Concurrent Chemo radiation in Nasopharyngeal Cancer

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Anatomy

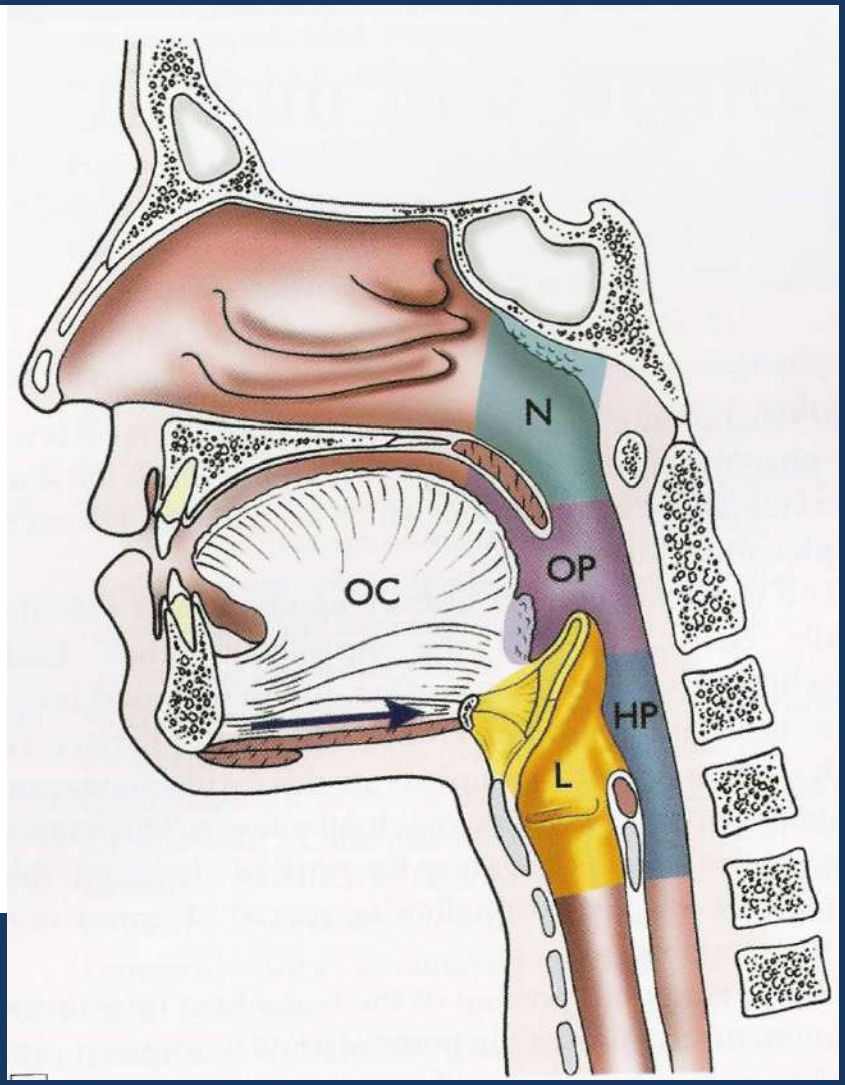
The pharynx is a musculomembraneous tube.

Interior of the pharynx is divided into 3 parts.

Oropharynx.

Nasopharynx.

Laryngopharynx.

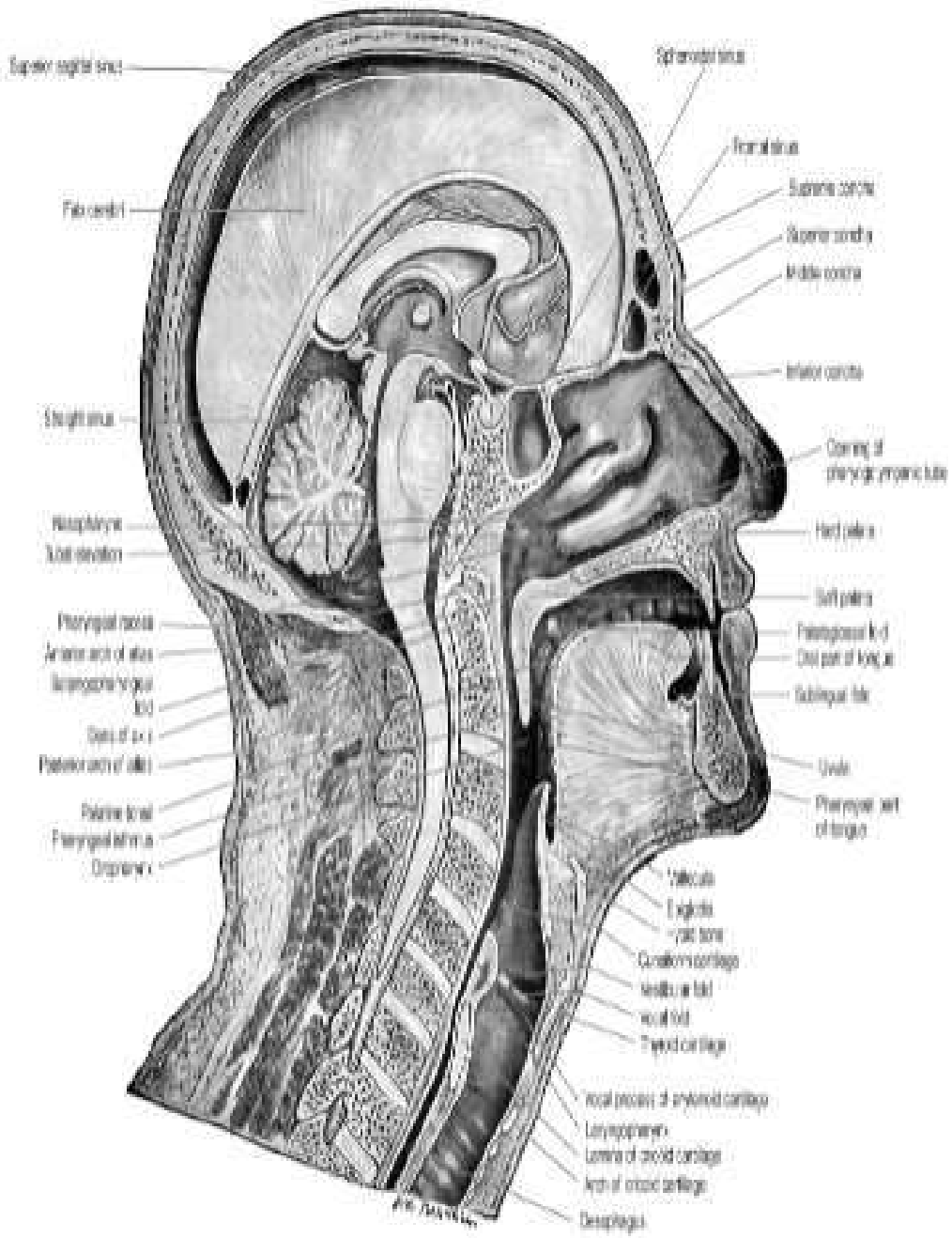


Nasopharynx

Present behind the nasal cavity and above soft palate.

Anterior wall is deficient.

Posterior wall and **roof** supported by sphenoid (body),basilar part of occipital,anterior arch of atlas.



Posterior wall and roof presents following features.

