Neoplasie del rinofaringe

Criticità nel timing terapia sistemica-radioterapia

Fabiola Paiar

CHEMOTHERAPY IN NASOPHARYNGEAL CANCER

Minimize the risk of distant recurrence through eradication of micro-metastases

Enhance the effects of radiation through synergistic agents

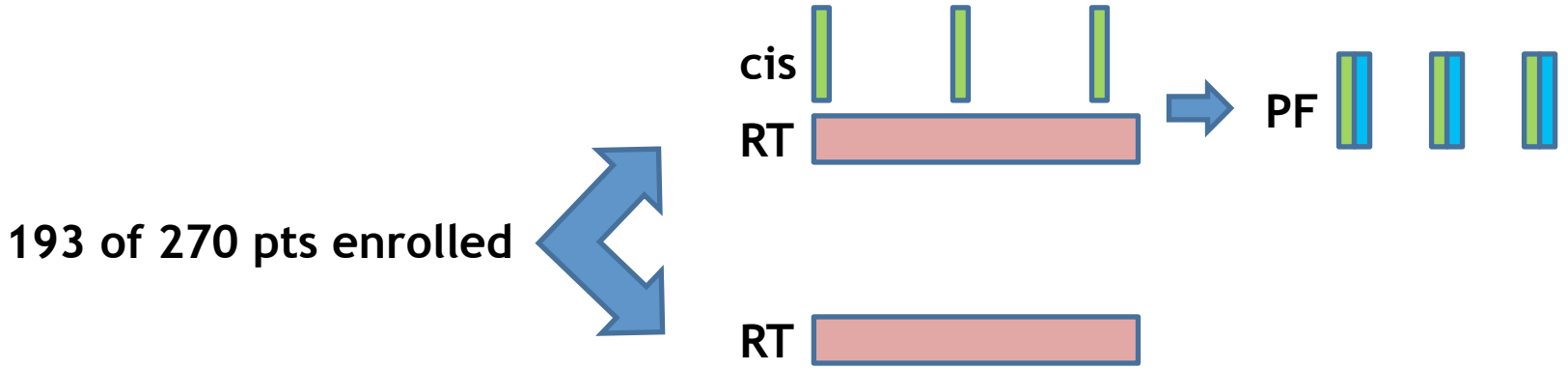
Facilitate planning of RT and to improve local disease control reducing the tumor volume prior to irradiation


I
N
D
ADJ

Chemoradiotherapy Versus Radiotherapy in Patients With Advanced Nasopharyngeal Cancer: Phase III Randomized Intergroup Study 0099

By Muhyi Al-Sarraf, Michael LeBlanc, P.G. Shanker Giri, Karen K. Fu, Jay Cooper, Te Vuong, Arlene A. Forastiere, George Adams, Wael A. Sakr, David E. Schuller, and John F. Ensley

ASCO 1996, JCO1998



Al-Sarraf, JCO, 1998

Intergroup 0099

- 3Y PFS 69% (CRT) *vs.* 24% (RT alone), $p<0.001$
- 3Y OS 78% (CRT
  47% (RT al .005
- Lo ol & distant mets
  proved

MIGLIORAMENTO DEL 31% SULLA OS A 3 ANNI E DEL 45% SULLA PFS RISULTATI CONFERMATI ANCHE A 5 ANNI

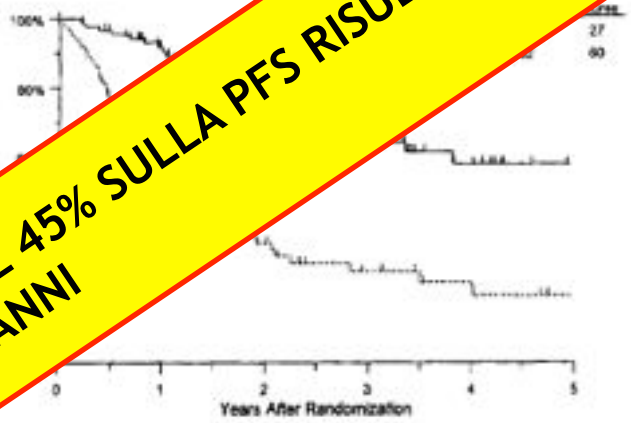


Fig 4. PFS for randomized patients on RT only and combined CT/RT.

