5 IV on day 1, repeat the cycle every 21 days for 6–8 courses

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Gemcitabine and Cisplatin Induction Chemotherapy in Nasopharyngeal Carcinoma

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Massachusetts/ Amerika : 2019

# Gemcitabine and Cisplatin Induction Chemotherapy in Nasopharyngeal Carcinoma

## METHODS

In a parallel-group, multicenter, randomized, controlled, phase 3 trial, we compared gemcitabine and cisplatin as induction chemotherapy plus concurrent chemoradiotherapy with concurrent chemoradiotherapy alone. Patients with locoregionally advanced nasopharyngeal carcinoma were randomly assigned in a 1:1 ratio to receive gemcitabine (at a dose of 1 g per square meter of body-surface area on days 1 and 8) plus cisplatin (80 mg per square meter on day 1), administered every 3 weeks for three cycles, plus chemoradiotherapy (concurrent cisplatin at a dose of 100 mg per square meter every 3 weeks for three cycles plus intensity-modulated radiotherapy) or chemoradiotherapy alone. The primary end point was recurrence-free survival (i.e., freedom from disease recurrence [distant metastasis or locoregional recurrence] or death from any cause) in the intention-to-treat population. Secondary end points included overall survival, treatment adherence, and safety.

# Gemcitabine and Cisplatin Induction Chemotherapy in Nasopharyngeal Carcinoma .....

**CONCLUSIONS**

Induction chemotherapy added to chemoradiotherapy significantly improved recurrence-free survival and overall survival, as compared with chemoradiotherapy alone, among patients with locoregionally advanced nasopharyngeal carcinoma. (Funded by the Innovation Team Development Plan of the Ministry of Education and others; ClinicalTrials.gov number, NCT01872962.)

Int J Clin Exp Med 2019;12(8):10682-10688
www.ijcem.com /ISSN:1940-5901/IJCEM0089645

*Original Article*

# Concurrent chemoradiotherapy via nimotuzumab combined with cisplatin improves clinical efficacy in middle-late staged nasopharyngeal carcinomas

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Hubei / China : 2019

# Concurrent chemoradiotherapy via nimotuzumab combined with cisplatin improves clinical efficacy in middle-late staged nasopharyngeal carcinomas

## Methods

- Patients in both groups were given three-di-mensional conformal radiotherapy.
- The nasopharyngeal primary target lesion was a high-risk target area with a radiological dose of 78 Gy/30 F, while surrounding tissues of the focal lesion were the low-risk target area, with a radiological dose of 60 Gy/30 F.
- During radiotherapy, the two groups of patients were given cisplatin concurrent chemotherapy by intravenous infusions of cisplatin 40 mg/m2, once/week, for 6 days in total. For the course of chemotherapy in the study group, 200 mg of nimotuzumab was given by intravenous infusions, once/week, for 6 days in total.

# Concurrent chemoradiotherapy via nimotuzumab combined with cisplatin improves clinical efficacy in middle-late staged nasopharyngeal carcinomas

**In summary**, nimotuzumab combined with cisplatin concurrent radio-chemotherapy will effectively improve the clinical efficacy of patients with middle-late staged nasopharyngeal carcinomas, reducing adverse reactions. This treatment method is worthy of clinical application and promotion.

National Comprehensive Cancer Network®

# NCCN Guidelines Version 2.2020
# Cancer of the Nasopharynx

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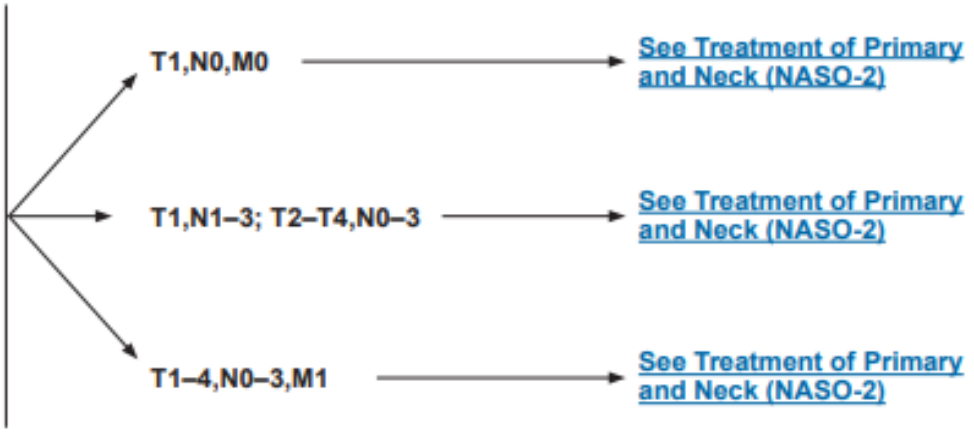
## WORKUP

