

Medical Oncology Perspective: Neoadjuvant/Induction Chemotherapy W/O Adjuvant Chemotherapy?

Amiran Matitashvili M.D.

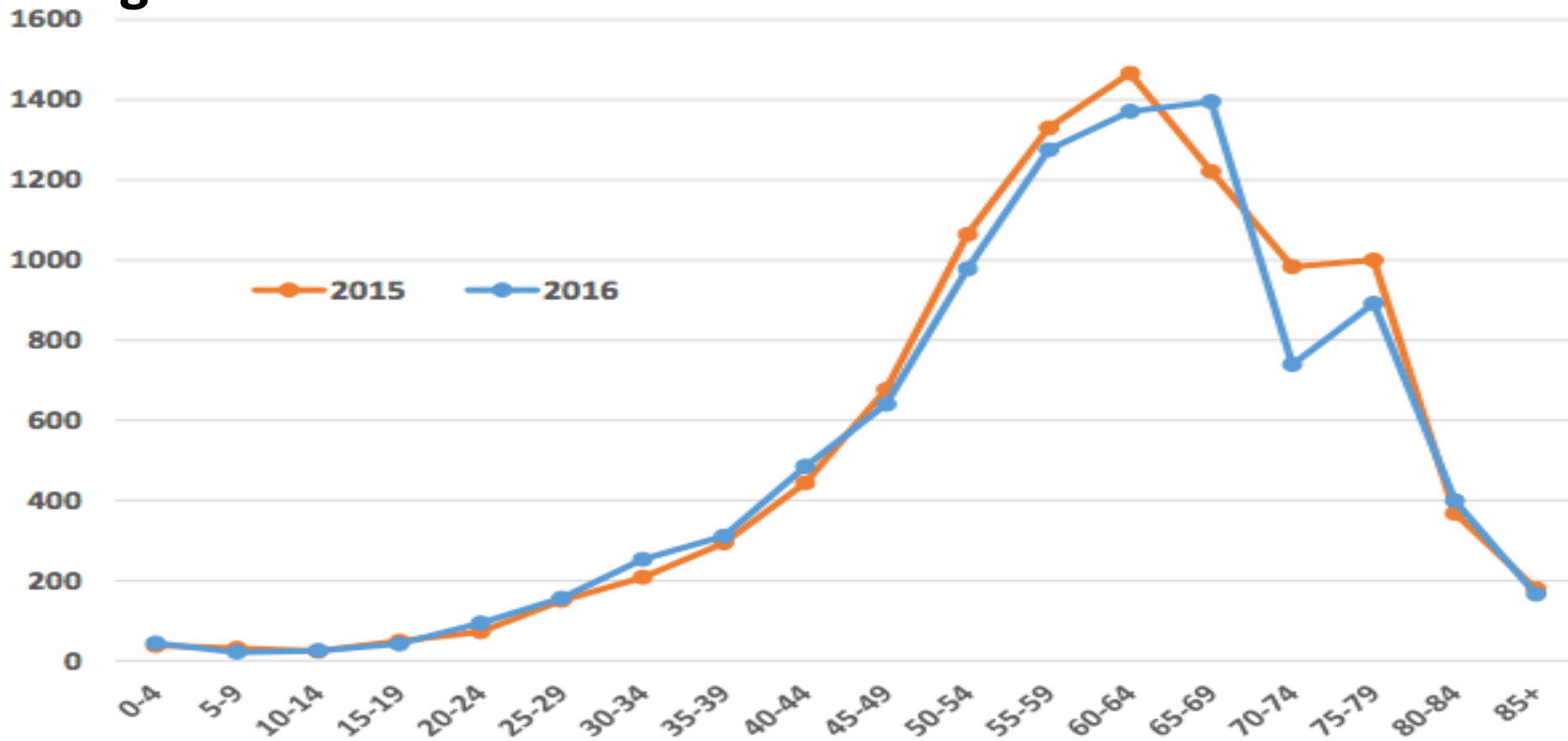
Mardaleishvili Medical Centre
Tbilisi, Georgia

**GEORGIAN
YOUNG
ONCOLOGISTS**

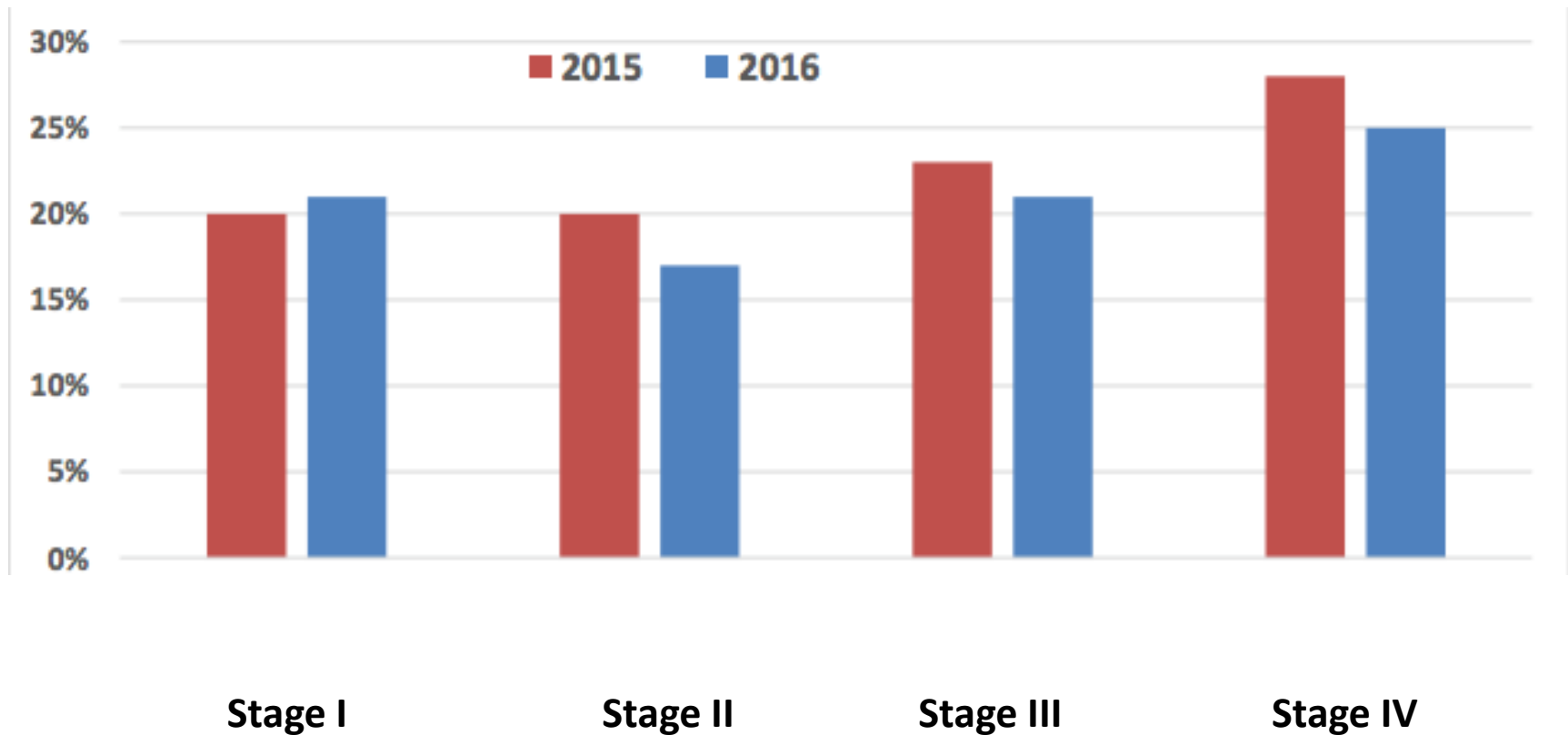
Cancer incidence In Georgia

2015 -2016

Cancer incidence in both sex distributed according age in Georgia



Cancer Incidence Distribution According Tumor Stage (%) 2015 - 2016



Cancer incidence In Georgia

2015

Tumor Type	Number
Head & Neck Cancer(Oral cavity, oropharynx , hypopharynx, Glottic cancer, nasopharynx)	347 (More than 80% of Head and Neck Cancer patients are treated at my Cancer Centre)
Breast Cancer	1885
GYO Cancers	1058
Thoracic malignancy	1192
GI tract malignancy	1714
CNS Tumors	222
Soft tissue and bone tumors	60

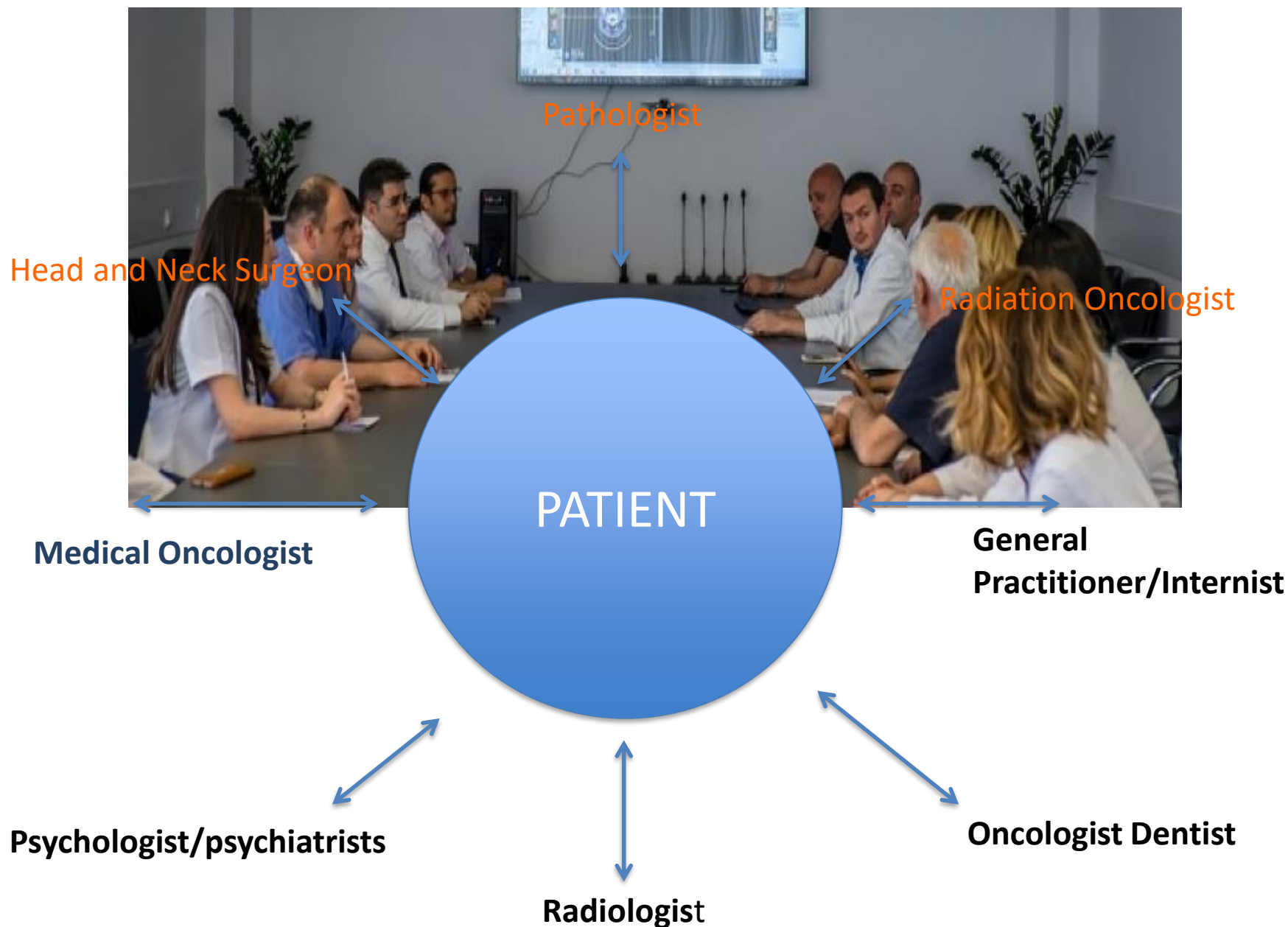
Survival Rate For Head and Neck Cancer

- The 5 year overall survival for mucosally based head and neck cancers remains about 60% for past few decades
 - Very dependent on site and stage