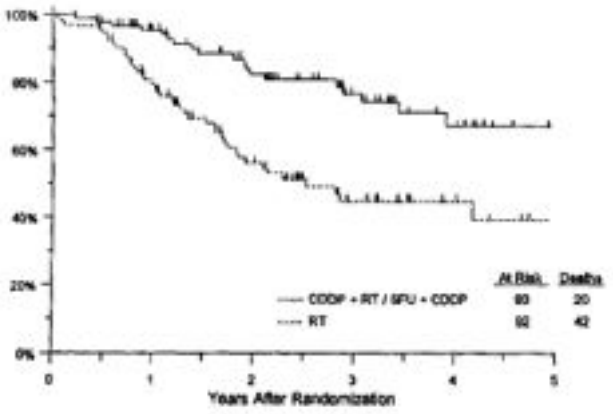


Fig 3. Overall survival for randomized patients on RT only and combined CT/RT.

Intergroup 0099

- Issues
  - Flawed study design
    - Are the benefits from chemo due to concurrent administration, adjuvant, or both?
  - Terminated early after interim analysis showed survival benefit
  - RT alone arm performed worse than expected
  - Old RT techniques
  - Many patients enrolled had WHO type I NPC (not EBV-associated)
  - Adjuvant PF chemotherapy only feasible in some patients

STUDI RANDOMIZZATI FASE III
RADIO-CHEMIOTERAPIA CONCOMITANTE VS RT ESCLU

Study (authors or trial)	RT (Gy)	Concurrent chemotherapy	Adjuv ch
Al-Sarraf et al (USA)	70	CDDP 100 mg/m² 3 cycles	
Chan et al (Hong Kong)	66 ± 10–20 Gy boost	CDDP 40 mg/m²	
Lin et al (Taiwan)	70–74	CDP	NA
Kwong et al (Hong Kong)	r 66–68 ± 10 Gy bo		CDDP/5FU + VBM 3 cycles
Zhang et al (Guangzhou)	70–74	mg/m²/wk	NA
Wee et al (Singapore)		CDDP 25 mg/m²/d × 4d 3 cycles	CDDP 20 mg/m²/d × 4d + 5FU 1000 mg/m²/d × 4d
Lee et al (Hong K	y boost	CDDP 100 mg/m² 3 cycles	CDDP 80 mg/m² + 5-FU 1000 mg/m² 3 cycles
	≥66 Gy in 5 or 6 fractions/week	CDDP 100 mg/m² 3 cycles	CDDP 80 mg/m² + 5-FU 1000 mg/m² 3 cycles
et al (Guangzhou)	70	CDDP 40 mg/m² weekly	CDDP 80 mg/m² + 5-FU 800 mg/m² 3 cycles

CONFERMA DEI RISULTATI DELL' INT-0099

CONTRIBUTO DELLA CHEMIOTERAPIA ADIUVANTE DOPO RADIOCHEMIOTERAPIA CONCOMITANTE

STUDI RANDOMIZZATI FASE III
CHEMIOTERAPIA ADIUVANTE VS SOLA

Trials fase III	PAZ	SCHEMA	%	OS %
ROSSI A ET AL Italia	229	Rt Rt→VCA	55.8 57.7	67.3 58.5
CHI KH ET AL Taiwan	157	Rt	49.5 54.4	60.5 54.5
KWONG DL ET AL Hong Kong		CDDP/5FU+VBM CRT (UFT) ±CDDP/5FU+VBM	62.5 65	80.4 83.1

NESSUN IMPATTO SIGNIFICATIVO SU OS E RFS

CHEMOTHERAPY IN LOCALLY ADVANCED NASOPHARYNGEAL CARCINOMA: AN INDIVIDUAL PATIENT DATA META-ANALYSIS OF EIGHT RANDOMIZED TRIALS AND 1753 PATIENTS

Bertrand Baujat, M.D.,* Hélène Audry, M.Sc.,* Jean Bourhis, M.D., Ph.D.*
Anthony T. C. Chan, M.D.,† Haluk Onat, M.D.,‡ Daniel T. T. Chua, M.D.,§ Dora L. W. Kwong, M.D.,§ Muhyi al-Sarraf, M.D.,‖ Kwan-Hwa Chi, M.D.,¶ Masato Hareyama, M.D.,*
Sing F. Leung, M.D.,† Kullathorn Thephamongkhol, M.D.,* and
Jean-Pierre Pignon, M.D., Ph.D.,* on behalf of the MAC-NPC Collaborative Group