- H&P[a,b] including a complete head and neck exam; mirror examination as clinically indicated
- Nasopharyngeal fiberoptic examination
- Biopsy of primary site or FNA of the neck[c]
- MRI with contrast of skull base to clavicle ± CT of skull base/neck with contrast to evaluate skull base erosion
- Imaging for distant metastases with FDG PET/CT and/or chest CT with contrast[d]
- Consider Epstein-Barr virus (EBV)/DNA testing[e]
- As clinically indicated:
  - Dental/prosthodontic evaluation[f]
  - Nutrition, speech and swallowing evaluations/therapy[g]
  - Audiogram
  - Consider ophthalmologic and endocrine evaluation
  - Smoking cessation counseling[a]
  - Fertility/reproductive counseling[h]

**Multidisciplinary consultation as clinically indicated**

## CLINICAL STAGING




[a] H&P should include documentation and quantification (pack years smoked) of tobacco use history. All current smokers should be advised to quit smoking, and former smokers should be advised to remain abstinent from smoking. For additional cessation support, refer to the Patient/Provider Smoking Cessation Resources in the NCCN Guidelines for Smoking Cessation.

[b] Screen for depression (See NCCN Guidelines for Distress Management).

[c] Image-guided (US or CT) needle biopsy of cystic neck nodes may offer better diagnostic yield than FNA by palpation alone for initial diagnosis in this setting.

[d] See Principles of Imaging (IMG-A).

[e] For nonkeratinizing or undifferentiated histology, consider testing for EBV in tumor and blood. Common means for detecting EBV in pathologic specimens include in situ hybridization for EBV-encoded RNA (EBER) or immunohistochemical staining for latent membrane protein (LMP). The EBV DNA load within the serum or plasma may be quantified using polymerase chain reaction (PCR) targeting genomic sequences of the EBV DNA such as BamHI-W, EBNA, or LMP; these tests vary in their sensitivity. The EBV DNA load may reflect prognosis and change in response to therapy.

[f] See Principles of Dental Evaluation and Management (DENT-A).

[g] See Principles of Nutrition: Management and Supportive Care (NUTR-A).

[h] See fertility and reproductive endocrine considerations in the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology.

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

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# NCCN Guidelines Version 2.2020
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| CLINICAL STAGING | TREATMENT OF PRIMARY AND NECK | FOLLOW-UP |
|---|---|---|
| T1,N0,M0 | Definitive RT to nasopharynx and elective RT[i] to neck | See Post Systemic Therapy/RT or RT Neck Evaluation (FOLL-A, 2 of 2) |
| T1,N1–3; T2–T4,N0–3 | Clinical trials (preferred)<br>or<br>Concurrent systemic therapy/RT[i,j] followed by adjuvant chemotherapy[i]<br>or<br>Induction chemotherapy[j,k] followed by systemic therapy/RT[i,j]<br>or<br>Concurrent systemic therapy/RT[i,j] not followed by adjuvant chemotherapy (category 2B) | See Post Systemic Therapy/RT or RT Neck Evaluation (FOLL-A, 2 of 2) |
| T1–4,N0–3,M1 | Clinical trials (preferred)<br>or<br>Platinum-based combination chemotherapy[i] → RT[i]<br>or<br>Concurrent systemic therapy/RT[i,j] as clinically indicated<br>and<br>Locoregional treatment to oligometastatic sites[i,j,l]<br>or<br>Observation | Follow-up (See FOLL-A) |

Recurrent or persistent disease (See ADV-3)

[i] See Principles of Radiation Therapy (NASO-A).
[j] See Principles of Systemic Therapy (SYST-A, 3 of 6).
[k] See Discussion on induction chemotherapy.

