Meta-Analysis in HNSCC

Cessal Thommachan Kainickal
Additional Professor, Head & Neck Oncology
RCC, Trivandrum

Contents

- Role of altered fractionation RT
- Role of Chemo along with RT
- Role of NACT prior to surgery
- Role of NACT prior to CCRT
- Adjuvant chemoRT in high risk patients
- Role of Chemotherapy in Ca Nasopharynx

March Meta Analysis

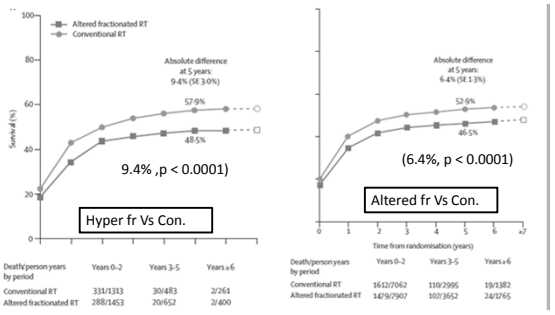
Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis

Jean Bourhis, Jens Overgaard, Hélène Audry, Kian K Ang, Michele Saunders, Jacques Bernier, Jean-Claude Horiot, Aurélie Le Maître, Thomas F Pajak, Michael G Poulsen, Brian O'Sullivan, Werner Dobrowsky, Andrzej Hliniak, Krzysztof Skladowski, John H Hay, Luiz H J Pinto, Carlo Fallai, Karen K Fu, Richard Sylvester, Jean-Pierre Pignon, on behalf of the Meta-Analysis of Radiotherapy in Carcinomas of Head and neck (MARCH) Collaborative Group*

15 Trials,6500 Pts
Median FU 6 yrs

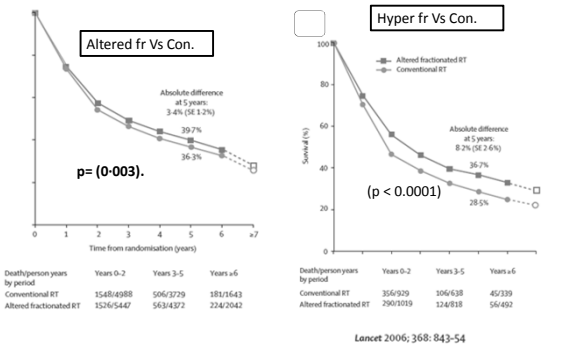
Lancet 2006; 368: 843-54

Local control



Lancet 2006; 368: 843-54

Over all survival



Lancet 2006; 368: 843-54

Conclusions - Altered fractionation

- Al fr.superior to conventional RT - local control (6.4%) and OS (3.4%)
- Hyper Fr Vs conventional RT – local control (9.4%) and OS (8.2%)
- Hyperfractionation Vs accelerated fractionation (8.2% vs 2% p= 0.02)
- Hyperfractionation and concurrent chemoradiation – similar results
- Limited data on head-to-head comparison

Lancet 2006, 368:843-54

Role of radiotherapy fractionation in head and neck cancers (MARCH): an updated meta-analysis

Benjamin Lacas, Jean Bourhis, Jens Overgaard, Qiang Zhang, Vincent Grégoire, Matthew Nankivell, Björn Zackrisson, Zbigniew Szutkowski, Rafal Suwiński, Michael Poulsen, Brian O'Sullivan, Renzo Corvò, Sarbani Ghosh Laskar, Carlo Fallai, Hideya Yamazaki, Werner Dobrowsky, Kwan Ho Cho, Beth Beadle, Johannes A Langendijk, Celia Maria Pais Viegas, John Hay, Mohamed Lotayef, Mahesh K B Parmar, Anne Auperin, Carla van Herpen, Philippe Maingon, Andy M Trotti, Cai Grau, Jean-Pierre Pignon*, Pierre Blanchard*, on behalf of the MARCH Collaborative Group†

1.Altered fractionation superior to conventional radiotherapy (p=.0023)- 5yr OS benefit 3.1%

Hyperfractionation Vs Conventional RT

OS benefit restricted to the hyperfractionated group

OS benefit of 8·1% at 5 yrs and of 3·9% at 10 years

2.CCRT Vs Altered fractionation- significantly worse with altered fr.

Lancet Oncol 2017; 18: 1221–37

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Radiotherapy- Main Dish

Systemic Rx-Dessert

Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: individual data

J P Pignon, J Bourhis, C Domenge, L Designé, on behalf of the MACH-NC Collaborative Group*

Trial category	Hazard ratio (95% CI)	Chemo-therapy effect (p)	Heterogeneity (p)	Absolute benefit	
				At 2 years*	At 5 years*
Adjuvant	0·98 (0·85–1·19)	0·74	0·35	1%	1%
Neoadjuvant	0·95 (0·88–1·01)	0·10	0·38	2%	2%
Concomitant	0·81 (0·76–0·88)	<0·0001	<0·0001	7%	8%
Total	0·90 (0·85–0·94)	<0·0001	<0·0001	4%	4%

Lancet 2000; **355:** 949–55

Radiotherapy and Oncology 92 (2009) 4–14

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Meta analysis

Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients

Jean-Pierre Pignon[a,*], Aurélie le Maître[a], Emilie Maillard[a], Jean Bourhis[b], on behalf of the MACH-NC Collaborative Group[1]