Cancer Research Centre (Mardaleishvili Medical Centre) Tbilisi, Georgia



MTD Meetings





Clinical Practice Guidelines for Patients with Locoregionally Advanced SCCHN

Surgery followed by RT or CCRT	Level of evidence I	Grade of recommendation A
Concomitant CT and RT	Level of evidence I	Grade of recommendation A
CCRT or ICT followed by RT for Organ preservation	Level of evidence II	Grade of recommendation A
Cetuximab + RT	Level of evidence II	Grade of recommendation B
ICT followed by CCRT (sequential Therapy)		Under evaluation





CCRT Standard Nonsurgical Therapy

- Adding more cytotoxic chemotherapy (ICT)
- Adding Targeted Therapy
- Adding a hypoxic sensitizer to concurrent CRT
- Immunotherapy

Role Of Induction Chemotherapy

- ICT does not have a clear established frontline role in the routine treatment of head and neck carcinomas of the major non-nasopharyngeal sites
- ICT  RT has an established role for organ Preservation in advanced and hypopharyngeal cancer
- ICT  Cisplatin based CCRT reduced distant metastases but it does not increase OS and is more toxic than CCRTalone

Randomized Trials of Sequential Therapy versus Concurrent CRT Only

Group	Regimen	Survival benefit
TTCC (Sp) ¹	 <div> TPF (or PF) x 3 → CCRT (P) </div> <div> CCRT (cisplatin) </div>	No
Boston (US) ²	 <div> TPF x 3 → CCRT (C or TAX) </div> <div> CCRT (cisplatin) </div>	No
Chicago (US) ³	 <div> TPF x 2 → CCRT (THFX) </div> <div> CCRT (THFX) </div>	No
GCTCC (It) ⁴	 <div> CCRT (PF) w/wo foregoing TPF </div> <div> BRT (Cetuximab) w/wo foregoing TPF </div>	Yes

¹Hitt R et al. Ann Oncol 2014; 25: 216-225; ²Haddad R et al. Lancet Oncol 2013; 14: 257-296

³Haddad R et al. ASCO 2012 (abstr. #5501); ⁴Ghi MG et al. ASCO 2013 (abstr. #6003) and ASCO 2014 (abstr. #6004)

INDUCTION CHEMOTHERAPY

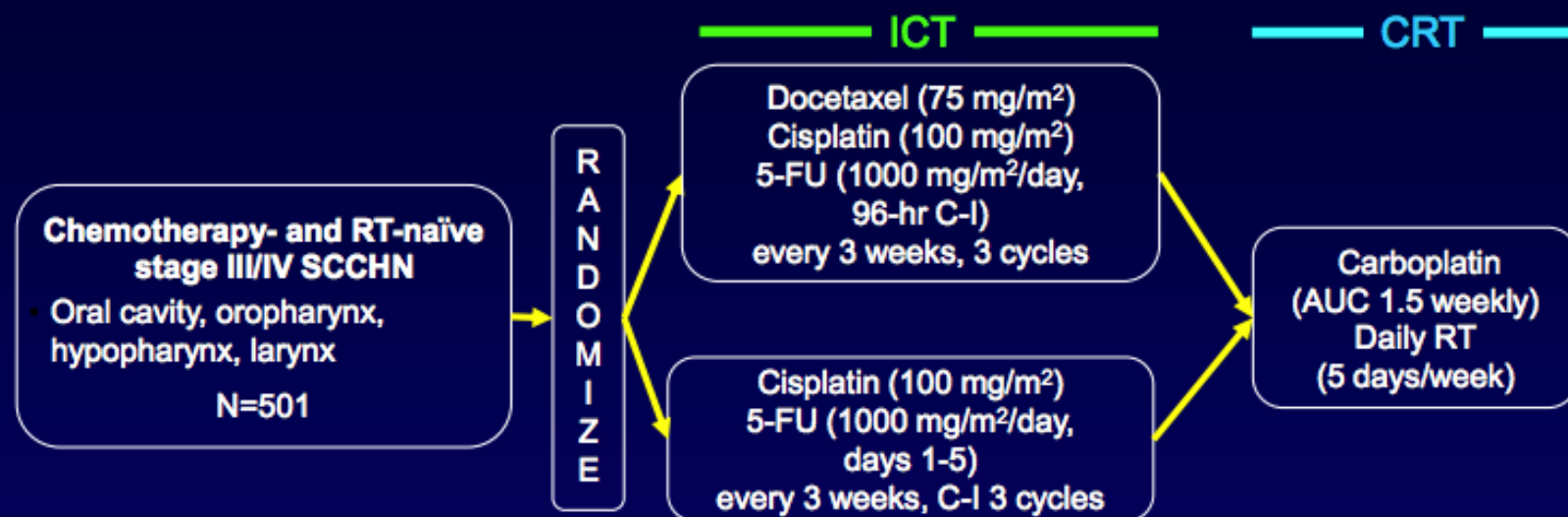
- **TAX 324 : DCF vs PF**

Did not include direct comparison to concurrent CRT

- **PARADIGM**

- **DeCIDE**

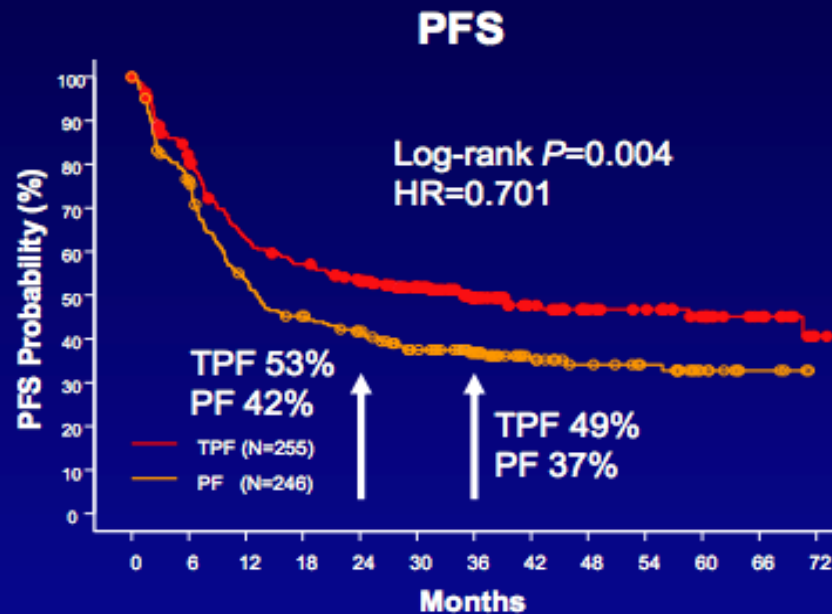
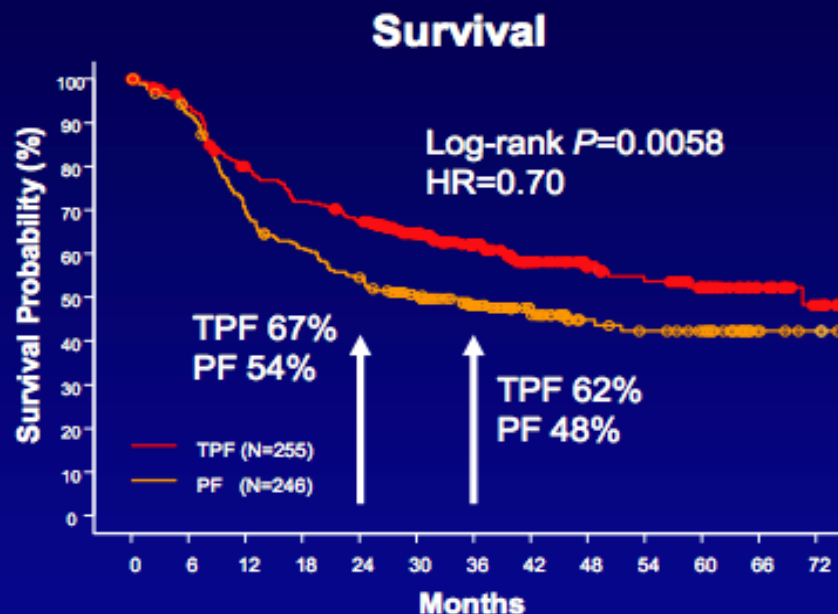
TAX 324: Docetaxel/Cisplatin/5-FU vs Cisplatin/5-FU Sequential Therapy in Advanced SCCHN



Response	TPF N=255 (95% CI)	PF N=246 (95% CI)	P Value
ORR (ICT)	72% (65.8-77.2)	64% (57.9-70.2)	0.07
CR (ICT)	17% (12.1-21.6)	15% (10.8-20.1)	0.66
ORR (ICT+CRT)	77% (70.8-81.5)	72% (65.5-77.1)	0.21
CR (ICT+CRT)	35% (29.4-41.5)	28% (22.5-34.1)	0.08

Posner, *N Engl J Med.* 2007;357:1705.

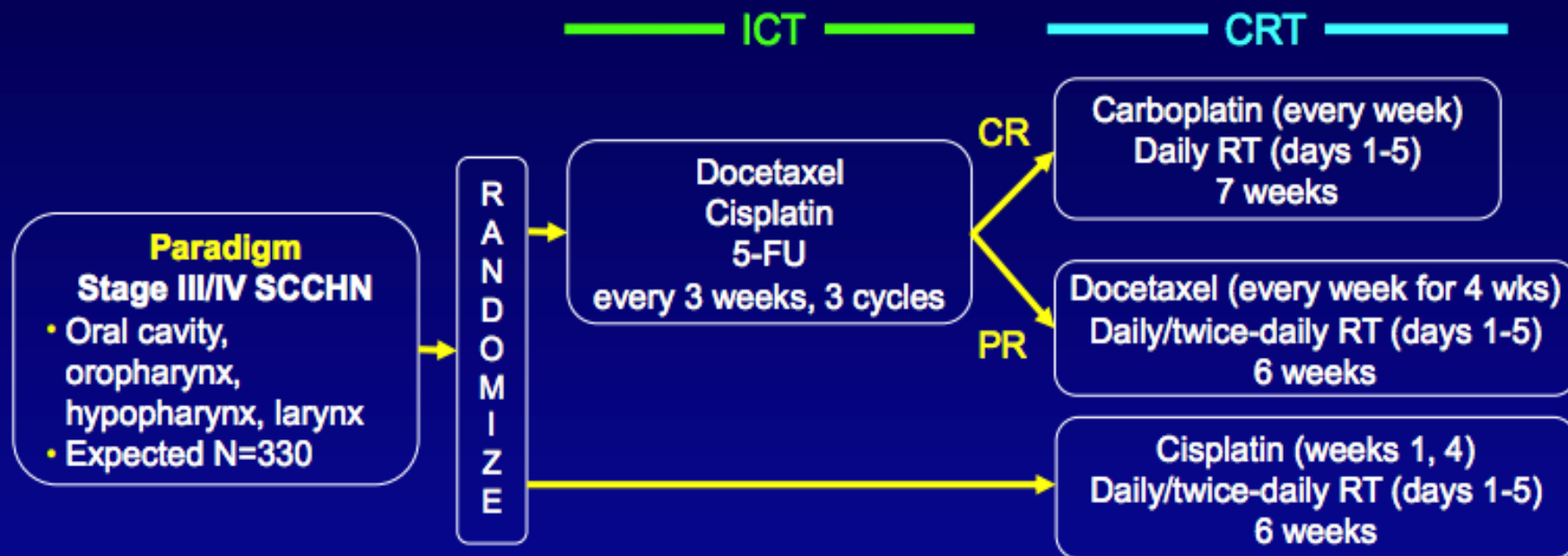
TAX 324: Docetaxel/Cisplatin/5-FU vs Cisplatin/5-FU Sequential Therapy in Advanced SCCHN: Results



- TPF significantly improves survival and PFS compared with PF in an ICT regimen followed by CRT

Posner. *N Engl J Med.* 2007;357:1705. Copyright © [2007] Massachusetts Medical Society. All rights reserved.

