

# Concurrent chemo-radiation in head-neck cancer

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## Roadmap

- Why do we need to use chemotherapy along with RT?
- Which sequencing strategy is 'best' (before, along with or after RT)?
- Which RT schedule (once-a-day or twice-a-day or with some gap)?
- Several drugs or one drug and which one?
- Which is better - intensified RT or chemo-RT?
- What about morbidity and its management?
- What should be our focus (as opposed to that of the West)?

## Why do we need to use chemotherapy along with RT?

Local control / survival by site and T stage when treated with RT alone				
Site	T1	T2	T3	T4
Oral cavity	88-98%	65-85%	15% (OS: 10-55%)	
OPH (tonsil)	90%	80%	70%	15-30%
OPH (base tongue)	75-85%		OS: 15-45%	
Nasopharynx	55-60% for all T stages			
Hypopharynx	70-80%		? 15%	
Larynx	85%	70%	64%	?

Local control of N stage with RT alone				
	N0	N1	N2	N3
	90%	70-80%	70% or lower	33%

## Goals for incorporation of CT

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- Desire for organ preservation in RESECTABLE & better local therapy for UNRESECTABLE H&N cancers
- Rationale for using upfront
  - Better drug delivery as tumor has intact vasculature
  - Reduce bulk in borderline resectable tumor / reduce extent of Sx
  - Early eradication of micro-metastatic disease
  - Perturb cell kinetics, kill hypoxic cells, inhibit tumor repopulation, enhance radiation induced apoptosis, sensitize cells to radiation, inhibit repair of radiation damage, decrease tumor mass and therefore blood delivery and oxygenation
- Potential disadvantages
  - Delay/compromise of definitive local treatment, proliferation of non-responsive tumors, increase therapy related morbidity, cost & duration

## Induction chemotherapy for head-neck cancers

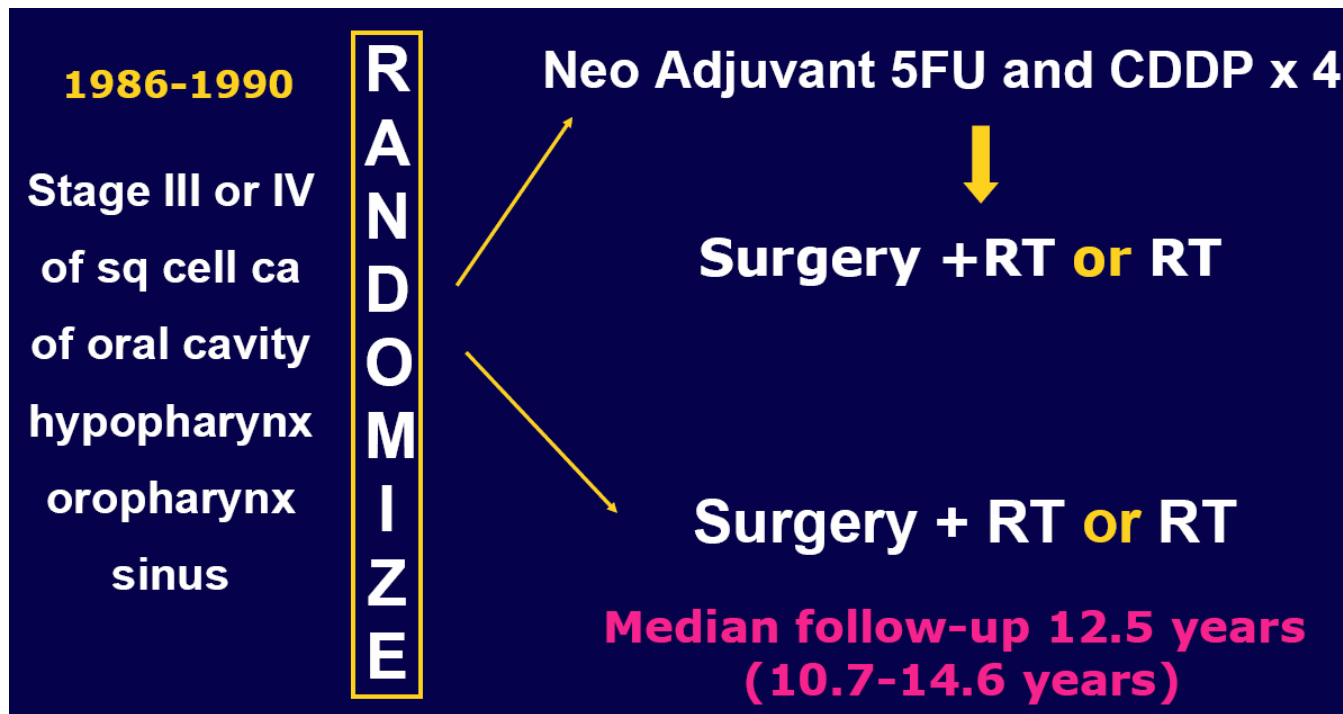
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- **At Least 31 randomized trials using neoadjuvant chemotherapy**
- **At least 11 randomized trials for operable disease, 14 trials for inoperable disease**
- **Common agents include cisplatin, and/or 5-FU, bleomycin, methotrexate, vincristine, mitomycin**
- **Response rates to induction chemotherapy : 37-98% for operable disease, 21-91% for inoperable disease**
- **No compelling evidence for an effect of chemotherapy on overall survival**

# Randomized Phase III trial of Neoadjuvant Chemotherapy in Head and Neck Cancer: 10-Year Follow-Up

[J Natl Cancer Inst 2004;96:1714 –7]

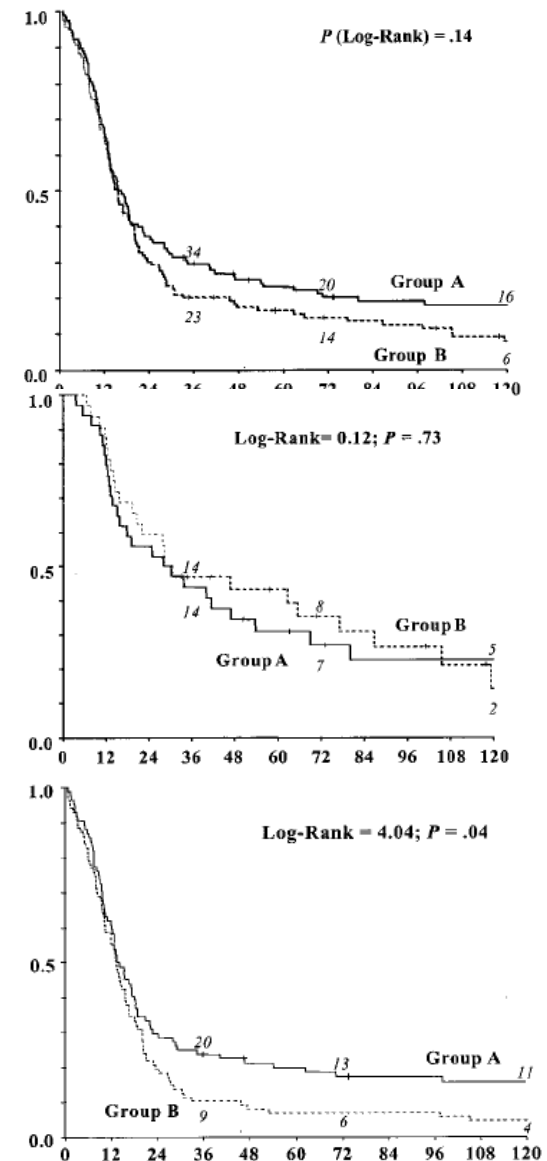
N=237, 70% inoperable  
Stratification by: Institution, stage, KPS and operability



