

# Locally advanced NPC

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## Nasopharyngeal cancer: EHNS–ESMO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up

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On behalf of the EHNS–ESMO–ESTRO Guidelines Working Group\*

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### -TREATMENT:

- Stage I – IIa: RADIOTHERAPY (IMRT)
- Stage IIb: RADIO (**CHEMO**) (IMRT)
- Stage III – IV: RADIO (IMRT)-CHEMO

Table 1. Meta-analysis of chemotherapy in nasopharyngeal carcinoma: description of eligible trials

Trial (reference)	Inclusion period	Stage (classification*)	Histologic type (WHO classification)	RT dose, duration	Chemotherapy		Patients randomized and analyzed (n)	Median follow-up (months)
					Timing	Dose × No. of cycles		
PWH-88 (13)	1988–91	III–IV (Ho)	3	T 66 Gy/6.5 wk, N– 58 Gy, N+ 65.5 Gy	Induction and adjuvant	Cisplatin 100 mg/m <sup>2</sup> × (2 + 4) 5-Fluorouracil 3000 mg/m <sup>2</sup> × (2 + 4), CI	77	35
AOCOA (18)	1989–93	II–IV (AJCC <1997)	2–3	T 66–74 Gy/6.5–7.5 wk; N– 60–66 Gy, N+ 66–76 Gy	Induction	Cisplatin 60 mg/m <sup>2</sup> × 2–3 Epirubicin 110 mg/m <sup>2</sup> × 2–3	334	65
VUMCA-89 (19)	1989–93	III–IV (AJCC <1997)	1–3	T 65–70 Gy/6.5–7.5 wk; N– 50 Gy, N+ 65 Gy	Induction	Bleomycin 15 mg/m <sup>2</sup> × 3 Bleomycin 60 mg/m <sup>2</sup> × 3, CI Epirubicin 70 mg/m <sup>2</sup> × 3 Cisplatin 100 mg/m <sup>2</sup> × 3	339	84
Japan-91 (20)	1991–98	I–IV (AJCC <1997)	1–3	T 66–68 Gy/6.5–7 wk, N– 50 Gy, N+ 66–68 Gy	Induction	Cisplatin 80 mg/m <sup>2</sup> × 2 5-Fluorouracil 3200 mg/m <sup>2</sup> × 2, CI	80	74
T-0099 (21)	1989–95	III–IV (AJCC <1997)	1–3	T 70 Gy/7 wk; N– 50 Gy, N+ 66–70 Gy	Concomitant and adjuvant	Cisplatin 100 mg/m <sup>2</sup> × 3 Cisplatin 80 mg/m <sup>2</sup> × 3 5-Fluorouracil 4000 mg/m <sup>2</sup> × 3, CI	193	110
PWHQEH-94 (22)	1994–99	II–IV (AJCC 1997)	1–3	T 66 Gy/6.5 wk; N– 58 Gy, N+ 65.5 Gy	Concomitant	Cisplatin 40 mg/m <sup>2</sup> , weekly	350	67
QMH-95 (23)	1995–2000	II–IV (AJCC 1997)	1–3	T 62.5–68 Gy/7 wk N 62.5–66 Gy/7 wk ± boost 10 Gy	Concomitant Adjuvant	UFT 600 mg daily, p.o. Cisplatin 100 mg/m <sup>2</sup> × 3 5-Fluorouracil 3000 mg/m <sup>2</sup> × 3 Vincristine 2 mg × 3 Bleomycin 30 mg × 3 Methotrexate 150 mg/m <sup>2</sup> × 3 Cisplatin 20 mg/m <sup>2</sup> × 9 weekly, CI Fluorouracil 2200 mg/m <sup>2</sup> × 9 weekly, CI Leucovorin acid 120 mg/m <sup>2</sup> × 9 weekly, CI	222	57
TCOG-94 (24)	1994–99	IV (AJCC <1997)	1–3	T 70–72 Gy/7–8 wk N– 50 Gy	Adjuvant		158	72