Paradigm: Phase III Sequential Therapy Trial in North America

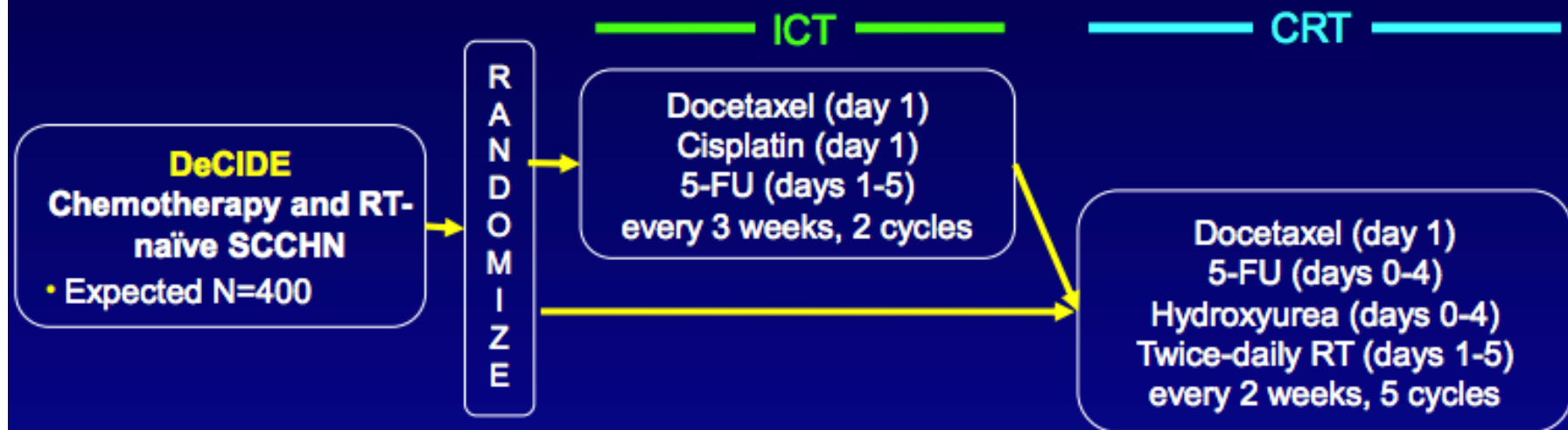


PARADIGM

- Arm 1: TPF x 3 → weekly carboplatin or docetaxel with accelerated RT
- Arm 2: Cisplatin x 2 with accelerated RT
- Enrolled 145 pts: oropharynx: 80, larynx: 24, hypopharynx: 15, and oral cavity: 26
- Study terminated early due to low accrual
- **3y OS was 73% vs 78% (p=0.77)**

Haddad et al., The PARADIGM trial: A phase III study comparing sequential therapy (ST) to concurrent chemoradiotherapy (CRT) in locally advanced head and neck cancer (LANHC). ASCO 2012. Abstract #5501.

Decide: Phase III Sequential Therapy Trial in North America



DECIDE

- Arm 1 (standard): 5 days of D 25 mg/m², F 600 mg/m², hydroxyurea 500 mg BID, and RT 150 cGy BID followed by a 9 day break
- Arm 2 (induction): 2 induction cycles (D 75 mg/m², P 75 mg/m², F 750 mg/m² day 1-5) → same CRT
- Enrolled 280 patients
- **3y OS 73% vs 75% (p=0.70)**

Cohen et al., DeCIDE: A phase III randomized trial of docetaxel (D), cisplatin (P), 5-fluorouracil (F) (TPF) induction chemotherapy (IC) in patients with N2/N3 locally advanced squamous cell carcinoma of the head and neck (SCCHN). ASCO 2012. Abstract #5501.

Role Of Induction Chemotherapy

ORGAN PRESERVATION

JNCI Journal of the National Cancer Institute Advance Access published January 27, 2009

ARTICLE

Phase 3 Randomized Trial on Larynx Preservation Comparing Sequential vs Alternating Chemotherapy and Radiotherapy

J. L. Lefebvre, F. Rolland, M. Tessaar, E. Bardat, C. R. Leemans, L. Geoffrois, P. Hupperets, L. Barzan, D. de Raucourt, D. Chevalier, L. Licita, F. Lunghi, R. Stupp, D. Lacombe, J. Bogaerts, J. C. Horiot, J. Bernier, J. B. Vermorken; for the EORTC Head and Neck Cancer Cooperative Group and the EORTC Radiation Oncology Group

EORTC 24954

RTOG 91-11

The **NEW ENGLAND JOURNAL of MEDICINE**

ESTABLISHED IN 1812

NOVEMBER 27, 2003

VOL. 349 NO. 22

Concurrent Chemotherapy and Radiotherapy for Organ Preservation in Advanced Laryngeal Cancer

Arlene A. Forastiere, M.D., Helmuth Goepfert, M.D., Moshe Maor, M.D., Thomas F. Pajak, Ph.D., Randal Weber, M.D., William Morrison, M.D., Bonnie Glisson, M.D., Andy Trotti, M.D., John A. Ridge, M.D., Ph.D., Clifford Chao, M.D., Glen Peters, M.D., Ding-jen Lee, M.D., Ph.D., Andrea Leaf, M.D., John Ensley, M.D., and Jay Cooper, M.D.

ABSTRACT

RTOG 91-11

- Patient selection
 - T3
 - Limited T4
- Patient exclusions
 - Large volume T4a
 - Extending through thyroid cartilage
 - Greater than 1 cm extension into base of tongue

RTOG 91-11

Phase III Trial to Preserve the Larynx

N = 547 stage III/IV

**S
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Location:

Glottic
Supraglottic

T Stage:

T2
T3
Early T4

N Stage:

N0, N1
N2, N3

**R
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Arm 1 : Neoadjuvant CT + RT
CR, PR → Cis + 5-FU → RT
x 1 Cycle

Cis + 5-FU X 2 Cycles

NR → Surgery → RT

Arm 2 : RT + cisplatin

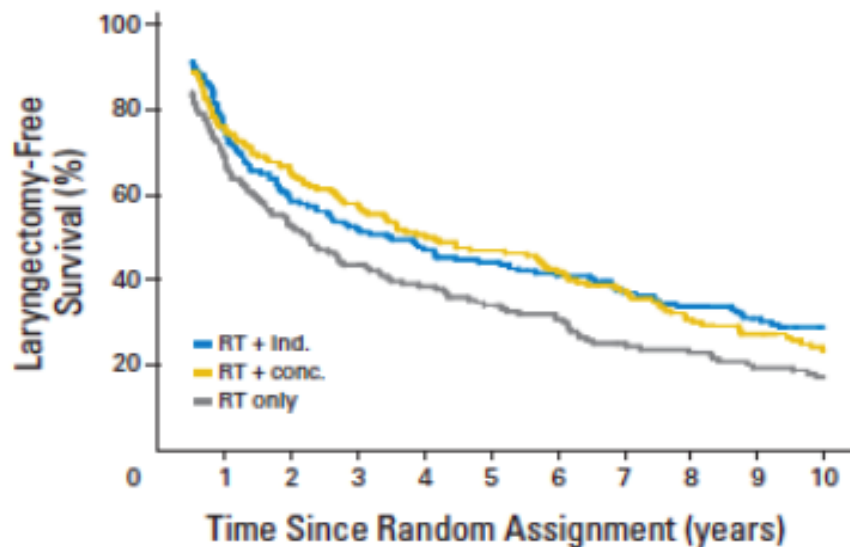
Arm 3 : RT Alone

Neck dissections for all pts with node > 3cm or multiple nodes, 8 weeks after RT

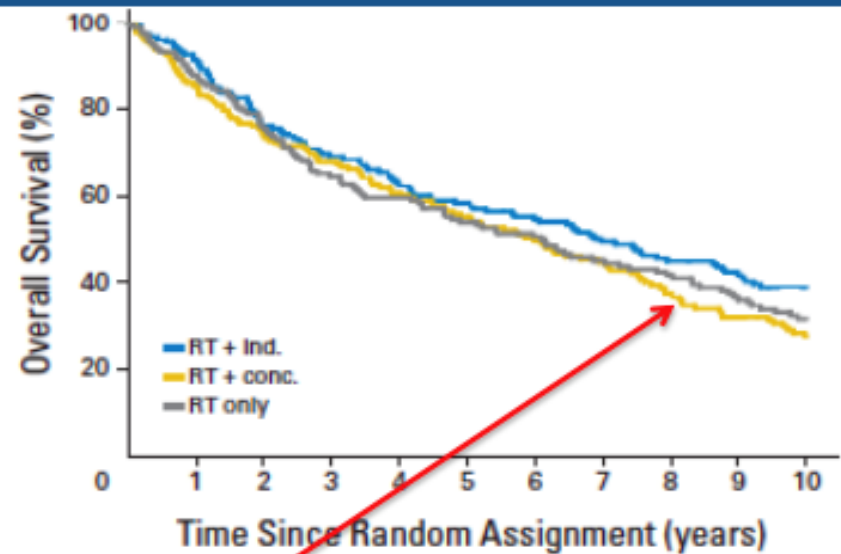
RTOG 91-11 at 3 years

Arm	LPR	LRC	OS	G3/4 (G5)
Neoadj CT	75%	61%	76%	66% (5)
Conc CT	88%	78%	74%	77% (9)
RT alone	70%	56%	75%	47% (5)

RTOG 91-11 10 year update: IC→RT produced higher rates of LFS than RT alone



No. at risk	174	130	98	87	78	72	65	56	51	44	37
RT + Ind.	174	130	111	96	83	76	67	58	45	38	30
RT + conc.	172	116	88	70	62	52	46	35	32	27	24
RT only											



No. at risk	174	157	128	116	104	96	88	76	69	61	52
RT + Ind.	174	146	126	113	100	90	80	70	56	46	36
RT + conc.	172	148	126	105	96	83	76	65	59	51	43
RT only											

