Chemoradiotherapy of Laryngeal Cancers

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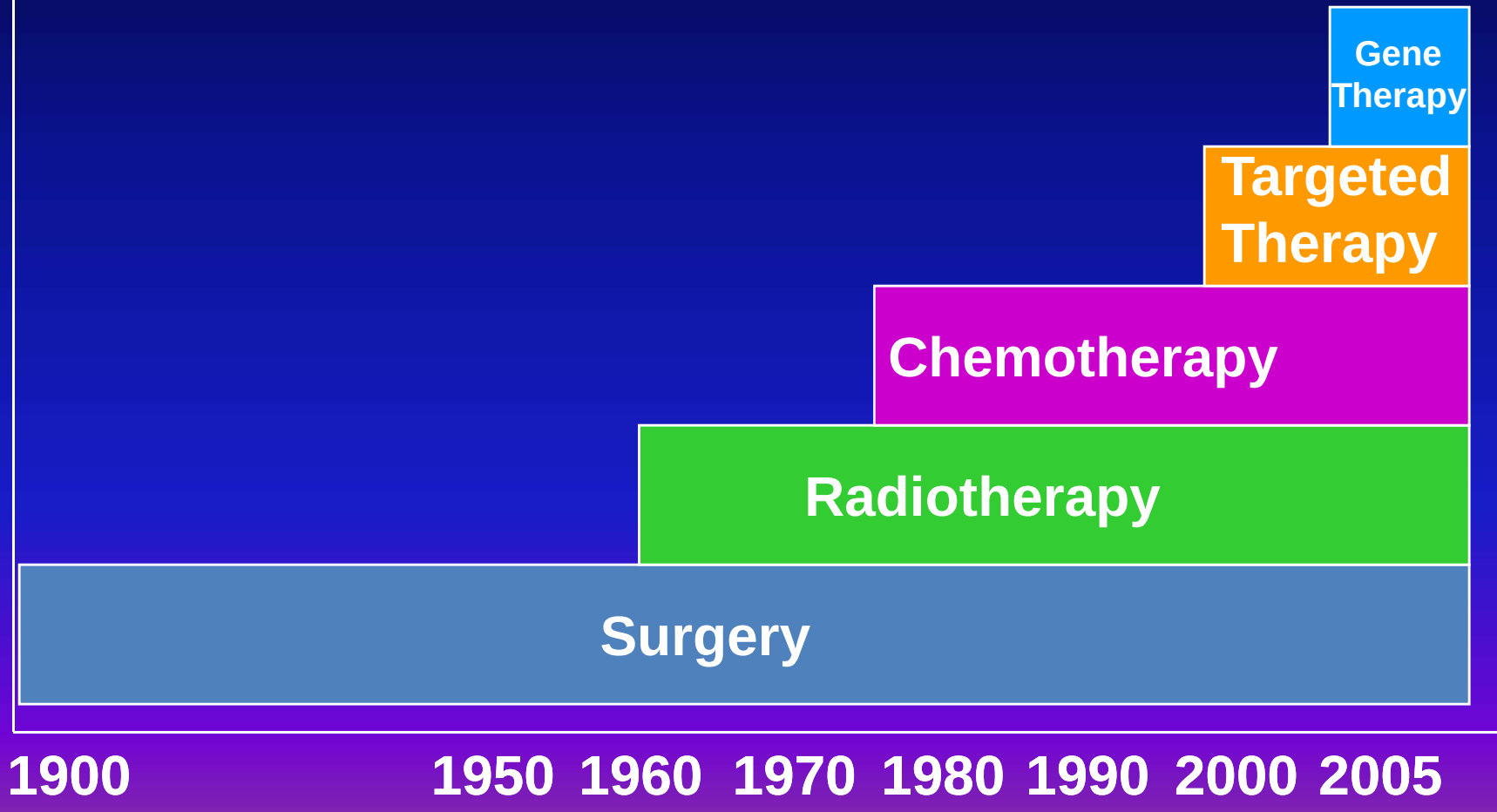
Development of Multimodal Therapy for Head & Neck Cancer



Multimodal Treatment Combinations

- RT → Surg
- Surg → RT
- RT → Surg → RT
- Surg → RT → Chemo
- Chemo → Surg → RT (± Chemo)
- Chemo → RT (± Chemo)
- Concurrent Chemo & RT
- Intraarterial Chemo
- Brachytherapy

Development of Multimodal Therapy for Head and Neck Cancer

Single modality treatments
Surgery – RT – Chemo Rx

Pre-operative radiotherapy

Post-operative radiotherapy

Induction chemotherapy with surgery + RT
Neoadjuvant chemo Rx
Organ preservation strategies
Concurrent chemo Rx & RT

Larymx

Larynx : Protective sphincter at the inlet of air passage.

Responsible for voice production.

Divided into-

Supraglottis –epiglottis,false cords,ventricle, arytenoids,aryepiglottic folds.

Glottis-true vocal cords , the ant.commisures.

Subglottis –below the vocal cords.

Situation and extent

- The larynx lies in the midline of the neck, extending from the root of the tongue to the trachea.
- In adult male it lies in front of the 3^{rd,} 4th 5th and 6th cervical vertebrae.
- In children and adult female it lies at a higher level.
- Length-44mm in males,36mm in females

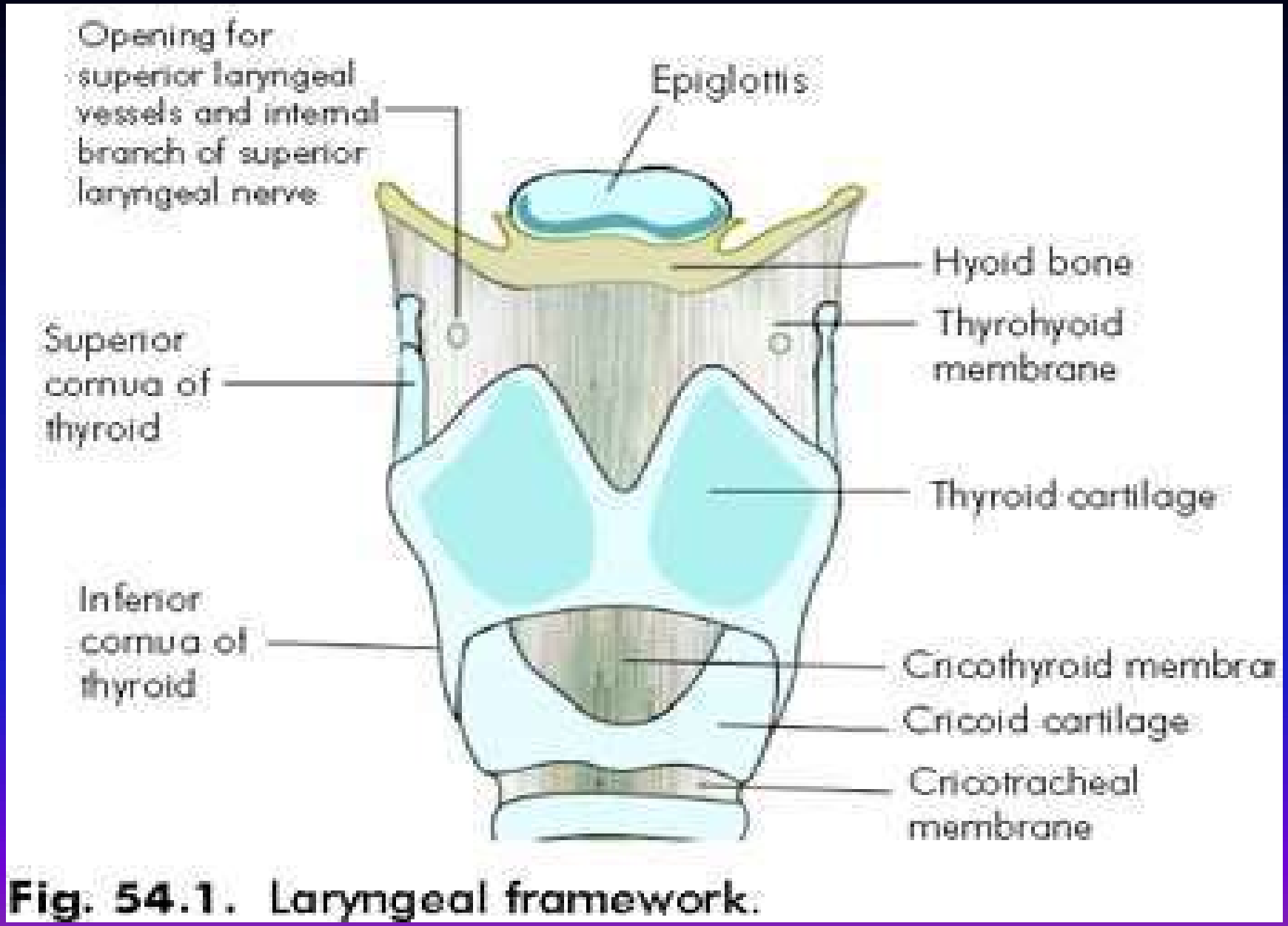


Fig. 54.1. Laryngeal framework.

Lymphatic drainage

- Supraglottis has a rich capillary lymphatic plexus.
- Pass through preepiglottic space and the thyrohyoid membrane and terminate mainly in the subdigastic nodes.
- Few drain to middle internal jugular nodes.
- Essentially no lymphatic capillary in the vocal cord.
- The subglottic area has few lymphatic capillaries.
- Lymphatic trunk pass through the cricothyroid membrane to the pretracheal (delphian) lymph node,some go to the paratracheal and inferior jugular nodes.

