

Role of Neoadjuvant Chemotherapy in Head and Neck Cancer



Ying Zhuo, MD



Treatment Timeline of Head and Neck Cancer in the Past Two Decades

- ❖ 1991-VALSG trial showed benefit of locoregional control and organ preservation by adding the induction chemotherapy prior to definitive radiation therapy for locally advanced laryngeal cancer.
- ❖ 1998-Brizel *et al.* showed benefit of locoregional control with concurrent chemo/radiation therapy for locally advanced head and neck cancer.
- ❖ 2004-GORTEC 94-01 trial showed a survival benefit of concurrent chemo/XRT compared to XRT alone in locally advanced oropharyngeal cancer
- ❖ 2005-Hitt *et al.* showed higher CR rate with induction chemotherapy of PCF followed by concurrent chemo/XRT compared to CF induction chemotherapy.



Rationale for Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy, or induction chemo, is the chemotherapy given prior to definitive locoregional treatment.

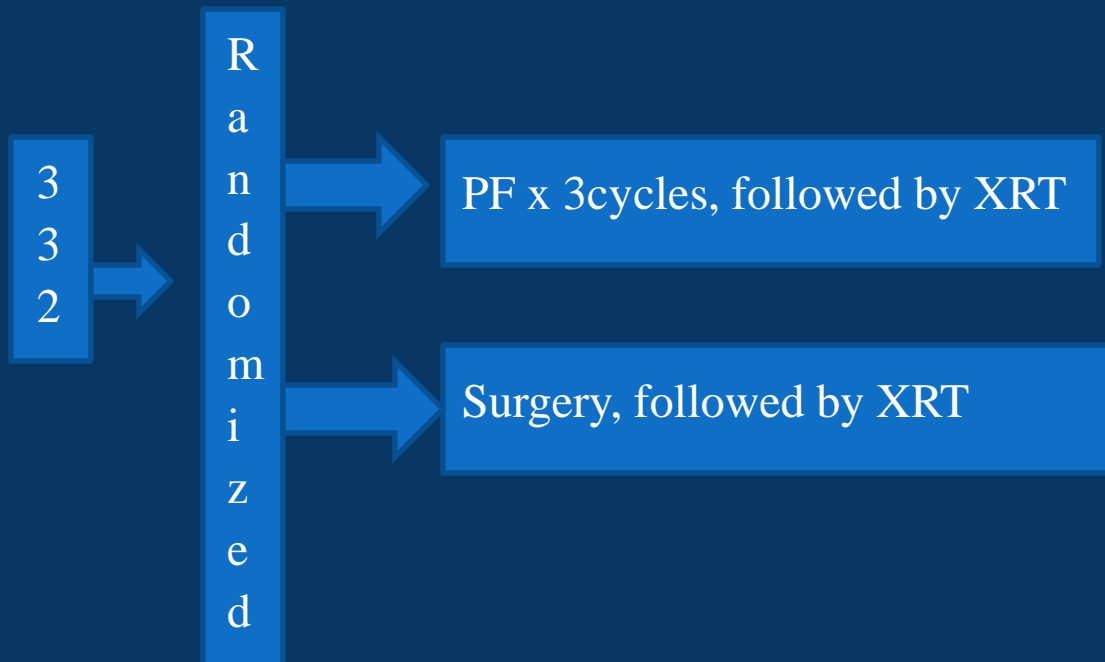
Advantage of induction chemo: 1. systemic treatment prior to locoregional definitive treatment eradicate the possible micrometastasis cancer cells to decrease the rate of distant recurrence, consequentially increase the OS. 2. Increase organ preservation rate. 3. increase response rate.

Disadvantage of induction chemo: 1. Increase toxicity. 2. Preclude or delay the delivery of the mainstay curative locoregional treatment.



VALSG Trial

Stage III & IV SCC of larynx. Unresectable cancers or distant metastases excluded



Median f/u: 33 Months

Primary end point: OS and DFS



	Induction Chemo+XRT	Surgery+XRT
2 yr OS (p=0.98)	68%	68%
Local recurrence (p=0.001)	12%	2%
Distant recurrence (p=0.001)	11%	17%
Larynx preservation at 2yr	64%	



Phase III clinical trials of induction chemo for local advanced head and neck cancer