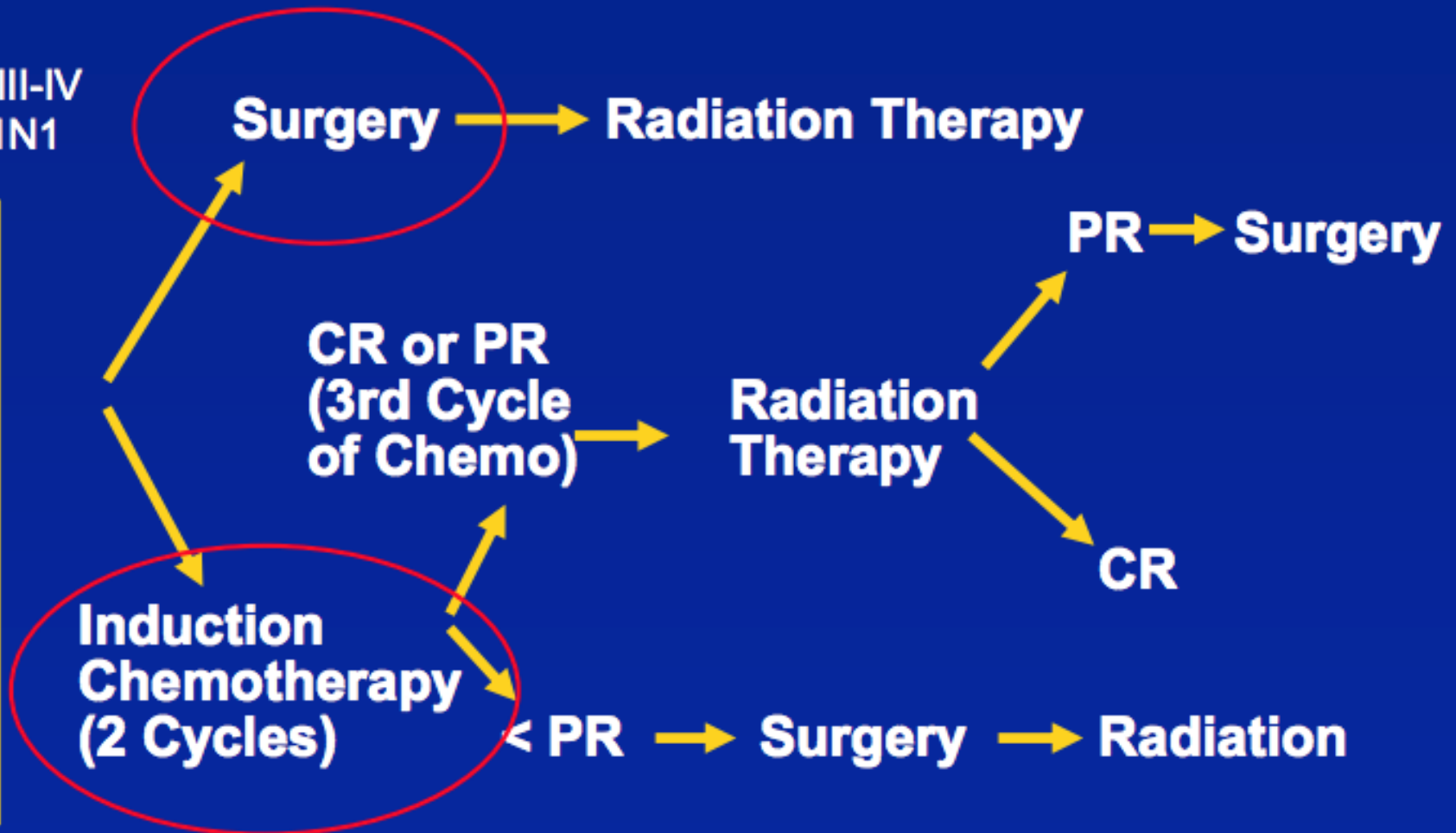
? Late “non-cancer related death” in CRT arm?

Forastiere JCO 2013

VA LARYNGEAL CA. STUDY

Stage III-IV
excl T1N1

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Induction Chemotherapy: Cisplatin and 5-FU

VAH Laryngeal Carcinoma Study

Patterns of First Failure – higher in CRT arm

	S + RT (N = 166)	CT + RT (N = 166)	P value
Persistent Disease	6 (4%)	15 (9%)	.042
Recurrent Disease			
Primary only	0 (0%)	21 (13%)	.001
Nodes (\pm prim)	15 (9%)	27 (16%)	.001
Distant Mets	30 (18%)	20 (12%)	.004

VAH Laryngeal Carcinoma Study

Cause of Death – similar in the end

Cause	S + RT (N = 166)	CT + RT (N = 166)
Local/Regional	20 (12%)	29 (17%)
Distant Mets	22 (13%)	20 (12%)
Second Primary	4 (2%)	7 (4%)
Complications	6 (4%)	4 (2%)
Other causes	22 (14%)	17 (10%)
Unknown	5 (3%)	10 (6%)
Total	79 (48%)	87 (52%)

VAH Laryngeal Carcinoma Study

at Four Years

	S + RT (N = 166)	CT + RT (N = 166)
Larynx preserved	20* (12%)	103 (62%)
Total laryngectomy	146 (88%)	63 (38%)
Patients alive	87 (52%)	79 (48%)
without larynx	79	27
with larynx	8 (5%)	52 (31%)

* Supraglottic Laryngectomy

Toxicity Profile

VA larynx, long term QOL: significant differences in mental health and pain

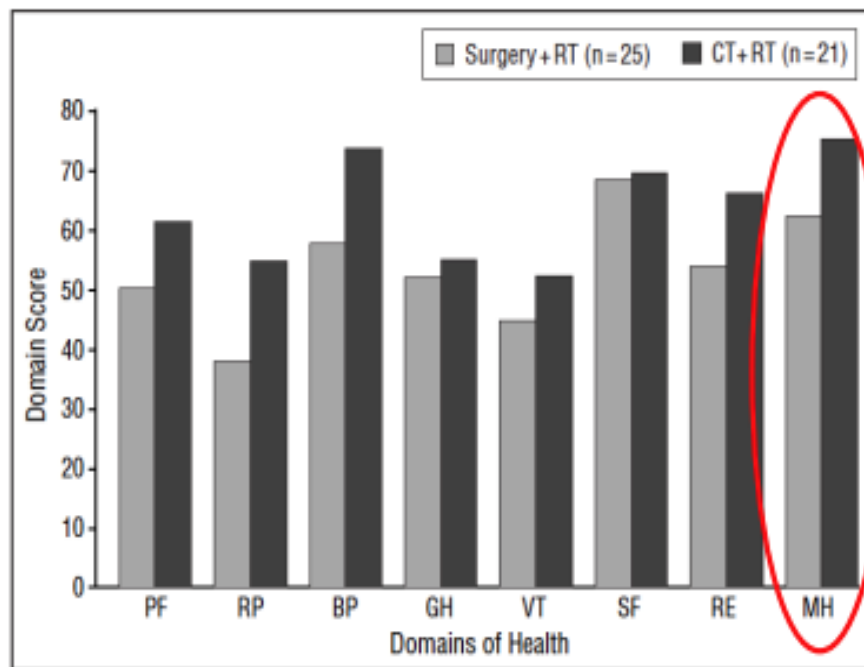


Figure 2. Comparison of health status for surgery and radiation therapy (RT) vs chemotherapy (CT) + RT patients for domains of the Medical Outcomes Studies Short-Form 36 instrument (see legend to Figure 1 for domains and expansion of abbreviations). $P < .05$ for mental health.

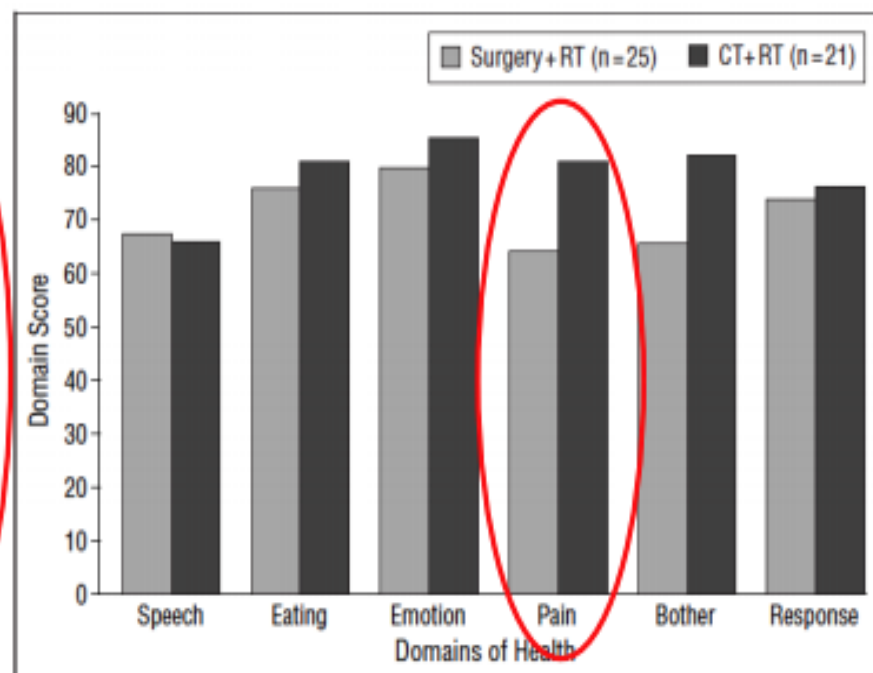


Figure 3. Comparison of health status for surgery and radiation therapy (RT) vs chemotherapy (CT) + RT patients for 6 domains of the Head and Neck Quality of Life (HNQOL) instrument. Response indicates the treatment item of HNQOL; bother, the overall bother item on the HNQOL. $P < .05$ for pain.

Questions ?

- Should induction-RT be an option along with concurrent chemoradiation?
- Should “induction” mean TPF or PF?
- Should induction be followed by chemoradiation instead of RT, in keeping with original TPF vs PF protocol?
- Which T3 cancers should have surgery and would they do better with partial larygectomy?
- Should “minimal” T4 cancers be considered for organ preservation?

Question: Induction...which chemotherapy?

GORTEC Trial

Randomized Trial of Induction Chemotherapy With Cisplatin and 5-Fluorouracil With or Without Docetaxel for Larynx Preservation

Yoann Pointreau, Pascal Garaud, Sophie Chapet, Christian Sire, Claude Tuchsais, Jacques Tortochaux, Sandrine Faivre, Stephane Guerif, Marc Alfonsi, Gilles Calais

JNCI 2009

Docetaxel	75
Cisplatin	75
5 FU	750

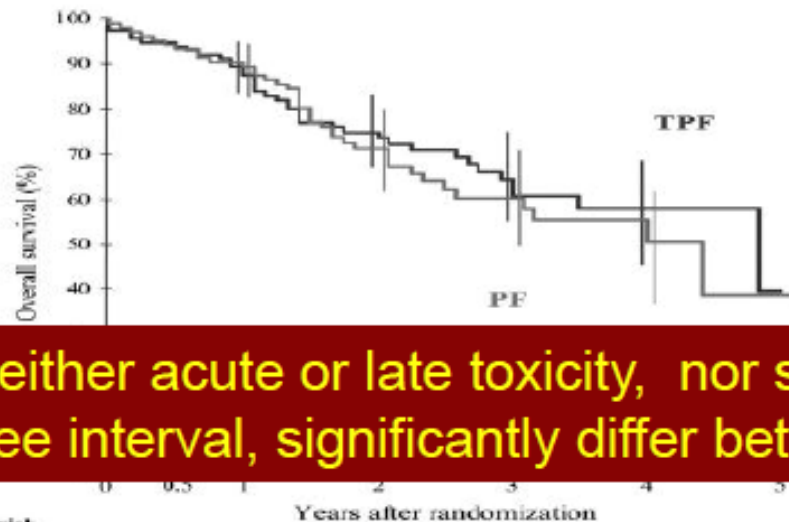
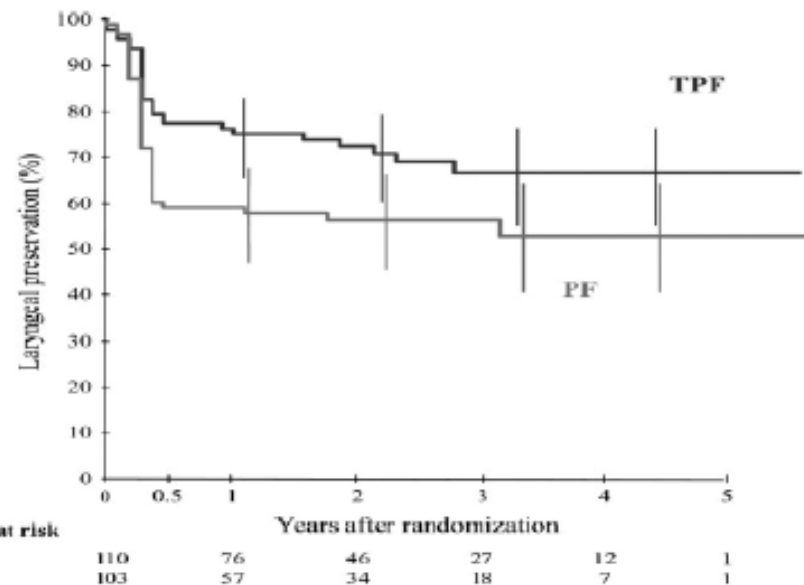
VS