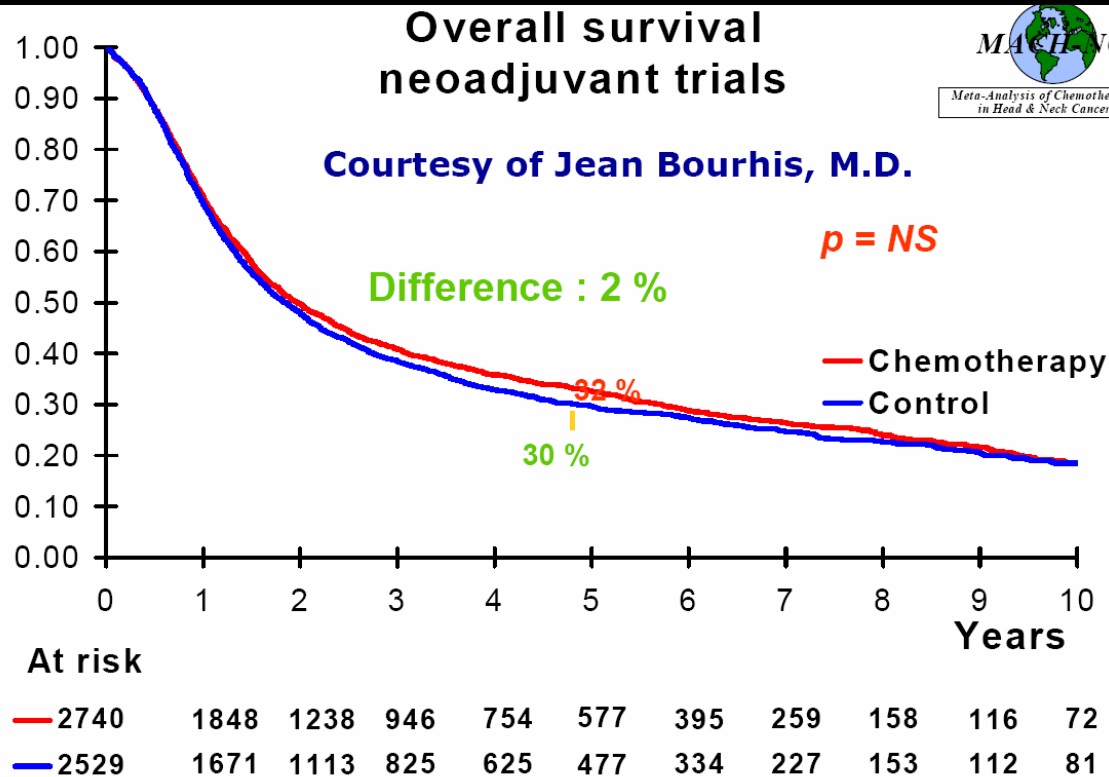
NACT: CDDP 100mg/m<sup>2</sup> day1, 5-FU 1000mg/m<sup>2</sup> day1-5, every 3 wks x 4cs  
PORT: 45-50Gy; Definitive RT: 65-70Gy

## Results – overall survival

Endpoint	CT + RT	RT	P
<b>All Patients (N=237)</b>			
5 year	23%	16%	0.13
10 year	19%	9%	
Endpoint	CT + RT	RT	P
<b>Operable Patients (n=69)</b>			
5 year	43%	31%	.73
10 year	23%	14%	
Endpoint	CT + RT	RT	P
<b>Inoperable Patients (n=170)</b>			
5 year	21%	8%	.04
10 year	16%	6%	



# Induction chemotherapy: summary



Though possible to get CR and high response rates after induction chemotherapy, **no evidence to suggest any impact on OS** on pooled results

**Not recommended as the standard of care**

## Alternating chemotherapy and radiotherapy vs. sequential chemo-radiotherapy

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- At least 6 randomized trials compared sequential CT and RT vs. alternating or concurrent CT and RT
- Alternating chemort: a.k.a. split course chemort
- Most common agents include cisplatin, and/or 5-FU, bleomycin, methotrexate, and vinblastine
- Most trials suggest improved DFS with the concurrent or alternating approach as compared with the sequential regimen
- Only one trial showed improved overall survival with alternating approach
- None of these trials had RT alone arm as a control

# Alternating CT-RT vs. once daily RT for advanced H&N cancers

[M Merlano, NEJM 327:1115, 1992]

Endpoint	CT + RT (n = 80)	RT (n = 77)	<i>P</i>
Complete response	43%	22%	0.037
Local-Regional Control	29%	8%	0.028
Distant Metastases	8%	7%	n.s.
5-yr. PFS	21%	9%	0.008
5-yr. Survival	24%	10%	0.01

# Alternating Chemoradiotherapy versus Partly Accelerated Radiotherapy in Locally Advanced Squamous Cell Carcinoma of the Head and Neck

*Results from a Phase III Randomized Trial*

Corvo` et al. *Cancer* 2001;92:2856–67.

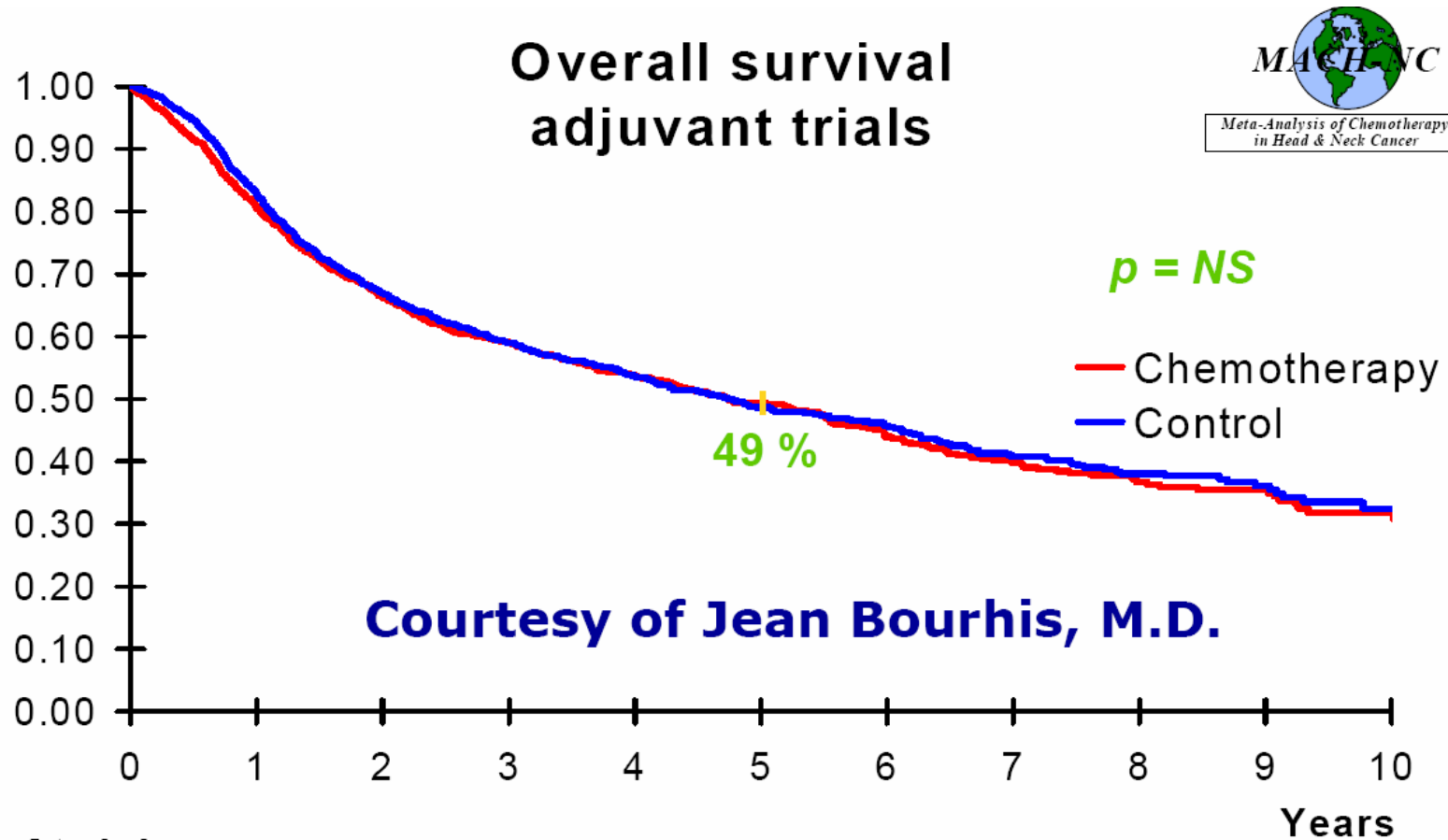
- Further extension of the alternating chemort trial
- Same exact design except the control group is **concomittant boost radiotherapy alone** to 75 Gy
- No statistically significant differences in the outcome of patients treated with either alternating chemort vs concomittant boost RT alone in terms of locoregional control, progression-free survival, or overall survival