[a] Department of Biostatistics and Epidemiology, Institut Gustave-Roussy, Villejuif, France
[b] Department of Radiotherapy, Institut Gustave-Roussy, Villejuif, France

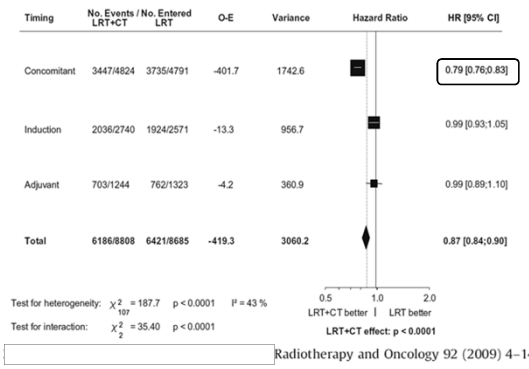
Editorial

Chemoradiotherapy of head and neck cancer – Can the bumble bee fly?

Jens Overgaard*

Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark

HR for Recurrence



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HR For death

Timing	No. Deaths / LRT+CT	No. Entered LRT	O-E	Variance	Hazard Ratio	HR [95% CI]
Concomitant	3171/4824	3389/4791	-326.4	1587.7		0.81 [0.78;0.86]
Induction	1877/2740	1813/2571	-40.0	900.7		0.96 [0.90;1.02]
Adjuvant	631/1244	661/1323	17.9	317.4		1.06 [0.95;1.18]
Total	**5679/8808**	**5863/8685**	**-348.5**	**2805.8**		**0.88 [0.85;0.92]**

Test for heterogeneity: $\chi^2_{107} = 179.8$ $p < 0.0001$ $I^2 = 41\%$

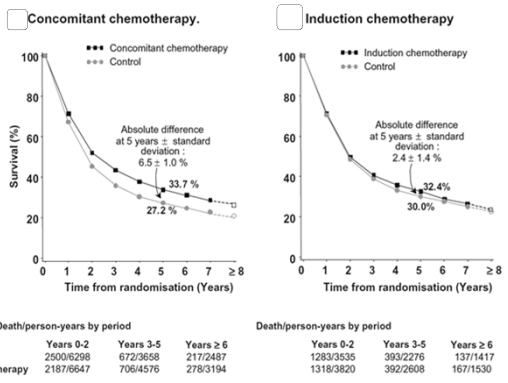
Test for interaction: $\chi^2_2 = 26.60$ $p < 0.0001$

0.5 1.0 2.0

LRT+CT better | LRT better

LRT+CT effect: p < 0.0001

Radiotherapy and Oncology 92 (2009) 4–14



Death/person-years by period

	Years 0-2	Years 3-5	Years ≥ 6
Control	2500/6298	672/3658	217/2487
Chemotherapy	2187/6647	706/4576	278/3194

Death/person-years by period

	Years 0-2	Years 3-5	Years ≥ 6
	1283/3535	393/2276	137/1417
	1318/3820	392/2608	167/1530

Radiotherapy and Oncology 92 (2009) 4–14

Type of chemotherapy	No. Deaths / LRT+CT	No. Entered LRT	O-E	Variance	Hazard Ratio	HR [95% CI]	p of interaction
(a) Poly chemotherapy							
5-FU and Platin	602/940	695/931	-92.2	317.6		0.75 [0.67;0.84]	p = 0.41
5-FU or Platin	495/743	543/795	-45.8	250.0		0.83 [0.74;0.94]	
Neither 5-FU nor Platin	62/115	85/129	-11.1	35.0		0.73 [0.52;1.01]	
Subtotal (a)	1159/1798	1323/1855	-149.0	602.6		0.78 [0.72;0.85]	
(b) Mono chemotherapy							
Mono Platin	703/1151	739/1059	-102.6	341.8		0.74 [0.67;0.82]	
Mono Other	1309/1875	1327/1877	-74.8	643.3		0.89 [0.82;0.96]	
Subtotal (b)	2012/3026	2066/2936	-177.4	985.1		0.84 [0.78;0.89]	
Total (a ... b)	**3171/4824**	**3389/4791**	**-326.4**	**1587.7**		**0.81 [0.78;0.86]**	

Test for heterogeneity: $\chi^2_1 = 1.69$ $p = 0.19$

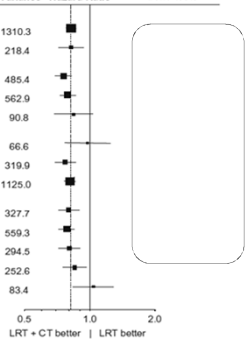
0.5 1.0 2.0

LRT+CT better | LRT better

Radiotherapy and Oncology 92 (2009) 4–14

by sex, performance status, stage and tumour site

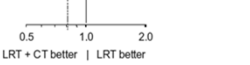
Category	No. Deaths / No. Entered LRT + CT	LRT	O-E	Variance	Hazard Ratio	Interaction and trend tests
Sex						
Male	2635/3882	2807/3847	-259.2	1310.3		
Female	483/788	508/788	-44.1	218.4		
Performance status						
0	923/1667	1084/1696	-135.1	485.4		
1	1210/1680	1179/1538	-131.8	562.9		
2 or 3	220/279	218/274	-15.8	90.8		
Stage						
I-II	133/251	155/286	-1.5	66.6		
III	661/1140	699/1094	-83.7	319.9		
IV	2268/3266	2430/3261	-240.9	1125.0		
Site						
Oral cavity	680/997	754/1020	-72.8	327.7		
Oropharynx	1123/1723	1219/1681	-138.3	559.3		
Larynx	607/1013	644/1012	-64.0	294.5		
Hypopharynx	546/760	563/757	-40.5	252.6		
Others	187/264	183/256	3.2	83.4		