RADIOTHERAPY

- Primary treatment – typical dose 66Gy in 33 fractions over 6½ weeks
- Post-operative (adjuvant) – indications include close or involved resection margins, poorly differentiated tumours, extensive lymph node involvement
- Palliative e.g. bleeding, pain

Is there a survival benefit for combining CT with locoregional treatment of SCCHN?

- Meta-analysis of CT in head and neck cancer (MACH-NC)
- 87 trials: 17,858 patients

Timing of CT	Absolute benefit after 5 years
Adjuvant	-2%
Neoadjuvant	2%
Concomitant CRT*	8%
Total*	5%

*$p<0.0001$ for effect of CT + logoregional treatment vs logoregional treatment alone

Pignon JP, et al. Lancet 2000;355:949–955; Bourhis J, et al. ASCO 2004 (Abstract and presentation No. 5505)

Need for update of MACH-NC 2000

- The IPD meta-analyssis (63 trials) showed that chemotherapy improved survival (4% at 5 years) in patients curatively treated for HNSCC with a higher benefit (8%) with concomitant chemotherapy.
- However the heterogencity of the results limited the conclusions and prompted the group to confirm the results on a more complete database by adding the randomized trials conducted between 1994 and 2000.

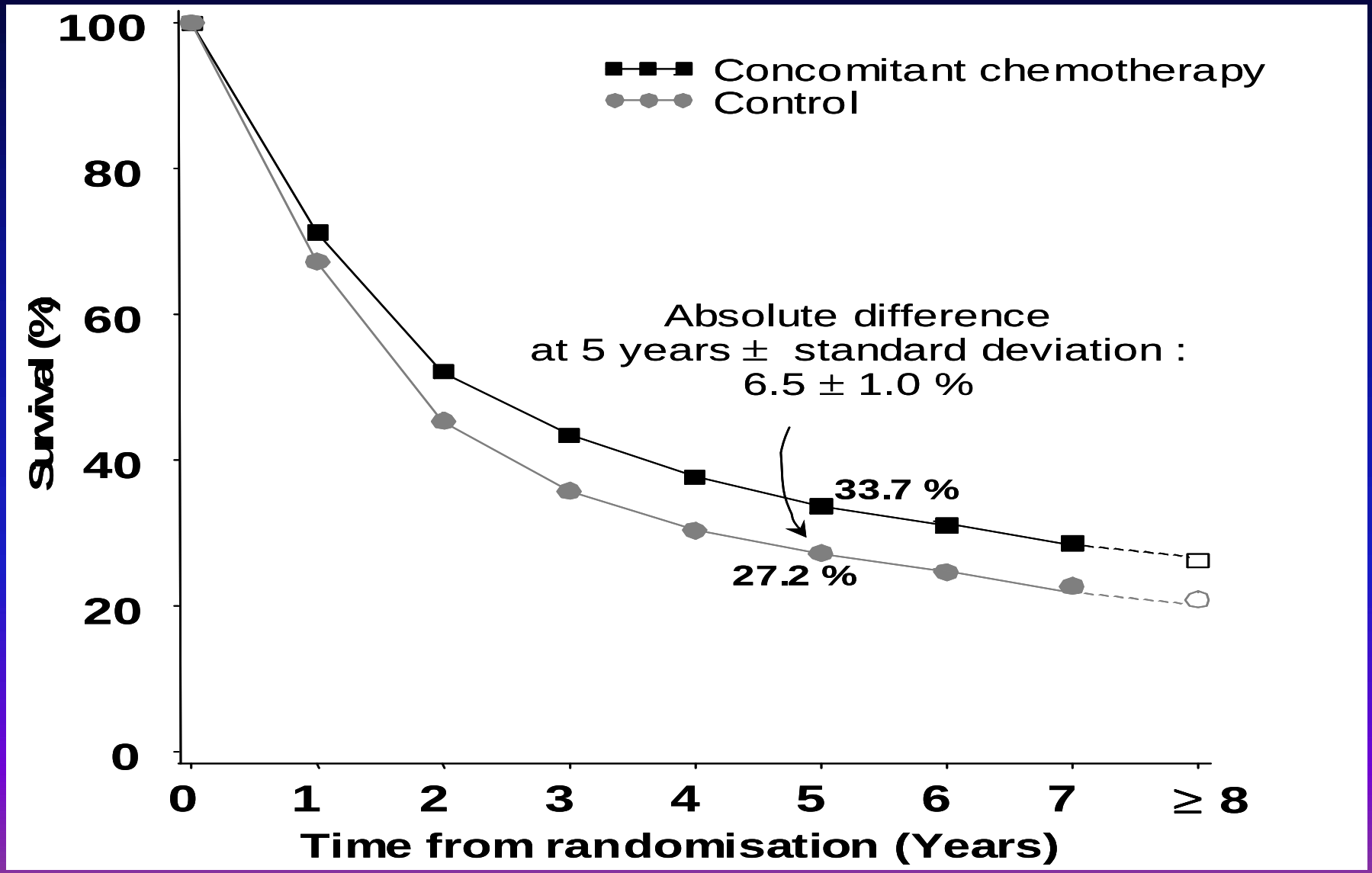
Methods
(MACH-NC 2009, Pignon et al)

- The updated IPD meta-analysis included trials comparing loco-regional treatment to loco-regional treatment + chemotherapy in HNSCC patients and conducted between 1965 and 2000
- The log rank-test, stratified by trial, was used to compare treatments
- The hazard ratios of death or relapse were calculated

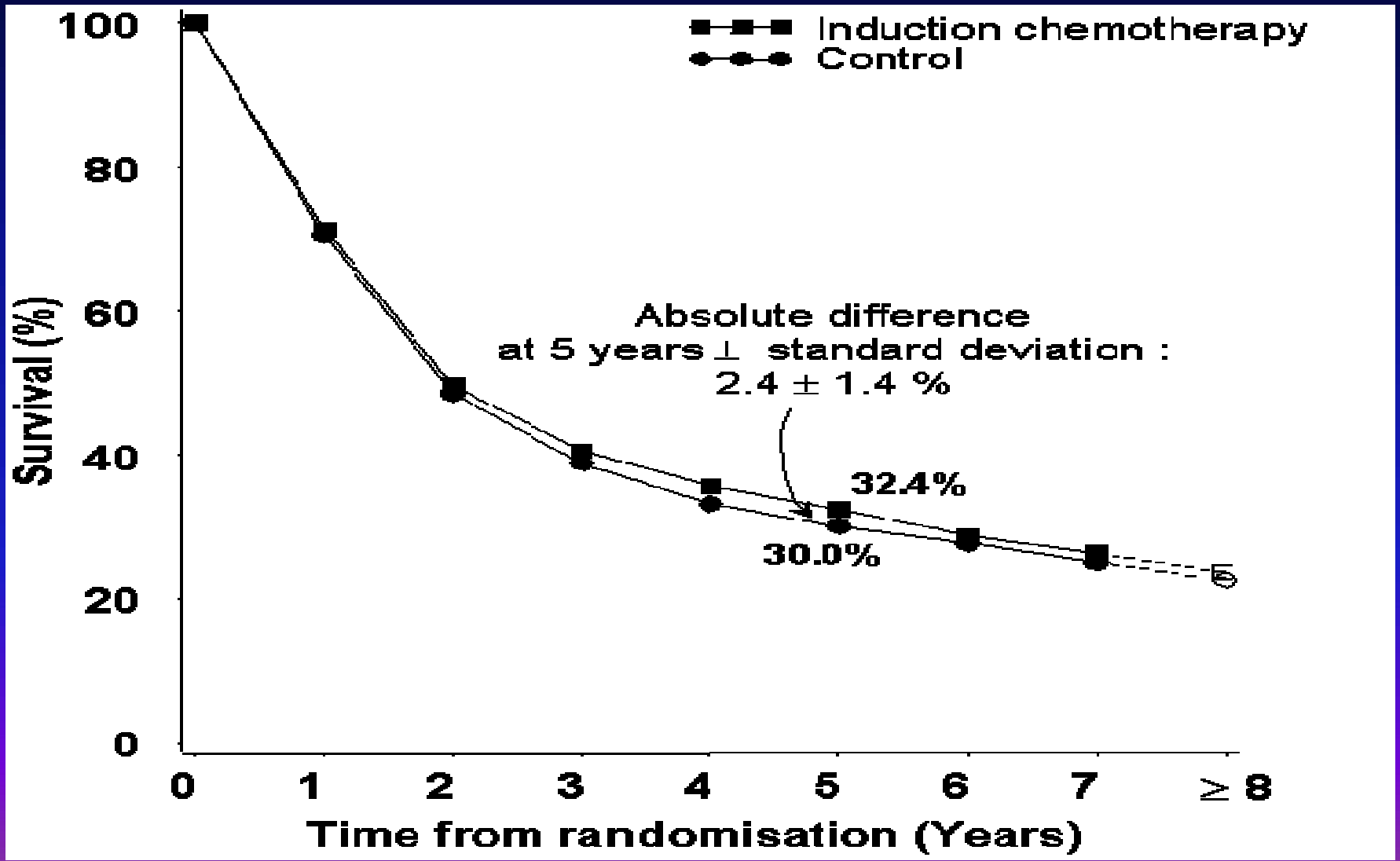
MACH-NC 2009: Results

- Absolute benefit of CT at 5 years: 6.5 %
- No difference between:
  - conventional vs. altered fractionation
  - Single agent vs. Multiple agent CT
- Decreasing effect of CT on survival with increasing age