- **Conclusions**
  - Chemotherapy added to RT in NPC yields a small but statistically significant improvement in survival
  - Benefit almost entirely from concurrent chemotherapy
- **However**
  - Heterogeneity of studies, patients, chemotherapy regimens, and radiotherapy techniques limits lessons learned
  - No clear chemotherapy regimen superior to others
  - More effective chemotherapy regimens may exist

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

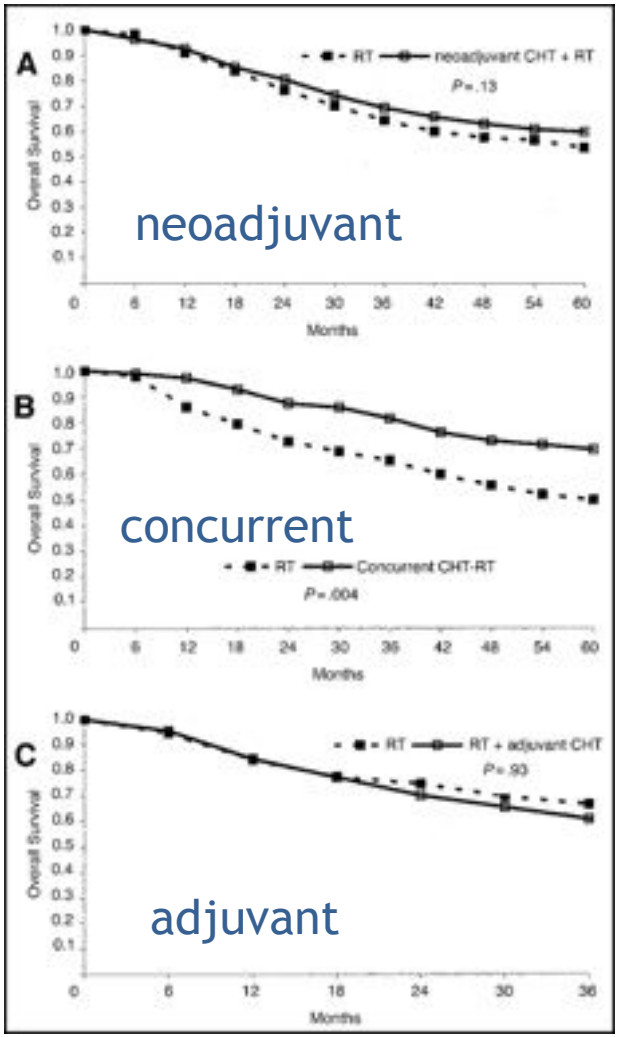
The Additional Value of Chemotherapy to Radiotherapy in Locally Advanced Nasopharyngeal Carcinoma: A Meta-Analysis of the Published Literature