Radiotherapy and Oncology 92 (2009) 4–14

Age

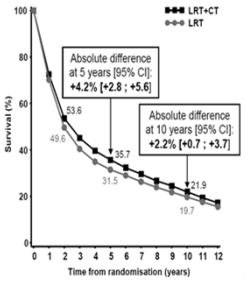
Category	No. Deaths / No. Entered LRT + CT	LRT	O-E	Variance	Hazard Ratio	Absolute difference at 5 years ± sd
Age						
Less than 50	803/1296	860/1288	-107.6	386.9		9.8 ± 2.1
51-60	1069/1645	1198/1661	-136.4	539.7		7.8 ± 1.8
61-70	972/1368	988/1330	-56.2	457.8		3.0 ± 1.9
71 or over	273/356	260/336	-3.5	114.7		-0.7 ± 3.9



Radiotherapy and Oncology 92 (2009) 4–14

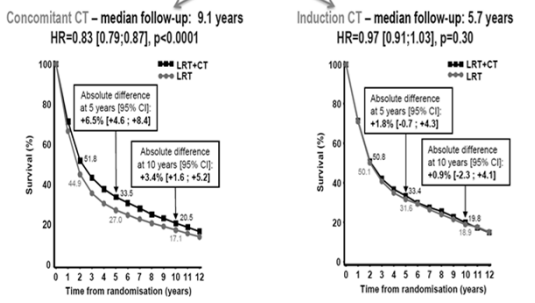
Radiotherapy versus radiotherapy + chemotherapy

20,092 patients and 13,904 deaths (69%)



Bourhis J et al. ESMO 2016

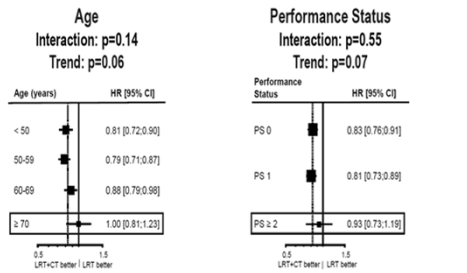
Concomitant chemotherapy gives the higher benefit



Bourhis J et al. ESMO 2016

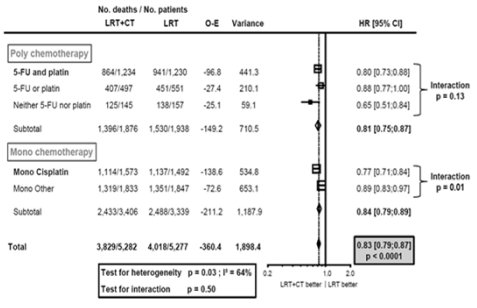
Subgroup analyses: overall survival

Performed on **concomitant** and recent trials only (at most 30 trials and 6,591 patients)



Bourhis J et al. ESMO 2016

Which chemotherapy should we used (concomitant trials) ?



Conclusions CCRT

- CCRT is superior to RT alone-OS&LCR
- Absolute benefit is 6.5 % at 5 yrs
- Induction chemo is not beneficial(Non taxane based)
- Maximum benefit of chemo in young pts
- Single agent is equivalent to combination
- Cisplatin is better than other agents

Radiotherapy and Oncology 100 (2011) 33–40

Contents lists available at ScienceDirect

Radiotherapy and Oncology

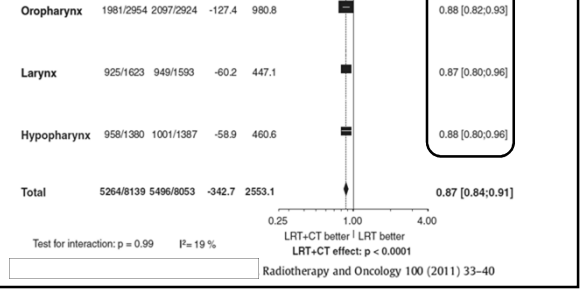
journal homepage: www.thegreenjournal.com

Meta-analysis of radiotherapy in HNSCC

Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): A comprehensive analysis by tumour site

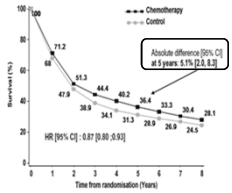
Pierre Blanchard [a,b,1], Bertrand Baujat [c,1], Victoria Holostenco [a], Abderrahmane Bourredjem [a], Charlotte Baey [a], Jean Bourhis [b], Jean-Pierre Pignon [b,*], on behalf of the MACH-CH Collaborative group [2]

[a] Biostatistics and Epidemiology Department; and [b] Radiotherapy Department, Institut Gustave Roussy, Villejuif, France; [c] Head and Neck Surgery, Hôpital Foch, Suresnes, France



Sub site benefit

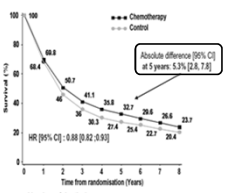
Oral cavity



Number of deaths/person-years:

	Years 0-2	Years 2-5	Years >=6
LRT+CT	1008/3031	253/2165	139/1620
LRT	1070/2846	280/1771	99/1204

Oropharynx



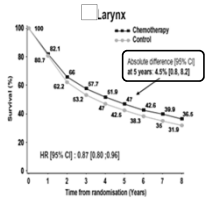
Number of deaths/person-years:

	Years 0-2	Years 2-5	Years >= 6
LRT+CT	1394/4092	434/2729	153/1444
LRT	1540/3951	433/2298	124/1255

Radiotherapy and Oncology 100 (2011) 33–40

Sub site benefit

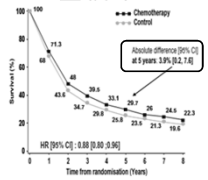
Larynx



Number of deaths/person-years:

	Years 0-2	Years 2-5	Years >= 6
LRT+CT	550/2628	253/2126	122/1387
LRT	591/2558	250/1923	108/1146

Hypopharynx



Number of deaths/person-years:

	Years 0-2	Years 2-5	Years >= 6
LRT+CT	687/1916	204/1177	67/669
LRT	764/1866	189/1059	48/564

Radiotherapy and Oncology 100 (2011) 33–40

Timing of Chemotherapy

		Timing of chemotherapy			Test of interaction*
		Adjuvant	Neoadjuvant	Concomitant	
Oral cavity	HR [95% CI]	0.83 [0.69; 1.01]	0.94 [0.84; 1.06]	0.81 [0.73; 0.90]	$p = 0.16$
	5-year abs benefit [CI]	+5.5% [−2.1; 13.1]	+3.8% [−1.1; 8.7]	+6.9% [2.8; 11.0]	
Oropharynx	HR [95% CI]	1.09 [0.87; 1.36]	1.05 [0.94; 1.16]	0.74 [0.69; 0.81]	$p < 0.0001$
	5-year abs benefit [CI]	−0.5% [−9.5; 8.5]	−0.6% [−4.9; 3.7]	+8.4% [5.1; 11.7]	
Larynx	HR [95% CI]	1.06 [0.85; 1.32]	1.13 [0.92; 1.38]	0.78 [0.70; 0.87]	$p = 0.002$
	5-year abs benefit [CI]	−1% [−9.4; 7.4]	−1.4% [−9.6; 6.8]	+5.4% [0.7; 10.1]	
Hypopharynx	HR [95% CI]	0.97 [0.75; 1.25]	0.94 [0.81; 1.09]	0.83 [0.73; 0.93]	$p = 0.31$
	5-year abs benefit [CI]	+0.5% [−10.5; 11.5]	+3.3% [−2.4; 9.0]	+3.2% [−1.7; 8.1]	

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European Journal of Cancer (2015) 51, 2596–2603

Available at www.sciencedirect.com

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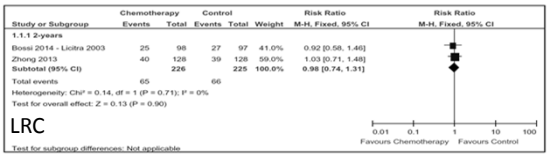
journal homepage: www.ejcancer.com

Induction chemotherapy prior to surgery with or without postoperative radiotherapy for oral cavity cancer patients: Systematic review and meta-analysis

Gustavo N. Marta [a,*], Rachel Riera [b], Paolo Bossi [c], Lai-ping Zhong [d], Lisa Licitra [e], Cristiane R. Macedo [a], Gilberto de Castro Junior [f], André L. Carvalho [g], William N. William Jr. [h], Luis Paulo Kowalski [i]



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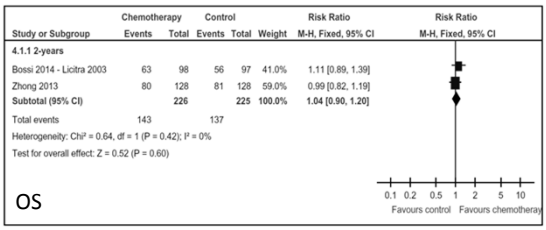
EJC (2015)51,2596-2603



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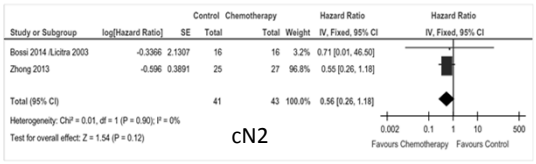

cN2

EJC (2015)51,2596-2603

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MACH-NC subset analysis of the effects of chemotherapy on survival at 5 yrs

Trial Category	No. of Trials	No. of Patients	Difference(%)	P-value
All trials	65	10850	+4	**<0.0001**
Adjuvant	8	1854	+1	0.74
Induction	31	5269	+2	0.10
PF	**15**	**2487**	**+5**	**0.01***
Other Chemo	16	2782	0	0.91
Concurrent	26	3727	+8	**<0.0001**

•Significance survival gain of 5% at 6 years in favour of PF
•No corroborative evidence obtained in a single large trial

Monnerat C. et . Annals of Oncology 13: 995-1006, 2002

Induction chemotherapy ⇨ ChemoRT

- ***1. IC 3 Drug Vs 2drug ⇨ RT/CRT***
- **No CCRT arm**
- ~~To know the best induction chemo~~
- ***2. CCRT Vs 3 Drug IC⇨ CCRT***
- To know best approach
- CCRT – control arm