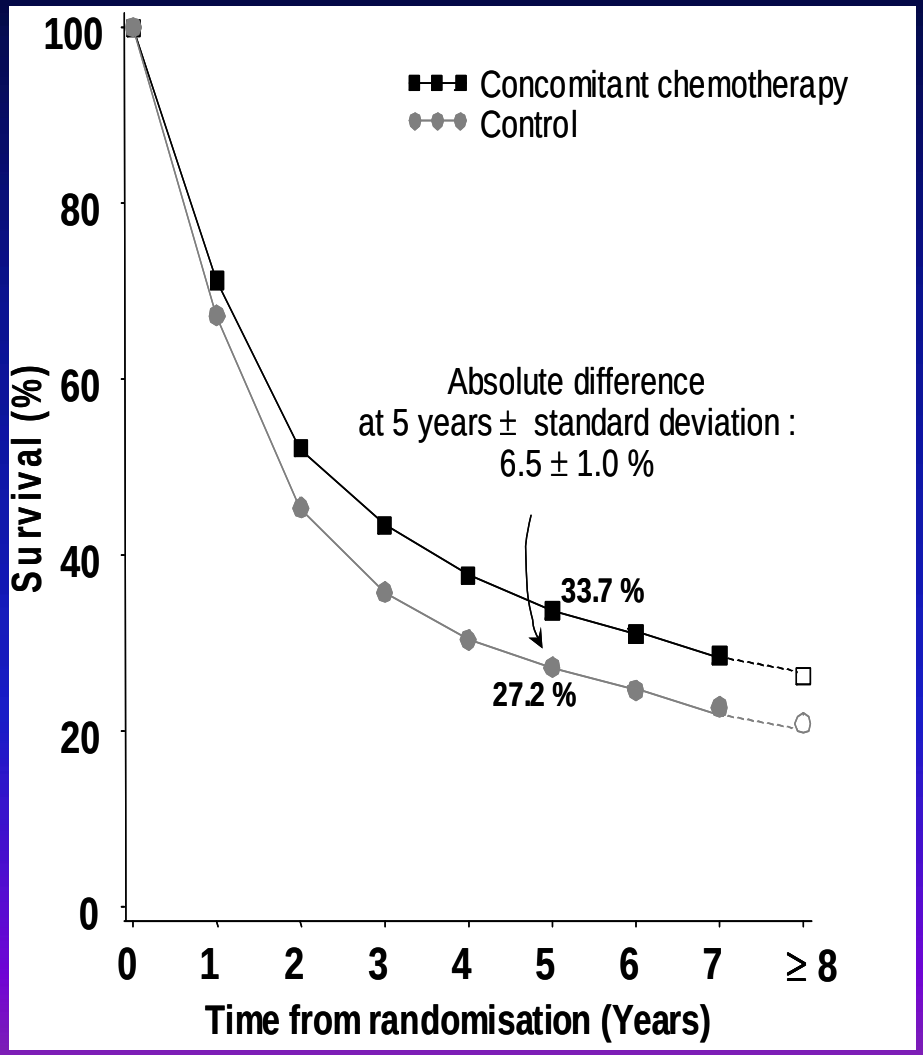
Overall survival
Concomitant chemotherapy