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

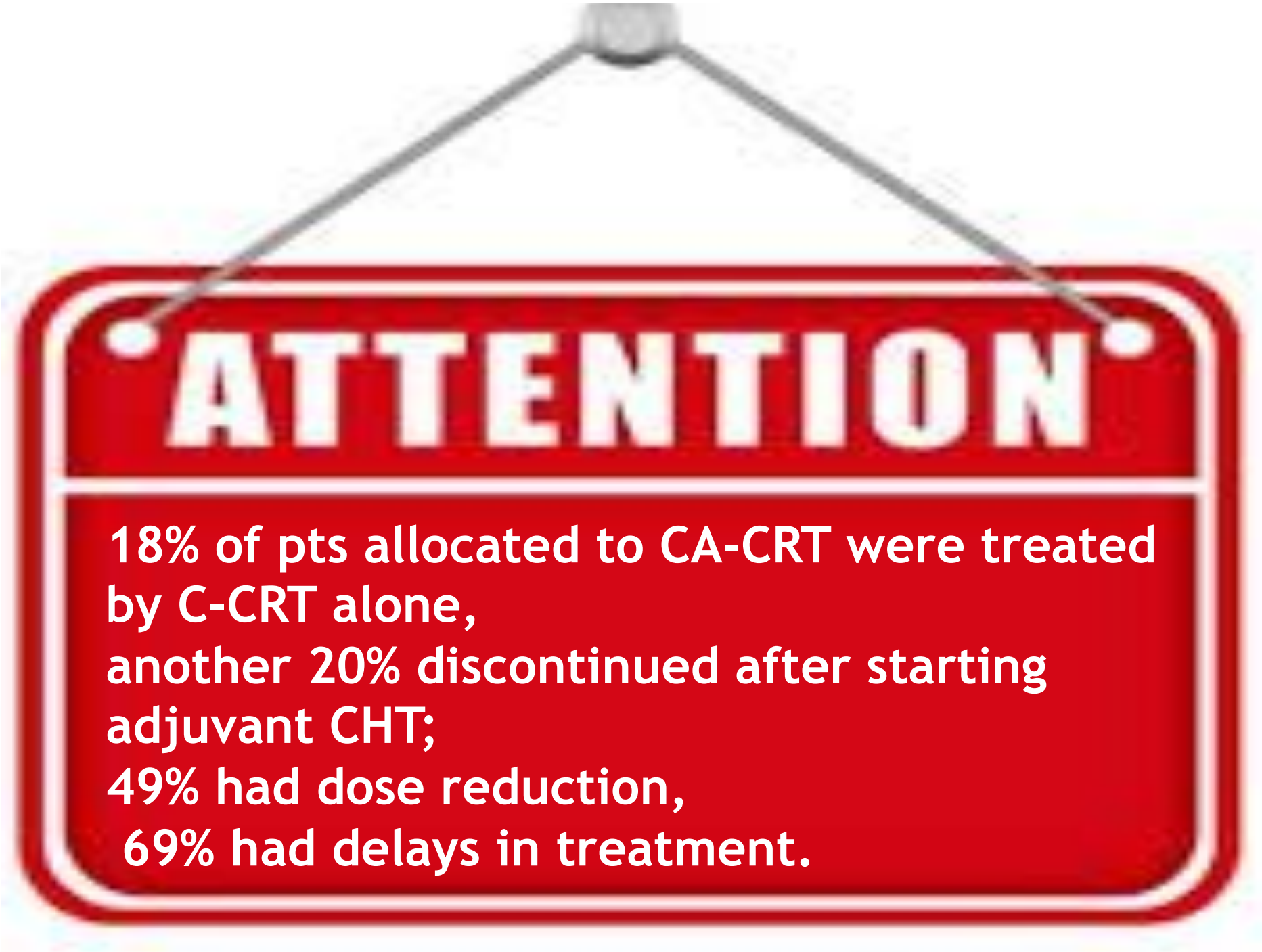
Ten randomized clinical studies → 2,450 patients.

a significant benefit in favor of the addition of chemotherapy was found (*P* = .01) with an absolute survival benefit of 4% after 3 years.

concomitant chemotherapy with radiation is the most effective approach to combine chemotherapy and radiation in NPC



Langendijk, J.A. et al. J Clin Oncol; 22:4604-4612 2004


ATTENTION
18% of pts allocated to CA-CRT were treated by C-CRT alone,
another 20% discontinued after starting adjuvant CHT;
49% had dose reduction,
69% had delays in treatment.

Factors contributing to the efficacy of concurrent–adjuvant chemotherapy for locoregionally advanced nasopharyngeal carcinoma: Combined analyses of NPC-9901 and NPC-9902 Trials

Anne W.M. Lee[a], Stewart Y. Tung[b], Roger K.C. Ngan[c], Rick Chappell[d], Daniel T.T. Chua[e], T.X. Lu[f], Lillian Siu[g], Terence Tan[h], L.K. Chan[a], W.T. Ng[a], T.W. Leung[b], Y.T. Fu[c], Gordon K.H. Au[a], C. Zhao[f], Brian O'Sullivan[g], E.H. Tan[h], W.H. Lau[c]

Findings

Comparison by intention-to-treat showed that the CRT, group achieved significant improvement in overall failure-free rate (FFR), locoregional-FFR and cancer-specific survival ($p \leqslant 0.019$); but the improvements for distant-FFR and overall survival (OS) were statistically insignificant ($p \geqslant 0.14$). Further exploratory studies based on actual treatment showed that an additional improvement achieved was a significant gain in OS (CRT_a versus RT_a group: 72% versus 63% at 5-year, $p = 0.037$). Multivariate analyses showed that the dose of cisplatin during the concurrent phase had significant impact on locoregional-FFR and OS, while that of fluorouracil during the adjuvant phase was significant for distant-FFR. The 5-year locoregional-FFR for patients who received 0–1, 2 and 3 concurrent cycles were 79%, 88% and 88%, respectively; the corresponding distant-FFR by adjuvant cycles were 68%, 78% and 77%, respectively.