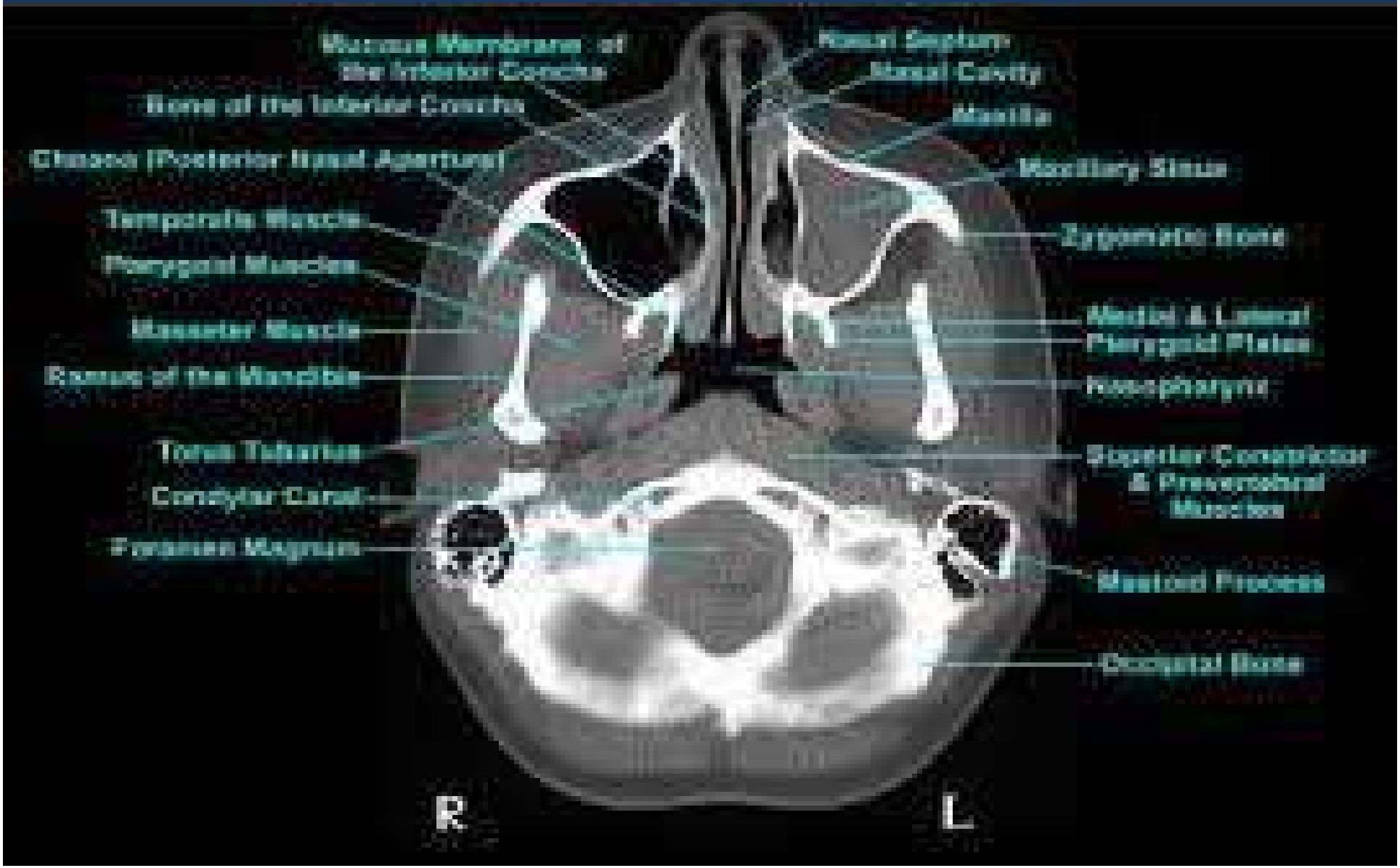
- The nasopharyngeal tonsils
- The pharyngeal bursa(pouch of Luschka)
- The pharyngeal hypophysis

Floor communicates with oropharynx through pharyngeal isthmus.

lateral wall presents the following features

- Nasopharyngeal opening of Auditory tube
- Tubal elevation
- Pharyngeal recess(Fossa of Rosenmuller)

Cross sectional anatomy of Nasopharynx



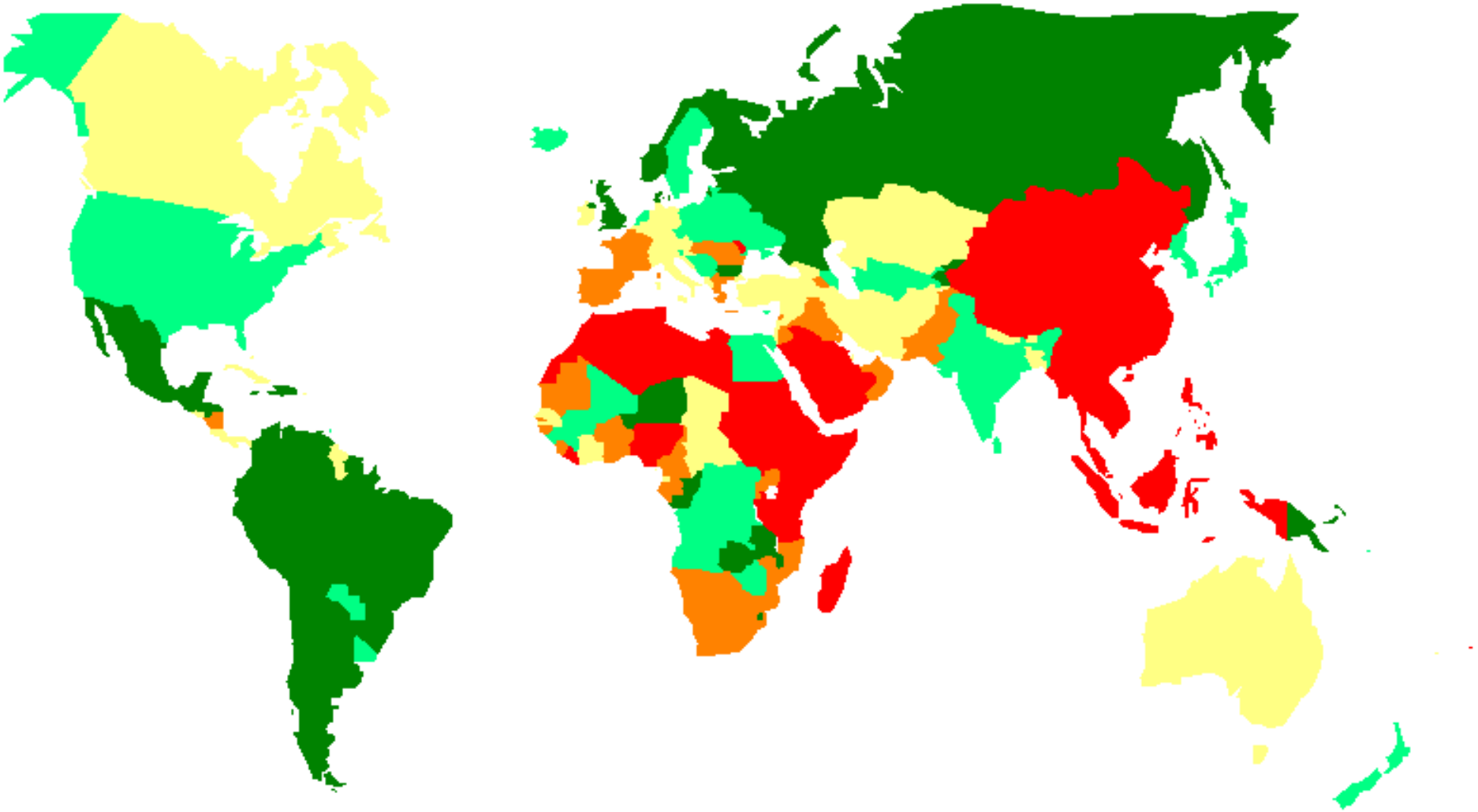
Nasopharyngeal Carcinoma (NPC)