Phase III Induction Chemotherapy –Taxanes

IC 3 Drug (TPF) Vs 2drug (PF) ⇨ RT/CRT

- TAX 323 /EORTC 24971 : Chemo → RT
- TAX 324 : Chemo → RT + Carboplatin q 1 week
- Madrid Study : Chemo → RT + Cisplatin q 3 weeks

Better OS &PFS

Published Ahead of Print on July 8, 2013 as 10.1200/JCO.2012.47.7802
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2012.47.7802

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Taxane-Cisplatin-Fluorouracil As Induction Chemotherapy in Locally Advanced Head and Neck Cancers: An Individual Patient Data Meta-Analysis of the Meta-Analysis of Chemotherapy in Head and Neck Cancer Group

Pierre Blanchard, Jean Bourhis, Benjamin Lacas, Marshall R. Posner, Jan B. Vermorken, Juan J. Cruz Hernandez, Abderrahmane Bourredjem, Gilles Calais, Adriano Paccagnella, Ricardo Hitt, and Jean-Pierre Pignon on behalf of the Meta-Analysis of Chemotherapy in Head and Neck Cancer, Induction Project, Collaborative Group

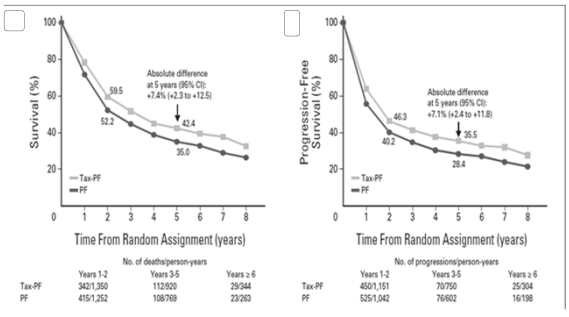
VOLUME 31 · NUMBER 23 · AUGUST 10 2013
JOURNAL OF CLINICAL ONCOLOGY EDITORIAL

No CCRT arm

Induction Chemotherapy Meta-Analysis in Head and Neck Cancer: Right Answer, Wrong Question

Arlene A. Forastiere, *Johns Hopkins University and Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD*
David J. Adelstein, *Cleveland Clinic, Taussig Cancer Institute, Cleveland, OH*
Judi Manola, *Dana-Farber Cancer Institute, Boston, MA*

OS PFS



No. of deaths/person-years

	Years 1-2	Years 3-5	Years ≥ 6
Tax-PF	342/1,350	112/920	29/344
PF	415/1,252	108/769	23/263

No. of progressions/person-years

	Years 1-2	Years 3-5	Years ≥ 6
Tax-PF	450/1,151	70/750	25/304
PF	525/1,042	76/602	16/198

Induction chemotherapy ⇨ ChemoRT

- **1. IC 3 Drug Vs 2drug ⇨ RT/CRT**
  No CCRT arm
- To know the best induction chemo
- **2. CCRT Vs 3 Drug IC ⇨ CCRT**
- To know best approach
- CCRT – control arm

CCRT Vs 3 Drug IC ⇨ CCRT

- Hitt trial
- DeCIDE
- PARADIGM

No benefit

Radiotherapy and Oncology 118 (2016) 238–243

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic review

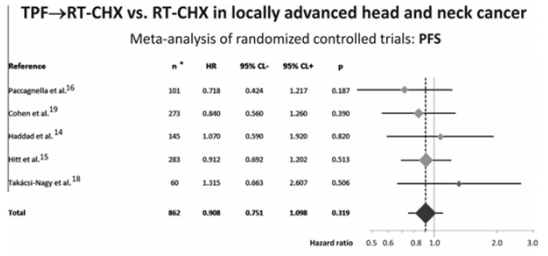
Induction chemotherapy followed by concurrent radio-chemotherapy versus concurrent radio-chemotherapy alone as treatment of locally advanced squamous cell carcinoma of the head and neck (HNSCC): A meta-analysis of randomized trials

Wilfried Budach [a], Edwin Bölke [a], Kai Kammers [b], Peter Arne Gerber [d], Klaus Orth [c], Stephan Gripp [a], Christiane Matuschek [a,*]

[a] Medical Faculty, Department of Radiation Oncology, Heinrich Heine University, Duesseldorf, Germany; [b] Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA; [c] Medical Faculty, Department of General, Visceral, and Thoracic Surgery, Asklepios Harz Hospitals, Goslar; and [d] Medical Faculty, Department of Dermatology, Heinrich Heine University, Dusseldorf, Germany

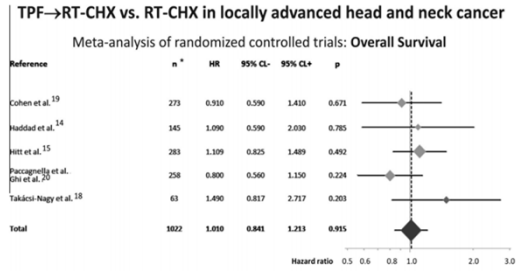
Radiotherapy and Oncology 118 (2016) 238–243

PFS



Radiotherapy and Oncology 118 (2016) 238–243

Overall Survival



Radiotherapy and Oncology 118 (2016) 238–243

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- Role of altered fractionation RT
- Role of Chemo along with RT
- Role of NACT prior to surgery
- Role of NACT prior to CCRT
- Adjuvant chemoRT in high risk patients
- Role of Chemotherapy in Ca Nasopharynx