Interpretation

Our results support the current practice of adding concurrent cisplatin plus adjuvant cisplatin-fluorouracil to radiotherapy for treating patients with locoregionally advanced NPC. The concurrent phase is important for locoregional control and survival, cisplatin 200 mg/m^2 in two concurrent cycles might be adequate. Additional chemotherapy using fluorouracil-containing combination contributed to improving distant control.

COMPLIANCE

Author	% Complete treatment				
	Induction/adjuvant chemotherapy		Concurrent chemotherapy		Radiotherapy
	≥2 cycles	≥3 cycles	≥2 cycles	≥3 cycles	
Concurrent–adjuvant					
Al-Sarraf [6]	60	55	86	63	73
Lee [7, 12]	81	76	94	60	99
Wee [8]	NR	57	NR	71	95
Chen [9]	68	61	90[2]	68[3]	99
Chen [21]	NR	63	NR	45	98

SHIFT FROM ADJUVANT TO INDUCTION CHEMOTHERAPY

ADVANTAGES

- Induction chemotherapy is likely to be much more tolerable.
- Upfront use of a potent combination of cytotoxic drugs at an optimal dose intensity would be more effective for reduction of distant failure.
- Induction chemotherapy could shrink the primary tumor to give wider margins around delicate normal structures.
- Regression of bulky lymph nodes by induction chemotherapy could minimize marked changes in the contour of the neck during subsequent RT.

SHIFT FROM ADJUVANT TO INDUCTION CHEMOTHERAPY

DISADVANTAGES

- Induction chemotherapy delays the commencement of RT (the primary modality for locoregional control).
- Induction chemotherapy could jeopardize the tolerance to subsequent concurrent chemotherapy (the most potent sequence for enhancing tumor control).

STUDI RANDOMIZZATI FASE III
CHEMIOTERAPIA DI INDUZIONE E RT VS RT ESCLUSI

Study (authors or trial)	Median follow-up (months)	Time point (years)	Treatment arm	N	Regimen			
Chan et al (Hong Kong) 1995	28.5	2	RT	40	66 Gy			76
			Induction-RT-adjuvant chemo	37			68	78
						NS	NS	NS
International Nasopharynx Cancer Study Group VUMCA I 1996	49	5				46	30	
					EC 3 cycles	40	40	
						NS	$P < 0.01$	SS
Chua et al (AOCOA) 1998	30			152	66–74 Gy	71	42	
			tion-RT	134	CDDP 60 mg/m² + Epi 110 mg/m² 2–3 cycles	78	48	
						NS	NS	NS
Ma et al (Guangzhou) 2001			RT	225	68–72 Gy ± 10–14 Gy boost w/EBRT or 20–24 Gy boost w/HDR	56	49	75
			Induction-RT	224	CDDP, 5-FU, Bleo 2–3 cycles	63	59	79
						NS	$P = 0.05$	NS
(Jap 20	49	5	RT	40	66–68 Gy	48	43	56
			Induction-RT	40	CDDP 80 mg/m² + 5-FU 800 mg/m² 2 cycles	60	55	74
						NS	NS	NS

NESSUN IMPATTO SIGNIFICATIVO SU OS E DFS

… New interest in induction CT

Induction-concurrent chemoradiotherapy

Author	No.	Stage		Chemotherapy scheme		Radiotherapy			Tumor control		
		Inclusion	% Stage IV	Induction/ adjuvant	Concurrent	Technique	Dose (Gy)	Time-point (year)	Locoregional-FFR	Distant-FFR	Overall survival
Induction–concurrent											
Rischin [22]	35	II–IVB	40	PEF	P	2D	60	4	97	94	90
Oh [23]	27	II–IVB	NA	PFLI	HF	NR	70	5	93	92	77
Chan [24]	31	III–IVB	39	JC	P	2D	66	2	90[a]	81 [a]	92
Al-Amro [25]	110	II–IVB	74	PE	P	2D	66	3	68	74	71
Johnson [26]	44	II–IVB	NA	PF	PF	2D	70	5	75 [a]	89 [a]	66
Lee [27]	49	IVA–B	100	PF	P	3D	70	3	77	75	71
Yau [28]	37	IVA–B	100	PG	P	3D	70	3	78	76	76
Mostafa [29]	36	III–IVB	61	PC	P	2D	70	3	64 [a]	86 [a]	68
Ferrari [30]	34	IIB–IVB	59	PF	P	3D	70	3	94	68	80
Airoldi [31]	40	III–IVB	44	PE	P	3D	70	5	70	75	77
Zheng [32]	60	IIB–IVB	43	NF	N	IMRT	70	3	NR	NR	86
Kong [33]	59	III–IVB	49	TPF	P	3D/ IMRT	70–76	1	98	96	100
Bae [34]	33	III–IVB	88	TPF	P	NR	68.4	3	NR	NR	86
Bossi [35]	30	III–IVB	57	TPF	P	IMRT	66–70	3	90 [a]	87 [a]	87
Airoldi [36]	30	III–IVB	53	JC	JC	3D	70	5	90	85	80
Sheung [37]	28	IIB–IVB	36	PEFL	PFL	Tomotherapy	70	3	88	78	84
Huang [38]	201	NA	NA	JU	J	2D	66–78	3	88	76	76
Hui [39]	34	III–IVB	44	TP	P	2D/ IMRT	66	3	NR	NR	94
Fountzilas [40]	72	IIB–IVB	43	PEC	P	2D/ 3D	66–70	3	76 [a]	86 [a]	67