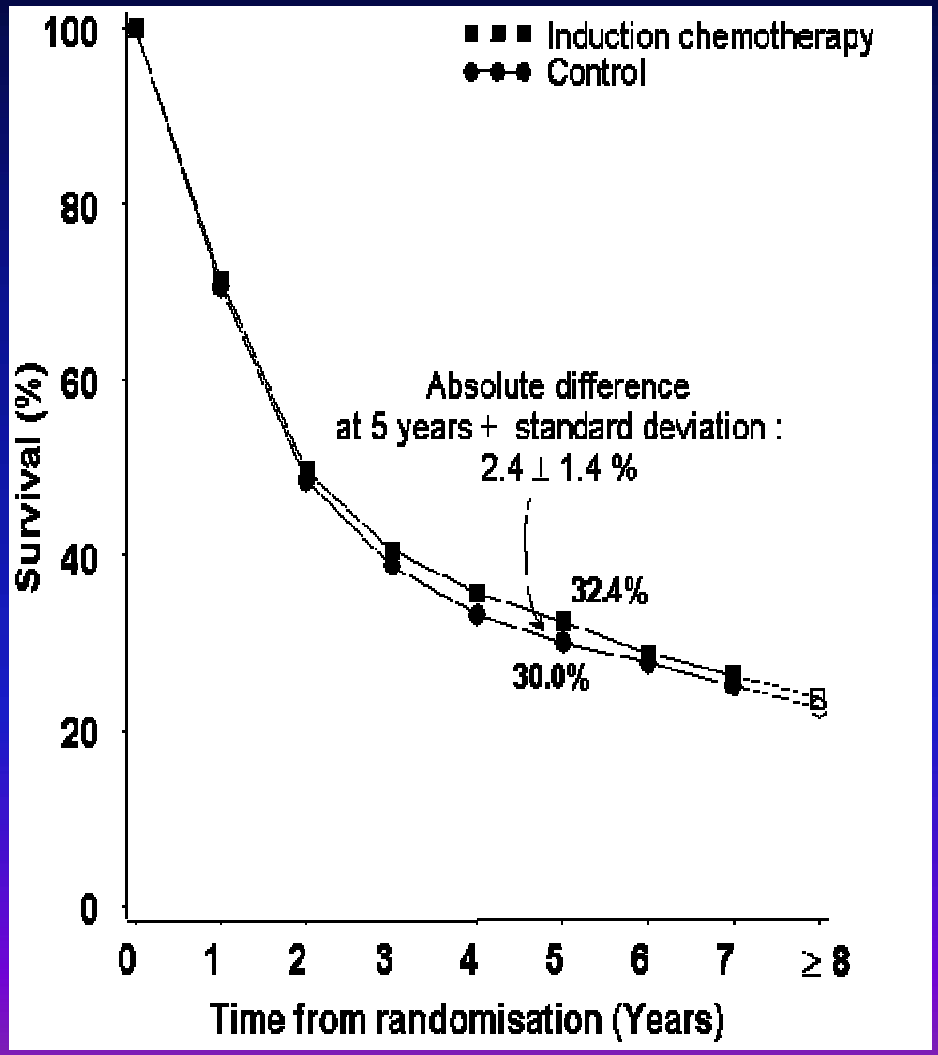


Overall survival -Induction chemotherapy

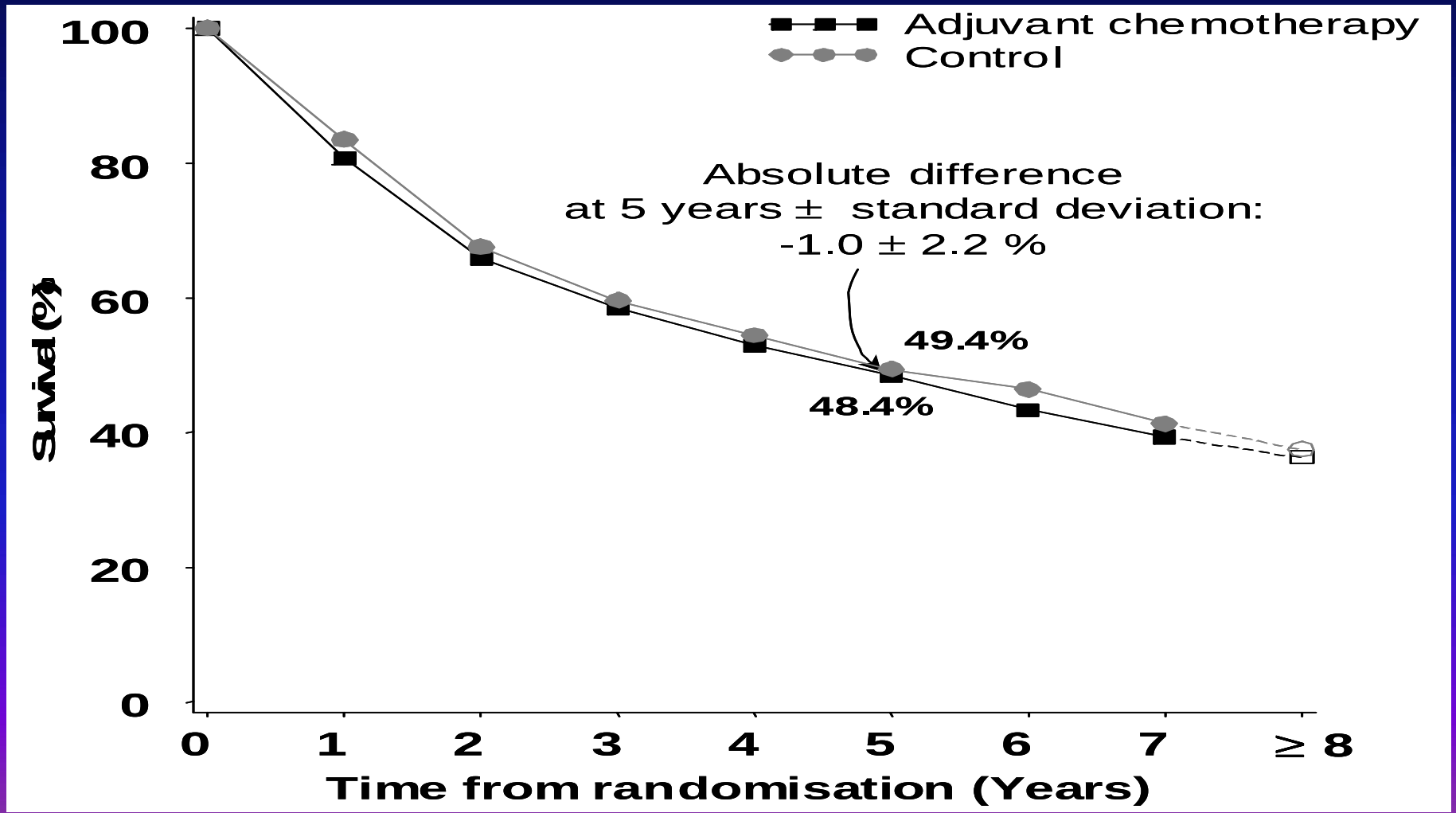


CCRT vs. Induction

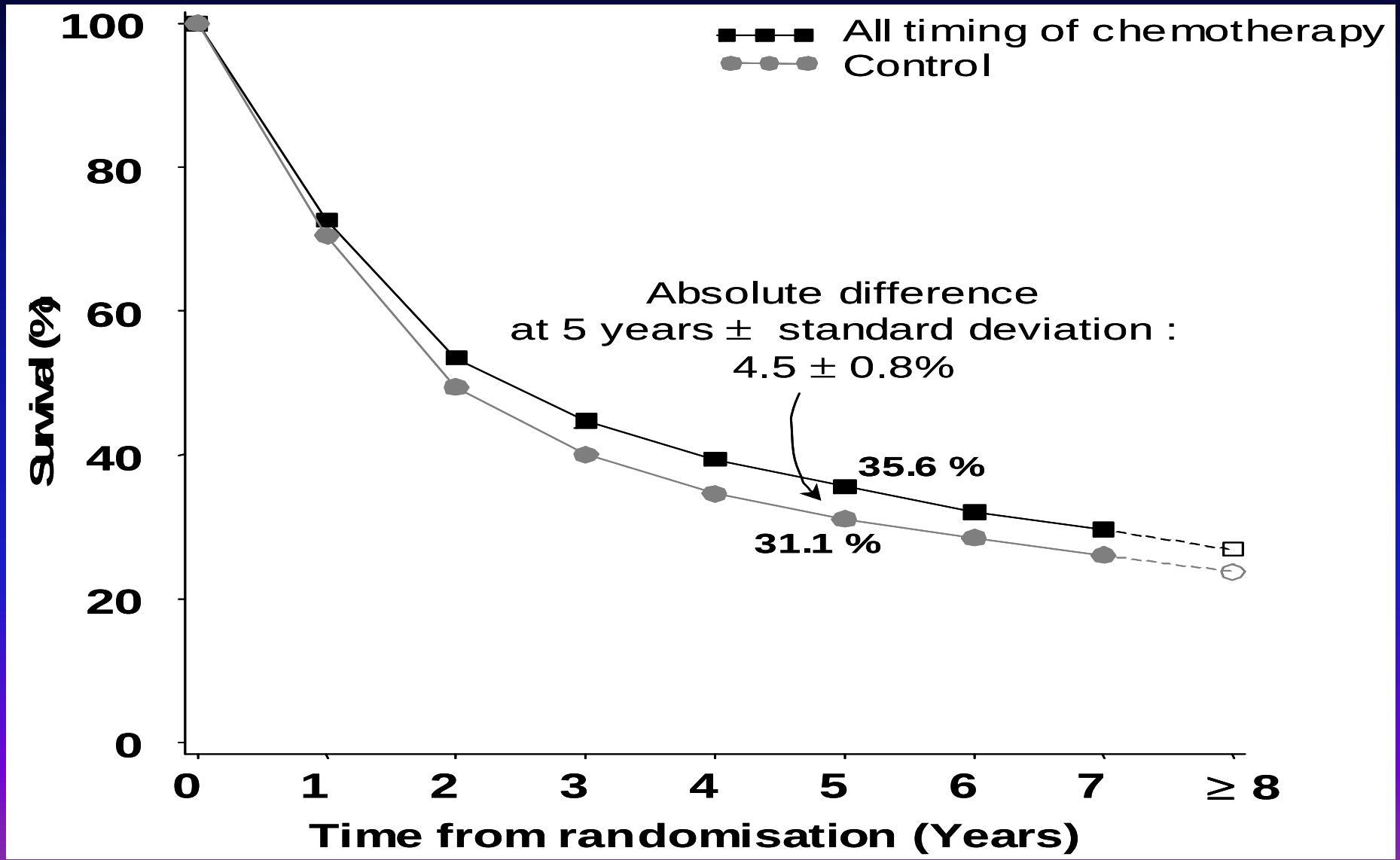




Overall survival -Adjuvant chemotherapy

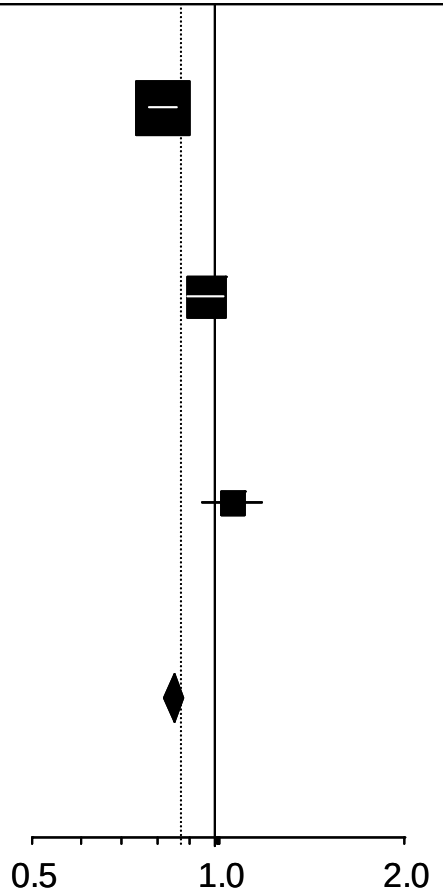


Overall Survival: All sequence of CT



Death: CCRT vs. RT alone

Timing	No. Deaths / No. Entered LRT+CT	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

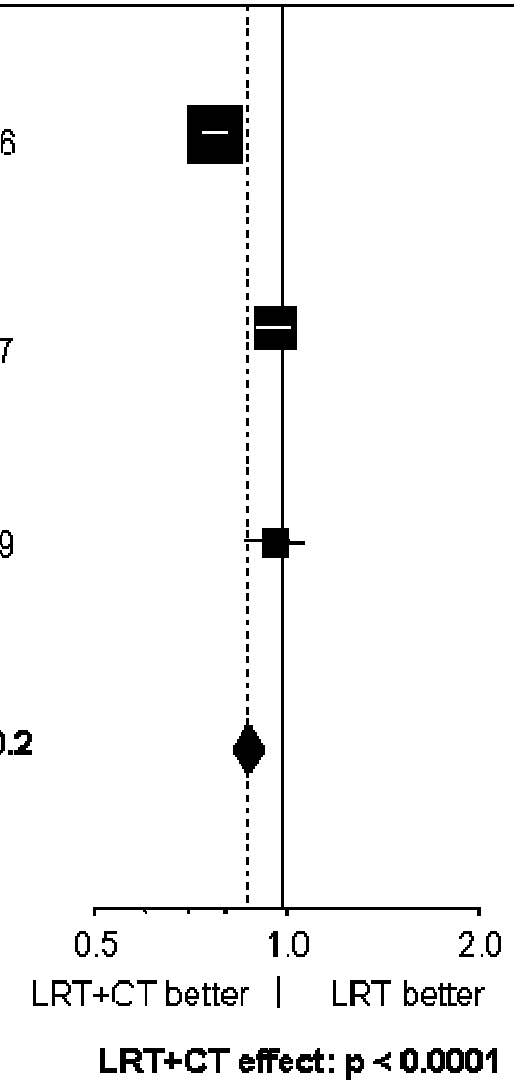
Test for interaction: $\chi^2_2 = 26.60$ p < 0.0001