- Arise from the epithelial lining of the nasopharynx.
- Fossa of Rosenmuller is the commonest site of origin.
- Results from the interplay of environmental, genetic and viral risk factors

Incidence & Mortality (World)

- 80,000 cases with 50,000 deaths annually
  - < 1 per 100,000/year incidence
  - 23rd most common cancer in the world
- 2-3 fold higher risk for males : females
- Broad racial/ethnic and geographic variation
  - 4th most common cancer in Hong Kong
- Highest incidence in Asian, N African/Mid east, and Arctic populations

Nasopharynx, Males
Age-Standardized incidence rate per 100,000



GLOBOCAN 2002, IARC

Other Etiologies

- Epstein-Barr Virus (EBV)

EBV DNA detected in ~100% of type II and III NPC

Type I is not as consistent

Also detected in NP dysplasia

- Salt-Preserved Fish & Meat
- Smoking causes a 2-6 fold increased risk

Particularly true for Type I

- Occupational exposures

Formalin

- Heat/combustion exposures
- Wood dust
- Chlorophenols

Pathology – WHO classification

- Nasopharyngeal carcinoma
  - Keratinizing squamous cell ca: type I
    - Similar with that in rest of aerodigestive tract
  - Non-keratinizing ca: type II and III
    - Differentiated non-keratinizing ca (type II)
    - Undifferentiated ca (type III)

Symptoms/signs

- Epistaxis and nasal obstruction/discharge
  - Mass in nasopharynx
- Tinnitus and hearing impairment
  - E-tube dysfunction, lateral extension
- Headache, diplopia, facial pain/numbness
  - Skull-base invasion, nerve palsy(5th/6th)
- Neck mass
- Signs of distant metastasis
  - Lung/bone/liver

AJCC

Tumour in nasopharynx (T)

T1	Tumour confined to the nasopharynx
T2	Tumour extends to soft tissues of oropharynx and/or nasal fossa
T2a	without parapharyngeal extension
T2b	with parapharyngeal extension
T3	Tumour invades bony structures and/or paranasal sinuses
T4	Tumour with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, or orbit

Regional lymph nodes (N)

The distribution and the prognostic effect of regional lymph node spread from nasopharynx cancer, especially of the undifferentiated type, is different from that of other head and neck mucosal cancers and justifies use of a different N classification scheme.

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa
N2	Bilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa
N3	Metastasis in a lymph node(s)
N3a	greater than 6 cm in dimension
N3b	extension to the supraclavicular fossa

AJCC

Stage grouping			
Stage 0	T1s	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T2a	N1	M0
	T2b	N0	M0
	T2b	N1	M0
Stage III	T1	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N0	M0
	T3	N1	M0
	T3	N2	M0
Stage IVA	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Standard approach to nasopharyngeal carcinoma

Stage	Denomination	Gold standard therapy
T1-2a N0 M0	Early stage	- IMRT alone - Conventional RT alone
From T2b N0 M0 to T4b N3 M0 also every T N2/3 M0	Locally advanced	- Neoadjuvant platinum-based CT followed by IMRT or CCRT (platinum-based) - Concurrent cDDP and RT
Every T every N M1	Metastatic	- Exclusive CT

RT: Radiotherapy; IMRT: Intensity modulated RT; CCRT: Concurrent chemoradiotherapy; CT: Comptued tomography.

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Treatment

- *Radiation Therapy is the mainstay*
  - Difficult surgical approach
  - Sensitive to radiotherapy
- RT volume (field) and dose
  - Primary tumor: 65-75 Gy
  - Involved neck: 65-70 Gy
  - Uninvolved neck: 50-60 Gy

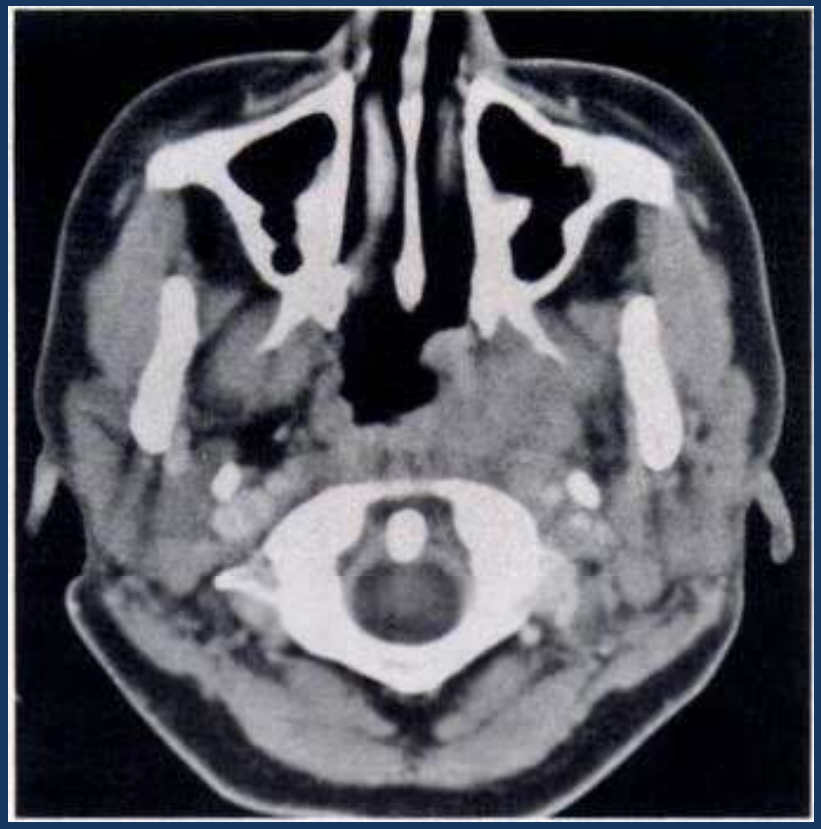


Fig.1- nasopharyngeal cancer, tumor has spread through pharyngobasilar fascia to involve parapharyngeal fat space.