TAXANES BASED INDUCTION CHEMOTERAPY FOLLOWED CCRT

AUTHOR	IC	≥ 2 CYCLES IC	≥ 3CYCLES IC	≥ 2 CYCLES ≥ 5 WCY	ES
Bossi 2011	docetaxel 75 mg/m2 cisplatin 75 mg/m2 5-FU 750 mg m2/day	NR	60		50
Bae 2010	Docetaxel (70 mg/m2) cisplatin (75 mg/m2) 5-FU (1,000 mg/m2/da for 4 days. 3 cycle	100		NR	97
Kong 2010	docetaxel 75 mg/m 2 , cisplatin 75 mg/m 2, 5 500 mg/m2/day1		86	66	NR
Hui 2009	docet	100	NA	74	10
Fou	mg/m2 el 175 mg/m2 latin 75 mg/m2 3 cycle	NR	86	72	40

TOLLERANCE AND COMPLIANCE TO INDUCTION CHEMOTHERAPY IS BETTER THAN ADJUVANT

Ongoing randomized trials to evaluate the therapeutic benefit of induction-concurrent chemoradiotherapy

Study				Endpoints
HKNPCSG 0501				
	Stage III or IV (n = 798)	CCRT[a*]	→ PF x 3	Progression free survival and overall survival
		PF x 3	→ CCRT[a*]	
		PX x 3	→ CCRT[a*]	
GORTEC				
	T2b-4, ≥ N1 (n = 260)	TPF x 3	→ CCRT[b]	Event free survival
		CCRT[b]		
China				
	T3-4N1 or any T4 with N2-3 (n = 362)	TPF x 3	→ CCRT[a]	Failure free survival
		CCRT[a]		
Singapore				
	Stage III or IV (n = 216)	GJPa x 3	→ CCRT[b]	Overall survival
		CCRT[b]		
Taiwan				
	Stage IV (n = 480)	MEPFL x 3	→ CCRT[b]	Disease free survival
		CCRT[b]		

Abbreviations:
T - taxotere, P - cisplatin, F - 5 fluorouracil, M - mitomycin, E - epirubicin, L - leucovorin, G - gemcitabine, J - carboplatin, Pa - paclitaxel, X - capecitabine

* with secondary randomization on fractionation (conventional vs. acceleration)

[a]3 weekly cisplatin, [b]weekly cisplatin

Note: Progression free survival - defining events for any failure or death
Failure free survival - defining events for any failure

CONCLUSION

Concurrent CRT is still the standard of care for locoregionally advanced nasopharyngeal cancer.

The exact role of adjuvant CT remains unclear because it has not been adequately tested and the compliance is difficult but in high risk patients it may play a role.

The reported failure-free rates and survival rates for IC-CRT are encouraging, and this strategy is an option to be considered especially for patients with extensive locoregional disease infiltrating/ abutting critical structures.

CONCLUSION

Studies on IC-CRT show that tolerance and compliance to induction chemotherapy are better than adjuvant chemotherapy however, the acute toxicity rates are similar.

the Clinical Practice Guidelines in Oncology by the National Comprehensive Cancer Network (NCCN) has included ICCRT as option for patients with locoregionally advanced NPC (Category 3 evidence).

Additional improvements are still needed to improve the quantity and quality of life of NPC patients.