## Alternating chemotherapy and radiotherapy vs. sequential chemo-radiotherapy: Conclusions

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- **Concurrent or alternating chemoradiotherapy is better than sequential chemoradiotherapy**
- **Alternating chemoradiotherapy appeared to be better RT alone using QD fx**
- **Alternating chemoradiotherapy does not result in better locoregional control, progression-free survival, and overall survival when compared to concomittant RT alone**
- **Don't recommend this approach as the standard of care for locally advanced H/N CA**

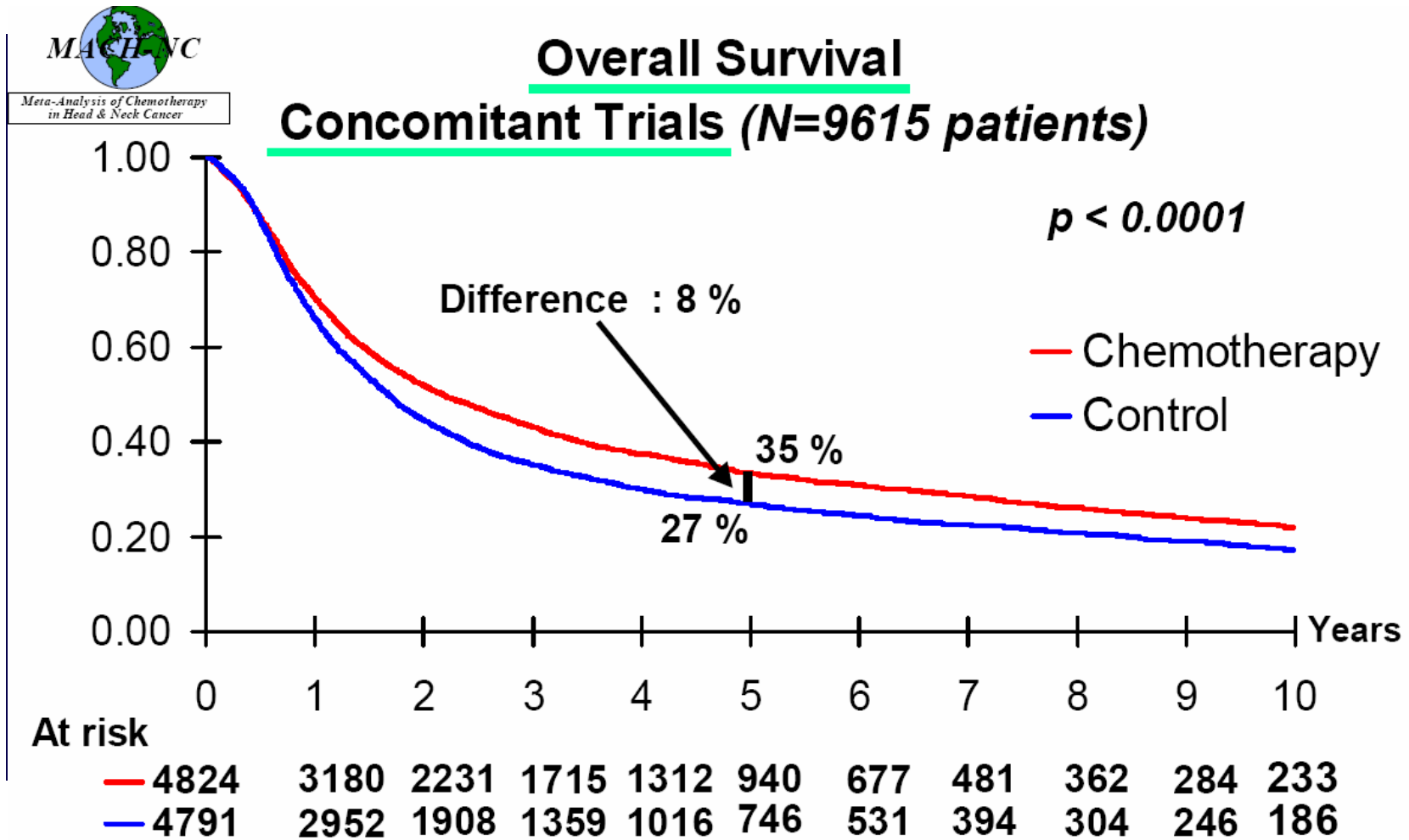
# Adjuvant therapy (i.e. following definitive loco-regional therapy)



**At risk**

— 1244	971	743	602	424	290	202	149	98	66	31
— 1323	1049	799	640	454	301	212	155	104	62	29

# Concurrent chemotherapy and radiotherapy



**Courtesy of Jean Bourhis, M.D.**

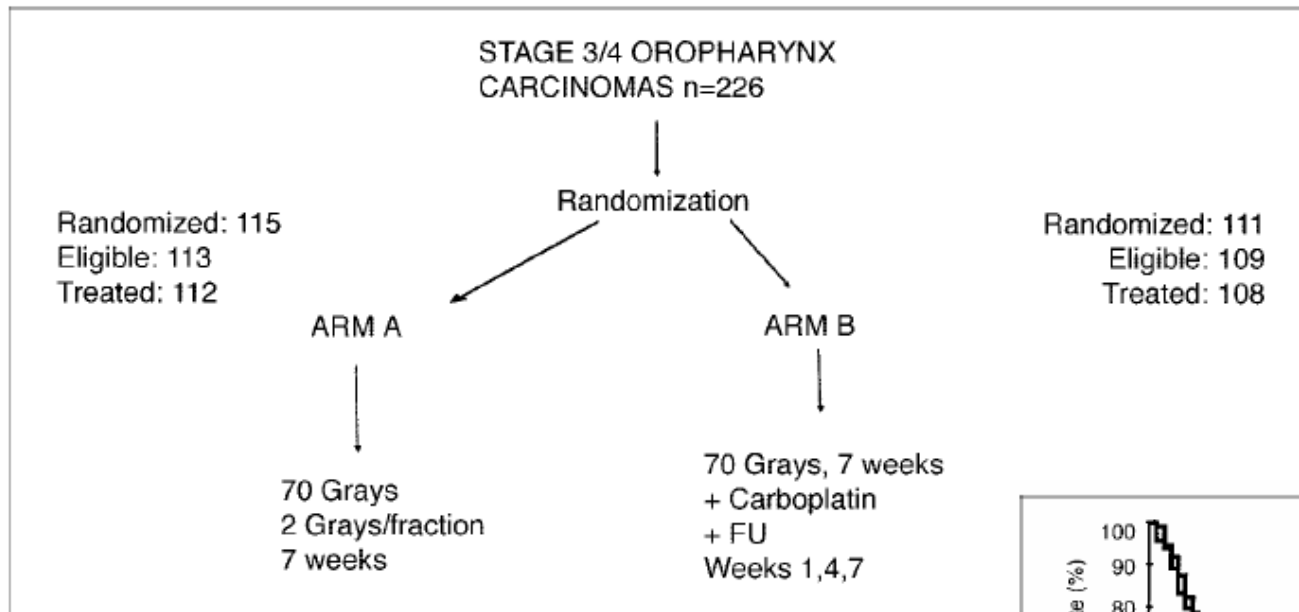
# Concurrent CT+RT (once daily fractionation)

Final Results of the 94-01 French Head and Neck Oncology and Radiotherapy Group Randomized Trial Comparing Radiotherapy Alone With Concomitant Radiochemotherapy in Advanced-Stage Oropharynx Carcinoma