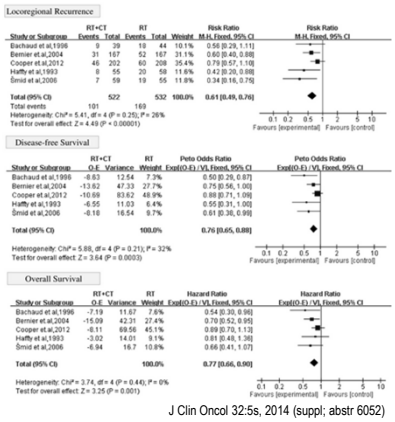
Is there a survival benefit in patients with advanced squamous cell carcinoma of the head and neck under chemoradiotherapy or radiotherapy alone after surgery administration: A systematic review and meta-analysis.

Jinbiao Shang, Jialei Gu, Qianbo Han, Yaping Xu, Xinmin Yu, Kejin Wang; Zhejiang Cancer Hospital, Hangzhou, China; Wenzhou Medical University, Zhejiang Cancer Hospital, Hangzhou, China

J Clin Oncol 32:5s, 2014 (suppl; abstr 6052)

Author/ year	Treatment arms	No. of pts.	Point in time*	Loco-regional recurrence	Disease-free survival	Overall survival	Median Survival, month
Bernier et.al,2004	CT+RT	167	5y	18%	47%†	53%	72
	RT	167		31%	36%	40%	32
				P=0.007	P=NR	P=NR	P=NR
			overall	NR	HR=0.75,*p*=0.04	HR=0.70,*p*=0.02	
				NR	95%CI=0.56-0.99	95%CI=0.52-0.95	
Cooper et.al,2012	CT+RT	202	10y	22.3%	20.1%	29.1%	NR
	RT	208		28.8%	19.1%	27%	NR
				P=0.10	P=0.25	P=0.31	
			overall	HR=0.73,	HR=0.88,	HR=0.89,	
				95%CI=0.49-1.07	95%CI=0.71-1.09	95%CI=0.70-1.12	
Bachaud et al,1996	CT+RT	39	5y	23%	45%	36%	40
	RT	44		41%	23%	13%	22
				P=0.08	P<0.02	P<0.01	P=NR
			overall	NR	HR=2.02	HR=1.89	
				NR	95%CI=1.17-3.48	95%CI=1.07-3.34	
Šmid et al,2006	CT+RT	59	5y	12%	53%	55%	68‡
	RT	55		35%	33%	37%	45
				P=0.026	P=0.035	P=0.091	
			overall	NR	HR=0.61,	HR=0.66,	
				NR	95%CI=0.37-0.97	95%CI=0.41-1.07	
Haffty et al,1993	CT+RT	55	5y	13%	67%	56%	NR
	RT	58		33%	44%	41%	NR
				P<0.015	P<0.03	NS	
			overall	NR	HR=0.55	HR=0.81	
				NR	95%CI=0.31-1.0	95%CI=0.48-1.36	

J Clin Oncol 32:5s, 2014 (suppl; abstr 6052)



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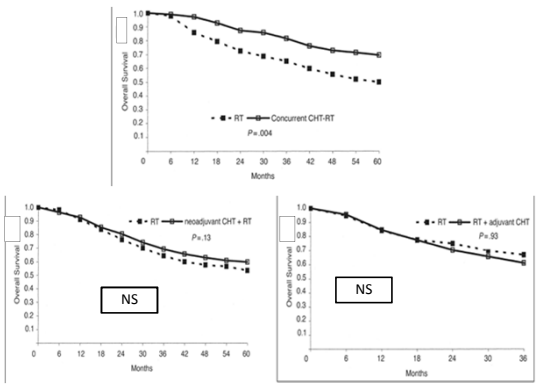
VOLUME 22 · NUMBER 22 · NOVEMBER 15 2004
JOURNAL OF CLINICAL ONCOLOGY
REVIEW ARTICLE

The Additional Value of Chemotherapy to Radiotherapy in Locally Advanced Nasopharyngeal Carcinoma: A Meta-Analysis of the Published Literature

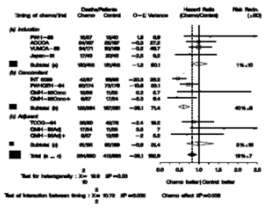
J.A. Langendijk, Ch.R. Leemans, J. Buter, J. Berkhof, and B.J. Slotman



Meta-analysis in NPC

MAC-NPC Collaborative Group

- To assess the impact of adding chemotherapy to RT on survival
- 8 trials, 1753 pts
- HR for death=0.82 (95% CI 0.71-0.95)
- 6% absolute survival benefit at 5 years
- Greatest benefit from concurrent chemo
  - HR=0.60 (concurrent)
  - HR=0.97 (adjuvant)
  - HR=0.99 (induction)



Baujat, IJROBP, 2006

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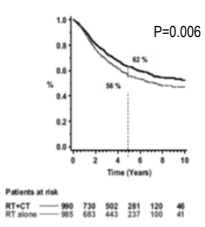
Baujat, IJROBP, 2006

Results

OS



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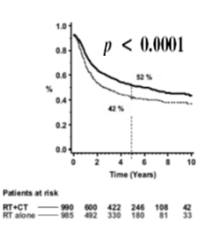