Cisplatin	100
5 FU	1000

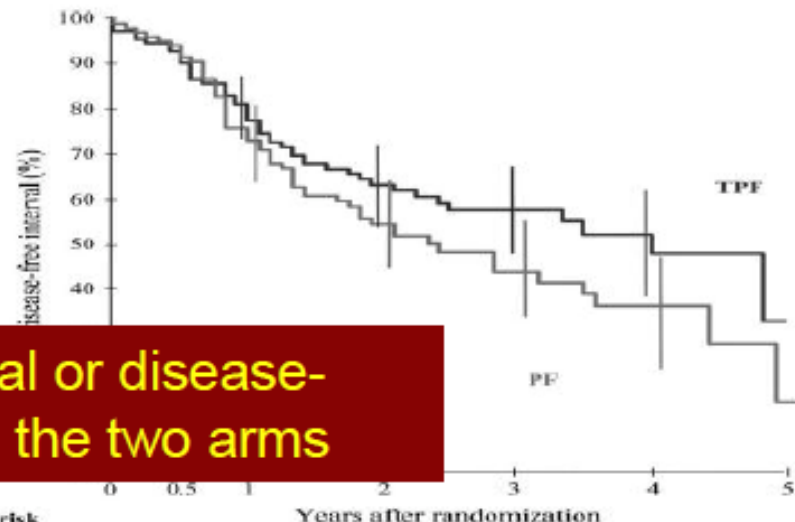
RADIOTHERAPY 70 Gy

Results

The main objective was larynx preservation .
Only the laryngectomy has been considered failure, regardless its function



Neither acute or late toxicity, nor survival or disease-free interval, significantly differ between the two arms



Organ preservation

CONCLUSIONS

1. ICT, Alternating CRT and Concurrent CRT are all acceptable approaches to organ preservation.
2. ICT should be regarded as the “best standard” because of a better survival profile than concurrent CRT and an easier delivery compared to alternating CRT.
3. There is evidence that TPF (European regimen) should be considered standard in organ preservation.

Research Areas of Induction Chemotherapy for Treatment De-intensification

- Induction Chemotherapy can be used as a tool to stratify patients by treatment response
- Applicable for good prognosis HPV associated OPC
- Ongoing Trial : OPTIMA - very interesting Clinical trial

E1308: A PHASE II TRIAL OF INDUCTION CHEMOTHERAPY FOLLOWED BY CETUXIMAB WITH LOW DOSE OR STANDARD DOSE IMRT IN PATIENTS WITH HPV-ASSOCIATED RESECTABLE SQUAMOUS CELL CARCINOMA OF THE OROPHARYNX

Induction Chemotherapy

Concurrent Chemoradiation

N=90 patients, 80 analyzable

Key Eligibility

- 1.OPSCC
- 2.HPV16 ISH + and / or p16+
- 3.Resectable stage III, IVA

Cisplatin 75mg/m² D1
Paclitaxel 90mg/m² D1,8,15
Cetuximab 250mg/m² D1,8,15
Q 21 days for 3 cycles

**R*
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CLINICAL CR

Low dose IMRT 54Gy/27fx** +
Cetuximab weekly

CLINICAL PR /SD

Full dose IMRT 69.3Gy/33fx** +
Cetuximab weekly

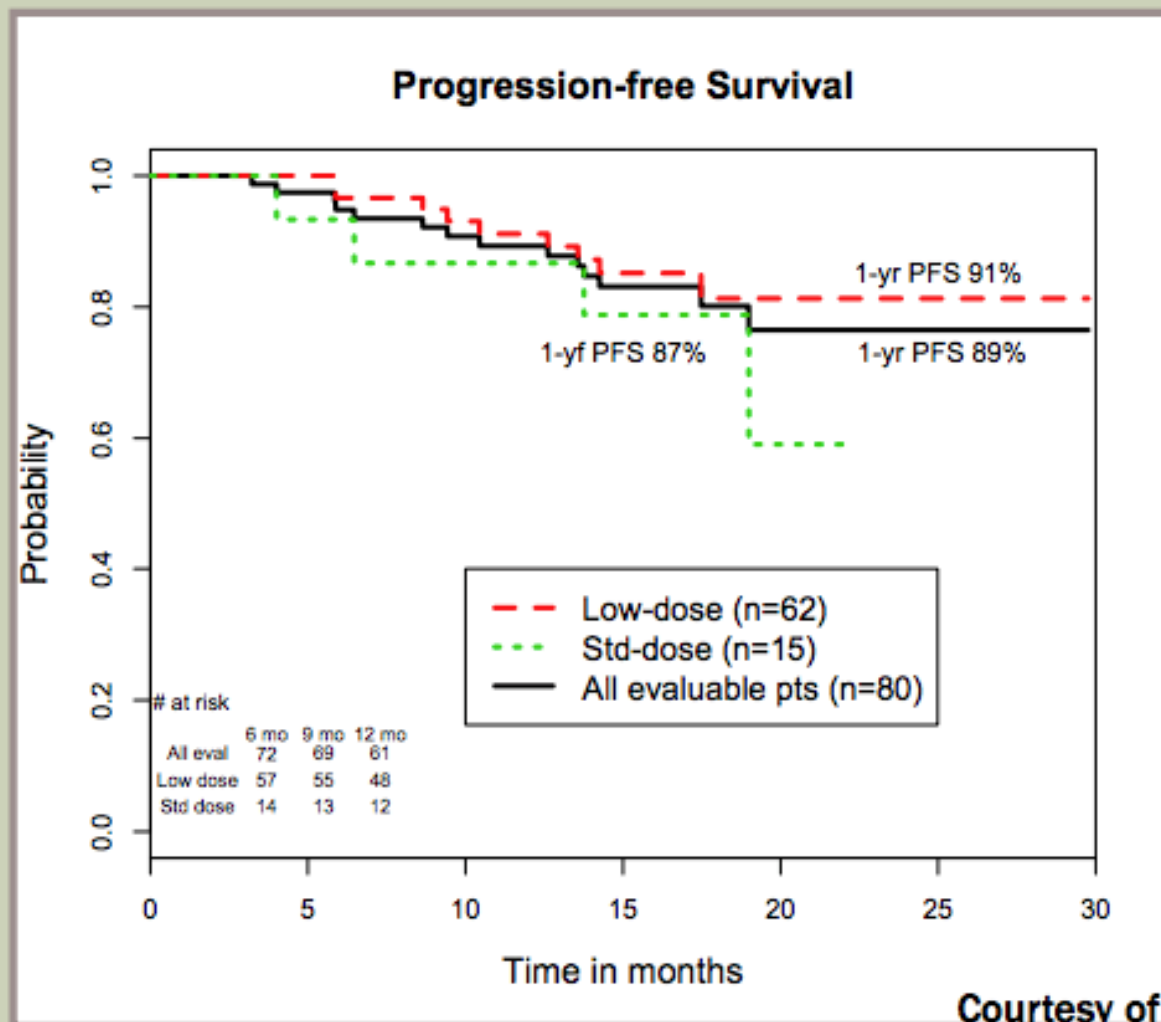
*Response Assessment

- : Direct visualization of primary
- : Clinical exam of neck
- : CT/MRI

**Uninvolved nodes get 51.3 Gy/27 fx

Courtesy of Barbara Burtness

RESULTS: PFS IN STANDARD AND LOW DOSE RT ARMS



Courtesy of Barbara Burtneess

ECOG 1308: 2-YEAR PRIMARY ENDPOINT

- For reduced-dose IMRT patients (78% of all patients), at 23 mo followup, PFS was 84%
 - overall survival 95%
 - primary site LC 94%
 - nodal control 95%
 - distant control 92%
- Patients with <10yrs smoking, T1-3 and N0-2b disease achieved 96% PFS and OS

OPTIMA Trial- Oropharynx Tumor Induction Response Stratified Therapy To Minimize Adverse Events

Low Risk

$\leq T3$ &
 $\leq N2B$ &
 ≤ 10 PYH

- 1) Carboplatin
AUC6,d1
- 2) Nab –
paclitaxel
100mg.m2
- 3) D1/d8/d15

High Risk

T4 or
 $\geq N2C$ or
 >10 PYH

Radiologic
Response

Low-dose RT
PTV1: 50 Gy

$>50\%$

30-50%

Low-dose CRT
PTV1: 45 Gy
PTV2: 30 Gy

$<30\%$

Standard CRT
PTV1: 75 Gy
PTV2: 45 Gy

Results

- Post-Treatment Biopsy/ND

Mean 7.3 weeks after RT/CRT(IQR 5.9-8.4)

Mean 26 nodes removed (IQR 18-33)

- Pathologic CR 91,5%

Low dose RT:94.7%(18/19)