Trial	Pt #	Regimen	Locoregional recurrence	Distant Mets	OS and LPR
VALSG (laryngeal)	332	PF+XRT vs surgery+XRT	12% vs 2% (p=0.001)	11% vs 17% (p=0.001)	68% vs 68% (2 yr), LPR=64%
EORTC (pyriform sinus)	202	PF+XRT vs surgery+XRT	29% vs 27% (NS)	25% vs 36% (p=0.041)	43% vs 57% (3 yr), LPR=42%
Paccagnella et al.	237	PF+locoregional tx vs locoregional tx	72% vs 71%	14% vs 38% (p=0.02)	37% vs 29% (2 yr, p=0.21)
Hitt et al.	382	PF+CRT (cis) vs PaPF +CRT	No difference	No difference	37 m vs 43 m (p=0.06)
EORTC24971 /TAX 323	358	PF+XRT vs TPF+XRT	81.2% vs 85.1%	10.3 vs 12.9%	14.5 m vs 18.8m (p=0.02)



Trial	Pt #	Regimen	Locoregional recurrence	Distant Mets	OS and LPR
TAX 324	501	PF+CRT(carbo) vs TPF+CRT	38% vs 30% (p=0.04)	9% vs 5% (p=0.14%)	48% vs 62% (p=0.006)
FHNORG	213	PF+locoregional tx vs TPF+locoregional tx	23.7% vs 18.6%	16 vs 12 (p=.38)	60% vs 60% (3 yr, p=.57), LPR 57.5% vs 70.3% (p=.03)



Drop out rate of induction chemo



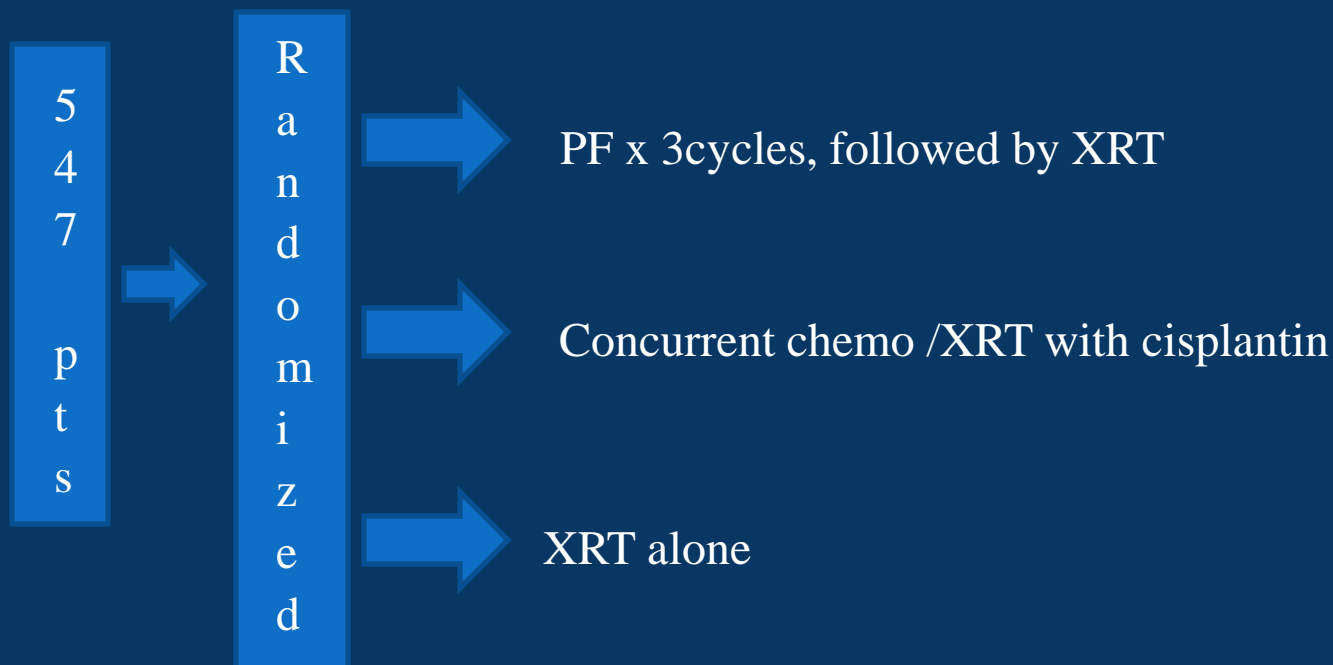
Phase III clinical trials of concurrent chemo/XRT for local advanced head and neck cancer