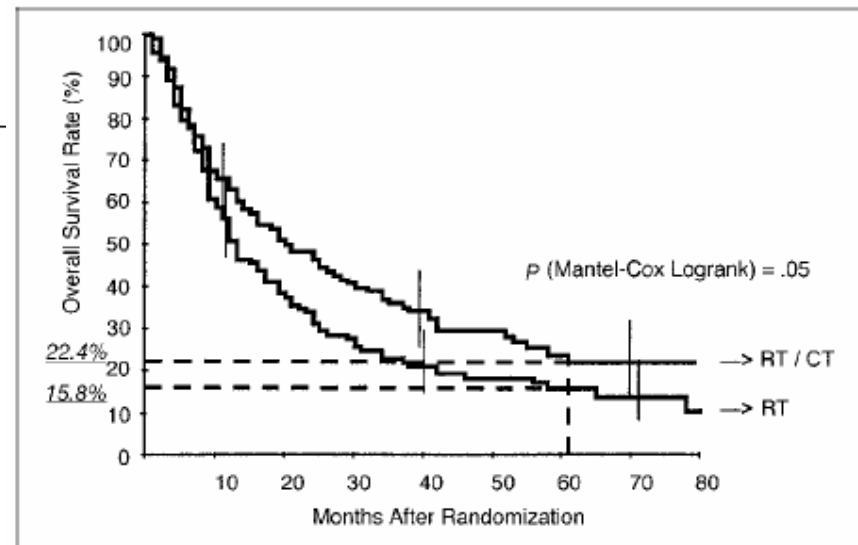
VOLUME 22 · NUMBER 1 · JANUARY 1 2004

JOURNAL OF CLINICAL ONCOLOGY

Denis et al *J Clin Oncol* 22:69-76.

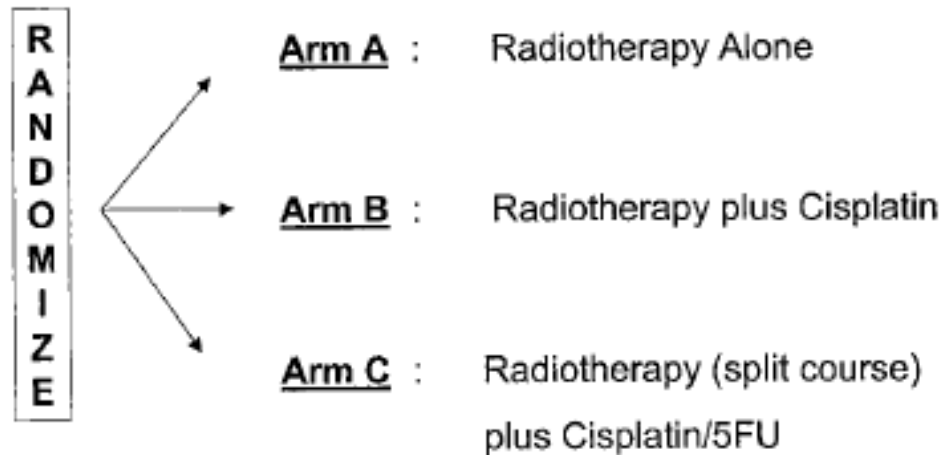


	CT+RT	RT	P
Median (mo)	20mo	13mo	
LRC (5-yr)	48%	25%	0.002
DFS (5-yr)	27%	15%	0.01
OS (5-yr)	22%	16%	0.05



# An Intergroup Phase III Comparison of Standard Radiation Therapy and Two Schedules of Concurrent Chemoradiotherapy in Patients With Unresectable Squamous Cell Head and Neck Cancer

ADELSTEIN ET AL *J Clin Oncol* 21:92-98. © 2003 by American Society of Clinical Oncology.



- N=295
- Median F/U 41 months

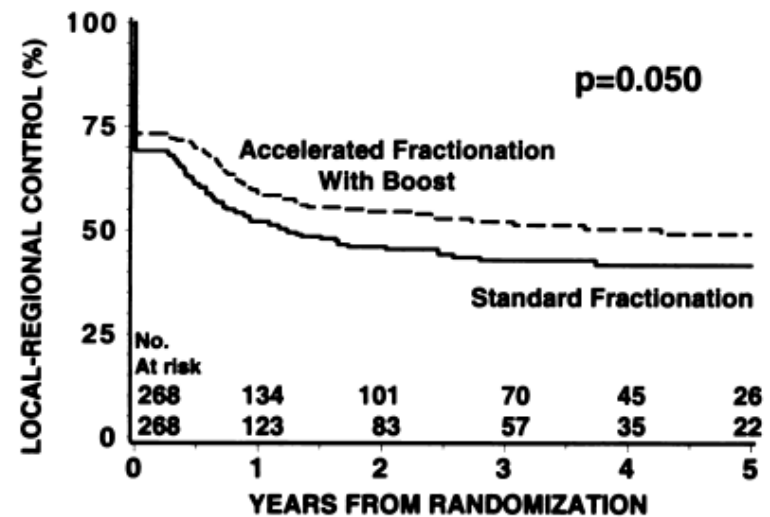
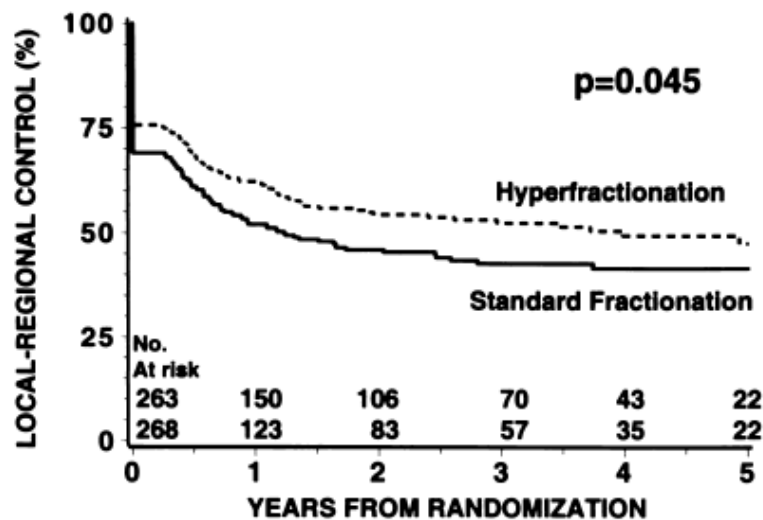
	<b>Arm A</b>	<b>Arm B</b>	<b>Arm C</b>
• 3 year OS	27%	<b>37%</b>	23%
• MS (mo)	13.8	<b>19.1</b>	12.6

- 3 cycles of CDDP + 70 Gy QD was superior

# Concurrent CT+ RT using altered fractionation

## Why?

- RTOG 90-03: HF or CBRT improves LRC compared to standard fractionation
- Meta-analysis of altered fractionation improves survival by 3%

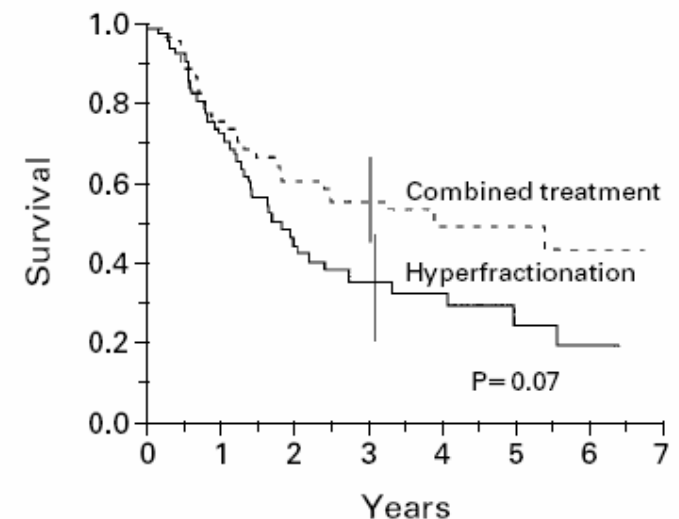


# HYPERFRACTIONATED IRRADIATION WITH OR WITHOUT CONCURRENT CHEMOTHERAPY FOR LOCALLY ADVANCED HEAD AND NECK CANCER

DAVID M. BRIZEL (N Engl J Med 1998;338:1798-804.)