[l] Can be used for select patients with distant metastasis in limited site or with small tumor burden, or for patients with symptoms in the primary or any nodal site.

## PRINCIPLES OF RADIATION THERAPY[1]

**DEFINITIVE:**
**RT Alone (for T1,N0 or patients who are not eligible to receive chemotherapy)**
- **PTV**
  - **High risk: Primary tumor and involved lymph nodes [this includes possible local subclinical infiltration at the primary site and at the high-risk level lymph node(s)]**
    - **66 Gy (2.2 Gy/fraction) to 70–70.2 Gy (1.8–2.0 Gy/fraction); daily Monday–Friday in 6–7 weeks[2,3]**
    - **69.96 Gy (2.12 Gy/fraction) daily Monday–Friday in 6–7 weeks[4]**
- **Low to intermediate risk: Sites of suspected subclinical spread**
  - **44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)[5]**

**CONCURRENT SYSTEMIC THERAPY/RT:[6]**
**(preferred for patients eligible for chemotherapy)**
- **PTV**
  - **High risk: typically 70–70.2 Gy (1.8–2.0 Gy/fraction); daily Monday–Friday in 7 weeks[2]**
  - **Low to intermediate risk: 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)[5]**

**IMRT is recommended for cancers of the nasopharynx to minimize dose to critical structures. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy.**

[1] See Radiation Techniques (RAD-A) and Discussion.
[2] Care should be taken to avoid critical neural structures; therefore, 1.8 Gy/fraction can be considered.
[3] For doses >70 Gy, some clinicians feel that the fractionation should be slightly modified (eg, <2.0 Gy/fraction for at least some of the treatment) to minimize toxicity. An additional 2–3 doses can be added depending on clinical circumstances.
[4] Lee NY, Zhang Q, Pfister DG, et al. Addition of bevacizumab to standard systemic therapy/RT for locoregionally advanced nasopharyngeal carcinoma (RTOG 0615): a phase 2 multi-institutional trial. Lancet Oncol 2012;13:172-180.
[5] Suggest 44–50 Gy in sequentially planned IMRT or 54–63 Gy with IMRT dose painting technique (dependent on dose per fraction).
[6] See Principles of Systemic Therapy (SYST-A).

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

# Recent Treatment of NPC Guideline NCCN 2020

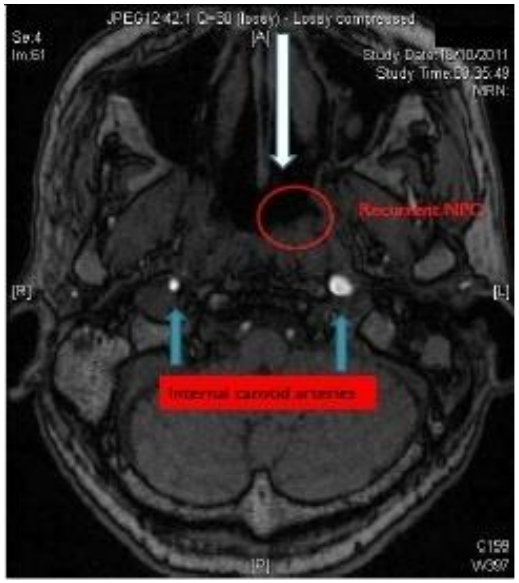
**T1N0M0** : Radiotherapy alone (± Chemotherapy sensitizer)