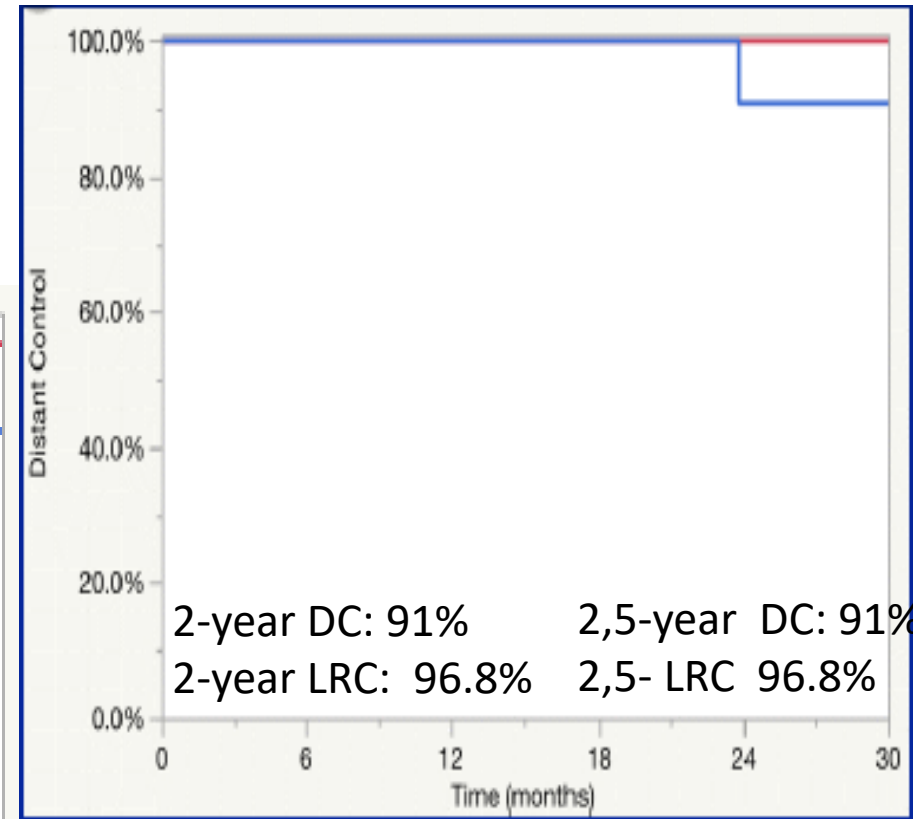
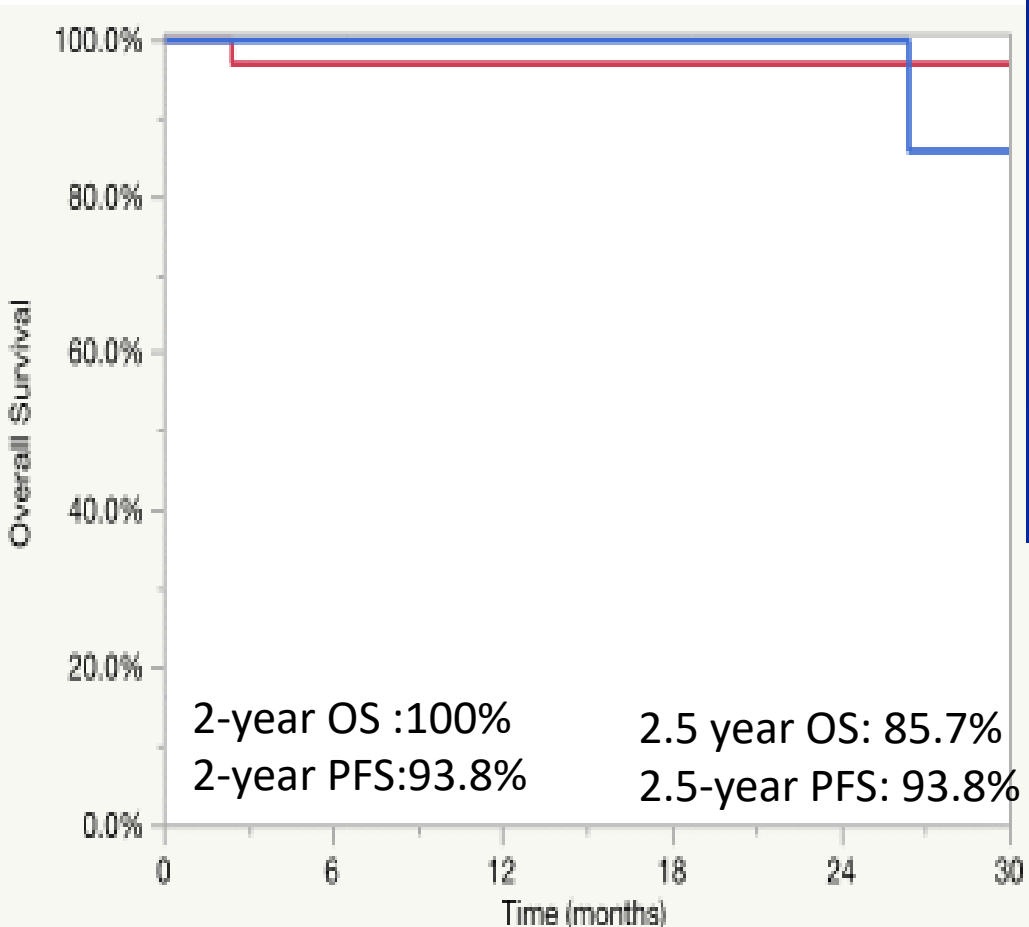
Low dose CRT(CRT: 89,3%25/28)

Low risk patient :100% (6/6)

High Risk patient:86,4%(19/22)

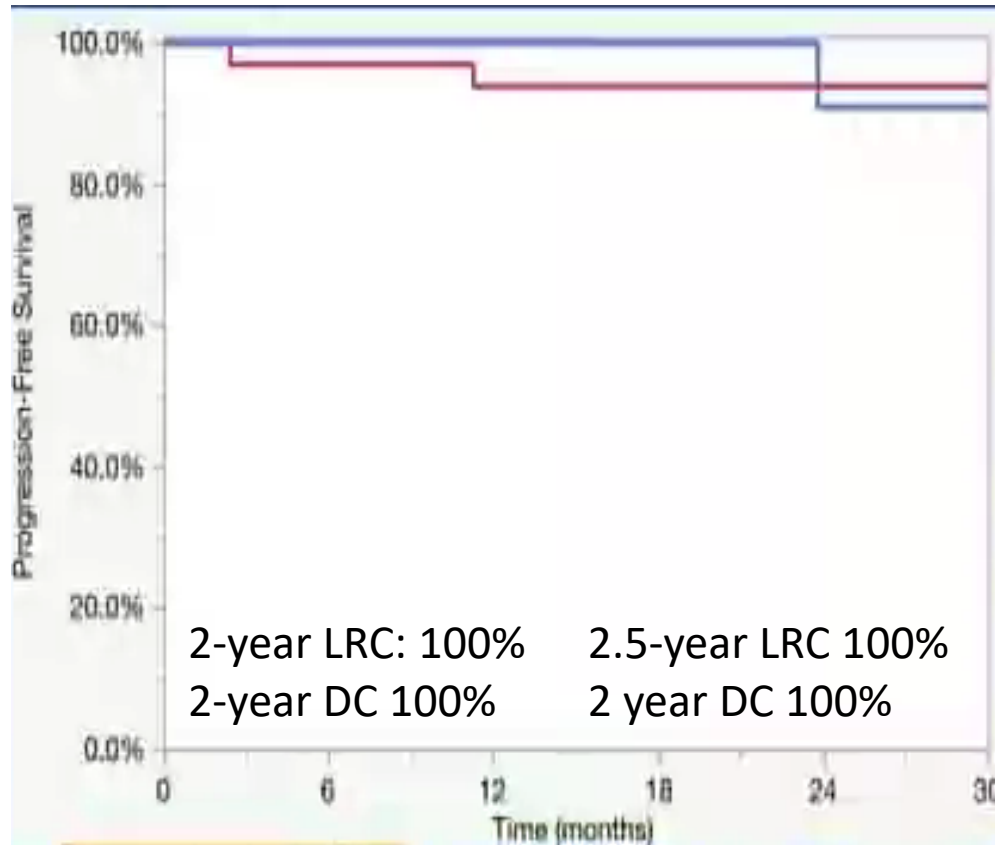
Optima Trial Results

OVERALL SURVIVAL

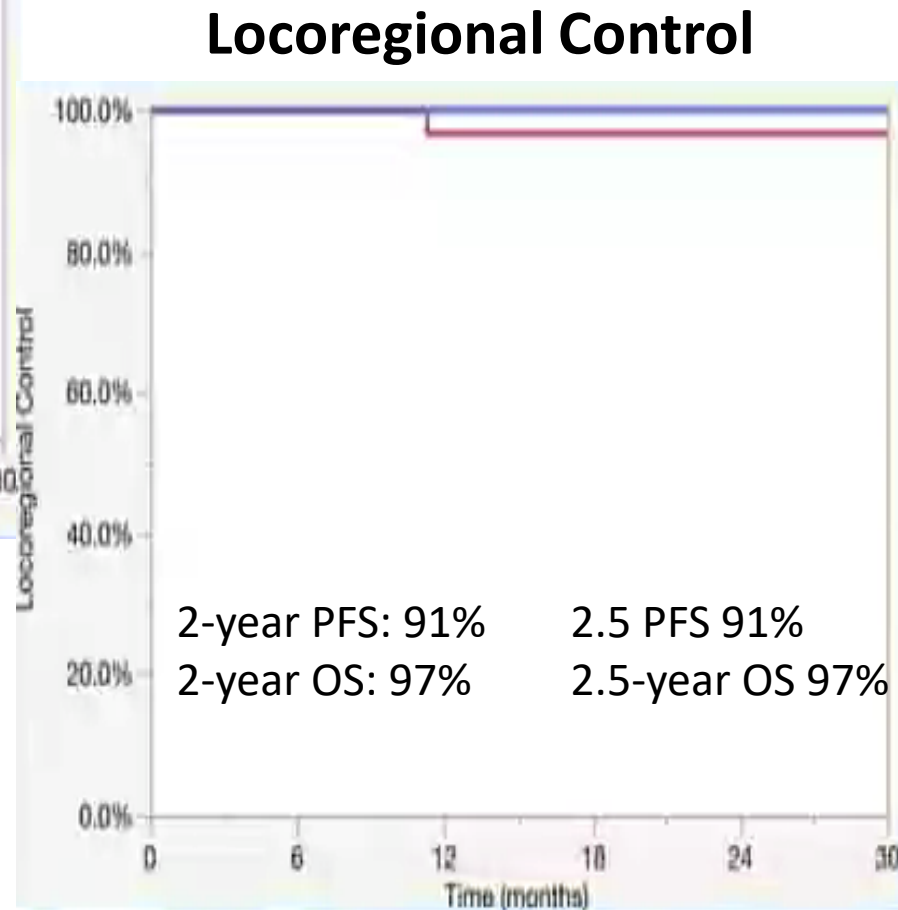


DISTANT CONTROL

Optima Trial Results



Progression Free Survival



GSTTC Italian Study Group

**A phase II-III study comparing
CRT vs cetuximab/RT
with or without induction TPF
(docetaxel/cisplatin/5-fluorouracil)
in locally advanced H&N cancer.
Efficacy results (NCT01086826).**

GSTTC Italian Study Group

- No Difference in toxicities, except neutropenia, 8% IC-CCRT versus 1% CCRT; $p=0.038$)
- Compliance to concomitant treatments was not affected by TPF

IC arms better for

OS($p=0.031$)

CRs($p=0.0028$)

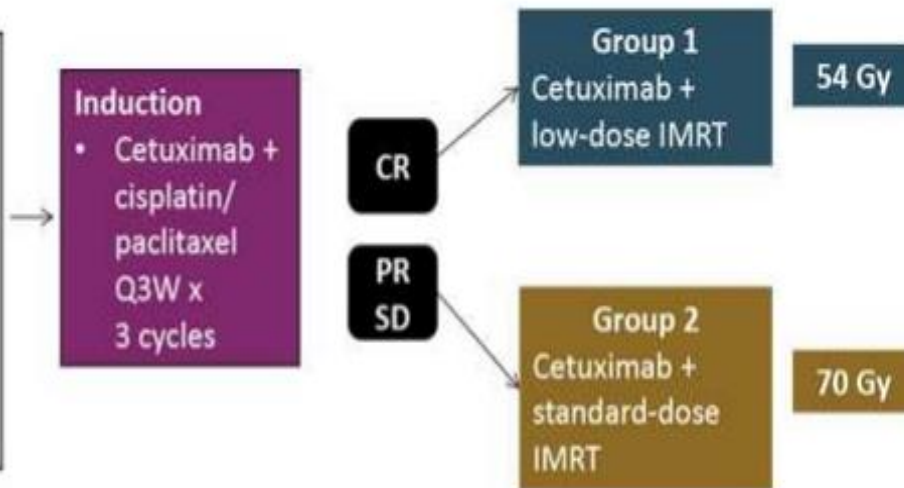
PFS($p=0.013$)

LRC($p=0.036$)

ECOG 1308 Trial

ECOG 1308: randomized Phase II trial

- Estimated N = 83
- No prior therapy for HNC
- Only HPV+ disease
- PS 0-1
- Resectable or potentially resectable



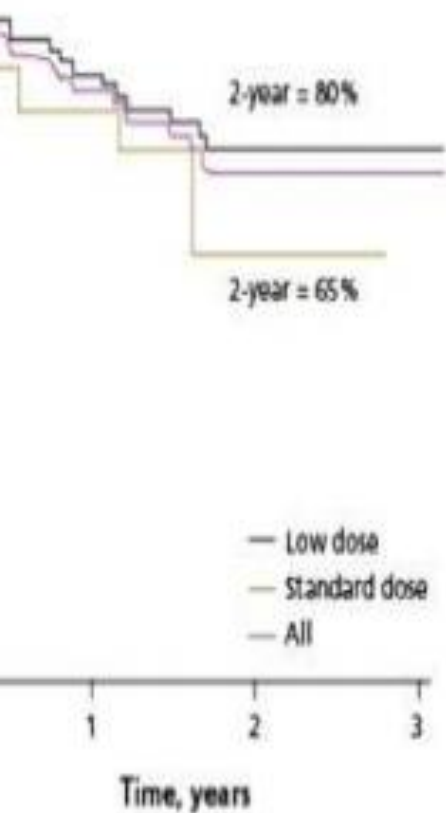
70% CR at primary
58% CR at nodal site

- Primary endpoint: 2-year PFS rate 85%
- Secondary endpoints: OS, QOL, overall response, toxicity, biomarkers