Trial	Pt #	Regimen	Local recurrence	Distant Mets	OS and LRC
Brizel et al.	122	XRT vs PF/XRT followed by PF	27 vs 16	6 vs 6	34% vs 55% (3 yr, p=0.07)
Adelstein et al.	271	XRT vs cis/XRT vs PF+split XRT followed by XRT or surgery	Not reported	17.9% vs 21.8% vs 19.1%	23% vs 37% vs 27% (3 yr, p=0.014, XRT vs CRT)
RTOG91-11 (larynx)	547	XRT vs cis/XRT vs PF+XRT	72% vs 35% vs 61% vs	16% vs 8% vs 9%	74% vs 75% vs 76% (2yr, NS)
Budach et al.	384	XRT vs 5fu+MMC/XRT	64 vs 42	19 vs 20	22.4% vs 15.8% (5 yr, p=0.05)



RTOG91-11 Trial

Stage III&IV SCC of the larynx. T1 or large –volume T4 primary tumor were excluded



Median f/u: 3.8 yrs

Primary end point: Preservation of the larynx.

Second end points: OS, DFS, local control, locoregional control , time to distant metastasis, LFS



	Concurrent chemo/XRT	Induction chemo+XRT	XRT alone
Preservation of the larynx	84%	72% (p=0.005)	67% (p<0.001)
LFS (2yr & 5yr)	66% & 46.6%	59% & 44.6% (p=0.49)	53% & 33.9% (p=0.01)
OS (2yr & 5yr)	74% & 54.6%	76% & 59.2%	75% & 53.5%
#of local failure at 2 yr	35	61 (p=0.004)	72(p<0.001)
Distant Metastasis (2yr & 5yr)	8% & 12%	9% & 15%	16% & 22% (p=0.03)
Total rates of severe toxic effects	82%	81%	61%



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 Group¹

(b): Hazard ratio of recurrence or death

Timing	No. Events / No. Entered LRT+CT	No. Entered LRT	O-E	Variance	Hazard Ratio	HR [95% CI]
Concomitant	3447/4824	3735/4791	-401.7	1742.6		0.79 [0.76;0.83]
Induction	2036/2740	1924/2571	-13.3	956.7		0.99 [0.93;1.05]
Adjuvant	703/1244	762/1323	-4.2	360.9		0.99 [0.89;1.10]
Total	6186/8808	6421/8685	-419.3	3060.2		0.87 [0.84;0.90]

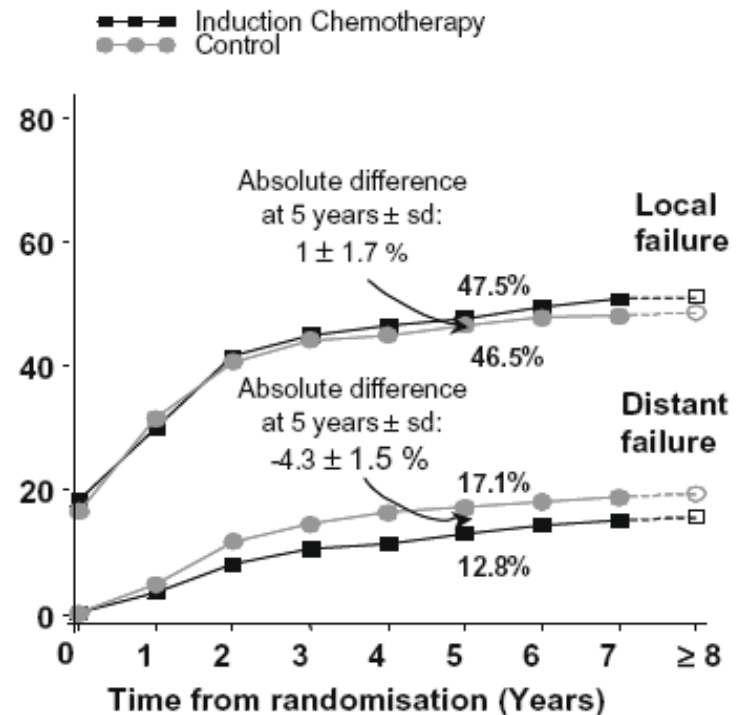
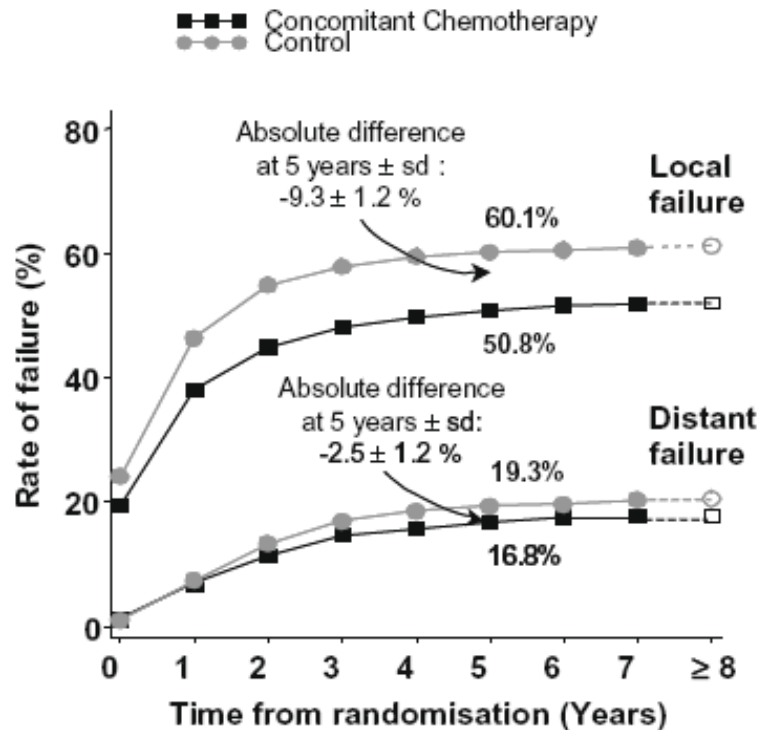
Test for heterogeneity: $\chi^2_{107} = 187.7$ $p < 0.0001$ $I^2 = 43\%$