Int. J. Radiation Oncology Biol. Phys., Vol. 64, No. 1, pp. 47–56, 2006

Articles

Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis

Pierre Blanchard, Anne Lee, Sophie Marguet, Julie Leclercq, Wai Tong Ng, Jun Ma, Anthony T C Chan, Pei-Yu Huang, Ellen Benhamou, Guopei Zhu, Daniel T T Chua, Yong Chen, Hai-Qiang Mai, Dora L W Kwong, Shie Lee Cheah, James Moon, Yuk Tung, Kwan-Hwa Chi, George Fountzilas, Li Zhang, Edwin Pun Hui, Tai-Xiang Lu, Jean Bourhis, Jean Pierre Pignon, on behalf of the MAC-NPC Collaborative Group*

Lancet Oncol 2015; 16: 645–55

Chemotherapy and Radiotherapy in NPC: Meta-analysis

	Overall survival	Progression-free survival	Locoregional control	Distant control	Cancer death*	Non-cancer death*
Induction	0·96 (0·80–1·16)	0·81 (0·69–0·95)	0·84 (0·66–1·07)	0·62 (0·48–0·79)	0·89 (0·73–1·09)	1·85† (1·05–3·29)
Adjuvant	0·87 (0·68–1·12)	0·80 (0·64–1·00)	0·61 (0·41–0·92)	0·80 (0·59–1·09)	0·84 (0·64–1·10)	1·08 (0·59–1·95)
Concomitant	0·80 (0·70–0·93)	0·81 (0·71–0·92)	0·82 (0·67–1·01)	0·74 (0·61–0·90)	0·74 (0·62–0·89)	1·20 (0·77–1·87)
Concomitant plus adjuvant	0·65 (0·56–0·76)	0·62 (0·53–0·72)	0·54 (0·41–0·71)	0·56 (0·45–0·70)	0·63 (0·52–0·77)	1·19 (0·77–1·85)
Overall	0·79 (0·73–0·86)	0·75 (0·69–0·81)	0·73 (0·64–0·83)	0·67 (0·59–0·75)	0·76 (0·69–0·84)	1·27 (0·99–1·64)
Overall test	p<0·0001	p<0·0001	p<0·0001	p<0·0001	p<0·0001	p=0·056
Interaction test (timing × treatment effect)	p=0·012	p=0·041	p=0·054	p=0·18	p=0·084	p=0·55
Residual heterogeneity test	p=0·36	p=0·62	p=0·78	p=0·031	p=0·54	p=0·25

Data are HR (95% CI) or p value. *Analyses based on 20 comparisons (4312 patients) because the cause of death was missing for three trials.[7,11,14] †No difference (HR 0·91, 95% CI 0·39–2·15) was seen in a sensitivity analysis, excluding one trial (239 patients)[14] that was a clear outlier.

Blanchard et al. Lancet Oncology 2015;16:645-55

VOLUME 35 · NUMBER 5 · FEBRUARY 10, 2017

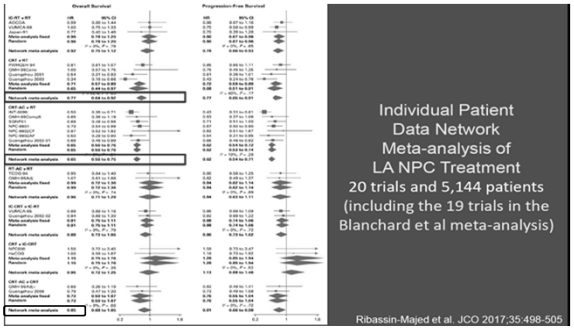
JOURNAL OF CLINICAL ONCOLOGY

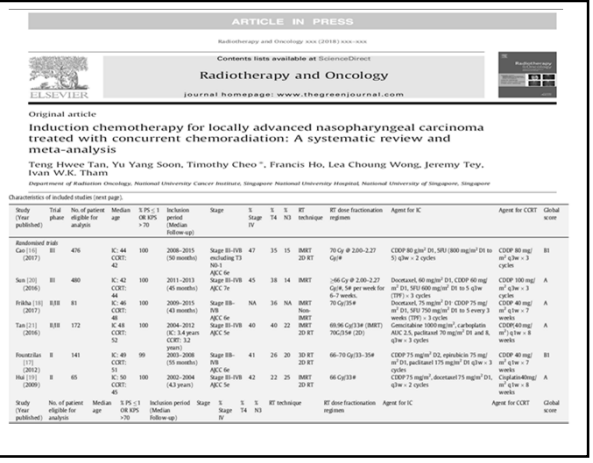
ORIGINAL REPORT

What Is the Best Treatment of Locally Advanced Nasopharyngeal Carcinoma? An Individual Patient Data Network Meta-Analysis

Laureen Ribassin-Majed, Sophie Marguet, Anne W.M. Lee, Wai Tong Ng, Jun Ma, Anthony T.C. Chan, Pei-Yu Huang, Guopei Zhu, Daniel T.T. Chua, Yong Chen, Hai-Qiang Mai, Dora L.W. Kwong, Shie-Lee Cheah, James Moon, Yuk Tung, Kwan-Hwa Chi, George Fountzilas, Jean Bourhis, Jean Pierre Pignon, and Pierre Blanchard, on behalf of the Meta-Analysis of Chemotherapy in Nasopharyngeal Collaborative Group

Results





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Radiotherapy and Oncology xxx (2018) xxx–xxx

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journal homepage: www.thegreenjournal.com

Original article

Induction chemotherapy for locally advanced nasopharyngeal carcinoma treated with concurrent chemoradiation: A systematic review and meta-analysis

Teng Hwee Tan, Yu Yang Soon, Timothy Cheo *, Francis Ho, Lea Choung Wong, Jeremy Tey, Ivan W.K. Tham

Department of Radiation Oncology, National University Cancer Institute, Singapore National University Hospital, National University of Singapore, Singapore

Characteristics of included studies (next page).