$I^2 = 41\%$

LRT+CT effect: p < 0.0001

Recurrence: CCRT vs. RT alone

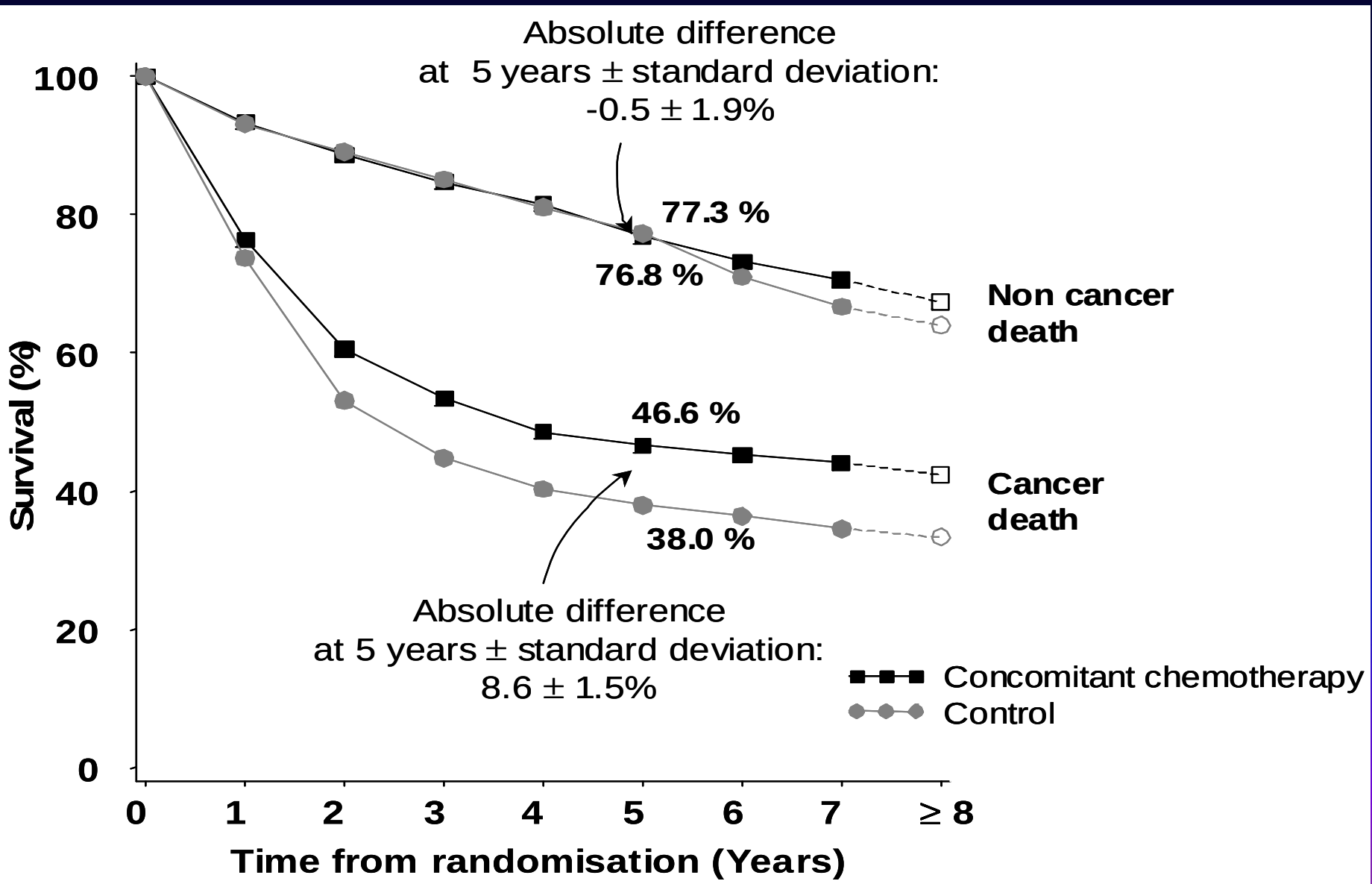
Timing	No. Deaths / No. Entered LRT+CT	LRT	O-E	Variance	Hazard Ratio	HR [95% CI]
Concomitant	3447/4824	3735/4791	-401.7	1742.6		0.79 [0.76;0.83]
Induction	2036/2740	1924/2571	-13.3	956.7		0.99 [0.93;1.05]
Adjuvant	703/1244	762/1323	-4.2	360.9		0.99 [0.89;1.10]
Total	**6186/8808**	**6421/8685**	**-419.3**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



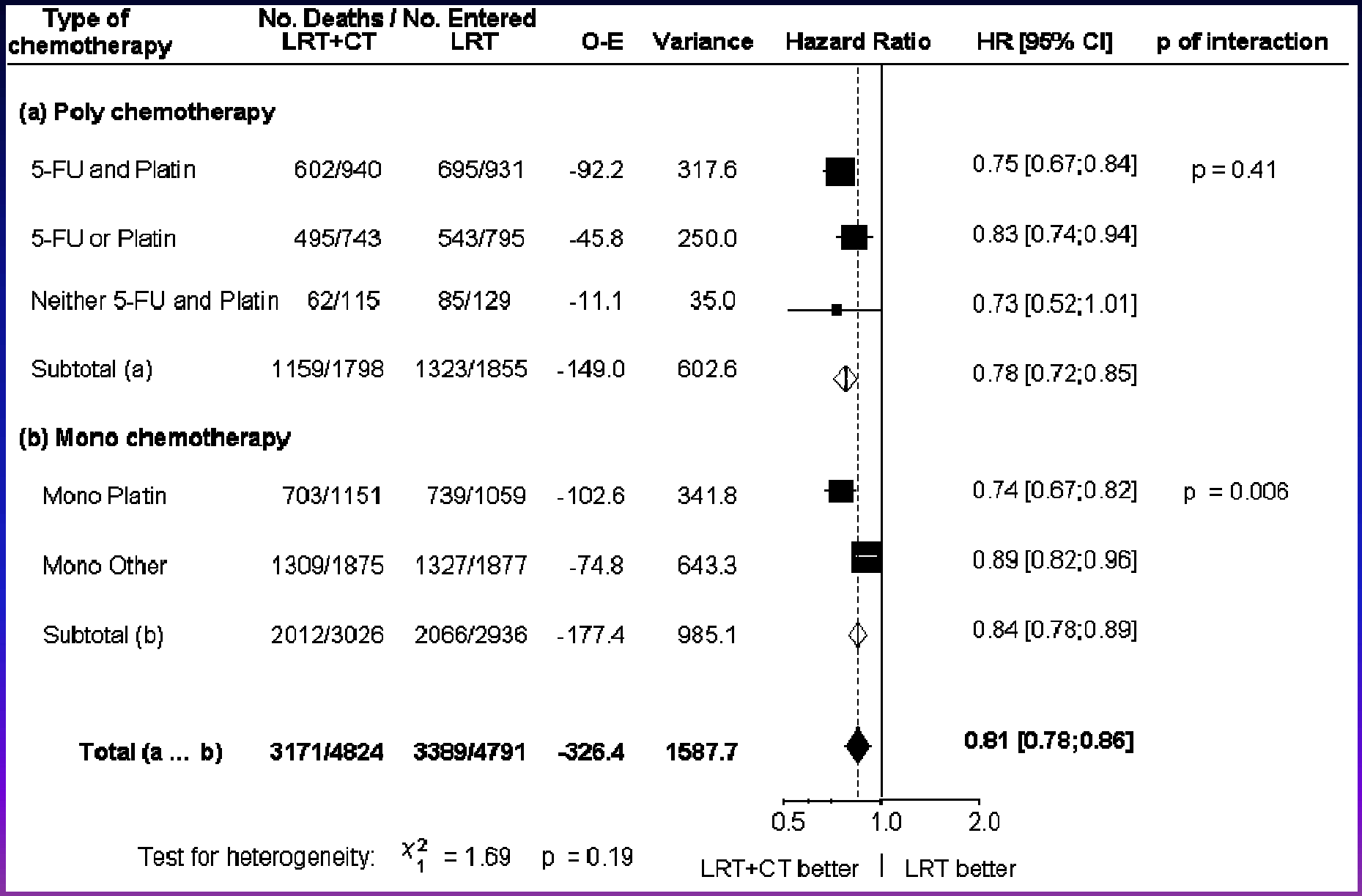
Test for heterogeneity: $\chi^2_{107} = 187.7$ p < 0.0001 $I^2 = 43\ \%$

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

Impact of CT on Cancer vs. Non-Cancer Deaths

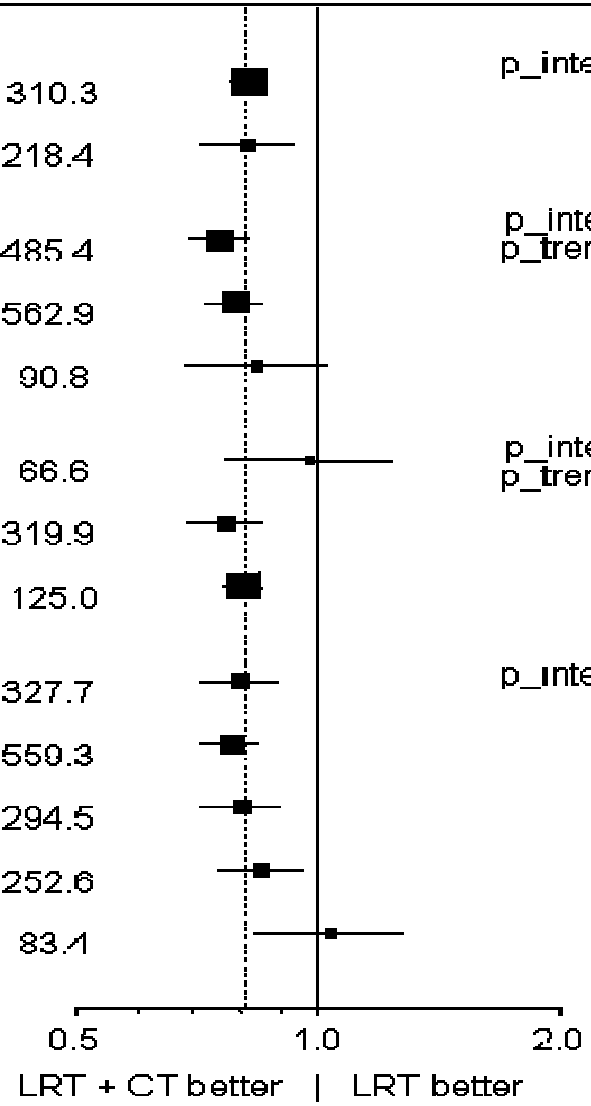


CT Drugs used: CCRT vs. RT alone



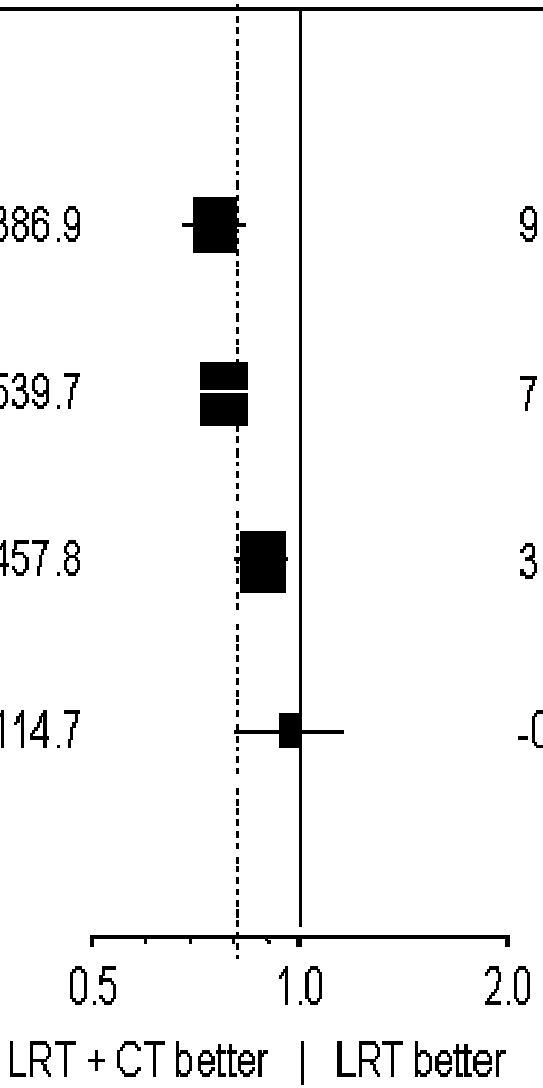
Patient Characteristics: CCRT vs. RT alone