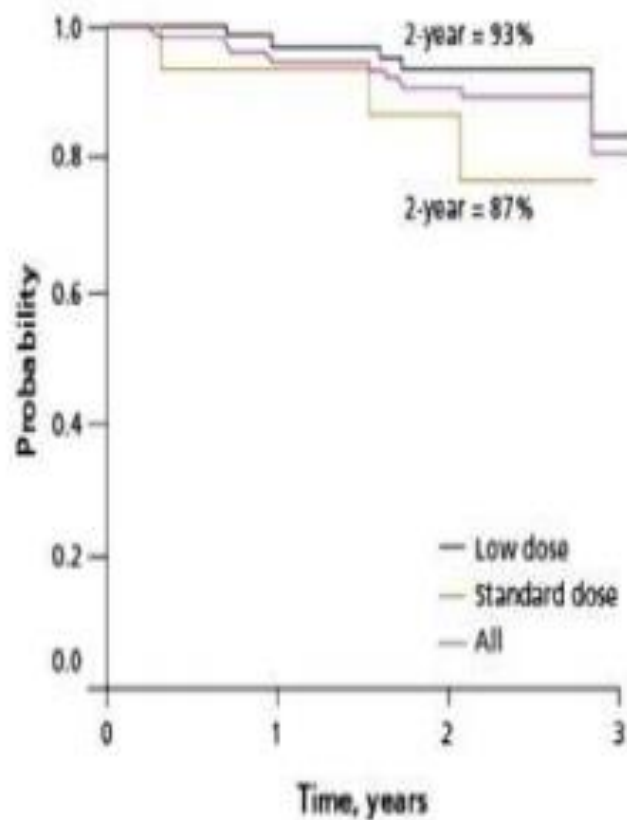
Results

1308

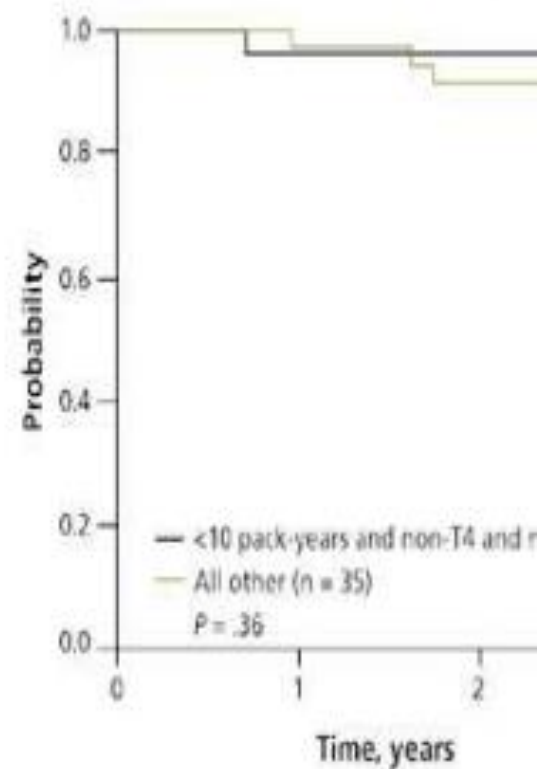
Recurrence-Free Survival by RT Dose



Overall Survival by RT Dose

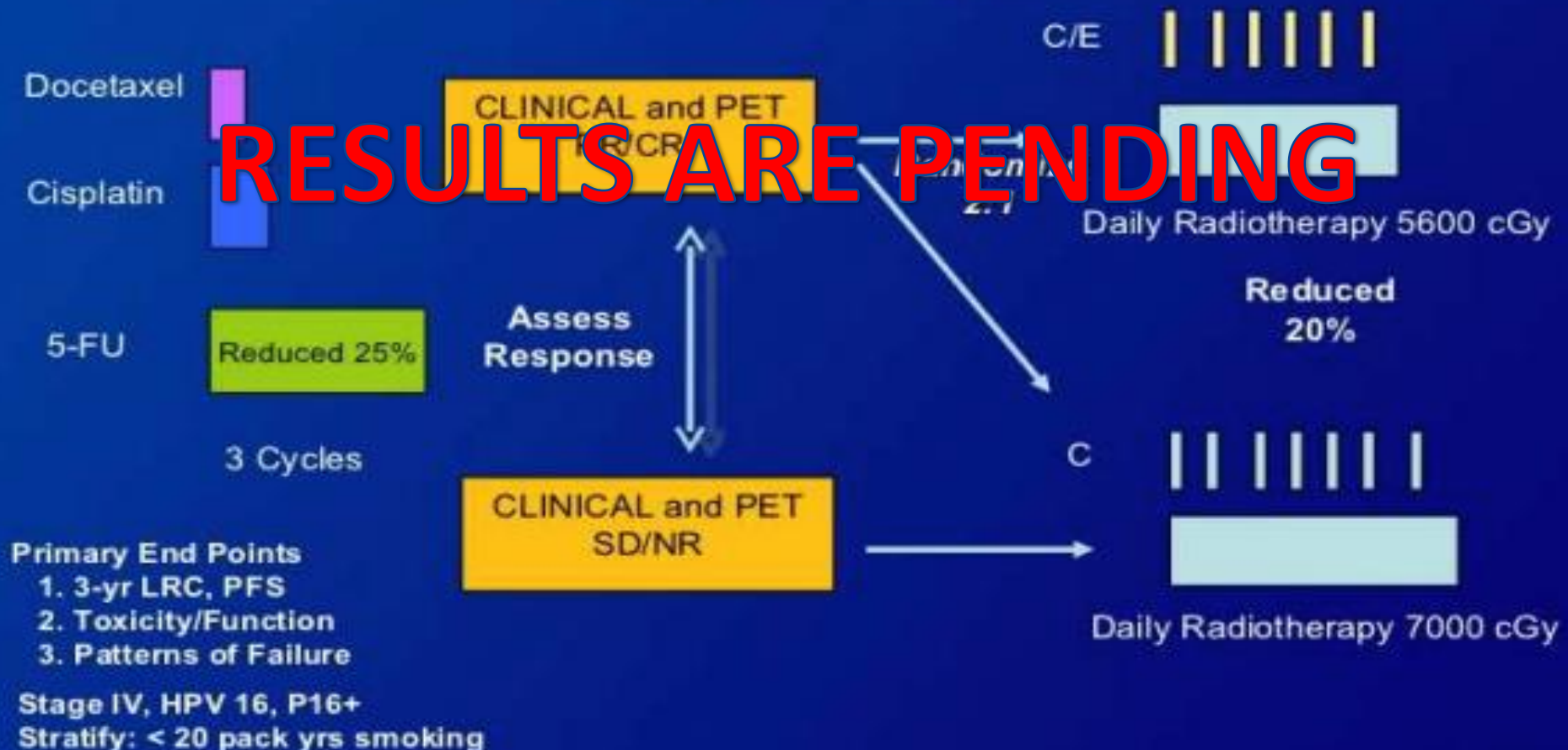


Overall Survival:
The Most Favorable Cohort vs



QUARTERBACK Trial

HPV+ Oropharynx Phase III: Reduced Dose Chemoradiotherapy for Induction PR/CR The Quarterback Trial



ROLE OF INDUCTION CHEMOTHERAPY
In

NASOPHARYNGEAL CARCINOMA

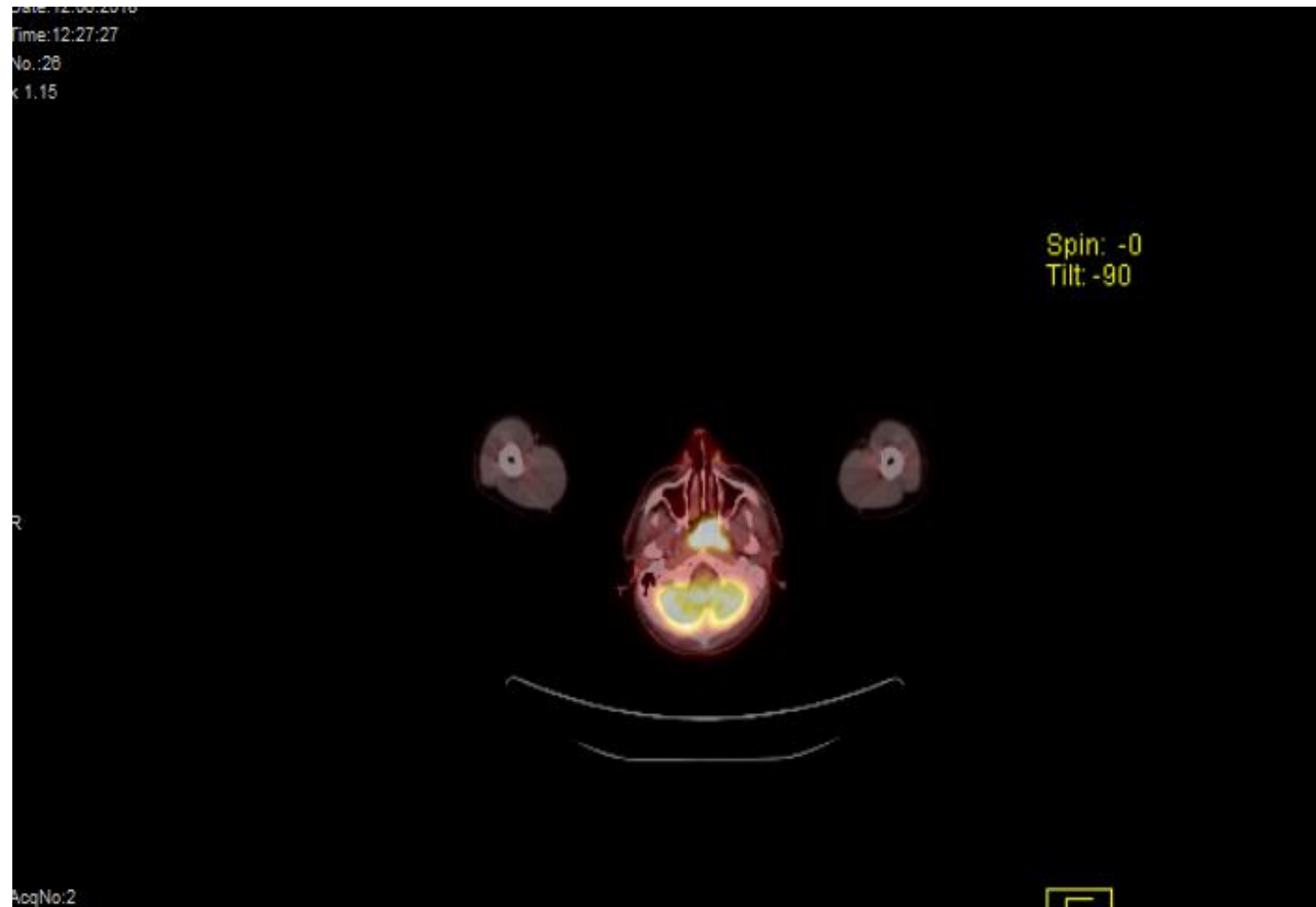
Clinical Case

- Patient: male 35 y old
- Patient was seen at our center in June 2018 when he admitted with complains on headace , nasal stiffnes, with some discharge , dizziness.
- Endoscopy and PET/CT scan was ordered

Diagnosis

- Endoscopy confirmed mass lesion at posterior wall of nasopharynx
- **Histology and Immunohistochemistry confirmed:** nasopharyngeal carcinoma non keratinized Grade 3