Stage III / IV	<b>R A N D O M I Z E</b>	<b>Arm 1 : HFx + CT</b>
Oropharynx		5FU + CDDP x 2
Hypopharynx		70 Gy 1.25 BID
Oral Cavity		(Split Course)
NPC and PNS		<b>Arm 2 : HFx Alone</b>
N=122		75 Gy 1.25 BID

	CT+RT	RT	P
CR	84%	73%	
LRC (5-yr)	70%	44%	0.01
DFS (5-yr)	60%	40%	0.08
OS (5-yr)	42%	28%	0.07



# Concomitant Cisplatin Significantly Improves Locoregional Control in Advanced Head and Neck Cancers Treated With Hyperfractionated Radiotherapy

**Huguenin et al**

<b>R A N D O M I Z E</b>	<p><b>Stage III and IV SCC</b></p> <p><b>Oropharynx Hypopharynx Larynx Oral Cavity</b></p> <p><b>N=224</b></p>	<p><b>Arm 1 : HFX RT Alone</b> 74.4 Gy BID</p> <p><b>Arm 2 : HFX RT + CT</b> 74.4 Gy BID + 2 cycles CDDP(20mg/m<sup>2</sup>) for 5 days</p>
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5-yr	CT+RT	RT	P
CR	64%	36%	0.01
LRC	51%	33%	0.03
Dist mets free	61%	40%	0.01
OS	46%	32%	0.15

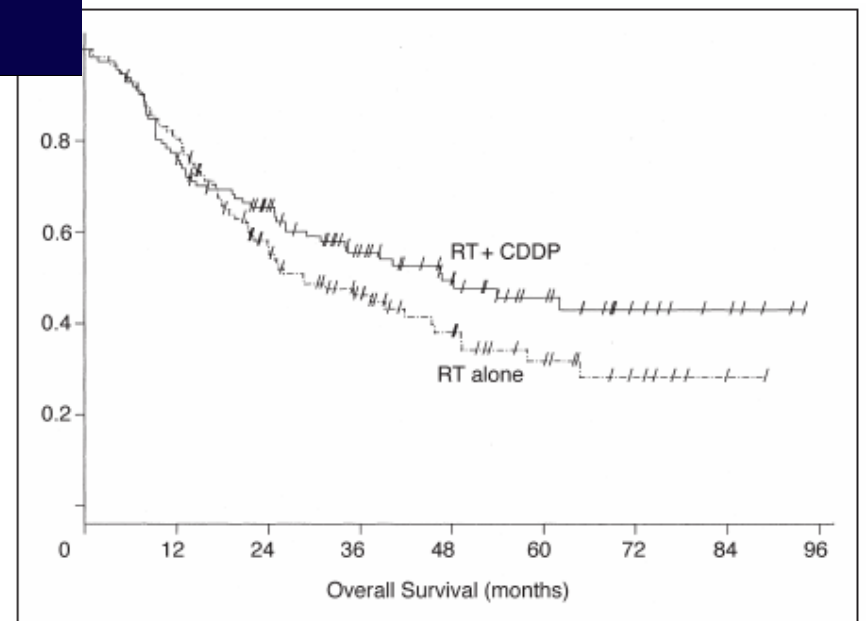


Fig 4. Overall survival ( $P = .147$ ). RT, radiation therapy; CDDP, cisplatin.

# Hyperfractionated Accelerated Chemoradiation With Concurrent Fluorouracil-Mitomycin Is More Effective Than Dose-Escalated Hyperfractionated Accelerated Radiation Therapy Alone in Locally Advanced Head and Neck Cancer: Final Results of the Radiotherapy Cooperative Clinical Trials Group of the German Cancer Society 95-06 Prospective Randomized Trial

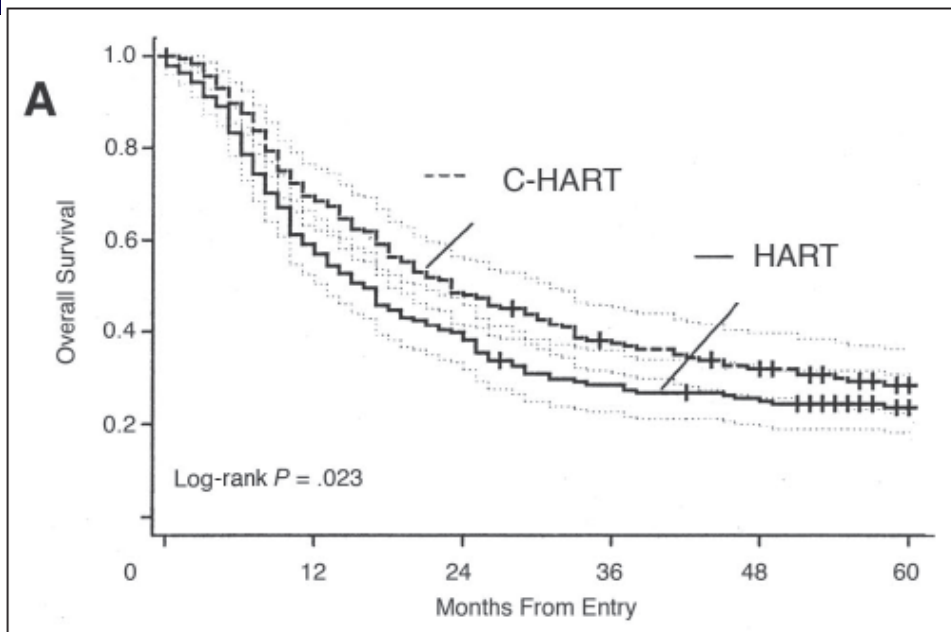
VOLUME 23 · NUMBER 6 · FEBRUARY 20 2005

Budach et al

JOURNAL OF CLINICAL ONCOLOGY

Stage III / IV	<b>R A N D O M I Z E</b>	<b>Arm 1 : Altered Fx + CT</b>
Oropharynx		5FU + MMC + 70.6 Gy (30 Gy QD then 1.4 Gy BID)
Hypopharynx		<b>Arm 2 : Altered Fx</b>
Oral Cavity		RT Alone: 77.6 Gy (14 Gy QD then 1.4 BID)
N=384		

5-Yr	CT+RT	RT	P
LRC	49.9%	37.4%	0.001
PFS	29.3%	26.6%	0.009
Dist mets free	51.9%	54.7%	0.575
OS	28.6%	23.7%	0.02