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		p_inter = 0.95
Female	483/788	508/788	-44.1	218.4		
Performance status						
0	923/1667	1084/1696	-135.1	485.4		p_inter = 0.59
1	1210/1680	1179/1538	-131.8	562.9		p_trend = 0.31
2 or 3	220/279	218/274	-15.8	90.8		
Stage						
I-II	133/251	155/286	-1.5	66.6		p_inter = 0.20
III	661/1140	699/1094	-83.7	319.9		p_trend = 0.60
IV	2266/3266	2430/3261	-240.9	1125.0		
Site						
Oral cavity	680/997	754/1020	-72.8	327.7		p_inter = 0.16
Oropharynx	1123/1723	1219/1681	-138.3	550.3		
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	83.1		



Age: CCRT vs. RT alone

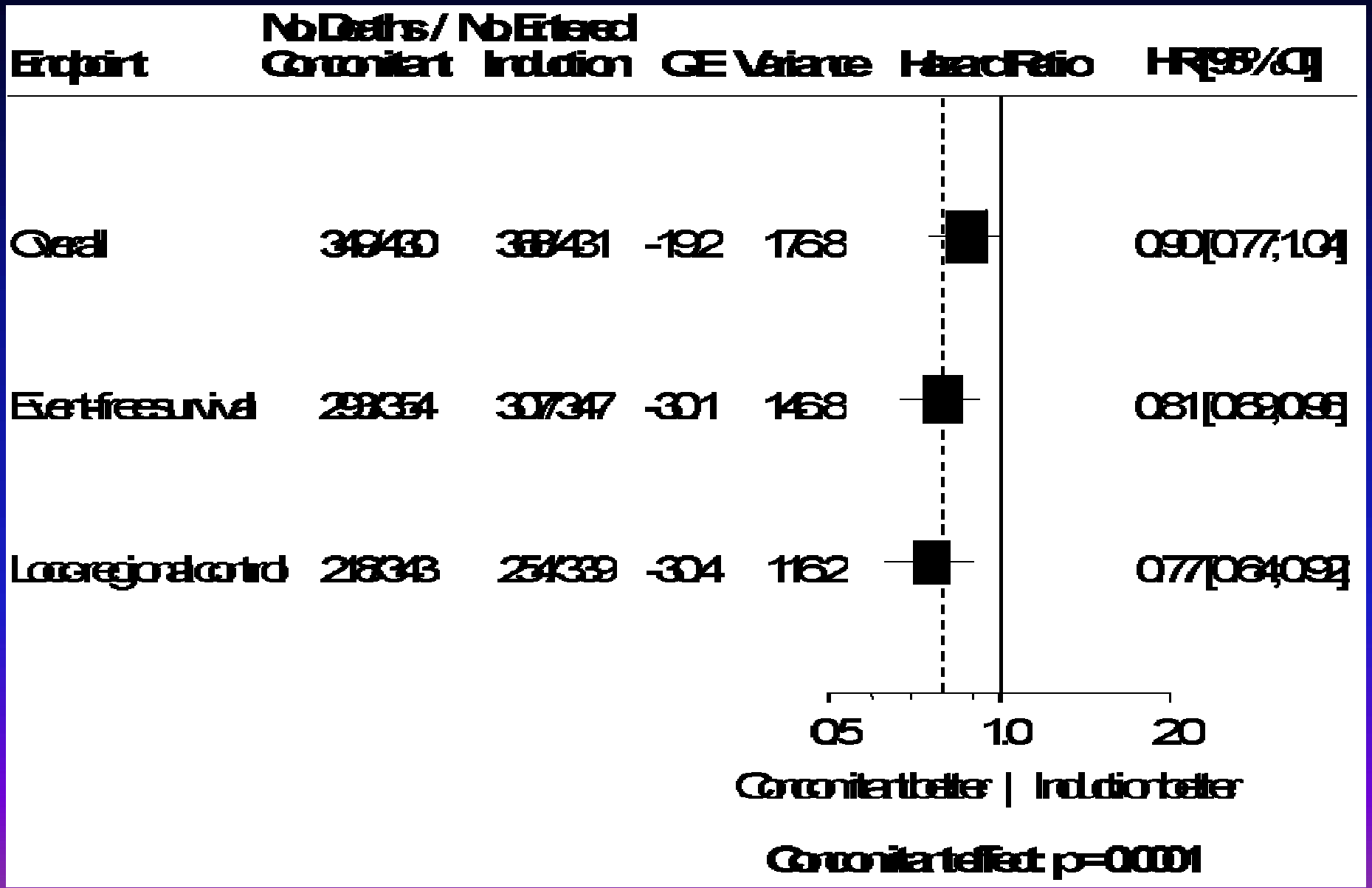
Category	No. Deaths / No. Entered LRT + CT	LRT	O-E	Variance	Hazard Ratio	Absolute difference at 5 years ± sd
Age						
Less than 50	803/1296	860/1288	-107.6	386.9		9.8 ± 2.1
51-60	1069/1645	1198/1661	-136.4	539.7		7.8 ± 1.8
61-70	972/1368	988/1330	-56.2	457.8		3.0 ± 1.9
71 or over	273/356	260/336	-3.5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