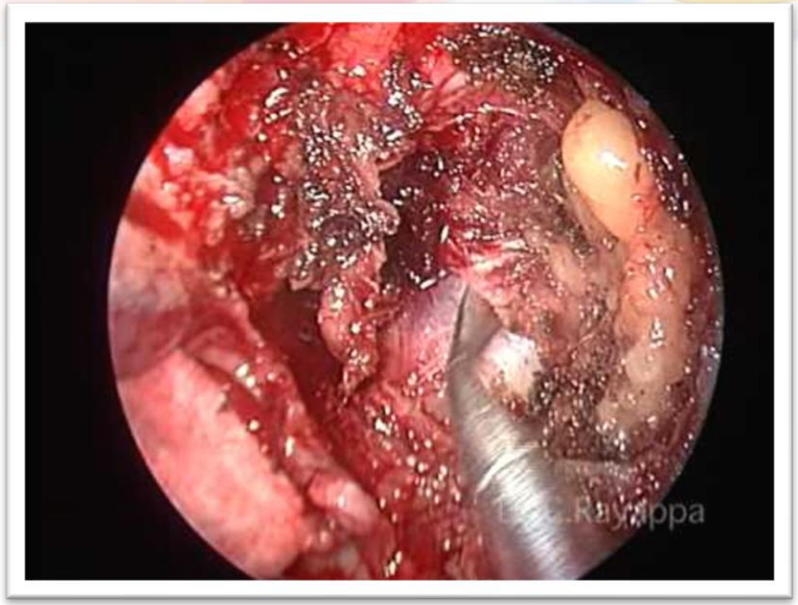
**T1N1-3; T2-4, N0-3, M0** : Chemoradiotherapy concurrent followed by adjuvant chemotherapy, or : induction chemotherapy followed by systemic chemo-radiotherapy, or: concurrent chemo-radiotherapy not followed by adjuvant chemotherapy

**T1-4, N0-3, M1** : Platinum-based combination chemotherapy, following with raditherapy or chemo-radiotherapy concurrent and adjuvant

# SURGERY

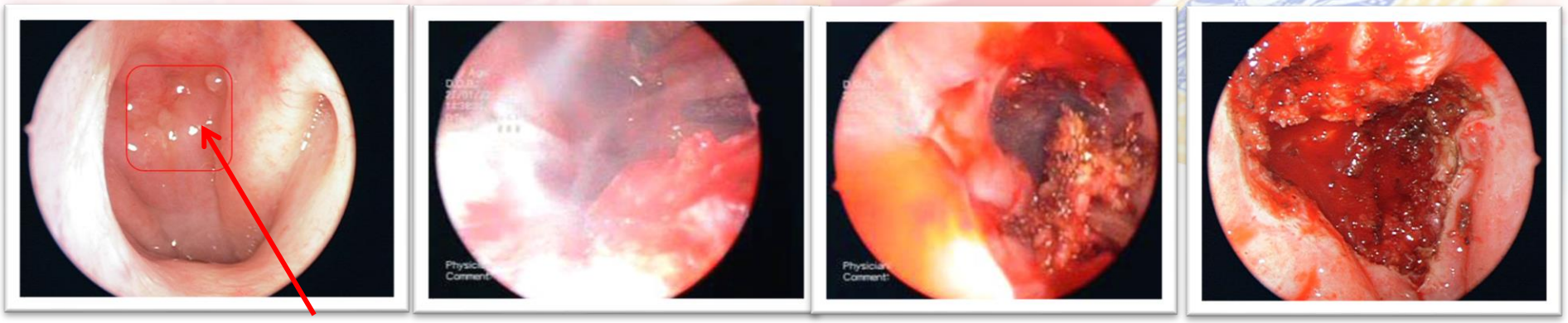
1. Nasopharyngectomy Endoscopic



Nasopharyngectomy endoscopic has recently emerged as a good salvage option with minimal morbidity in other regions is a safe and effective salvage procedure for treating rT1 and rT2 NPC with minimal morbidity

# Nasopharyngectomy Endoscopic.....



**Mass**

(Lau WY, Chong HM, Yu HC, Ngan KC, 2012)

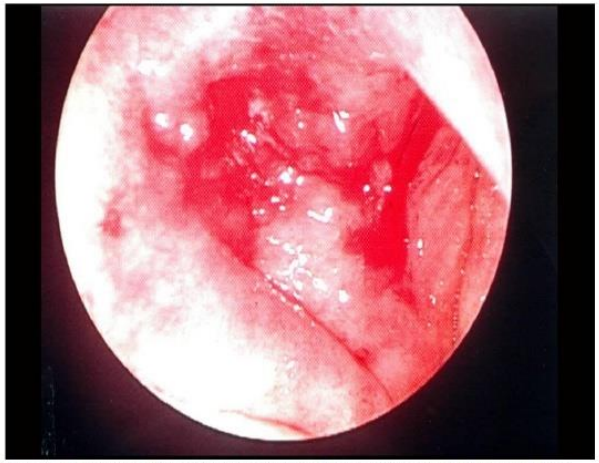


Fig. 1. Recurrent NPC is detected in the right fossa of Rosenmullar. The dotted line presents the planned mucosal incision.