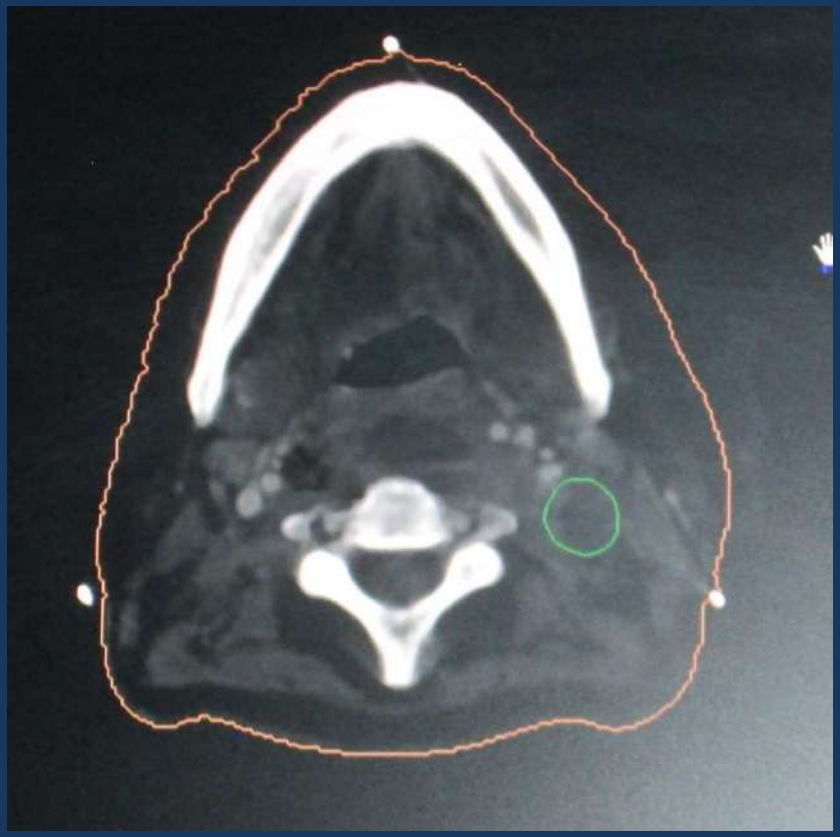


Fig.2- CT image showing level II neck nodes.

Steps of conventional planning

- Clinical evaluation & assessment
- Patient set up supine
- Immobilised with thermoplastic mask
- Planning X-rays or CT scan done
- Conventional set up : 3 fields; 2 lateral opposed for primary and upper neck, matched to 1 anterior field for lower neck.

Portals for conventional RT

B/L parallel opposed portals for primary & upper neck

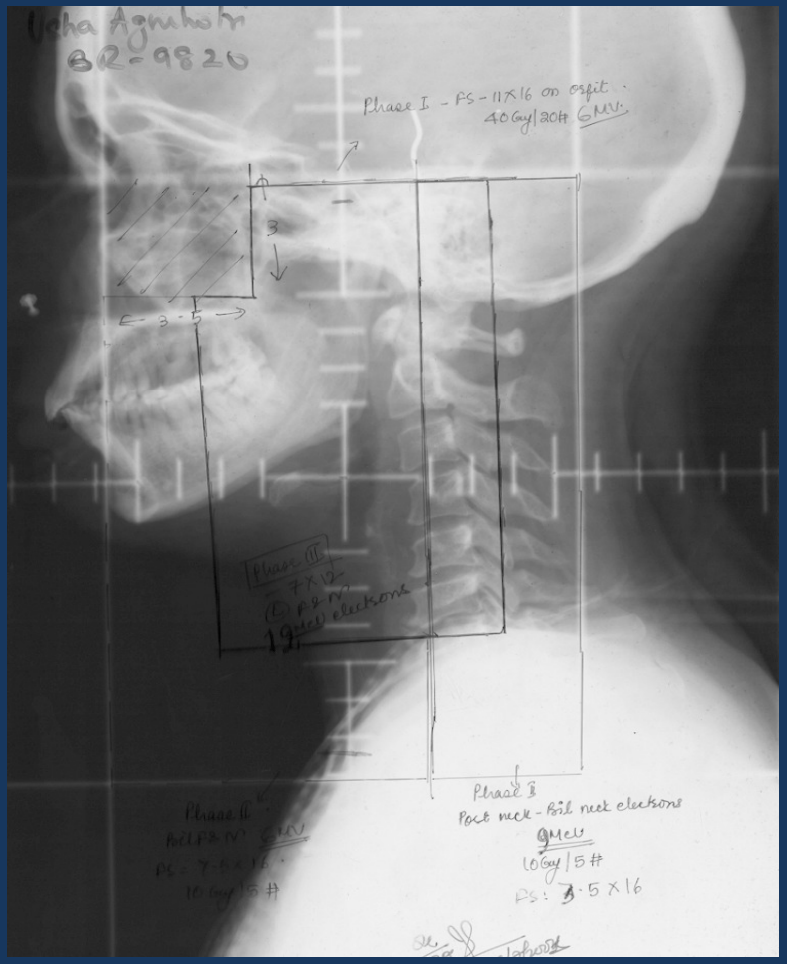
- Superior : 2 to 2.5 cm above the zygomatic arch and splits the pituitary fossa. In case of base of skull involvement or intracranial extension it is taken 4.0 to 5.0 cm above the zygomatic arch or 1 cm above the pituitary fossa.
- Inferior : at the thyroid notch
- Anterior : encompasses posterior ½ of nasal cavity or moved forward to cover the extensions if any.
- Posterior : kept open to cover the posterior triangle.

Portals for conventional RT

Single anterior portal for lower neck

- Superior : matched to the inferior border of the lateral fields.
- Inferior : extend below to cover the lower edge of clavicles.
- Lateral : cover medial 2/3rd of the clavicle.

Portals for conventional RT



Dose prescription

- Phase I : 40 to 44 GY in 20 to 22 fractions @ 2GY/#.
- Phase II : fields are shrinked to avoid the spinal cord. The primary tumor is boosted to an additional 20 to 25 GY.

  T1 & T2 tumor : 60 to 65 GY

  T3 & T4 tumor : 70 to 75 GY.

Dose to neck nodes : 45 to 50 GY to N0 neck.

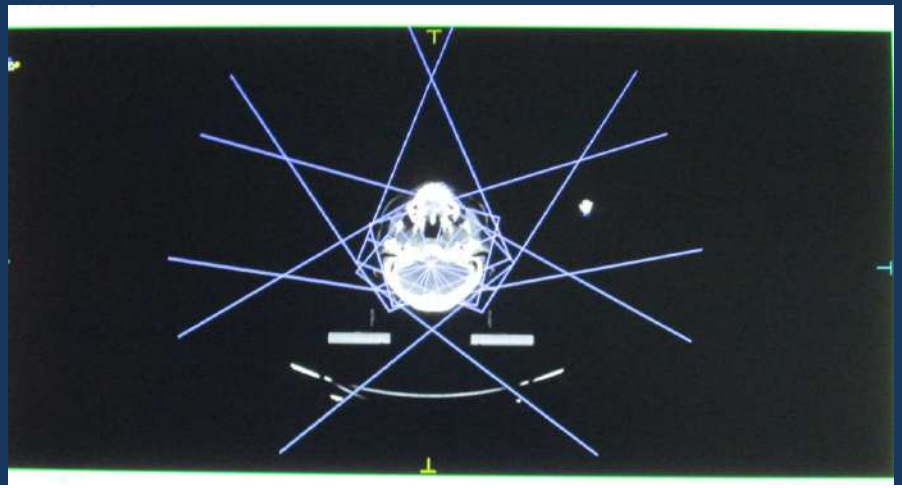
if nodes are palpable, an additional boost is given preferably by Electrons.