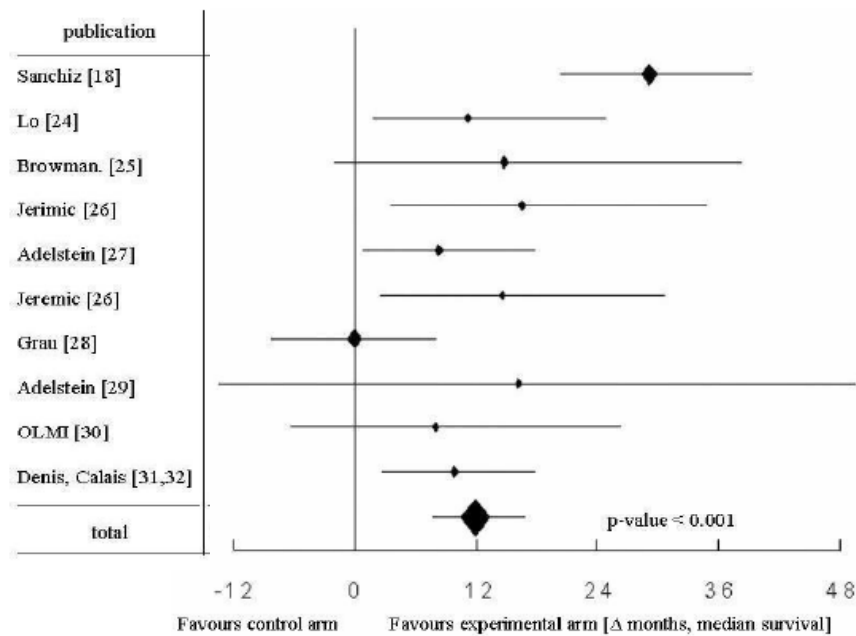


# In the setting of concomitant CT in H&N is altered fractionation needed?

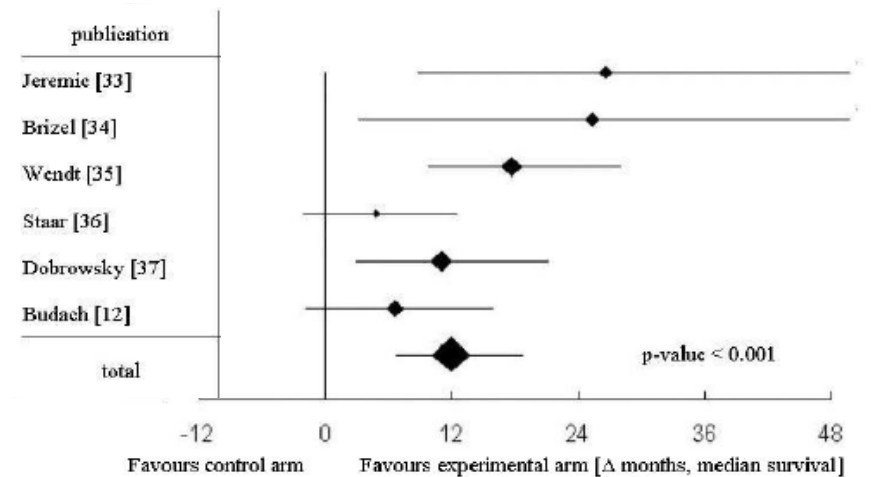
**A meta-analysis of hyperfractionated and accelerated radiotherapy and combined chemotherapy and radiotherapy regimens in unresected locally advanced squamous cell carcinoma of the head and neck**

BMC Cancer 2006, 6:28 doi:10.1186/1471-2407-6-28

W Budach\*<sup>1</sup>, T Hehr<sup>2</sup>, V Budach<sup>3</sup>, C Belka<sup>2</sup> and K Dietz<sup>4</sup>



CFRT vs. CFRT+ Chemo



HFRT/AFRT vs. HFRT/AFRT+Chemo

...being addressed by RTOG

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**RTOG 0129**  
**Phase III Trial of Concurrent RT and CT for**  
**Locally Advanced Head and Neck Cancer (Closed)**

Stage III and IV

SCC

Oral Cavity

Oropharynx

Larynx

Hypopharynx

**R**  
**A**  
**N**  
**D**  
**O**  
**M**  
**I**  
**Z**  
**E**

Arm 1 : **AFX-CB**

72 Gy/42 FXS/6 wks

+ CDDP 100 mg/m<sup>2</sup>

days 1 and 22

Arm 2 : **Standard FX:**

70 Gy/ 35 Fx

CDDP 100 mg/m<sup>2</sup>

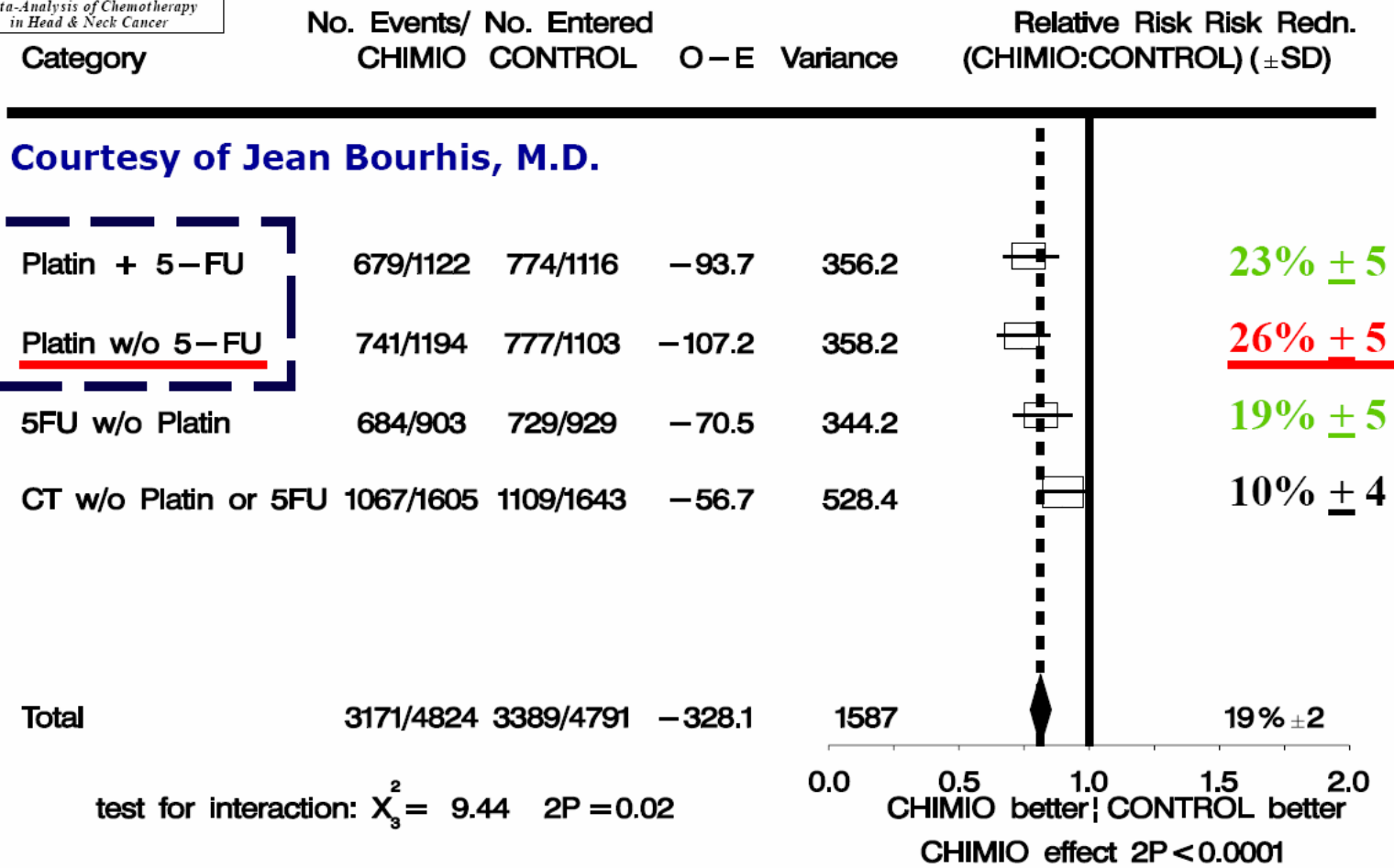
I.V. on days 1, 22, 43.

# Which chemotherapy should be used? View point 1



Meta-Analysis of Chemotherapy  
in Head & Neck Cancer

## Concomitant trials : effect by type of CT

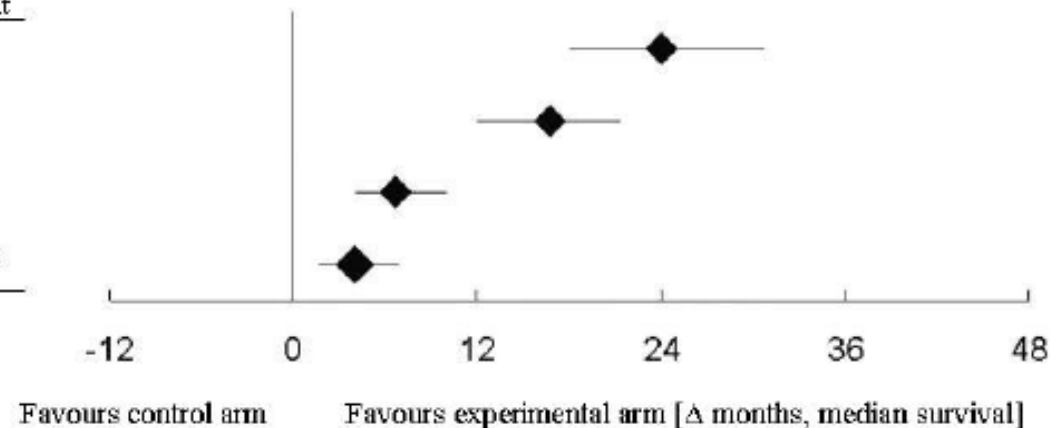


## Which chemotherapy should be used? View point 2

**A meta-analysis of hyperfractionated and accelerated radiotherapy and combined chemotherapy and radiotherapy regimens in unresected locally advanced squamous cell carcinoma of the head and neck**

W Budach<sup>\*1</sup>, T Hehr<sup>2</sup>, V Budach<sup>3</sup>, C Belka<sup>2</sup> and K Dietz<sup>4</sup>