Test for interaction: $\chi^2_2 = 35.40$ $p < 0.0001$

0.5 1.0 2.0
LRT+CT better | LRT better
LRT+CT effect: $p < 0.0001$



(a) All trials



Local failure and distant failure /person-years by period

	Years 0-2	Years 3-5	Years \geq 6
Local failure			
Control	2509/8969	127/2812	18/2016
Chemotherapy	2045/9789	162/3881	21/2822
Distant failure			
Control	382/9817	82/3026	9/2195
Chemotherapy	370/10438	96/4010	10/2896

	Years 0-2	Years 3-5	Years \geq 6
Local failure			
Control	942/5335	70/1897	16/1202
Chemotherapy	1049/5737	85/2165	27/1245
Distant failure			
Control	183/5717	45/2025	11/1328
Chemotherapy	143/6207	46/2329	16/1391



Planned or ongoing phase III trials comparing concurrent chemoradiation to induction chemotherapy followed by concurrent chemoradiation

Group	Sites	Stage	Resectable unresectable	Induction regimen	Concurrent chemotherapy	Radiation regimen	Primary endpoint
University of Chicago (DeCIDE)	All	N2/ N3	Both	TPF × 2	DFHX	See (1)	3-year OS
SWOG/ECOG	Oropharynx	III– IV	Resectable**	TPF × 3*	P	Conventional	2-year OS
Dana Farber Cancer Center (PARADIGM)	All	III– IV	Both	TPF × 3	See (2)	See (3)	3-year OS
Spanish Head and Neck Cancer Cooperative Group	All	III– IV	Unresectable	TPF or PF × 3	P	Conventional	TTF
Italian multicenter trial	Oral cavity/oropharynx hypopharynx	III– IV	Inoperable	TPF × 3	PF × 2 or cetuximab	Conventional	3-year OS***

(1) Twice daily, day 1–5 every 14 days.

(2) CRT after IC: in case of PCR at primary site and CCR in lymph nodes: weekly carboplatin; otherwise: weekly D × 4; CRT alone arm: weekly P × 4.

(3) In case of PCR at primary site and CCR in lymph nodes: conventional radiation; otherwise and in concurrent chemoradiation alone arm: accelerated concomitant boost.

*Nonresponders after 1 cycle undergo surgery; **only T1-2, N1 excluded; ***a second primary endpoint is to compare the tolerability of CRT versus radiotherapy with cetuximab.

Abbreviations: T, docetaxel; P, cisplatin; F, fluorouracil; CCR, clinical complete response; PCR, pathological complete response; OS, overall survival; TTF, time to treatment failure; DFHX, docetaxel day 1–5, fluorouracil day 0–4, hydroxyurea day 0–4 every 14 days; CRT, concurrent chemoradiation; IC, induction chemotherapy.