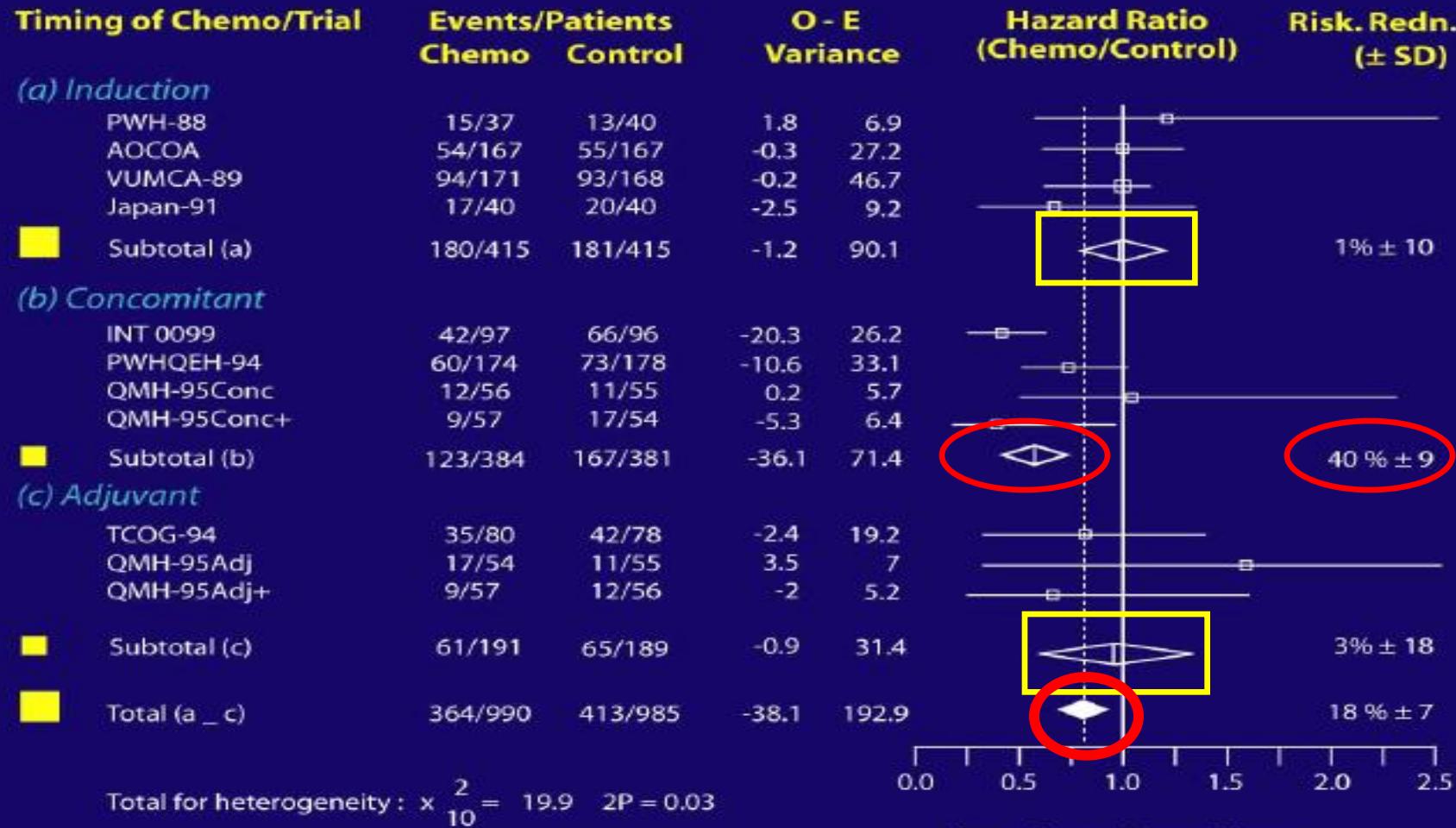
*Baujat et al, IJROBP 2006*

# Individual patient Data Meta-Analysis

*Baujat et al, IJROBP 2006*

## Overall Survival

## MAC NPC Collaboration



Chemo effect 2P = 0.006

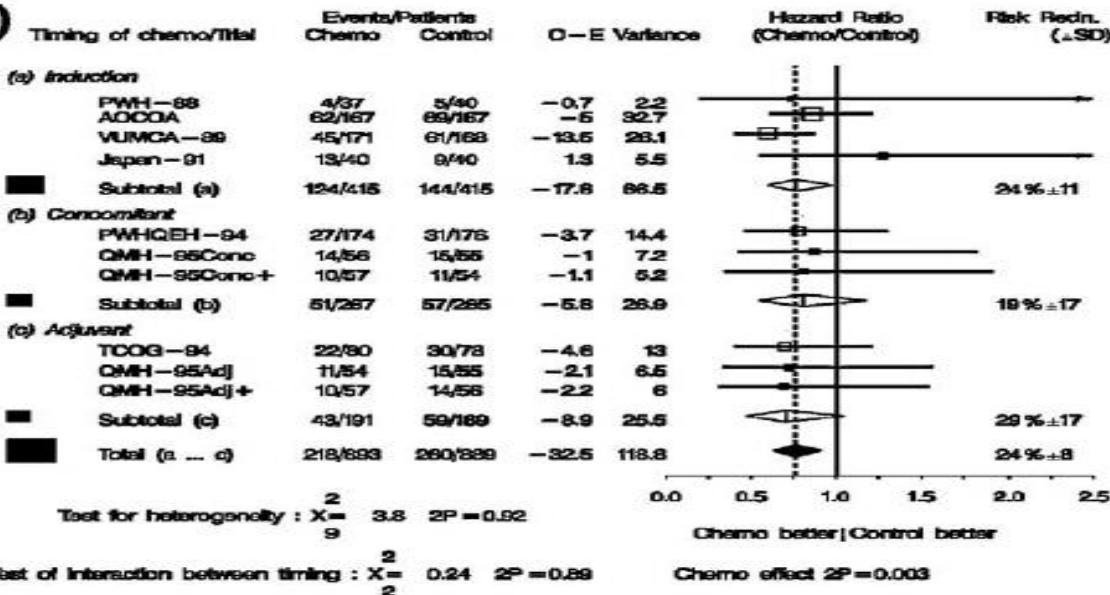
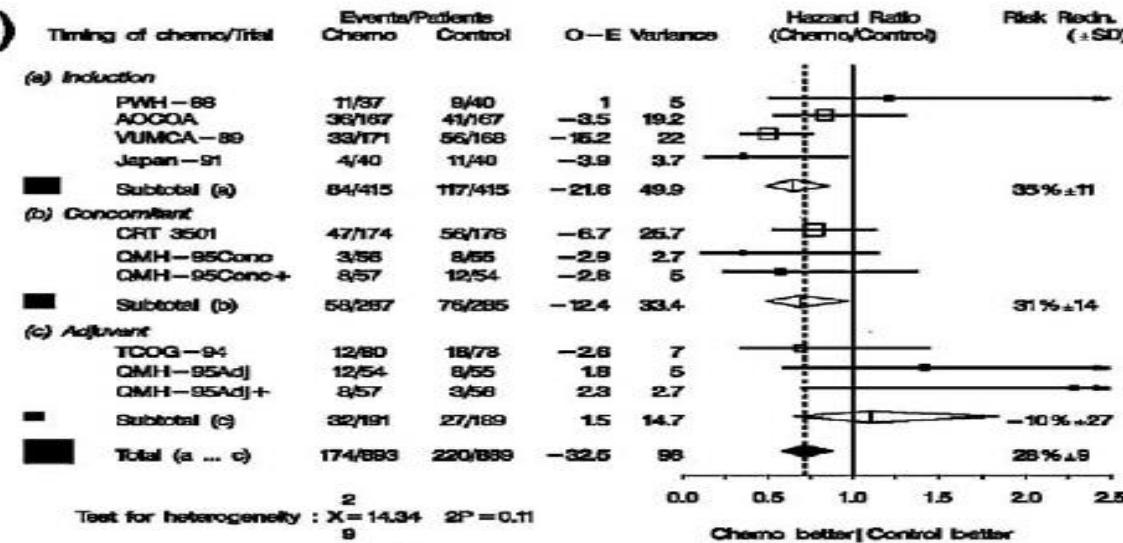
**(a)**

**LRC**
**(b)**

**DM**

Table 3. Treatment effect on overall and event-free survival according to patient characteristics

Characteristic	Patients receiving RT+CT/RT (n)	Hazard ratio of death (95% CI)	p (t for test for trend)	Hazard ratio of tumor failure or death (95% CI)	p (t for test for trend)
Gender					
Male	742/727	0.81 (0.69–0.95)		0.76 (0.66–0.87)	
Female	248/258	0.85 (0.62–1.16)	0.81	0.74 (0.58–0.96)	0.89
Age (y)					
≤40	326/285	0.85 (0.63–1.14)		0.67 (0.52–0.85)	
41–50	308/327	0.77 (0.59–1.01)		0.80 (0.64–1.00)	
>50	356/373	0.86 (0.70–1.05)	0.85 (t)	0.79 (0.66–0.95)	0.31 (t)
Performance status*					
0	380/368	0.89 (0.71–1.11)		0.78 (0.64–0.94)	
1	342/340	0.71 (0.55–0.92)		0.66 (0.53–0.83)	
2	17/21	1.55 (0.65–3.69)	0.73 (t)	1.40 (0.65–3.02)	0.92 (t)
T stage (AJCC 1997)					
T1	267/272	0.68 (0.51–0.90)		0.69 (0.54–0.87)	
T2	350/363	0.83 (0.64–1.07)		0.82 (0.66–1.02)	
T3–T4	373/350	0.90 (0.73–1.12)	0.12 (t)	0.73 (0.60–0.88)	0.80 (t)
N stage (AJCC 1997)†					
N0	91/83	1.02 (0.61–1.69)		0.65 (0.42–1.00)	
N1–N2	620/643	0.82 (0.68–0.99)		0.79 (0.68–0.93)	
N3	242/219	0.68 (0.52–0.88)	0.24 (t)	0.64 (0.51–0.81)	0.47 (t)
WHO histologic type‡					
1	29/26	0.30 (0.15–0.59)		0.18 (0.09–0.36)	
2–3	958/959	0.85 (0.73–0.98)	0.003	0.78 (0.69–0.89)	<0.0001
Total	990/985	0.82 (0.71–0.94)	0.006	0.76 (0.67–0.86)	<0.0001

# Updated MA

- 19 trials
- Median Fup 7 yrs
- Benefit of CT on OS@5 yrs = 6.4%
- Timing significant: CT/RT w/o adjuv CT
- PFS; LRC; DM
- Age, sex, stage: NS