Morbidity from RT

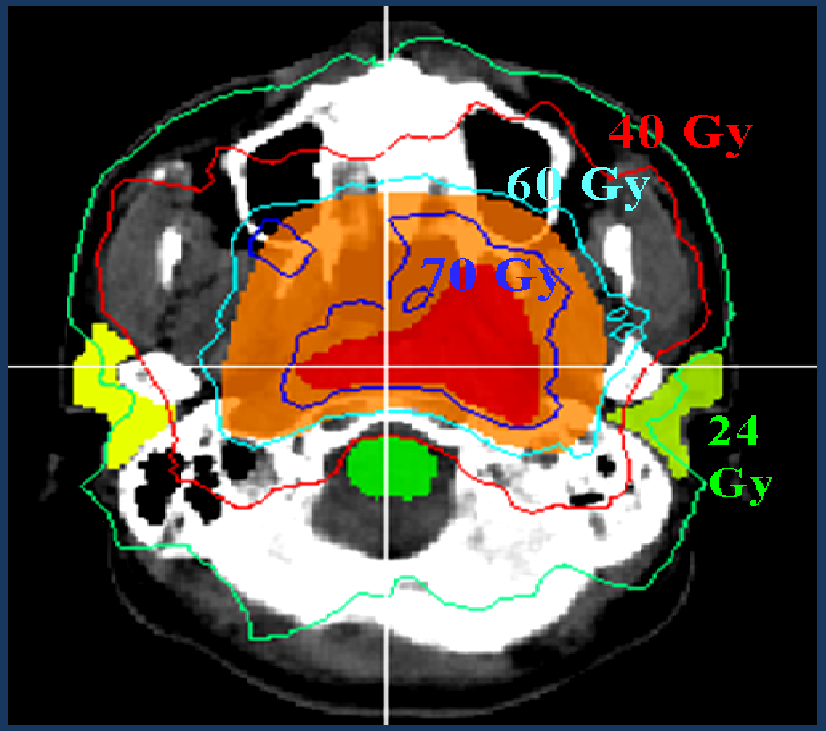
- Acute Toxicity
  - Mucositis
  - Dermatitis
  - Pharyngitis
  - Otitis
- Chronic Toxicity
  - Xerostomia
  - sub cutaneous fibrosis
  - radiation myelitis
  - cranial neuropathy
  - endocrine dysfunction
  - temporal lobe necrosis
  - hearing loss
  - otitis media
- Dose-limiting organ
  - Brain stem
  - Spinal cord
  - Pituitary-hypothalamic axis
  - Temporal lobes
  - Eyes
  - Middle/inner ears
  - Parotid glands

Need for newer techniques

- 3DCRT
- IMRT
- IGRT
- SRS (boost)
- Rapid arc
- VMAT
- Proton



- Development of computerized 3D treatment plans is an important technical advance for Nasopharyngeal cancer with its typically concave tumor volume and proximity to critical structures.



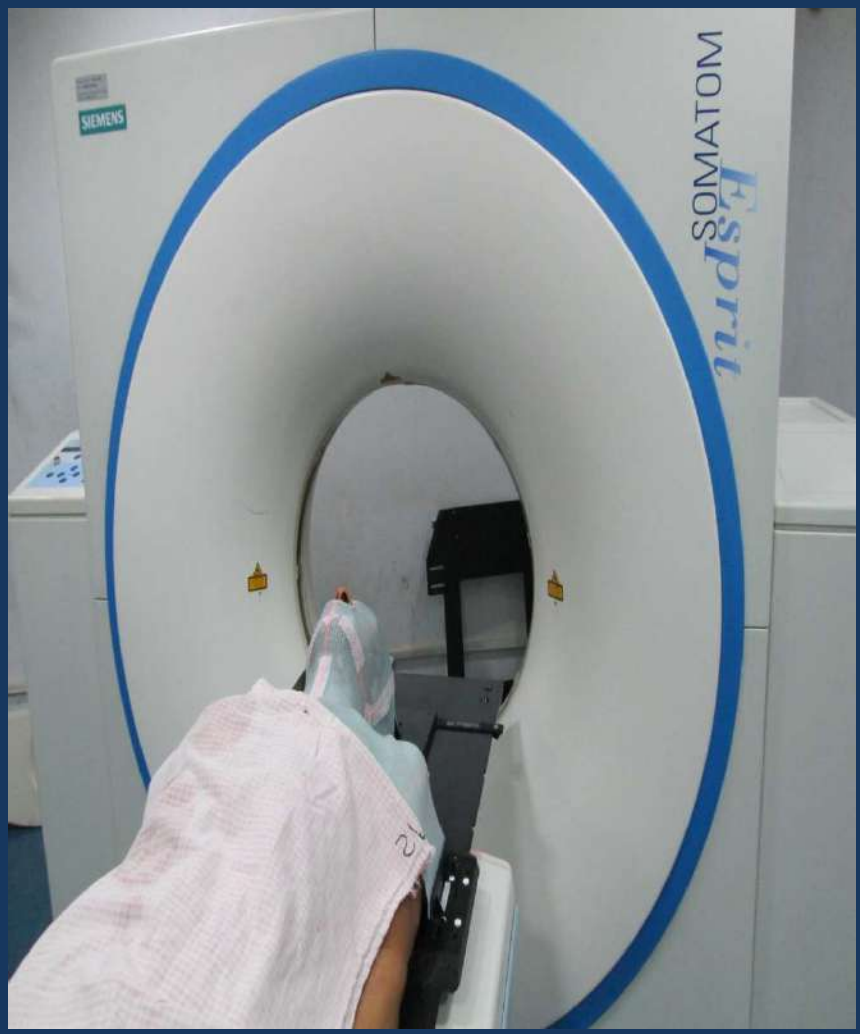
Rationale of IMRT in cancer nasopharynx

1. Anatomically complex H&N region
2. Treat target volumes adjacent to critical or sensitive normal tissues
3. Lack of organ motion in the H&N region
4. Allows for dose escalation , allows for concomitant boost.

Steps of IMRT

- Clinical evaluation & assessment
- Simulation
- Planning CT/MRI/PET-CT scan
- Target volume Delineation: Gross target volume, Clinical target volume, Planning target volume.
- Dose prescription : PTV dose and Organ at risk (OAR) constraint
- IMRT Planning, Dose Volume Histogram
- Quality Assurance
- Execution of IMRT