Study (Year published)	Trial phase	No. of patient eligible for analysis	Median age	% PS ≤ 1 OR KPS >70	Inclusion period (Median follow-up)	Stage	% Stage IV	% T4	% N3	RT technique	RT dose fractionation regimen	Agent for IC	Agent for CCRT	Global score
Randomized trials														
Cao [14] (2017)	III	476	IC: 44 CCRT: 42	100	2008–2015 (50 months)	Stage III–IVB excluding T3 N0-1 AJCC 6e	47	35	15	IMRT 2D RT	70 Gy @ 2.00–2.27 Gy/#	CDDP 80 g/m² D1, 5FU 800 mg/m² D1 to 5) q3w × 2 cycles	CDDP 80 mg/m² q3w × 3 cycles	B1
Sun [20] (2016)	III	480	IC: 42 CCRT: 44	100	2011–2013 (45 months)	Stage III–IVB AJCC 7e	45	38	14	IMRT	>66 Gy @ 2.00–2.27 Gy/#, 54 per week for 6–7 weeks	Docetaxel, 60 mg/m² D1, CDDP 60 mg/m² D1, 5FU 600 mg/m² D1 to 5 q3w (TPF) × 3 cycles	CDDP 100 mg/m² q3w × 3 cycles	A
Frikha [18] (2017)	II/II	81	IC: 46 CCRT: 35	100	2009–2015 (43 months)	Stage IIB–IVB AJCC 6e	NA	36	NA	IMRT Non-IMRT	70 Gy/35#	Docetaxel, 75 mg/m² D1 CDDP 75 mg/m² D1, 5FU 750 mg/m² D1 to 5 every 3 weeks (TPF) × 3 cycles	CDDP 40 mg/m² q1w × 7 weeks	A
Tan [21] (2016)	II/II	172	IC 48 CCRT: 52	100	2004–2012 (IC: 3.4 years CCRT: 3.2 years)	Stage III–IVB AJCC 5e	40	40	22	IMRT 2D RT	69.96 Gy/33# (IMRT) 70G/35# (2D)	Gemcitabine 1000 mg/m², carboplatin AUC 2.5, paclitaxel 70 mg/m² D1 and 8, q3w × 3 cycles	CDDP,40 mg/m² q1w × 8 weeks	A
Fountzilas [17] (2012)	II	141	IC: 49 CCRT: 51	99	2003–2008 (55 months)	Stage IIB–IVB AJCC 6e	41	26	20	3D RT 2D RT	66–70 Gy/33–35#	CDDP 75 mg/m² D2, epirubicin 75 mg/m² D1, paclitaxel 175 mg/m² D1 q3w × 3 cycles	CDDP 40 mg/m² q1w × 7 weeks	B1
Hui [19] (2009)	II	65	IC: 50 CCRT: 45	100	2002–2004 (43 years)	Stage III–IVB AJCC 5e	42	22	25	IMRT 2D RT	66 Gy/33#	CDDP 75 mg/m², docetaxel 75 mg/m² D1, q3w × 2 cycles	Cisplatin 40mg/m² q1w × 8 weeks	A

Study (Year published)	No. of patient eligible for analysis	Median age	% PS ≤ 1 OR KPS >70	Inclusion period (Median follow-up)	Stage	% Stage IV	% T4	% N3	RT technique	RT dose fractionation regimen	Agent for IC	Agent for CCRT	Global score

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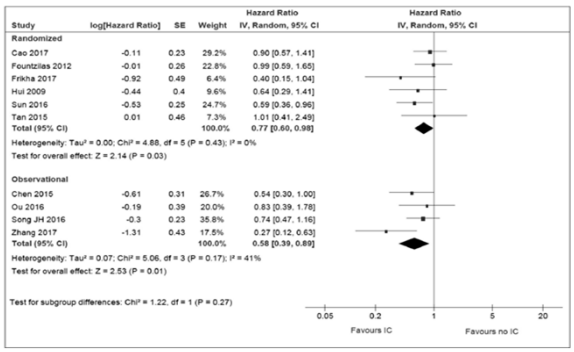

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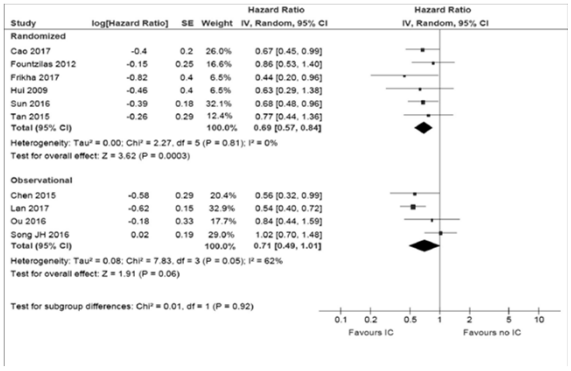

Thank you