*Baujat et al, ASCO 2014*

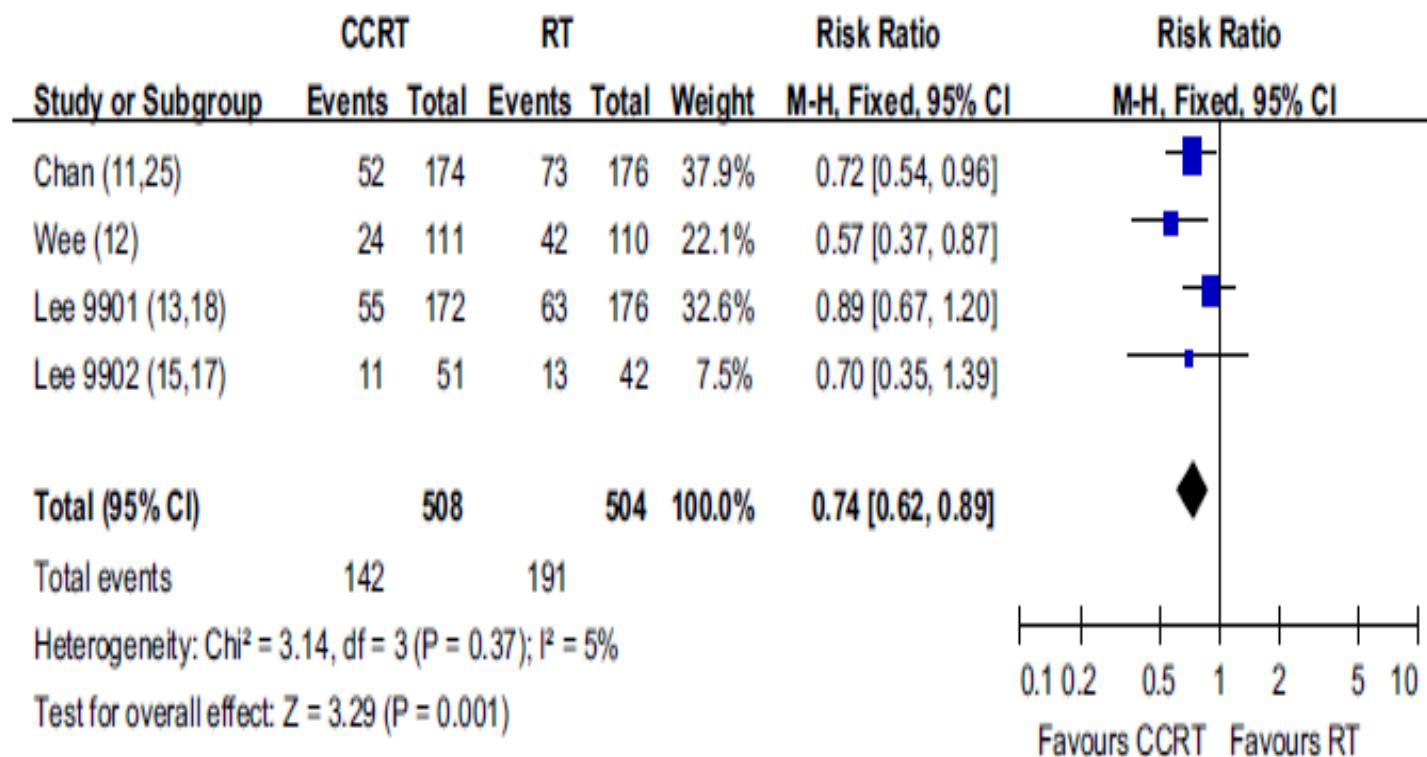
## RESEARCH ARTICLE

## Open Access

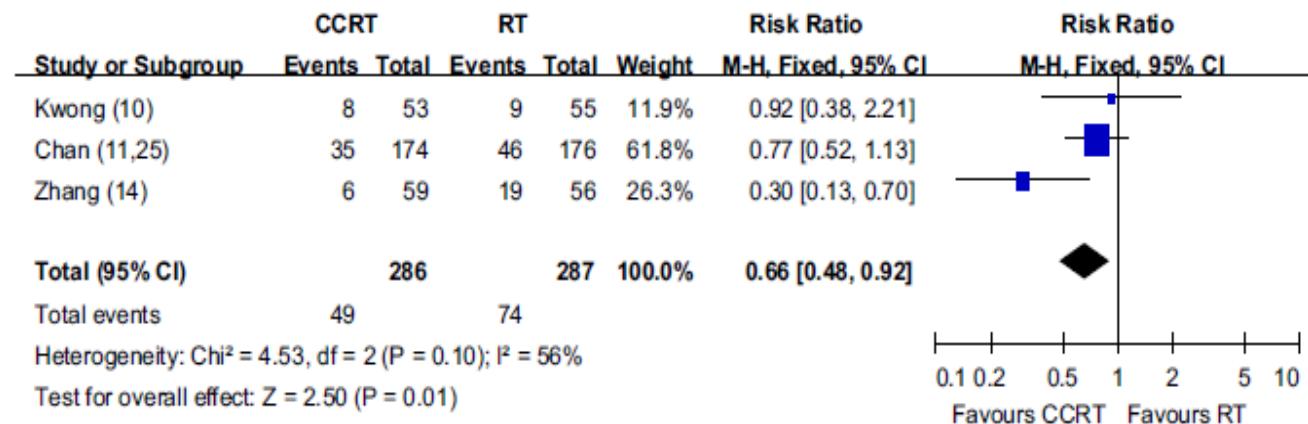
# The role of concurrent chemoradiotherapy in the treatment of locoregionally advanced nasopharyngeal carcinoma among endemic population: a meta-analysis of the phase iii randomized trials

Li Zhang<sup>1†</sup>, Chong Zhao<sup>2†</sup>, Bijesh Ghimire<sup>1</sup>, Ming-Huang Hong<sup>3</sup>, Qing Liu<sup>3</sup>, Yang Zhang<sup>3</sup>, Ying Guo<sup>3\*</sup>, Yi-Jun Huang<sup>4\*</sup>, Zhong-Zhen Guan<sup>1</sup>