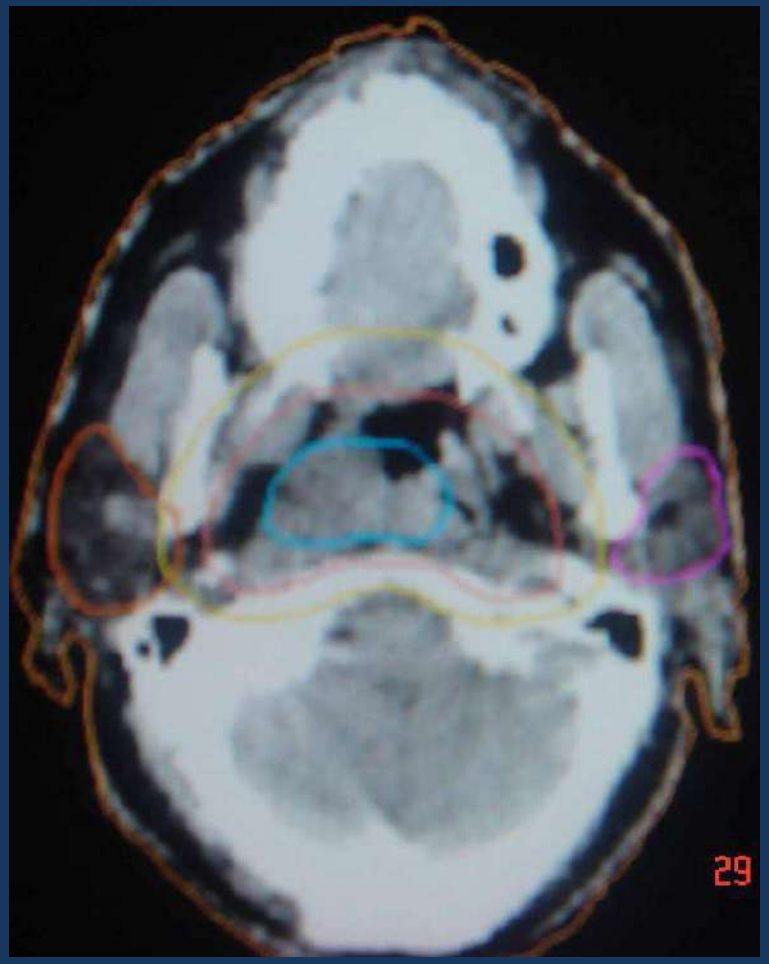
Steps of IMRT

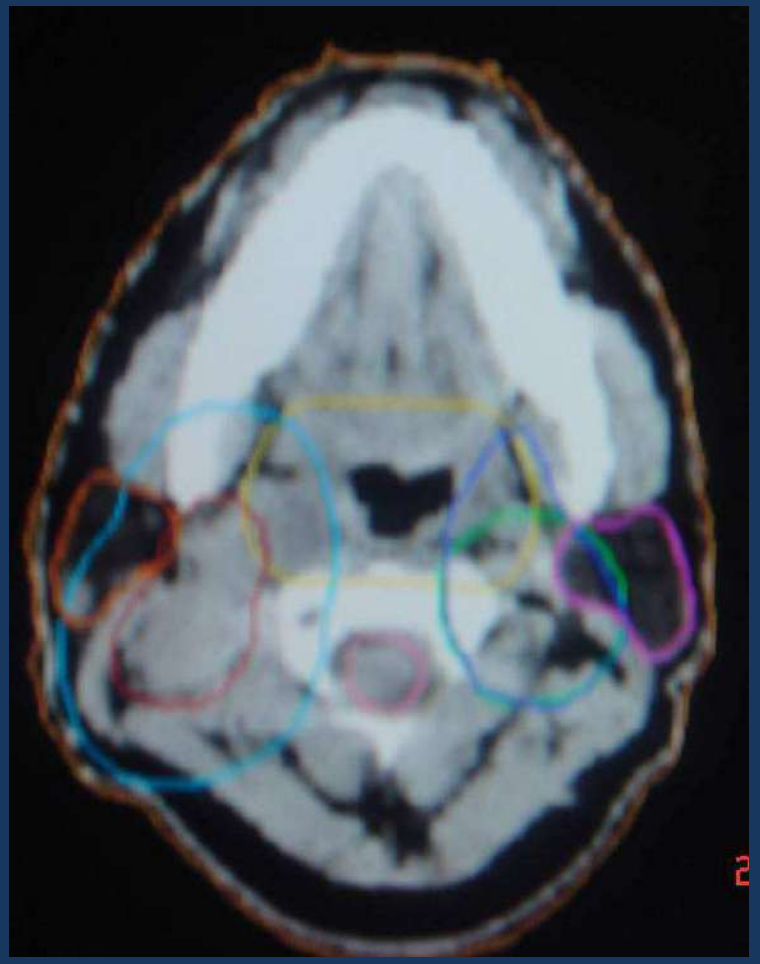


Contouring guidelines

- GTV = gross disease
- CTV = entire nasopharynx, sphenoid sinus, cavernous sinus, base of skull, posterior ½ of nasal cavity, posterior 1/3 of maxillary sinuses, post. Ethmoid sinus, pterygoid fossa, lateral & posterior pharyngeal wall, retropharyngeal nodes, & b/L cervical nodes including level V & SCF.
- PTV = 5mm to 1cm.

Contouring of primary disease and palpable neck nodes





Dose prescription

- PTV 1 : 70GY/35# @ 2GY/#
- PTV2 : 61.25GY/35# @ 1.75GY/#
- PTV 3 : 52.5 GY/30# @ 1.75GY/#

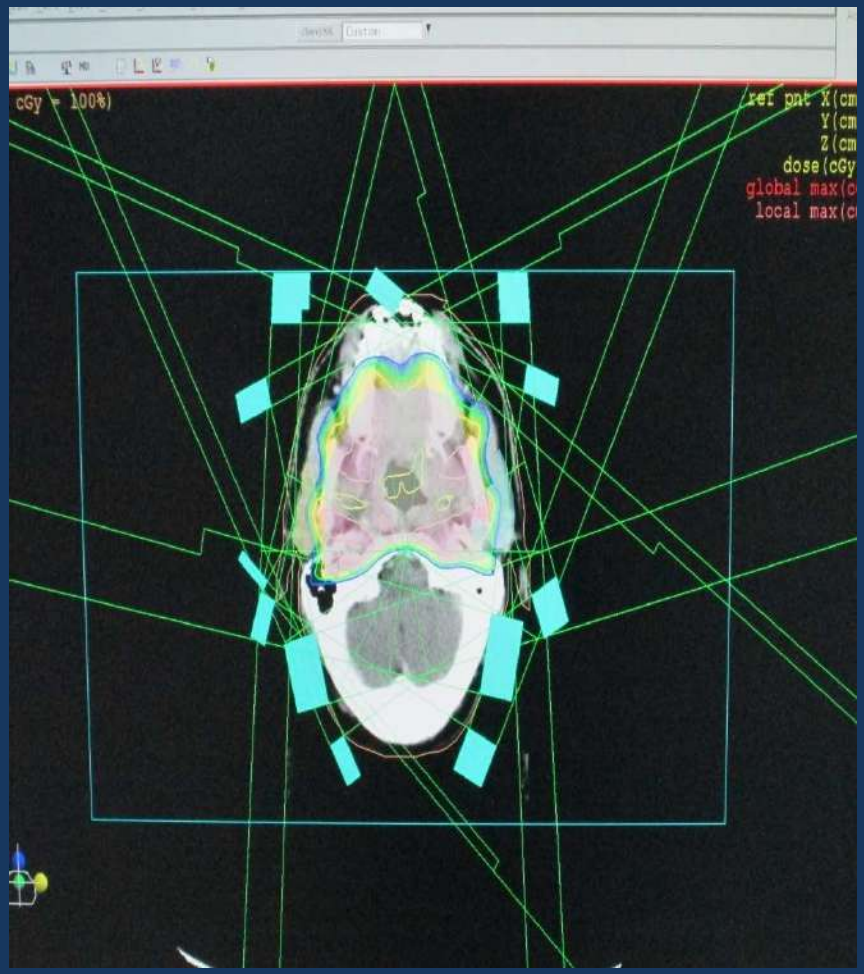
OAR Constraints

OARs	Constraints
Spinal cord	Dmax ≤ 40 Gy
Brainstem	Dmax ≤ 54 Gy V55< 5 cc V50<few cc
Optical nerves	Dmax ≤ 50 Gy
Chiasma	Dmax ≤ 50 Gy
Mandible	Dmax ≤ 66 Gy (Dmax ≤ 100% prescribed dose – no hot spots)
Parotids	V15<67% V30<50% V45<25% Dmean<30 Gy ..as low as possible with priority for PTV coverage