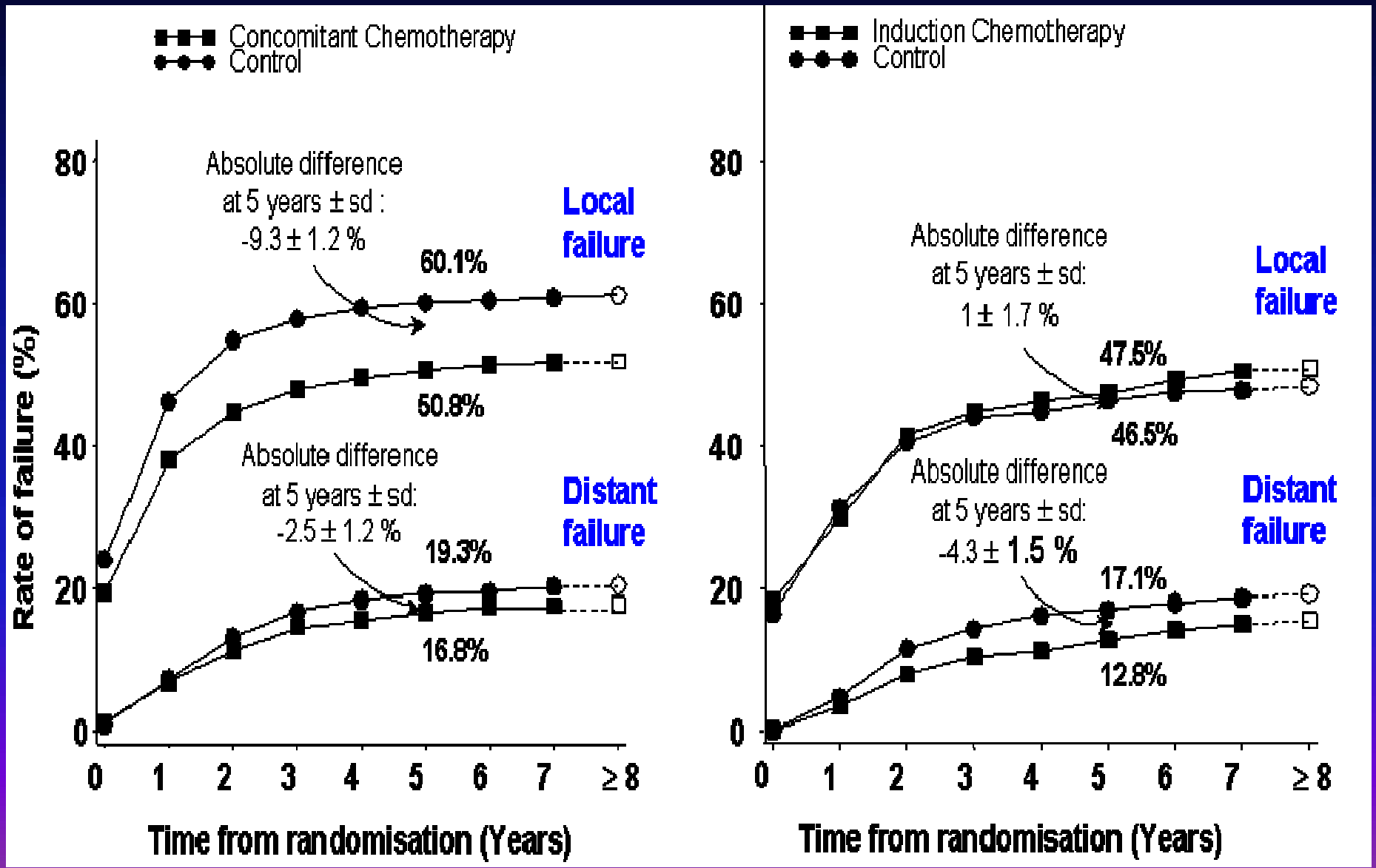
p_inter = 0.02

p_trend = 0.003

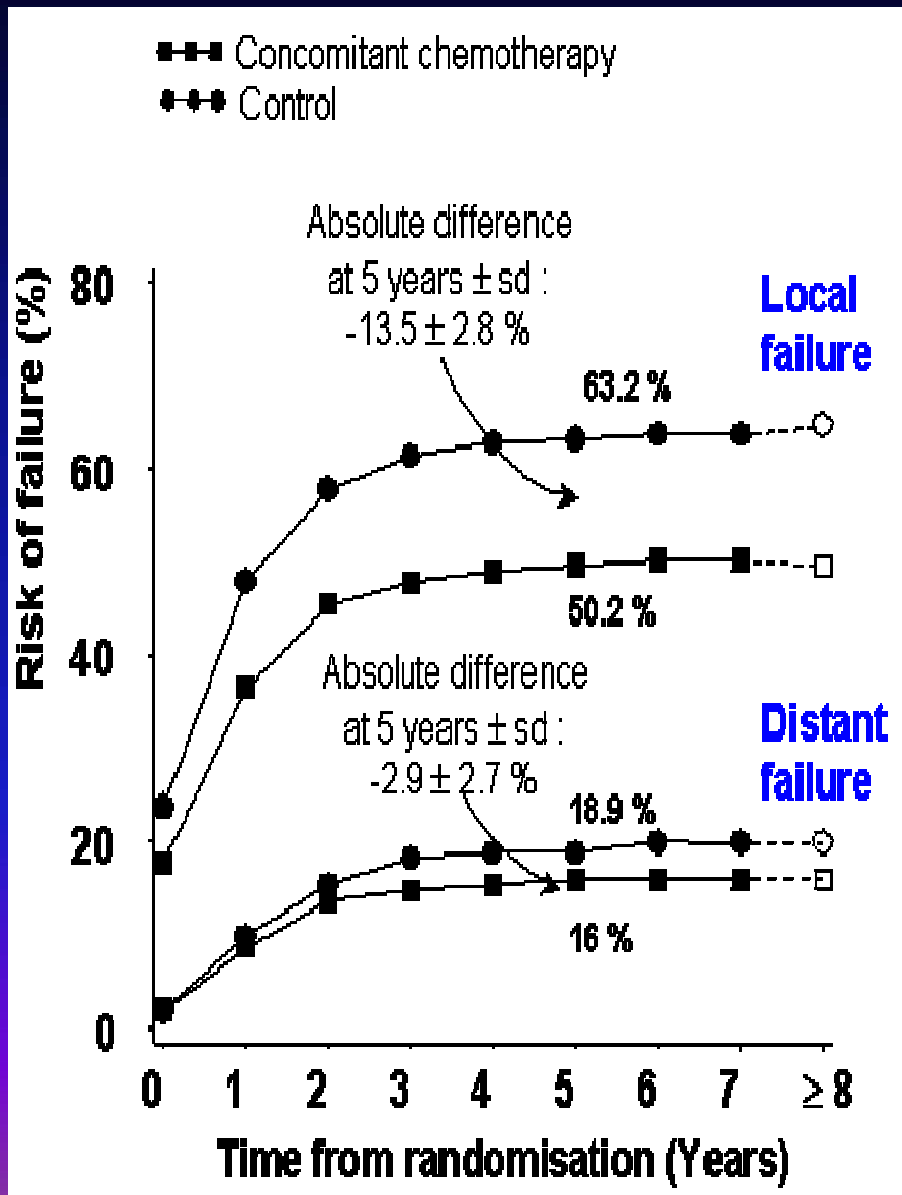
End Points

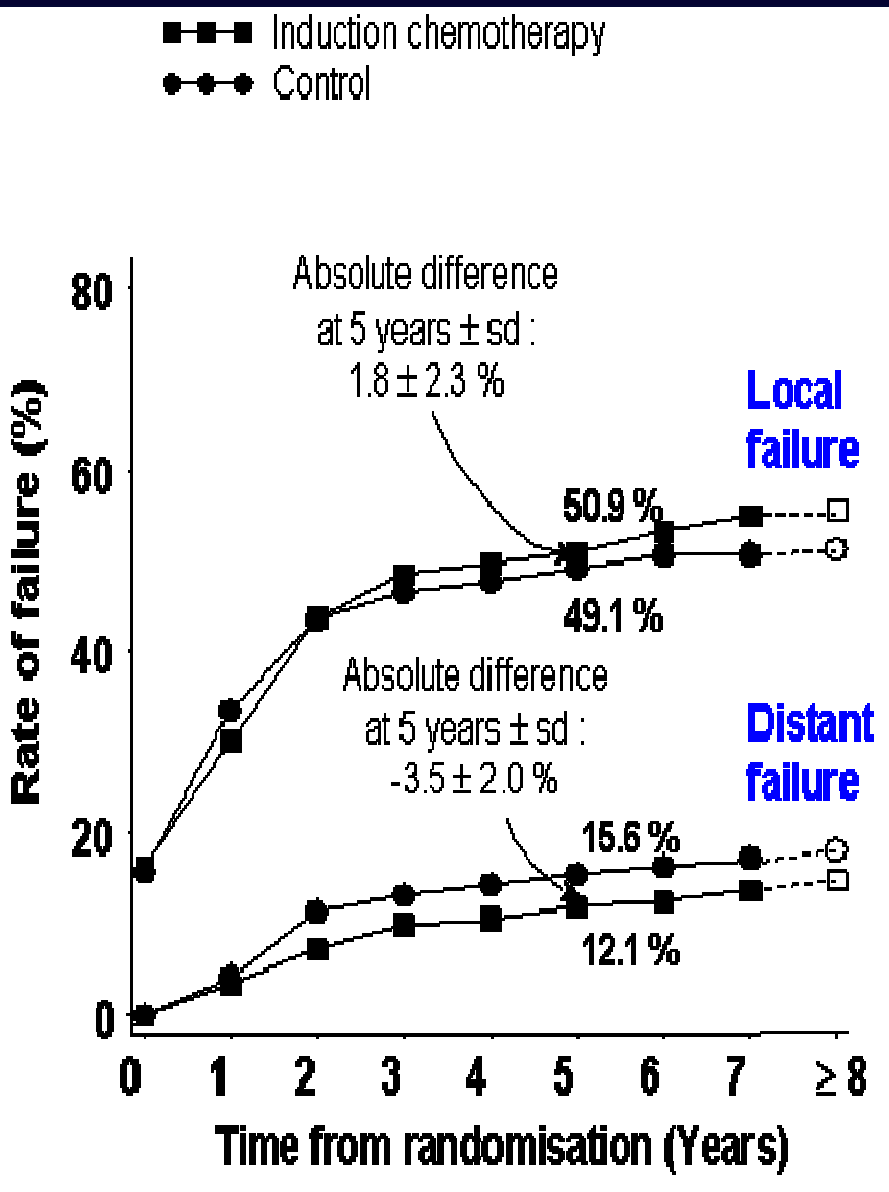

Endpoint
No Deaths/ No Entered
Concomitant Induction
GE Variance
Hazard Ratio
HR[95%CI]
Overall
349/430 388/431
-192
1768
0.90[0.77,1.04]
Event free survival
293/354 307/347
-301
1468
0.81[0.69,0.96]
Loco regional control
216/343 254/339
-304
1162
0.77[0.64,0.92]
0.5
1.0
2.0
Concomitant better | Induction better
Concomitant effect: p=0.0001

Failure Rates: CCRT vs. Induction



Failure Rates: CCRT vs. Induction: 5FU + Platinum





Outlook

- **This meta-analysis clearly demonstrates that Radiotherapy with PF chemotherapy can contribute substantial clinical benefit to the management of patients with locally advanced head and neck cancer.**
- **However, there remains considerable room for improvement, particularly in terms of long-term survival outcomes , treatment induced side effects /complications**

Concurrent chemoradiotherapy

CONCURRENT CHEMOTHERAPY

- Most commonly single agent Cisplatin for 2–3 doses if given every 3 weekly
- Pignon meta-analysis showed an 8% absolute survival benefit when chemo added to RT
- Several randomised trials in unresectable disease show significant improvement in local control and survival
- Regarded by most clinicians as the best time to give chemotherapy
- Increased toxicity (especially mucositis) means only suitable for fit patients

Sanchiz F et al.