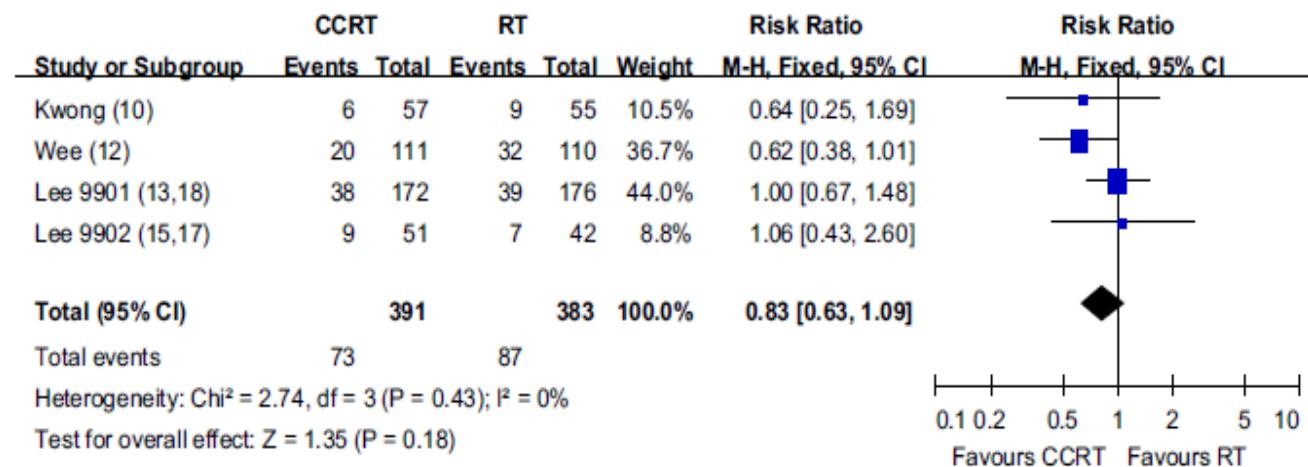
## C 5 years Overall Survival



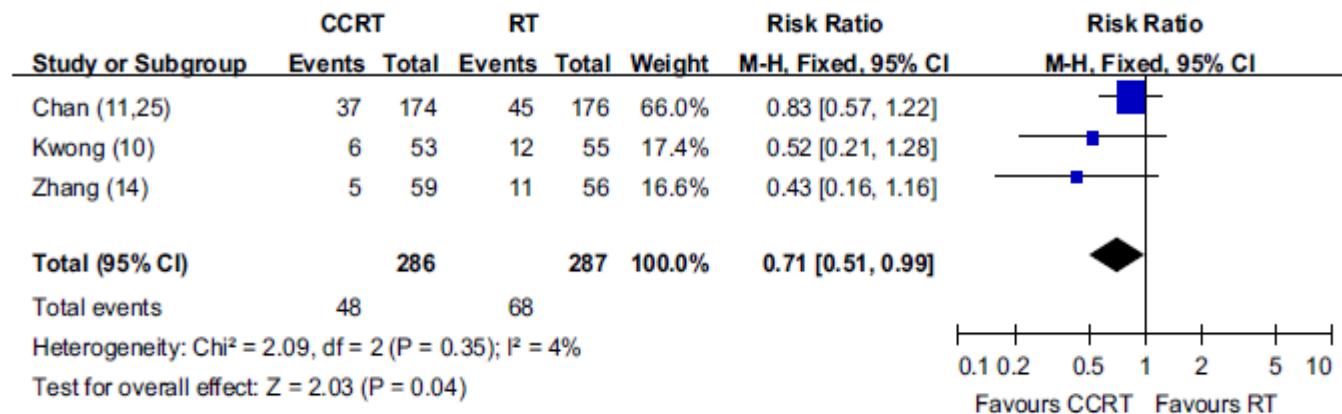
## B 3 years Overall Survival (without adjuvant)



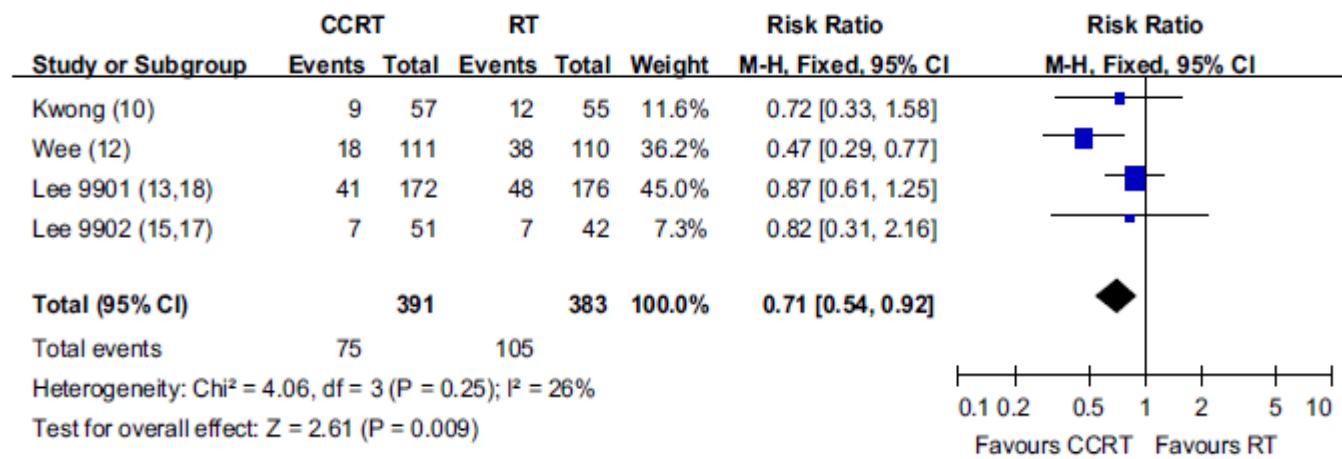
## C 3 years Overall Survival (with adjuvant)



## B 3 years Distant metastasis (without adjuvant)



## C 3 years Distant metastasis (with adjuvant)



DOI:<http://dx.doi.org/10.7314/APJCP.2012.13.11.5747>

*Chemoradiotherapy Followed by Adjuvant Chemotherapy Versus Chemoradiotherapy Alone for NPC*

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## RESEARCH ARTICLE

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# **Comparison of Concurrent Chemoradiotherapy Followed by Adjuvant Chemotherapy Versus Concurrent Chemoradiotherapy Alone in Locoregionally Advanced Nasopharyngeal Carcinoma: a Meta-analysis of 793 Patients from 5 Randomized Controlled Trials**

**Zhong-Guo Liang, Xiao-Dong Zhu\*, Zhi-Rui Zhou, Song Qu, You-Qin Du,  
Yan-Ming Jiang**

APJCP, 2012

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**RESEARCH ARTICLE**

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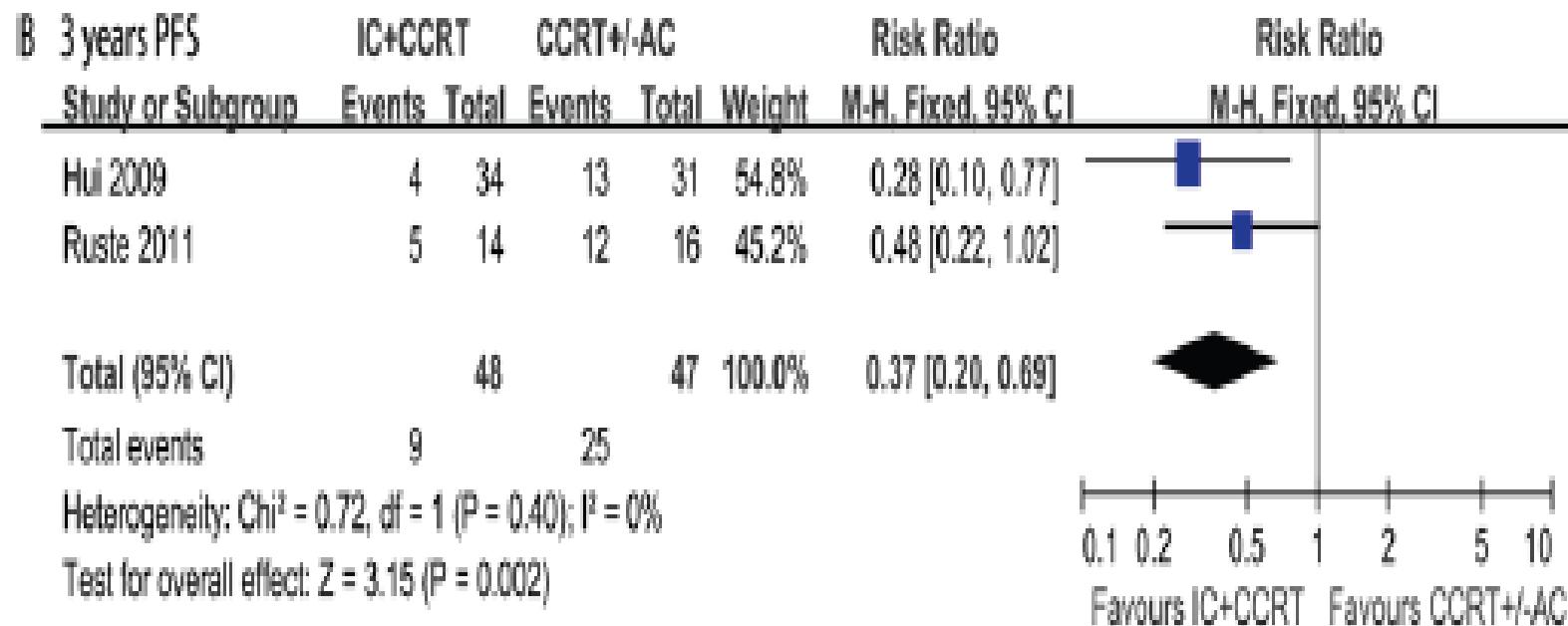
**Induction Chemotherapy Followed by Concurrent Chemoradiotherapy Versus Concurrent Chemoradiotherapy with or without Adjuvant Chemotherapy for Locoregionally Advanced Nasopharyngeal Carcinoma: Meta-analysis of 1,096 Patients from 11 Randomized Controlled Trials**