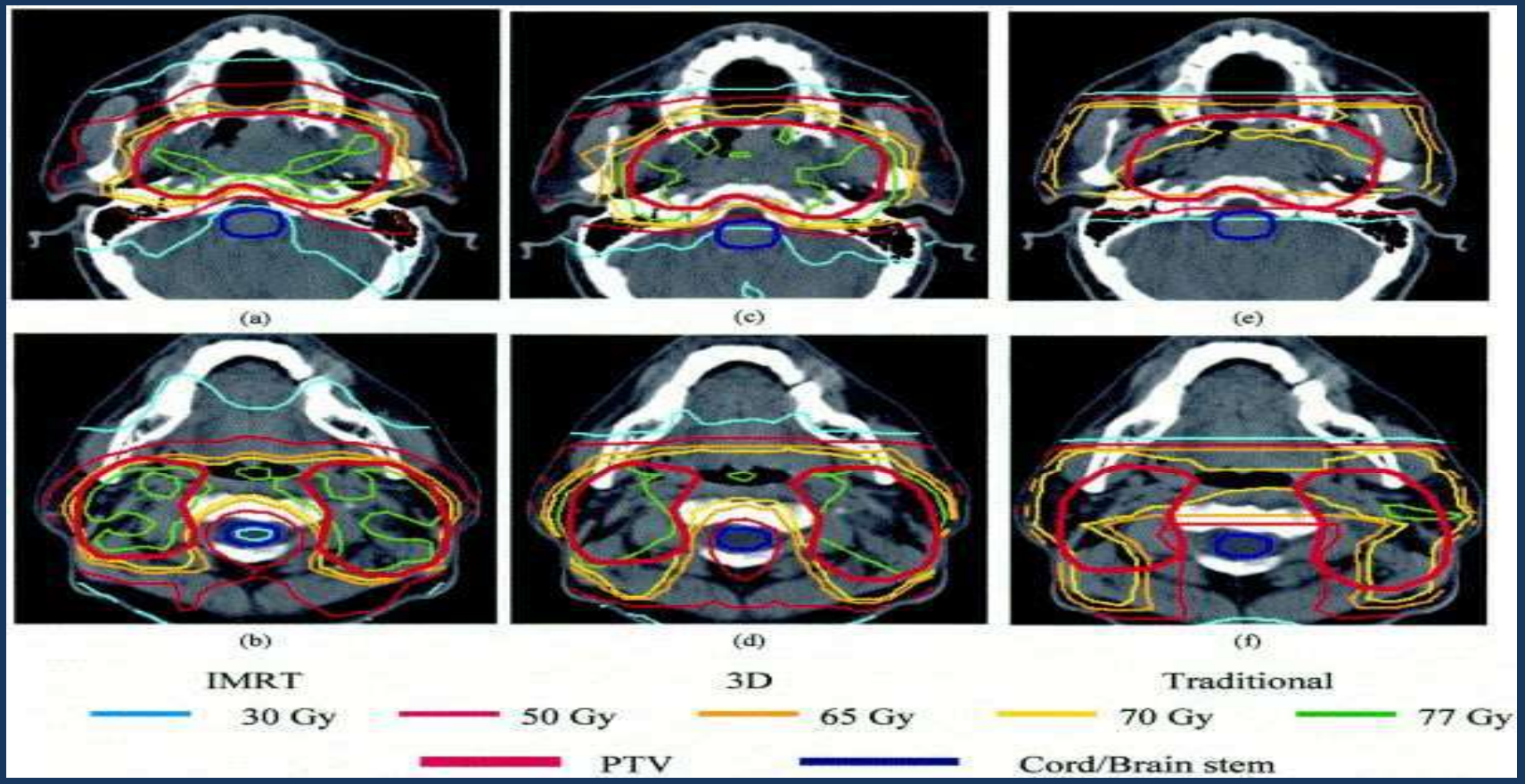
OARs	Constraints
Larynx	V20<60% V30<50% V50<20%
Tyroid	V45<50% V50<40%
Esophagous	V20<60% V30<30% V50<20%
Mucosa	V20< 50% V30< 40% V50< 20%
Lung apex	V30< 50%
Inner Hear	Dmax<50 Gy
Bone	Dmax< 65 Gy V55<20%

Try to optimize "as low as possible" without compromising the PTV coverage

Plan evaluation and Treatment



Comparison of different treatment plans



Axial dose distributions through the center of the nasopharynx and neck for the intensity-modulated radiation therapy (IMRT) [(a), (b)], three-dimensional (3D) conformal [(c), (d)], and traditional [(e), (f)] treatment plans. Note the relatively poor coverage of the skull base and medial nodal regions using the traditional plan and the improved dose conformality of the IMRT plan.

Results of Radiotherapy alone

STAGE	5 Yr SURVIVAL
EARLY DISEASE	90 – 95%
LOCALLY ADVANCED	50%

To improve the results in locally advanced cases chemotherapy was incorporated.

Chemoradiation in Cancer Nasopharynx

- It is the most chemo and radiosensitive entity of all head & neck cancer.
- High incidence of distant metastasis.
- Integration of chemotherapy in radiotherapy has resulted in improved disease outcomes.

Chemo radiotherapy

- **An improved therapeutic index is the goal**
  - More effect of chemo radiotherapy on the tumor compared to the effect of chemo radiotherapy on normal tissue toxicity
- **Classically there are 4 ways to define the interaction**
  - spatial cooperation
  - toxicity independence
  - radioprotectors
  - radiation sensitizers
    - Steel & Peckham IJROBP 5:85, 1979

Locally advanced disease

- Various trials and meta-analysis have shown a clear advantage in terms of locoregional control, disease free & overall survival in favour of addition of chemotherapy to radiation.

Incorporate chemotherapy

- Induction (neo adjuvant)
- Concurrent
- Adjuvant
- Combination

Induction → Concurrent

Concurrent → Adjuvant

Chemo-radiation trials

Trial	Phase	Pts	Study design	Main end-point	Results
Lin JC et al[4]	III	284	Exclusive RT alone *vs* cDDP-5FU + RT	5-year DFS	Experimental arm better ($P < 0.0012$)
Chan AT et al[5]	III	350	Exclusive RT alone *vs* cDDP-5FU + RT	2-year PFS	Experimental arm better ($P < 0.016$)
Zhang L et al[12]	III(m)	1608	Exclusive RT alone *vs* cDDP based CT + RT	5-year OS	Experimental arm better ($P < 0.001$)
Yang AK et al[13]	III(m)	1993	Exclusive RT alone *vs* cDDP based CT + RT	5-year OS	Experimental arm better ($P < 0.05$)
Lu H et al[17]	II	22	IMRT + cDDP	1 year OS	96%
Ekenel M et al[34]	II	100	IMRT+ cDDP-Cet	ORR	100%

RT: Radiotherapy; IMRT: Intensity modulated RT; CT: Comptued tomography; ORR: Overall response rate; DFS: Disease-free survival.

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Meta- analysis of chemoradiation trials

- The main objective of this meta-analysis was to determine the clinical benefit of concurrent chemoradiotherapy (CCRT) compared with radiation alone (RT) in the treatment of nasopharyngeal carcinoma (NPC) patients in endemic geographic areas.