Chemotherapy	Delta Months	LCL	UCL	N weight
5-fluorouracil	24.0	18.1	30.8	887
Cisplatin	16.2	11.8	21.4	903
Carboplatin	6.7	3.7	10.1	822
Mitomycin C	4.0	1.6	6.9	1169



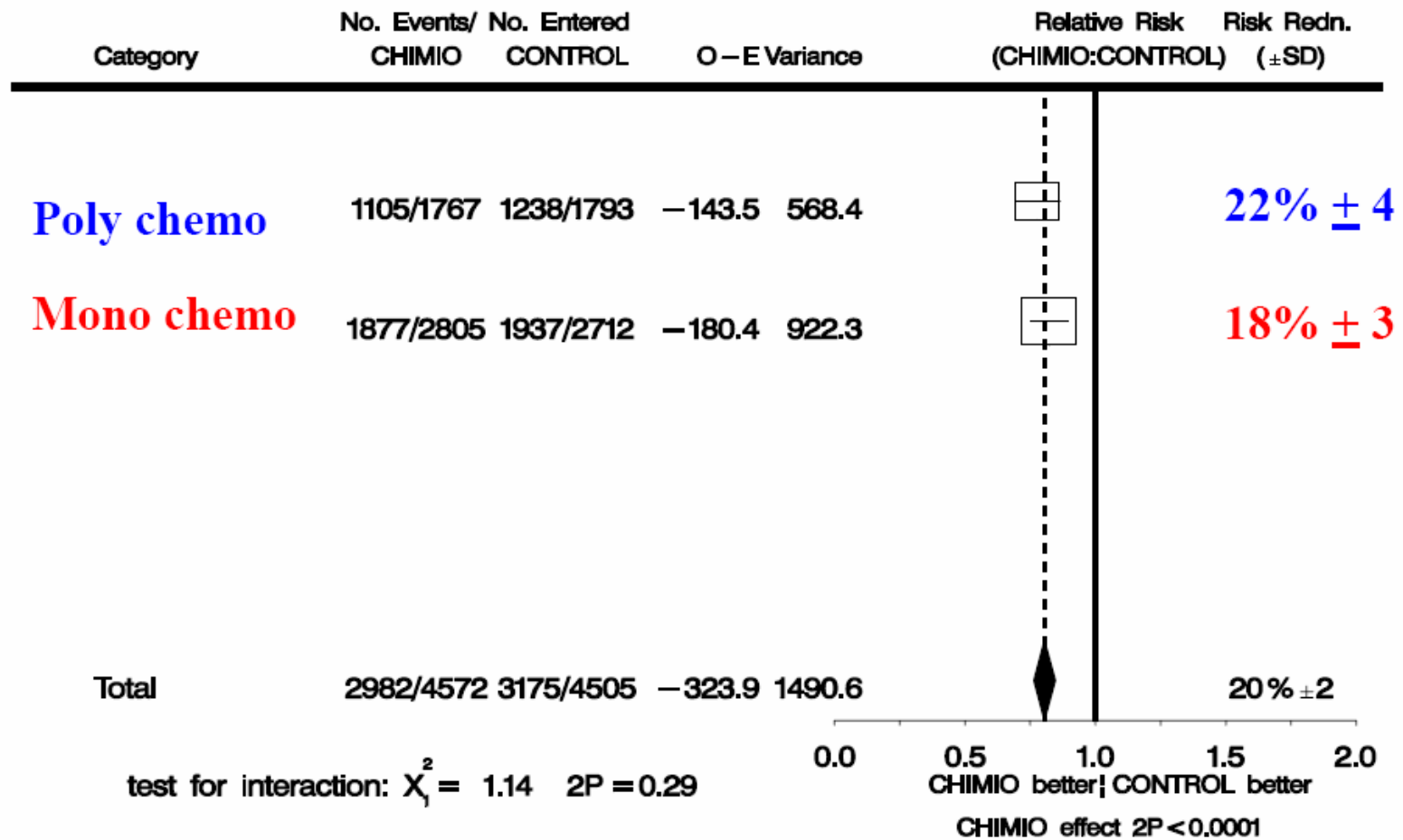
# Several drugs or one drug?