**Zhong-Guo Liang, Xiao-Dong Zhu\*, Ai-Hua Tan, Yan-Ming Jiang, Song Qu,  
Fang Su, Guo-Zeng Xu**

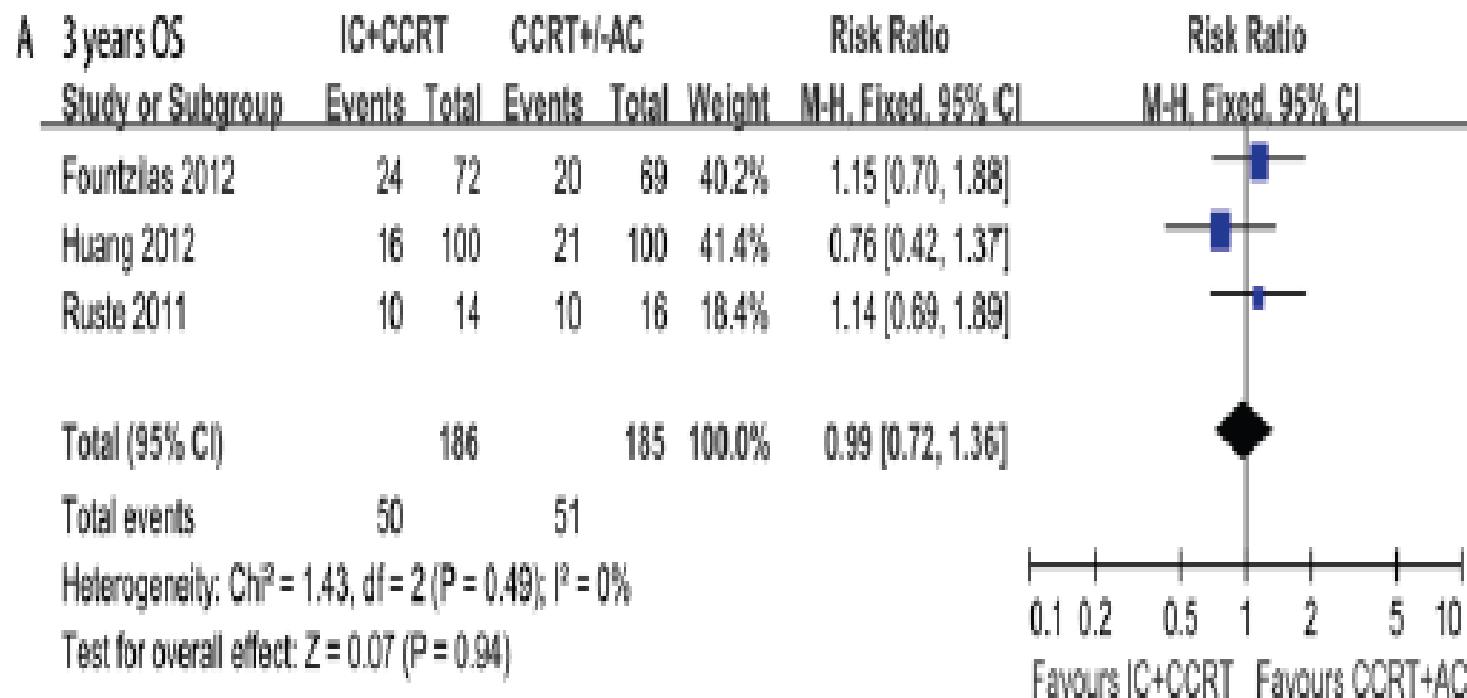
**APJCP, 2013**

**Table 1. Inclusion Criteria of Eligible Trials**

Study	Group	No. of patients	Inclusion period	Stage	Radiotherapy	Chemotherapy		
						IC	CC	AC
He et al., 2009	IC+CCRT	38	2004.4-	1992 Fuzhou	2.0Gy/Fx5F/wk, primary site:68-72Gy, positive nodes: 64-66Gy, the prevention dose for neck: 50Gy.	Cisplatin 80 mg/m <sup>2</sup> d1, 5-fluorouracil 800 mg/m <sup>2</sup> , d1-5, q3wks for 2 cycles.	Cisplatin 40 mg/m <sup>2</sup> d1, qwk for 6 cycles.	\
	CCRT	36	2006.5	stage III-IVa				
Ma et al., 2009	IC+CCRT	49	2003.5-	1992 Fuzhou	2.0Gy/Fx5F/wk, primary site:70Gy,the prevention dose for neck:50-55Gy.	Taxol 135 mg/m <sup>2</sup> d1, cisplatin 20 mg/m <sup>2</sup> , d1-5 and 5-fluorouracil 1000 mg/m <sup>2</sup> ,d1-5, q3wks for 2 cycles.	Cisplatin 20 mg/m <sup>2</sup> d1-5, 5-fluorouracil 1000 mg/m <sup>2</sup> , d1-5, for 2 cycles.	\
	CCRT	49	2006.8	stage III-IVa				
Hui et al., 2009	IC+CCRT	34	2002.11-	1997 UICC	2.0Gy/Fx5F/wk, nasopharyngeal-66Gy.	Docetaxel 75 mg/m <sup>2</sup> and cisplatin 75 mg/m <sup>2</sup> , q3wk for 2 cycles	Cisplatin 40 mg/m <sup>2</sup> /wk for 8 cycles	\
	CCRT	31	2004.11	stage III-IVb				
Sun et al., 2009	IC+CCRT(A)	76	2005.5-	1992 Fuzhou	Conventional radiotherapy: 2.0Gy/Fx5F/wk, primary site-70Gy, positive nodes-66-70Gy,	Group A: Cisplatin 80 mg/m <sup>2</sup> , 5-fluorouracil 3 g/m <sup>2</sup> , q3wks for 2 cycles.	Cisplatin 80 mg/m <sup>2</sup> , q3w for 2 cycles.	\
	IC+CCRT(B)	66	2008.9	stage III-IVa	pharyngeal extension and residual nodes-50Gy.	Group B: Taxol 135 m/m <sup>2</sup> , Carboplatin (AUC=6), q3wks for 2 cycles.		
	CCRT(C)	71			IMRT: GTVnx:68Gy,GTVnd:60-66Gy, CTV1:60Gy,CTV2:54Gy.			
Ruste et al., 2011	IC+CCRT	14	2005-	1997 UICC	2.0Gy/Fx5F/wk, primary site:70Gy, N0 disease:50Gy, nodes<2cm: 66 Gy, nodes greater than 2cm:70Gy	Cisplatin 20 mg/m <sup>2</sup> d1-4 and 5-fluorouracil 1000 mg/m <sup>2</sup> d1-4, q4wks for 3 cycle.	Cisplatin 25 mg/m <sup>2</sup> d1-4 q3wks for 3 cycle.	Cisplatin 20 mg/m <sup>2</sup> d1-4 5-fluorouracil 1000 mg/m <sup>2</sup> d1-4, q4wks for 3 cycle.
	CCRT+AC	16	2007	stage III-IVb				
Xu et al., 2011	IC+CCRT	25	2008.8-	Chinese	IMRT: GTVnx: 70.4-76.4Gy, GTVnd: 68Gy, CTV1: 60-62Gy, (2008) CTV2: 54-57Gy.	Docetaxel 75 mg/m <sup>2</sup> ,cisplatin 75 mg/m <sup>2</sup> d1, 5-fluorouracil 2.5 mg/m <sup>2</sup> , CIV120h, q3wks for 2 cycles.	Cisplatin(40 mg/m <sup>2</sup> ), qwk for 5 cycles.	\
	CCRT	20	2009.7	stage III-IVa				
He et al., 2011	IC+CCRT	50	2008.12-	2002 AJCC	Total dose: 70Gy	Docetaxel 75 mg/m <sup>2</sup> and cisplatin 25 mg/m <sup>2</sup> d1-3, 5-fluorouracil 800 mg/m <sup>2</sup> , CIV96h, q3wks for 3 cycles.	Cisplatin 90 mg/m <sup>2</sup> d1, q3wks for 3 cycles.	\
	CCRT	50	2010.1	stage III-IVa				
Fountzilas et al., 2012	IC+CCRT	72	2003.10-	2002 AJCC	2.0Gy/Fx5F/wk, 66 Gy to clinically involved nodes <3 cm, 70 Gy to nodes≥3 cm and 50 Gy to uninvolved cervical and supraclavicular areas.	Cisplatin 75 mg/m <sup>2</sup> , epirubicin 75 mg/m <sup>2</sup> and paclitaxel 175 mg/m <sup>2</sup> , q3wks for 3 cycles.	Cisplatin 40 mg/m <sup>2</sup> , qwk	\
	CCRT	69	2008.2	stage IIb-IVb				
Chen et al., 2012	IC+CCRT	30	2009.1-	Chinese	IMRT: GTVnx: 66-70.4Gy, GTVnd: 66-70.4Gy, CTV1:6 0-64Gy, CTV2: 50-54Gy.	Docetaxel 75 mg/m <sup>2</sup> , cisplatin 75 mg/m <sup>2</sup> d1, and 5-fluorouracil 500 mg/m <sup>2</sup> , d1-5, q3wks for 2 cycles.	Cisplatin 40 mg/m <sup>2</sup> , qwk	\
	CCRT	30	2010.1	stage (2008)				
Cui et al., 2012	IC+CCRT	35	2008.5-	2002 AJCC	2.0Gy/Fx5F/wk, primary site:68-74Gy, positive node: 66-70Gy, the prevention dose for neck: 54-60Gy.	Nedaplatin 80 mg/m <sup>2</sup> d1, 5-fluorouracil 500 mg/m <sup>2</sup> , d1-5, q3wks for 2 cycles.	The experimental group: Nedaplatin 80 mg/m <sup>2</sup> d1,q3wk	Cisplatin 80 mg/m <sup>2</sup> d1, 5-fluorouracil 500 mg/m <sup>2</sup> .
	CCRT+AC	35	2009.12	stage III-IVb			The control group: cisplatin 100 mg/m <sup>2</sup> , q3wk	d1-5, q3wks for 2 cycles.
Huang et al., 2012	IC+CCRT	100	2003.9-	1992 Fuzhou	2.0Gy/Fx5F/wk, primary site:66-78Gy, positive nodes: 60-70Gy, the prevention dose for neck 50-54Gy.	Carboplatin (AUC=6), 5-fluorouracil 750 mg/m <sup>2</sup> ,d1-5, q3wks for 2 cycles.	Carboplatin (AUC=6), q3wks for 3 cycles.	\
	CCRT	100	2006.5	stage III-IVa				