- This is the first meta-analysis of CCRT vs. RT alone in NPC treatment which included studies (7 TRIALS, 1608 PTS) only done in endemic area. *The results confirmed that CCRT was more beneficial compared with RT alone.*

The role of concurrent chemoradiotherapy in the treatment of locoregionally advanced nasopharyngeal carcinoma among endemic population: a meta-analysis of the phase III randomized trials

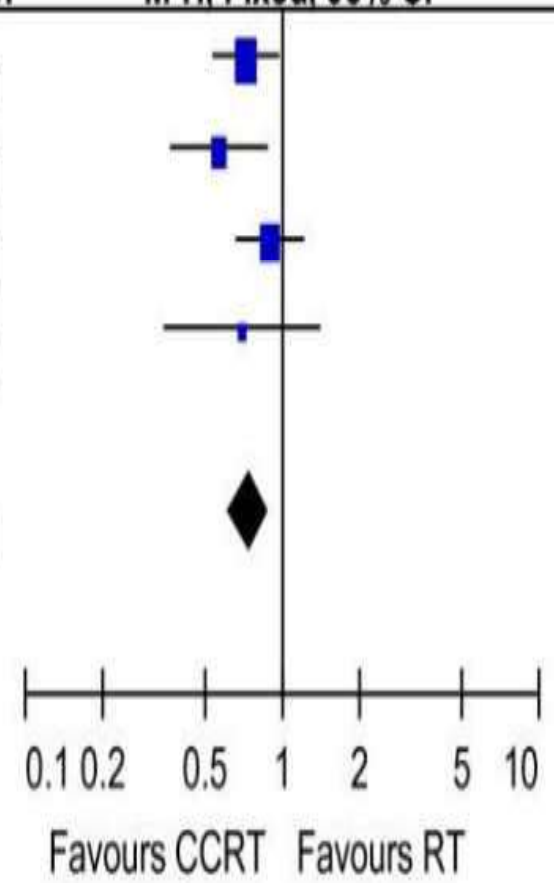
BMC Cancer. 2010; 10: 558.
Published online 2010 October 15.

C 5 years Overall Survival

Study or Subgroup	CCRT Events	CCRT Total	RT Events	RT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chan (11,25)	52	174	73	176	37.9%	0.72 [0.54, 0.96]
Wee (12)	24	111	42	110	22.1%	0.57 [0.37, 0.87]
Lee 9901 (13,18)	55	172	63	176	32.6%	0.89 [0.67, 1.20]
Lee 9902 (15,17)	11	51	13	42	7.5%	0.70 [0.35, 1.39]
Total (95% CI)		**508**		**504**	**100.0%**	**0.74 [0.62, 0.89]**
Total events	142		191			

Heterogeneity: $Chi^2 = 3.14$, $df = 3$ ($P = 0.37$); $I^2 = 5\%$

Test for overall effect: $Z = 3.29$ ($P = 0.001$)



Meta- analysis of chemoradiation trials

Another meta-analysis included 18 trials enrolling a total of 1993 patients from China. Yank AK,Liu TR, Guo x, QI gl, Chen FJ.

ARM	3Yr SURVIVAL	5Yr SURVIVAL	DISTANT METS. RATE
RT	56.38%	41.09%	38.71%
CT + RT	68.74%	51.91%	26.19%

The result demonstrated that chemoradiotherapy increased overall survival by 12% at 3 years, and 11% at 5 years after treatment. After chemoradiotherapy, the rate of distant metastasis was reduce by 12%.

Drugs used in Chemoradiation trials

- Cisplatin alone or in combination with 5-FU , Paclitaxel.
- Dose schedule: Cisplatin 30mg/m^2/weekly for 6 to 7 cycles or,

  100mg/m^2 3 weekly.

Interestingly, a combined analysis of two large studies (NPC-9901 and the NPC-9902) revealed that the dose of cisplatin during the concurrent phase of concurrent chemo-radiotherapy had a significant impact on locoregional control.

IMRT ± Chemo for NPC (Single Institutions)

Center	N	Stage	FU (mo)	LC	DM-Free
Bucci IJROBP, 2004(abs)	118	50% T3-4	30	96% (4-year data)	72%
Kam IJROBP, 2004	63	51% T3-4	29	92% (3-year data)	79%
Wolden IJROBP, 2006	74	51% T3-4	35	91% (3-year data)	78%

Adjuvant chemotherapy
The Intergroup- 0099

- The Intergroup-0099 was the first randomized trial to compare concurrent chemo-radiotherapy followed by adjuvant chemotherapy with RT alone.
- In this study, concurrent chemo-radiotherapy consisted of cisplatin (100 mg/m^2 every 21 d) for three cycles, followed by adjuvant cisplatin (80 mg/m^2 on day 1) and 5-fluorouracil (1000 mg/m^2 on days 1-4 every 4 wk).
- *A statistically significant advantage in the chemo-radiation arm was seen in terms of overall survival, disease-free-survival, locoregional failure rate and time to distant metastases.*

Adjuvant chemotherapy trials

Trial	Phase	Pts	Study design	Main end-point	Results
Al-Sarraf M et al[18]	III	147	Exclusive RT alone *vs* CCRT followed by cDDP-5FU	3-year PFS	Experimental arm better ($P < 0.01$)
Chen Y et al[19]	III	316	Exclusive RT alone *vs* CCRT followed by cDDP-5FU	2-year OS	Experimental arm better ($P < 0.003$)
Lee AW et al[20]	III	348	Exclusive RT alone *vs* CCRT followed by cDDP-5FU	5-year PFS	Experimental arm better ($P < 0.035$)
Park KH et al[21]	II	43	cDDP-5-FU + RT followed by cDDP-Epi-Ble CT	ORR	100%
Hu W et al[22]	II	54	w Pac + RT followed by cDDP-Pac CT	ORR	100%
Leung TW et al[10]	II	48	HFRT + cDDP based CT followed by cDDP-5FU CT	3-year DFS	71%

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Neo- adjuvant chemotherapy

- The role of neo-adjuvant chemotherapy followed by concurrent chemo-radiotherapy or RT is a matter of outstanding interest.
- Several clinical phase II trials from Western countries have proved that induction chemotherapy based on the administration of cisplatin, 5-fluorouracil and taxanes, may significantly improve treatment outcomes in patients with squamous cell carcinoma of the head and neck.
- An interesting approach may be to employ the same chemotherapy or a similar regimen in locally advanced NPC patients.

Neoadjuvant chemotherapy trials

Trial	Phase	Pts	Study design	Main end-point	Results
Al-Amro A et al[23]	II	110	Neo cDDP-Epi and followed by cDDP + RT	ORR	100%
Airoldi M et al[24]	II	30	Neo cbdca-Pac followed by RT + cbdca-Pac	ORR	87%
Ferrari D et al[25]	II	34	Neo cDDP-5FU followed by RT + cDDP	ORR	85.3%
Lu X et al[26]	II	58	Neo cbdca-Tax followed by cbdca + RT (arm A) *vs* neo cbdca-5FU followed by cbdca + RT (armB)	1-year DFS	no difference between arm A and B
Mosatafa E et al[27]	II	36	Neo cDDP-Pac followed by cDDP-RT	ORR	89%
Hui EP et al[28]	II	65	Neo cDDP-Tax followed by cDDP + RT (arm A) *vs* cDDP + RT (arm B)	3-year OS	Arm A better than arm B ($P < 0.012$)
Bossi P et al[29]	II	45	Neo cDDP-Tax-5FU followed by cDDP + RT	ORR	98%
Cho S et al[30]	II	19	Neo cDDP-Tax-5FU followed by cDDP + RT	ORR	93%
Bae WK et al[32]	II	33	Neo cDDP-Tax-5FU followed by cDDP + RT	ORR	99%
Kong L et al[6]	II	52	Neo cDDP-Tax-5FU followed by cDDP + RT	ORR	90.2%
Ekenel M et al[34]	II	59	Neo cDDP-Tax followed by cDDP + RT	ORR	95%
Lin S et al[35]	II	370	Neo cDDP based CT followed by IMRT	3-year OS	90%

RT: Radiotherapy; IMRT: Intensity modulated RT; CT: Comptued tomography; ORR: Overall response rate; DFS: Disease-free survival.

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Conclusion

- Although several cytotoxic agents have been used both in the neoadjuvant and adjuvant setting with promising results, *exclusive concurrent chemo-radiotherapy remains the recommended approach at the present time,* as additional evidence is required to support the use of chemotherapy in the adjuvant/neo-adjuvant setting.