PET/CT Images



Treatment

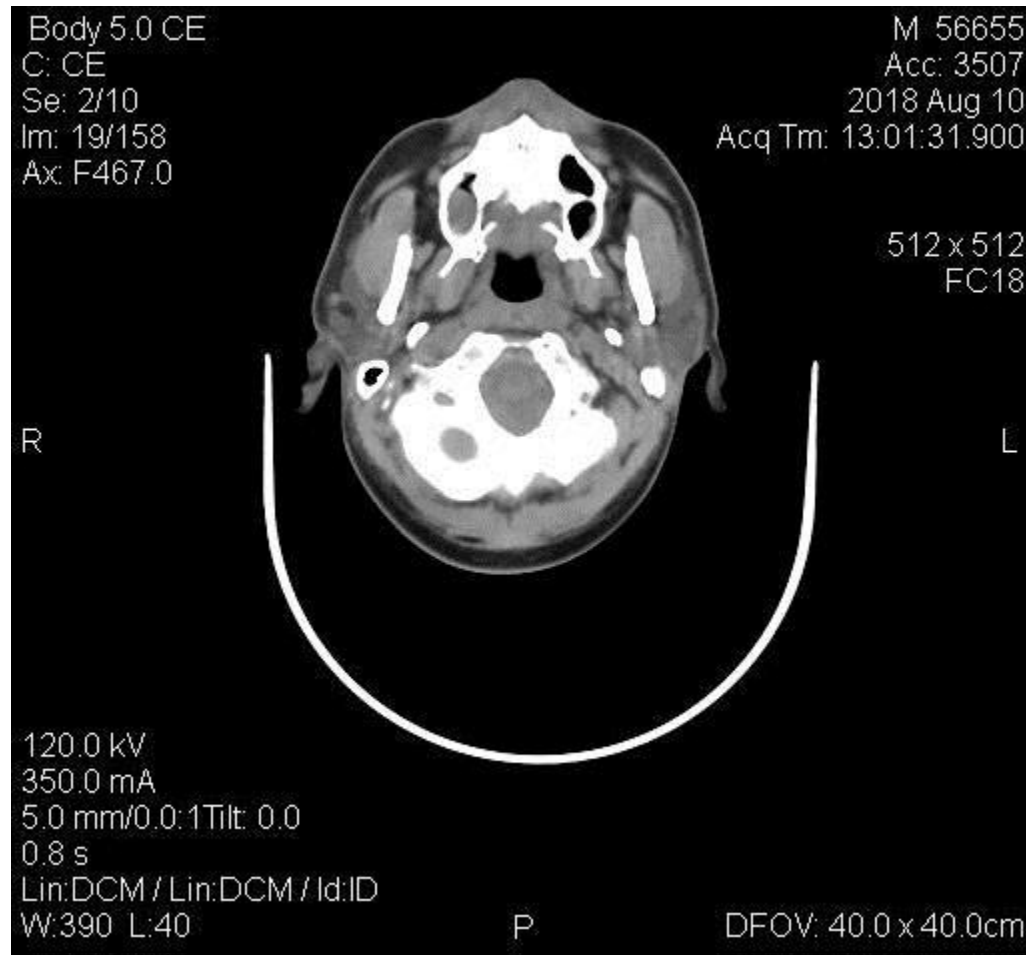
- **Induction chemotherapy with DCF regimen :**

Cisplatin 75mg/m²

Docetaxel 75mg/m²

5-FU 750mg /m² -96 hour pump infusion

CT Images after 3 cycles of IC treatment



Post IC Treatment

- Patient started CRT with platinum based chemotherapy

Induction Chemotherapy Role In Nasopharyngeal Carcinoma

Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial



Ying Sun, Wen-Fei Li*, Nian-Yong Chen*, Ning Zhang*, Guo-Qing Hu*, Fang-Yun Xie*, Yan Sun*, Xiao-Zhong Chen, Jin-Gao Li, Xiao-Dong Zhu, Chao-Su Hu, Xiang-Ying Xu, Yuan-Yuan Chen, Wei-Han Hu, Ling Guo, Hao-Yuan Mo, Lei Chen, Yan-Ping Mao, Rui Sun, Ping Ai, Shao-Bo Liang, Guo-Xian Long, Bao-Min Zheng, Xing-Lai Feng, Xiao-Chang Gong, Ling Li, Chun-Ying Shen, Jian-Yu Xu, Ying Guo, Yu-Ming Chen, Fan Zhang, Li Lin, Ling-Long Tang, Meng-Zhong Liu, Jun Ma*

Pts < 60 yrs

Excluded T3-T4N0

TPF at reduced doses (60-60-600)

Results

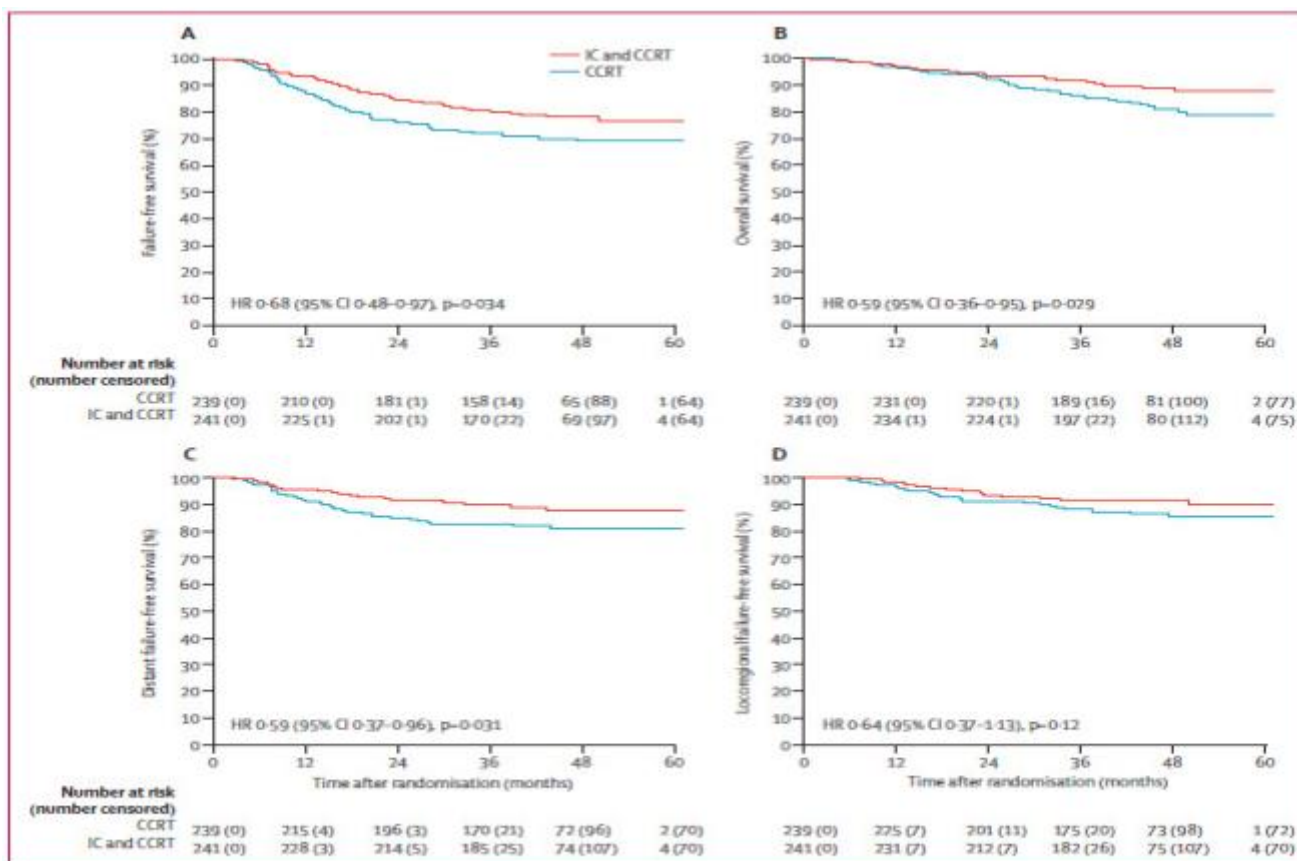


Figure 2: Kaplan-Meier survival curves for the two treatment groups

(A) Failure-free survival, (B) overall survival, (C) distant failure-free survival, and (D) locoregional failure-free survival, all from the start of treatment. Hazard ratios (HRs) were calculated with the unadjusted Cox proportional-hazards model; p values were calculated with the unadjusted log-rank test. CCRT=concurrent chemoradiotherapy. IC=induction chemotherapy.

Neoadjuvant Chemotherapy Followed by Concurrent Chemoradiotherapy (NCRT+CCRT) Versus CCRT Alone in Locoregionally Advanced Nasopharyngeal Carcinoma

A Phase III Multicentre Randomised Controlled Trial

Ming-Yuan Chen, MD., PhD.; Ming-Huang Hong, MD.

Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, Guangzhou, China

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

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Excluded T3N0, N1

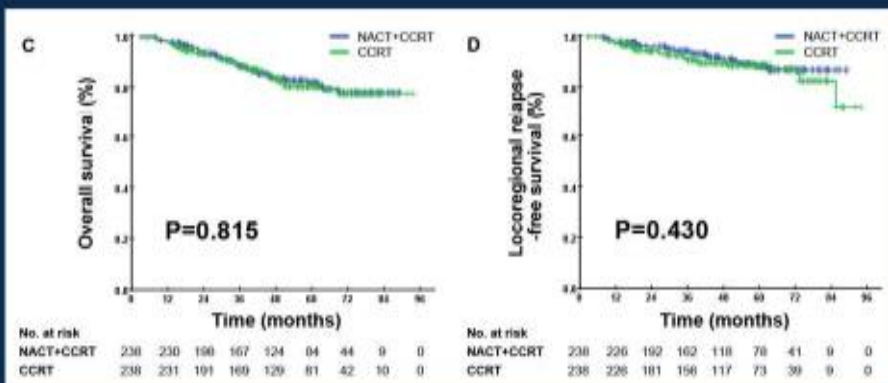
Presented By Ming-Yuan Chen at 2017 ASCO Annual Meeting

Efficacy analysis

- Intention-to-treat Analyses
- Per-protocol Analyses

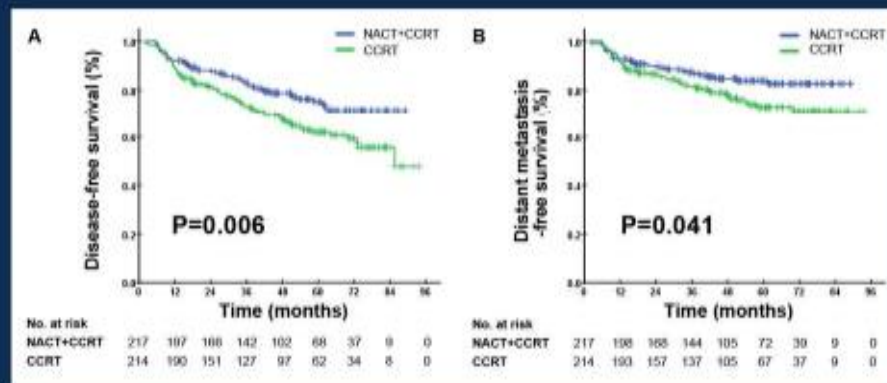
OS

LRRFS



OS

LRRFS



PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

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Presented by: Ming-Yuan Chen

Presented By Ming-Yuan Chen at 2017 ASCO Annual Meeting

Induction Chemotherapy 2018

- Has established role in organ preservation strategies
- Decreases the occurrence of distant metastases
- TPF –chemotherapy regiment is most effective regimen

THANK FOR YOUR ATTANTION