Meta-Analysis of Chemotherapy  
in Head & Neck Cancer

## Concomitant only Poly vs mono CT

MACH-NCZ Concomitant : Overall Survival, Poly or mono CT

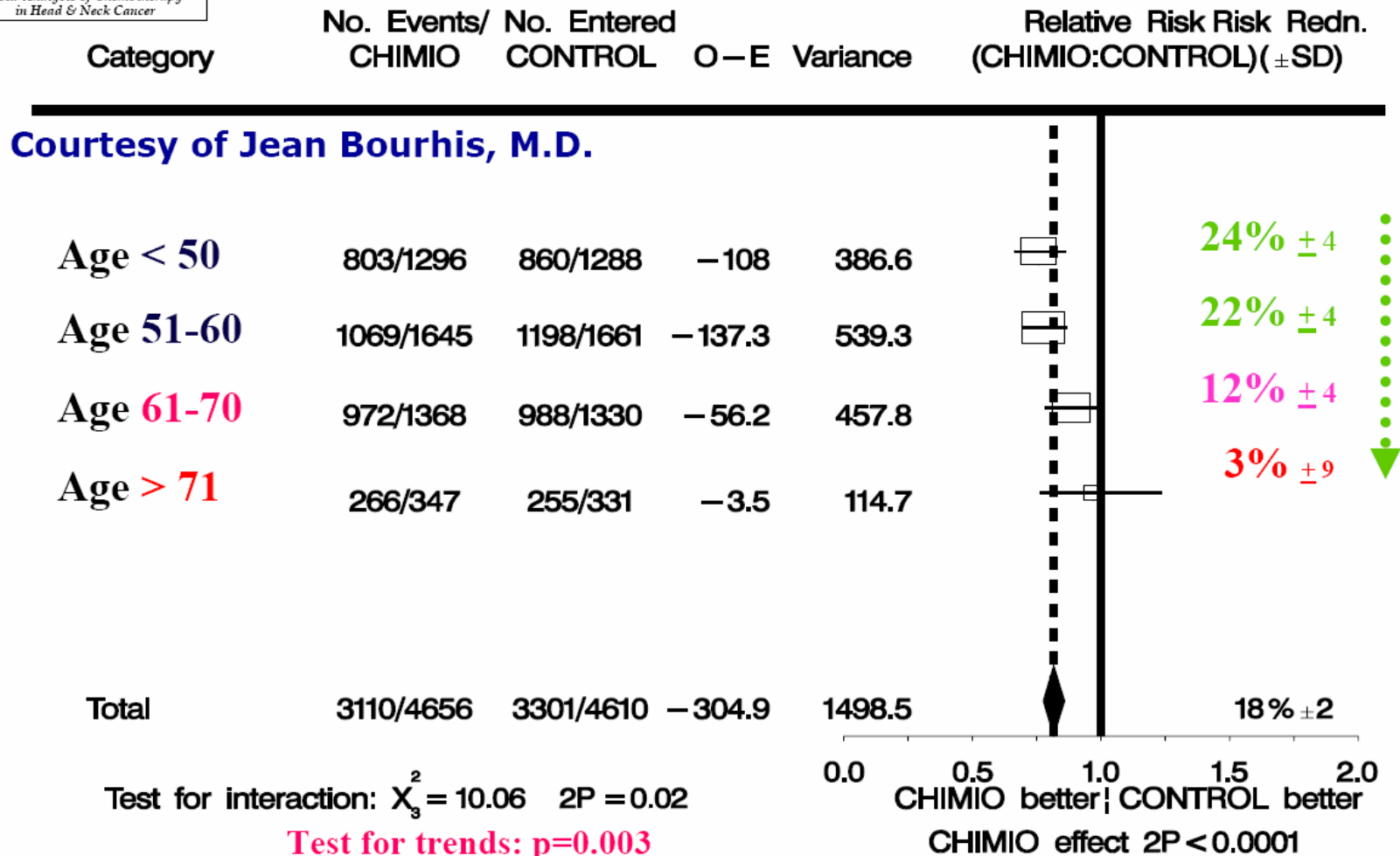


# Same treatment for young or elderly?



Meta-Analysis of Chemotherapy  
in Head & Neck Cancer

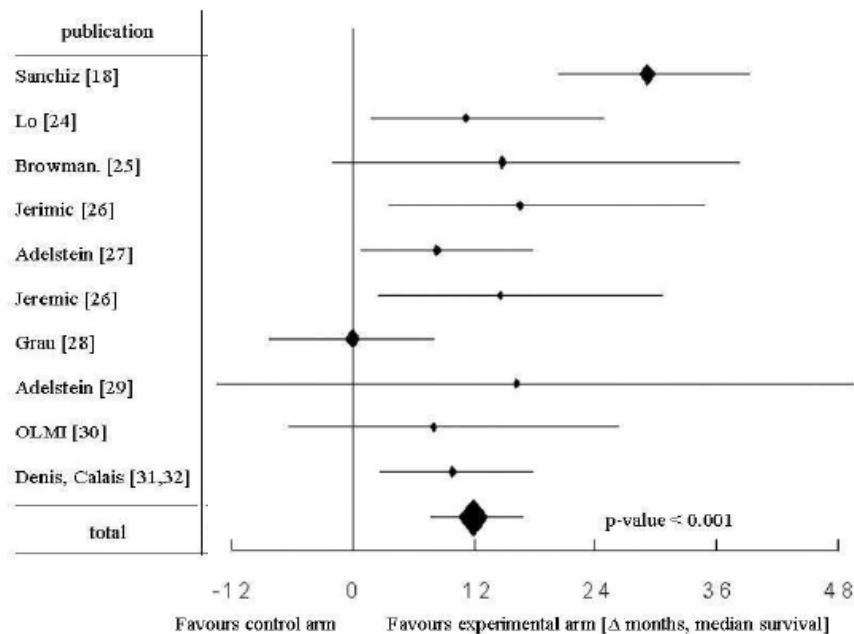
## Survival, concomitant trials by age



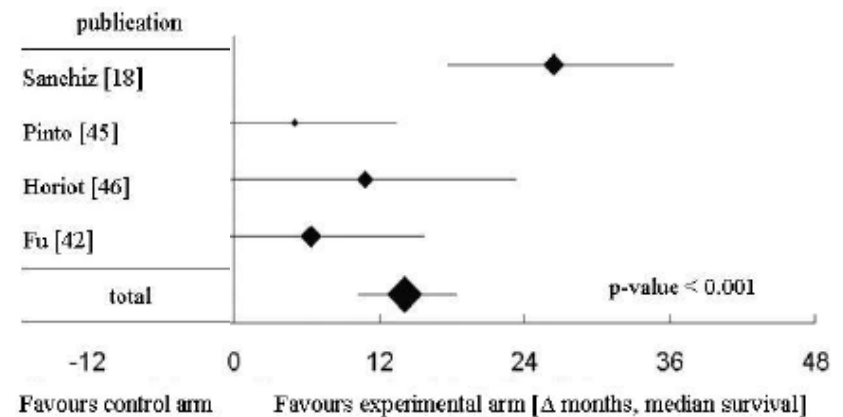
# What is there to choose between chemo + RT vs. intensified RT ?

**A meta-analysis of hyperfractionated and accelerated radiotherapy and combined chemotherapy and radiotherapy regimens in unresected locally advanced squamous cell carcinoma of the head and neck**

W Budach\*<sup>1</sup>, T Hehr<sup>2</sup>, V Budach<sup>3</sup>, C Belka<sup>2</sup> and K Dietz<sup>4</sup>



CFRT vs. CFRT+ Chemo



HFRT vs. CFRT

## **Morbidity in the West (Acute)**

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- **Acute Grade 3 / 4 toxicity can be as high as 89% with CCRT**
- **Acute severe toxicities can result in treatment breaks which can offset any benefit from aggressive treatments**
- **Agents used in randomized studies to minimize acute mucosal reactions have been disappointing: Sucralfate**
- **Agents that seem promising: vitamin E in oil solution rinse, ice chips, benzydamine**
- **Efforts are needed to test agents to decrease acute mucosal toxicities**

## Morbidity in the West (Late)

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- **Patients complain of permanent xerostomia (Significantly decreased with IMRT)**
- **Patients can be on long-term feeding tube due to inability to swallow secondary to stricture formation**
- **Concomittant Boost RT alone to 3.5 Gy per day (2 Gy AM + 1.5 Gy PM boost) resulted in high grade 2 late mucosal and skin fibrosis complications**
- **Conformal techniques such as IMRT further reduced rate of xerostomia and even skin fibrosis.**

## SGPGI data on tolerance to RT +/- concurrent CT

<i>Protocol</i>	<i>Gr III mucositis</i>	<i>Time in excess of ideal</i>	<i>%Wt loss</i>	<i>Tube feeds</i>	<i>IV fluids</i>	<i>Mortality ≤30 days</i>
RT (70Gy/7wk) n=95	25%	3.4 days, SD 11.2 30% ≤ 51days	-	3%	4%	7.3%
CDDP+RT (70Gy/7wk) n=95	Data ?	4.7 days, SD 12.2 34% ≤ 51days	-	1%	0	9.5%
RT (accelerated) (70Gy/6wk) n=36	67%	3.4 days, SD 6.4 53% ≤ 44days	8.5% (2-25)	19%	56%	13.8%
CDDP+RT (acc.) (70Gy/6wk) n=202	76%*	1.2 days, SD 7.3 69% ≤ 44days 82% ≤ 46days*	10% (0-26)	25%*	55%	10.4%*

* RTOG 99-14:	53%	78% ≤ 46days		84%		4%
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## Why were we losing patients on Rx?

- Many patients succumbed to pneumonia, dehydration and sepsis (1.3% grade III neutopenia) (99-14: 30% grade III hematologic toxicity)

70Gy/35fx/6 weeks + CDDP 35mg/m<sup>2</sup> wkly: 2004-2005, n=68

- Acute % wt loss : 9% (SD 5, range 0-26%) BUT
- Long term wt loss: 14% (SD 8.6, range 0-39%) (median FU 8 mo)
- At least 4 long term follow up patients had > 2 episodes of pneumonia each

<i>Site (no)</i>	<i>OC (82)</i>	<i>OPH (160)</i>	<i>LAR (79)</i>	<i>HYPO (73)</i>	<i>p-value</i>
% dead within 30 days of Rx (42/428)	6.1%	10%	7.6%	20.5%	0.02

## PEG program

70Gy/35fx/6 weeks + CDDP 35mg/m<sup>2</sup> wkly: 2004-2005, n=68



Variable	No PEG (n=47)	PEG (n=21)	P-value
70Gy within 43 days	70%	81%	0.35
Mucositis (Gd. III & IV)	41 (87%)	20 (95%)	0.19
% Wt loss (mean, SD)	10, 5.2	6.9, 3.8	0.01
NG tube	6 (13%)	-	-
IV fluid support + lipid +/- protein	43 (92%)	1 (4.5)	0.00
Blood transfusion	12 (26%)	3 (14%)	0.30
Mortality	5 (10.6%)	1 (4.5%)	0.43

Lal P, Bajpai R et al.  
2005

PEGs must be ensured to reduce or prevent treatment associated morbidity and mortality

## Let us conclude

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Lets hear your answers!!!

- Why do we need to use chemotherapy along with RT?
- Which sequencing strategy is 'best' (before, along with or after RT)?
- Which RT schedule (once-a-day or twice-a-day or with some gap)?
- Several drugs or one drug and which one?
- Which is better - intensified RT or chemo-RT?
- What about morbidity and its management?
- What should be our focus (as opposed to that of the West)?

# Our team at SGPGI

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## Radiation Oncologists

S Ayyagari (Retd)  
NR Datta  
Shaleen Kumar  
Punita Lal  
Neeraj Rastogi  
Sushma Agrawal  
Shalini Singh

## Past/Present residents

YS Nagar  
Manish Pandey  
Narendra Kumar  
Ranjeet Bajpai  
Anu Tewari  
Anurita Srivastava  
Rohini Khurana  
Anshu Goel

## Medical Physicists

KJ Maria Das  
D Rajasekhar  
Karthik Raj  
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Senthil Kumar

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