Liang Z APJCP, 2013



## original article

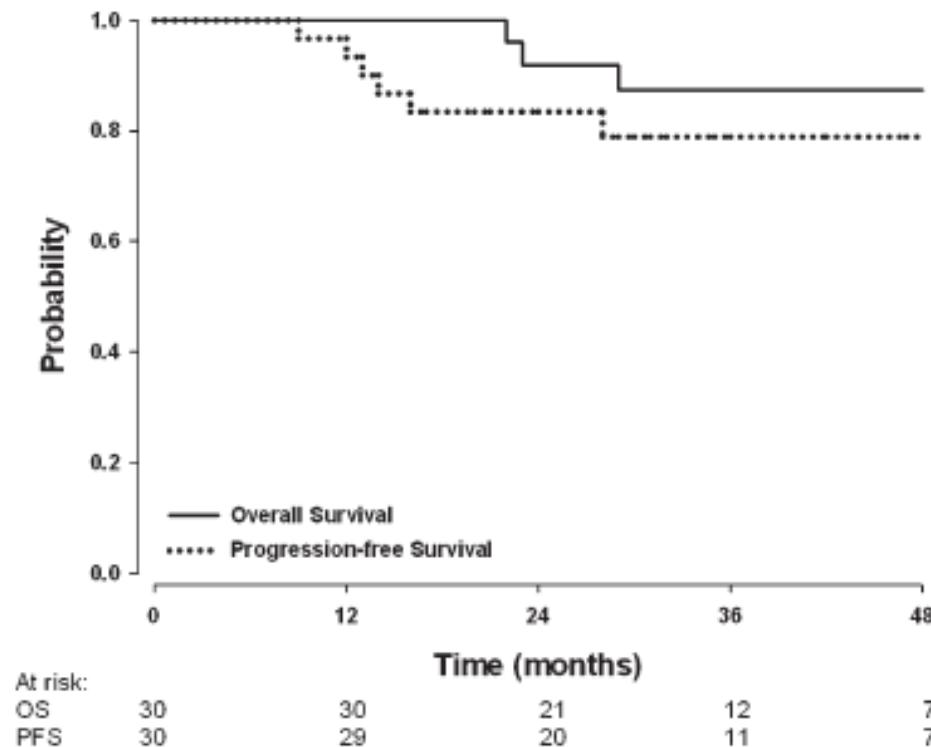
Annals of Oncology 22: 2495–2500, 2011  
doi:10.1093/annonc/mdq783  
Published online 11 March 2011

**Docetaxel, cisplatin and 5-fluorouracil-based induction chemotherapy followed by intensity-modulated radiotherapy concurrent with cisplatin in locally advanced EBV-related nasopharyngeal cancer**

P. Bossi<sup>1</sup>, E. Orlandi<sup>2</sup>, C. Bergamini<sup>1</sup>, L. D. Locati<sup>1</sup>, R. Granata<sup>1</sup>, A. Mirabile<sup>1</sup>, D. Parolini<sup>1</sup>, M. Franceschini<sup>2</sup>, C. Fallai<sup>2</sup>, P. Olmi<sup>2</sup>, P. Quattrone<sup>3</sup>, P. Potepan<sup>4</sup>, A. Gloghini<sup>5</sup>, R. Miceli<sup>6</sup>, F. Mattana<sup>6</sup>, G. Scaramellini<sup>7</sup> & L. Licitra<sup>1\*</sup>

<sup>1</sup>Department of Medical Oncology; <sup>2</sup>Department of Radiotherapy; <sup>3</sup>Pathologic Unit; <sup>4</sup>Department of Radiology; <sup>5</sup>Department of Molecular Biology; <sup>6</sup>Statistics Unit;  
<sup>7</sup>Department of Otorhinolaryngology, Tumor National Institute, Milan, Italy

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**Figure 1.** Kaplan-Meier overall survival (OS) and progression-free survival (PFS) curves.

Annals of Oncology Advance Access published September 23, 2011

original article

Annals of Oncology  
doi:10.1093/annonc/mdr401**A phase II study of concurrent cetuximab–cisplatin and intensity-modulated radiotherapy in locoregionally advanced nasopharyngeal carcinoma**B. B. Y. Ma<sup>1\*</sup>, M. K. M. Kam<sup>1</sup>, S. F. Leung<sup>1</sup>, E. P. Hui<sup>1</sup>, A. D. King<sup>2</sup>, S. L. Chan<sup>1</sup>, F. Mo<sup>1</sup>, H. Loong<sup>1</sup>, B. K. H. Yu<sup>1</sup>, A. Ahuja<sup>2</sup> & A. T. C. Chan<sup>1</sup><sup>1</sup>State Key Laboratory in Oncology in South China, Sir YK Pao Centre for Cancer, Department of Clinical Oncology, Hong Kong Cancer Institute, The Chinese University of Hong Kong; <sup>2</sup>Imaging and Interventional Radiology, Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong, China

Received 9 November 2010; revised 26 April 2011; revised 3 May 2011; accepted 20 July 2011

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→ Addition of bevacizumab to standard chemoradiation for locoregionally advanced nasopharyngeal carcinoma (RTOG 0615): a phase 2 multi-institutional trial