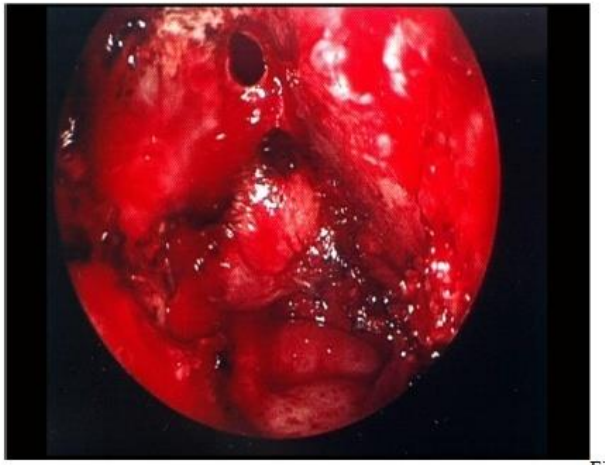


Fig The incision is made in the spheno-ethmoid recess and connects with the right torus tubarius. The specimen is retracted to expose the right sphenoid ostium and pharyngobasilar fascia which attaches to the sphenoid-clivus junction.

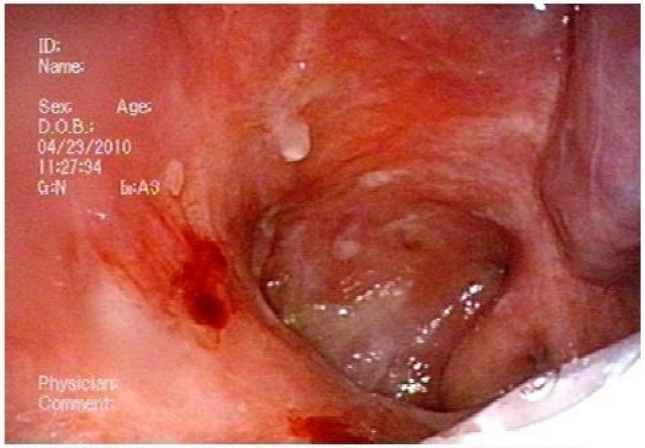



Fig. 4. Follow up nasopharynyoscopy 2 years after surgery, the defect is well epithelialized and no local recurrence was detected.

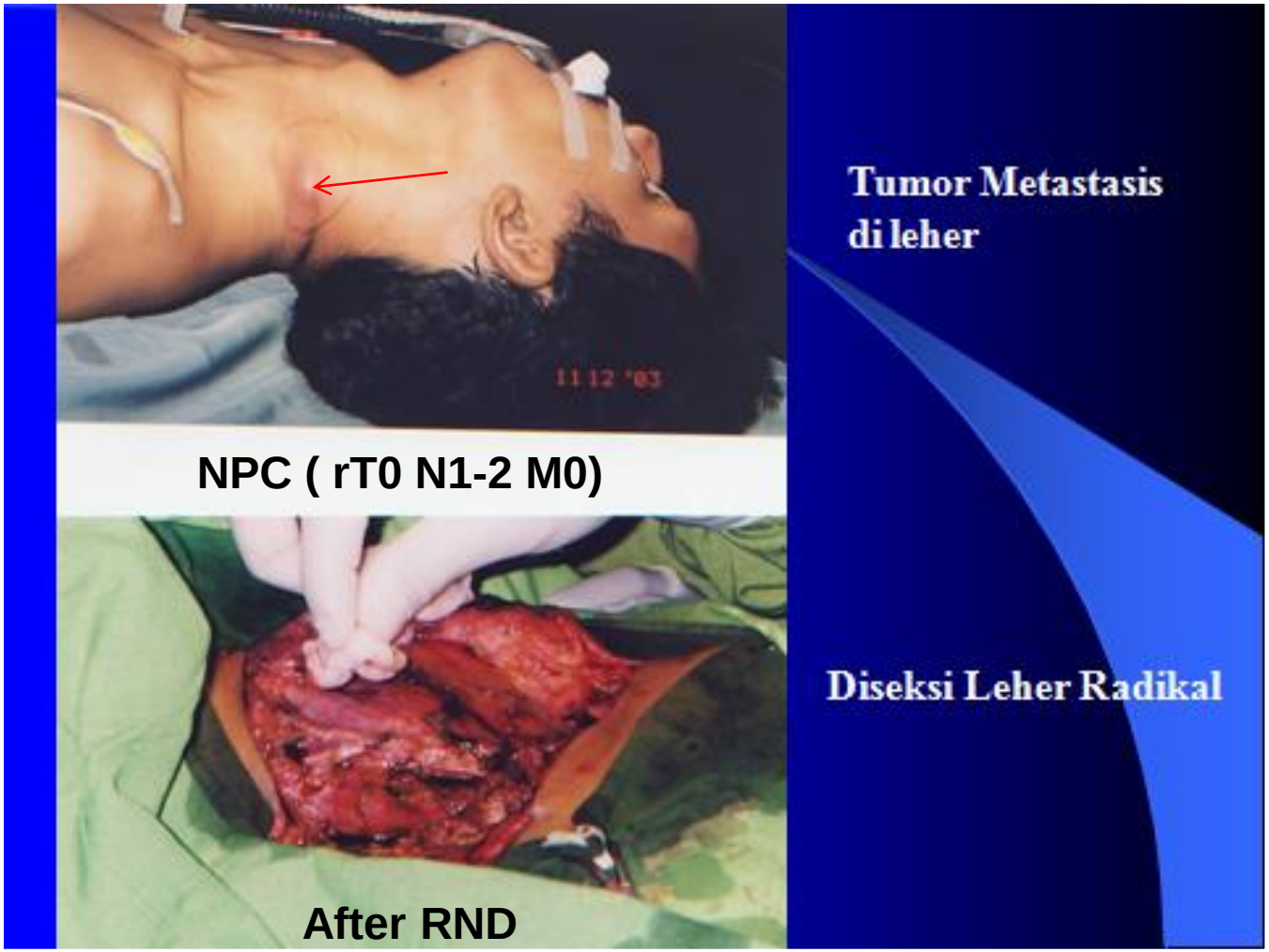
(Sheng-Po Hao, 2013)

# Endoscopic Nasopharyngectomy

(Sheng-Po Hao, 2013)

- Research in Hongkong → **12 pts**
- 8 cases after 1 course and 4 cases after 2 course of CRT
- Preoperative evaluation with MRI and PET
- rT1 in 9 pts, rT2 in 1 pts and rT3 in 2 pts
- Endoscopic nasopharngectomy was carried out with Diode LASER
- Navigation assistance was applied in rT2 (1) case and rT3 (2) cases
- Follow up in the out patient clinic for 9 to 50 month (mean 29,4 month)
- **The overall survival rate at 2 years is 87,5%**

# 2. Neck dissection




**MRI, PET scan**
**NF biopsy**

↓

**No tumor**

Arch Otolaryngol Head Neck Surg. 2012;138(6):572-576. doi:10.1001/archoto.2012.832

# Summary

1. The recent of NPC therapy was using **IMRT** (or IGRT) more effective than 3-DRT
2. Integrated chemo-radiotherapy it mean combined radiotherapy (**3 DRT / IMRT )** with **chemotherapy** (Cisplatin base and 5 FU, Paclitaxel, Docetaxel,or Gemcitabine) can increase the response rate and survival of NPC patients
4. Recently, reported new more effective combination which is **targeted therapy** (e.g. Cetuzimab, Nimotuzumab)
5. Current treatment of NPC → **NCCN Guidelines 2020**
6. Several studies reported minimally invasive **nasopharyngectomy endoscopic** is a feasible treatment for small tumor or recurrence after treatment (rNPC) with good result.

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