Nancy Y Lee, Qiang Zhang, David G Pfister, John Kim, Adam S Garden, James Mechalakos, Kenneth Hu, Quynh T Le, A Dimitrios Colevas, Bonnie S Glisson, Anthony T C Chan, K Kian Ang

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VOLUME 28 · NUMBER 28 · OCTOBER 1 2010

JOURNAL OF CLINICAL ONCOLOGY

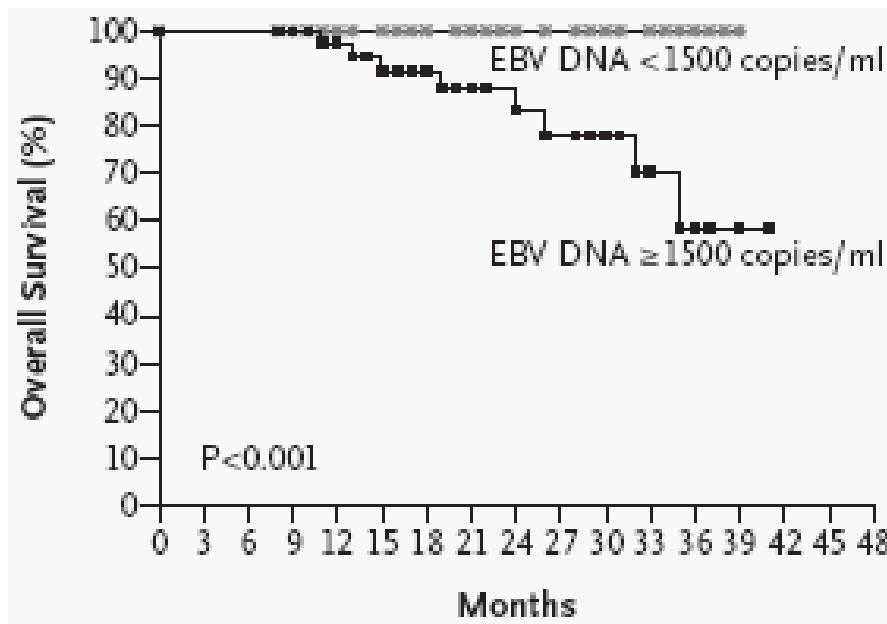
ORIGINAL REPORT

## Pretreatment Quality of Life As a Predictor of Distant Metastasis and Survival for Patients With Nasopharyngeal Carcinoma

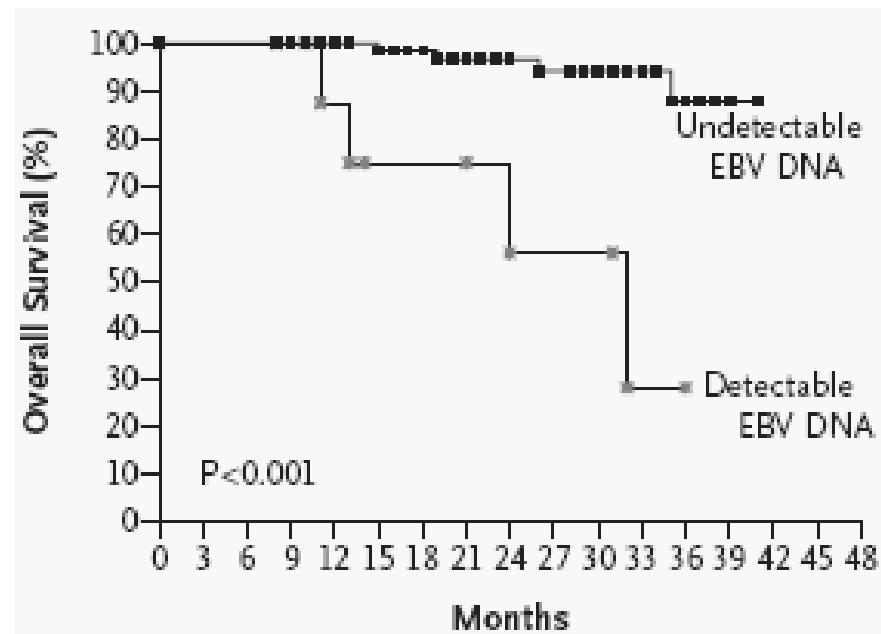
*Fu-Min Fang, Wen-Ling Tsai, Chih-Yen Chien, Hui-Chun Chen, Hsuan-Chih Hsu, Tai-Lin Huang, Tsair-Fwu Lee, Hsuan-Ying Huang, and Chien-Hung Lee*

# Prognostic/Predictive Factors

- OS according to **EBV DNA value**



**Pre-treatment value**



**1 week post treatment**

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## Prognostic value of a microRNA signature in nasopharyngeal carcinoma: a microRNA expression analysis

Na Liu\*, Nian-Yong Chen\*, Rui-Xue Cui\*, Wen-Fei Li, Yan Li, Rong-Rong Wei, Mei-Yin Zhang, Ying Sun, Bi-Jun Huang, Mo Chen, Qing-Mei He, Ning Jiang, Lei Chen, William CS Cho, Jing-Ping Yun, Jing Zeng, Li-Zhi Liu, Li Li, Ying Guo, Hui-Yun Wang†, Jun Mat

**Lancet Oncology 2012**

# Eight-Signature Classifier for Prediction of Nasopharyngeal Carcinoma Survival

*Hai-Yun Wang, Bing-Yu Sun, Zhi-Hua Zhu, Ellen T. Chang, Ka-Fai To, Jacqueline S.G. Hwang, Hao Jiang, Michael Koon-Ming Kam, Gang Chen, Shie-Lee Cheah, Ming Lee, Zhi-Wei Liu, Jing Chen, Jia-Xing Zhang, Hui-Zhong Zhang, Jie-Hua He, Fa-Long Chen, Xiao-Dong Zhu, Ma-Yan Huang, Ding-Zhun Liao, Jia Fu, Qiong Shao, Man-Bo Cai, Zi-Ming Du, Li-Xu Yan, Chun-Fang Hu, Ho-Keung Ng, Joseph T.S. Wee, Chao-Nan Qian, Qing Liu, Ingemar Ernberg, Weimin Ye, Hans-Olov Adami, Anthony T. Chan, Yi-Xin Zeng, and Jian-Yong Shao*

**JCO 2011**

# **A multicenter randomized controlled trial (RCT) of adjuvant chemotherapy (CT) in nasopharyngeal carcinoma (NPC) with residual plasma EBV DNA (EBV DNA) following primary radiotherapy (RT) or chemoradiotherapy (CRT).**

***Anthony T. C. Chan***

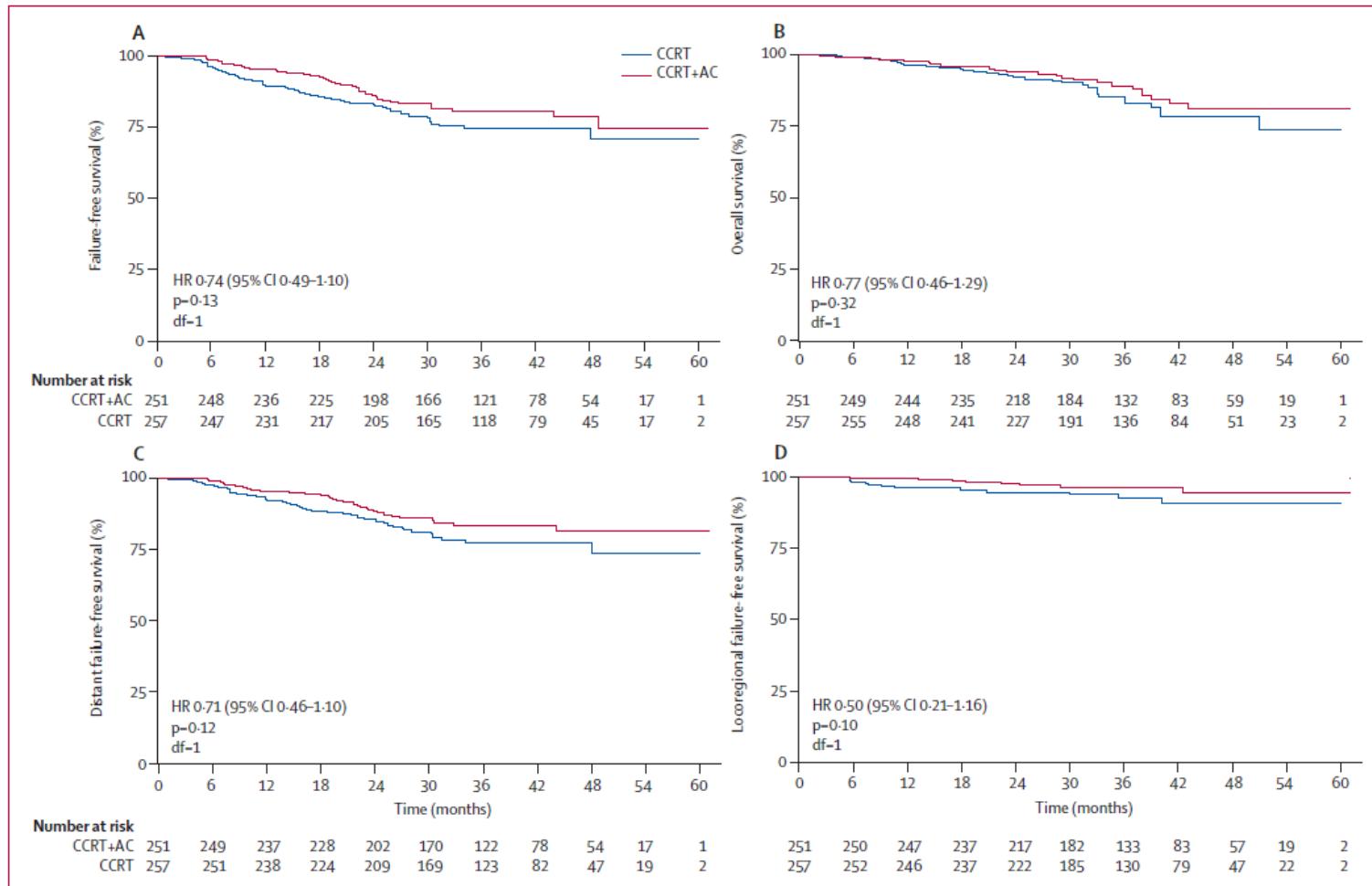
**ASCO 2012**

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**Concurrent chemoradiotherapy plus adjuvant chemotherapy  versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 3 multicentre randomised controlled trial**

*Lei Chen, \* Chao-Su Hu, \* Xiao-Zhong Chen, \* Guo-Qing Hu, Zhi-Bin Cheng, Yan Sun, Wei-Xiong Li, Yuan-Yuan Chen, Fang-Yun Xie, Shao-Bo Liang, Yong Chen, Ting-Ting Xu, Bin Li, Guo-Xian Long, Si-Yang Wang, Bao-Min Zheng, Ying Guo, Ying Sun, Yan-Ping Mao, Ling-Long Tang, Yu-Ming Chen, Meng-Zhong Liu, Jun Ma*

Lancet Oncology 2012



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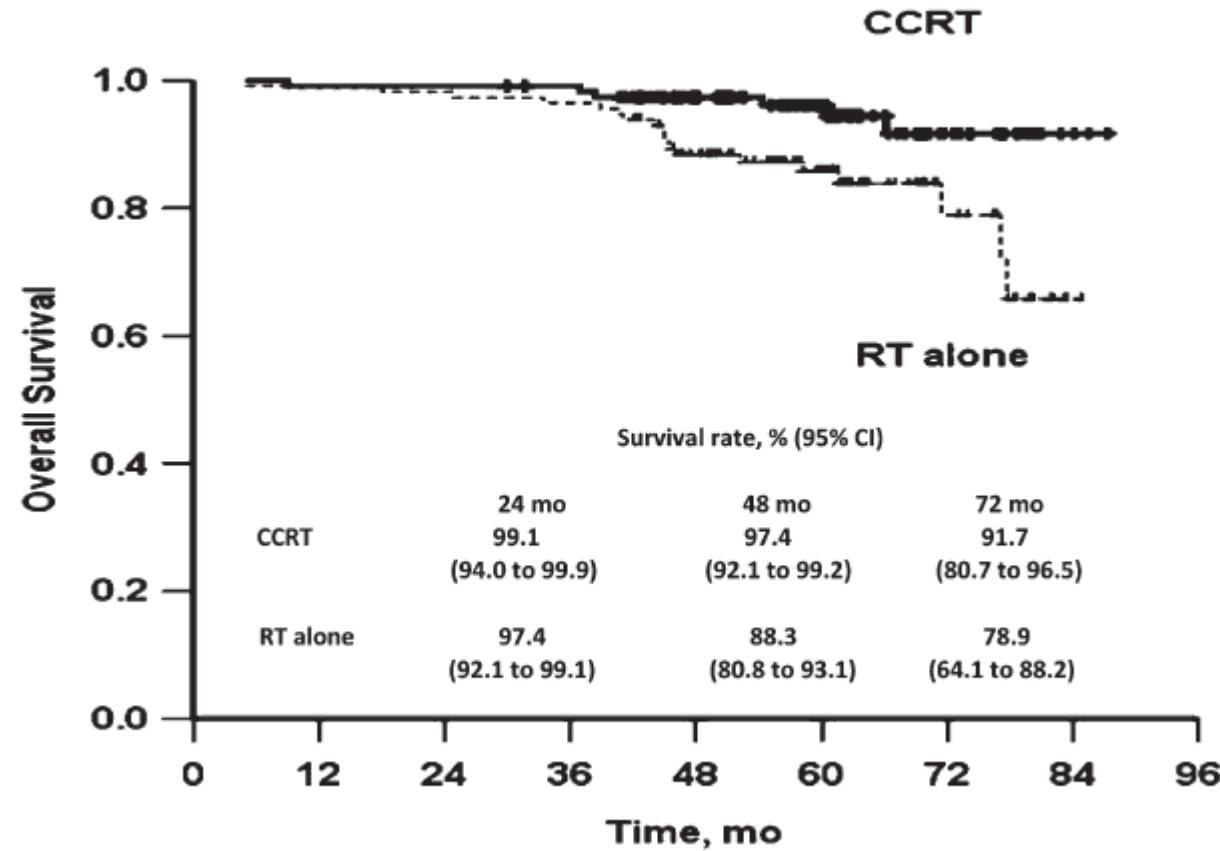
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**ARTICLE**

# **Concurrent Chemoradiotherapy vs Radiotherapy Alone in Stage II Nasopharyngeal Carcinoma: Phase III Randomized Trial**

Qiu-Yan Chen, Yue-Feng Wen, Ling Guo, Huai Liu, Pei-Yu Huang, Hao-Yuan Mo, Ning-Wei Li, Yan-Qun Xiang, Dong-Hua Luo, Fang Qiu, Rui Sun, Man-Quan Deng, Ming-Yuan Chen, Yi-Jun Hua, Xiang Guo, Ka-Jia Cao, Ming-Huang Hong, Chao-Nan Qian, Hai-Qiang Mai

JNCI, 2011



Chen JNCI, 2011

# Conclusions

- **Rare disease**
- **CT is beneficial in NPC**
- **Refinement of pts selection for neoadjuvant/adjuvant CT based on prognostic factors and biology**
- **Biological agents**