859 pts, HNSCC stage III/IV

- Conventional RT — 60Gy/30fx, 2Gy/d
- HFxRT — 70.4Gy, 1.1Gy bid
- CCRT (conventional RT) — 5FU 250mg/m2, qod

Oral cavity	29%
Nasopharynx	11%
Hypopharynx	14%
Larynx	36%
Other	10%

	RR	10yr OS	10yr DFS
A: RT	67.8%	17%	17%
B: HFxRT	90%	40%	31%
C: CCRT	96.3%	42%	37%
p		<0.01(A v B) <0.01(A v C)	<0.01(A v B) <0.01(A v C)

Int J Radiat Oncol Biol Phys. 1990; 19: 1347-1350

Browman GP et al

175 pts, HNSCC T3/T4

CCRT

RT alone

Identical RT in both arms

RT: 60Gy/30fx, conventional

C/T: 5-FU 1200mg/m2/d, infusion D1-D3, D22-D24

Oral cavity	12%
Oropharynx	42%
Hypopharynx	14%
Larynx	27%
Other	5%

	Complete response	3yr PFS	3yr OS
CCRT	68%	40%	58%
RT	56%	30%	42%
p value	0.04	0.057	0.08

More mucositis, weight loss, and skin toxicity in CCRT arm

Journal of Clinical Oncology 1994; 12: 2648-2653

Aldelstein DJ et al

100 pts, HNSCC stage III/IV

RT alone

CCRT

RT: 66-72Gy, conventional, 1.8-2Gy/fx

Cisplatin: 20mg/m2/d
5FU: 1000mg/m2/d

Infusion,
D1-D4
D22-D25

Oral cavity	4%
Oropharynx	44%
Hypopharynx	16%
Larynx	36%

Residual dz
or recurrence

Primary site resection +/- neck dissection

5yr	OS	RFS	Dist. Mets-free survival	OS with primary site preserve	Local control without resection
RT	48%	51%	75%	34%	45%
CCRT	50%	62%	84%	42%	77%
p value	0.55	0.04	0.09	0.004	<0.001

→ Survival benefit from better local control

Cancer 2000; 88: 876-883

Aldelstein DJ et al

100 pts, HNSCC stage III/IV

RT alone

CCRT

RT: 66-72Gy, conventional, 1.8-2Gy/fx

Cisplatin: 20mg/m2/d
5FU: 1000mg/m2/d

Infusion,
D1-D4
D22-D25

Residual dz
or recurrence

Primary site resection +/- neck dissection

Oral cavity	4%
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CCRT	50%	62%	84%	42%	77%
p value	0.55	0.04	0.09	0.004	<0.001

→ Survival benefit from better local control

Cancer 2000; 88: 876-883

GORTEC

226 pts, oropharynx III/IV

- CCRT: Carbo 70mg/m2/d, D1-D4; 5FU 600mg/m2/d, D1-D4; q3w, 3 cycles
- RT alone: Identical RT in both arms; RT: 7000cGy/35fx, conventional

Dose delivery

	RT dose
RT	6920 cGy
CCRT	6960 cGy

	1st	2nd	3rd
Carbo	98%	86%	66%
5FU	98%	88%	67%

3yr	DFS	OS	Dist. mets	LR control
CCRT	31%	51%	11%	66%
RT	20%	42%	11%	42%
p value	0.04	0.02	NS	0.02

Journal of National Cancer Institute 1999; 91:2081-2086

Jeremic B et al, Japan

130 pts, HNSCC stage III/IV

- CCRT (HFxRT)
- HFxRT alone

Identical RT in both arms
RT: 77Gy/70fx/35d, 1.1Gy bid
C/T: 5FU 6mg/m2/d, 5days/wk

Oral cavity	21%
Oropharynx	37%
Hypopharynx	16%
Larynx	17%
Nasophaynx	9%

5yr	OS	PFS	Local recur.-PFS	Dist. Mets-PFS
CCRT	46%	41%	50%	86%
RT	25%	25%	36%	57%
p value	0.0075	0.0068	0.041	0.0013

Similar stomatitis, esophagitis in both arm,
more leukopenia and thrombocytopenia in CCRT arm

Journal of Clinical Oncology 2000; 18: 1458-1464

ECOG RTOG

295 pts, HNSCC unresectable III/IV

A: RT alone

RT: 7000cGy/35fx, conventional identical in three arms

B: CCRT

Cisplatin 100mg/m2, D1, D22, D43

C: CCRT (RT 3000cGy)

CR or unresectable

CCRT (RT 4000cGy)

PR

surgery

CCRT (RT 3000cGy)

Cisplatin 75mg/m2, D1
5FU 1000mg/m2/d x 4d

q4w x 3

Oral cavity	13%
Oropharynx	59%
Hypopharynx	19%
Larynx	9%

	3y OS	Dist. Mets as first site	Treatment compliance
A	23%	17.9%	92.6%
B	37%	21.8%	85.1%
C	27%	19.1%	73%
p	0.014 (A vs B)	NS	0.001(A vs C) 0.05(B vs C)

Journal of Clinical Oncology 2003; 21: 92-98

Taylor SG et al

RT 70Gy/35fx

215 pts, HNSCC stage III/IV, unresectable

C/T → RT (A) — Cisplatin 100mg/m2, D1; 5-FU 1000mg/m2, D1-D5 — Q3w x 3

CCRT (B) — Cisplatin 60mg/m2, D1; 5-FU 800mg/m2, D1-D5 — Qw x 7

Sinus	1%
Oral	32%
Oropharynx	23%
Nasopharynx	6%
Hypopharynx	27%
Larynx	11%

	LR recurrence	Dist Mets	3-yr OS	3-yr dz specific survival
A	55%	10%	36%	41%
B	41%	7%	42%	55%
			NS	p=0.011

	A	B
% Cisplatin	97%	88%
% 5-FU	97%	79%
% RT(>65Gy)	78%	81%
% RT delay	No difference	

Journal of Clinical Oncology 1994; 12: 385-395

Concurrent chemoradiotherapy

- Enhance locoregional control
- Minimal effect in distant metastasis
- Improve survival
  - Superior than sequential chemoradiotherapy
  - Disease nature: local recurrence predominant
- Enhance RT toxicity
  - Mucositis, skin toxicity, BW loss
  - Leukopenia depends on C/T type

Brockstein B et al

PFLI

Cisplatin 100mg/m2, D1
5FU 640mg/m2/d, CVI, D1-D5
Leucovorin 100mg q4h po, D1-D6
INF-α 2MU/m2/d, D1-D6

q3w

PFLI-FHX

164 pts → Induction C/T x 3 → CCRT

FHX

5FU 800mg/m2/d x 5/wk
Hydroxyurea 1000mg q12h, 11doses/wk
RT 6000cGy/30fx

(C/T)HF2X

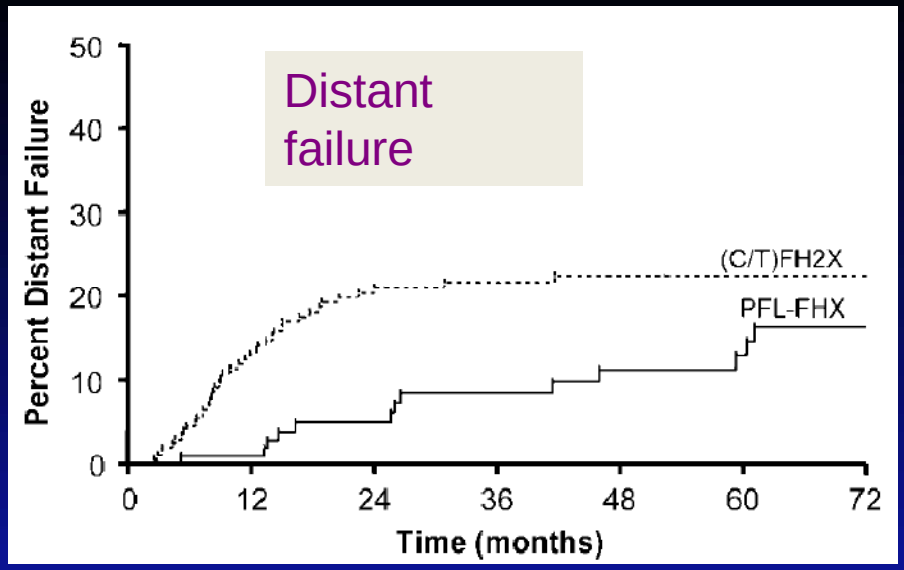
230 pts → Intensified CCRT

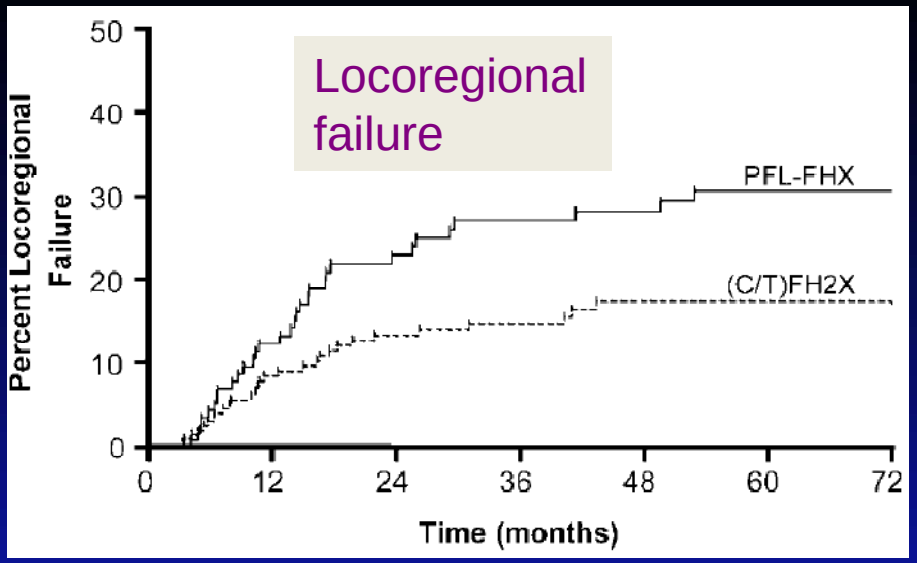
Cisplatin 100mg/m2, D1
or
Paclitaxel 100mg/m2, D1
q3w x 3

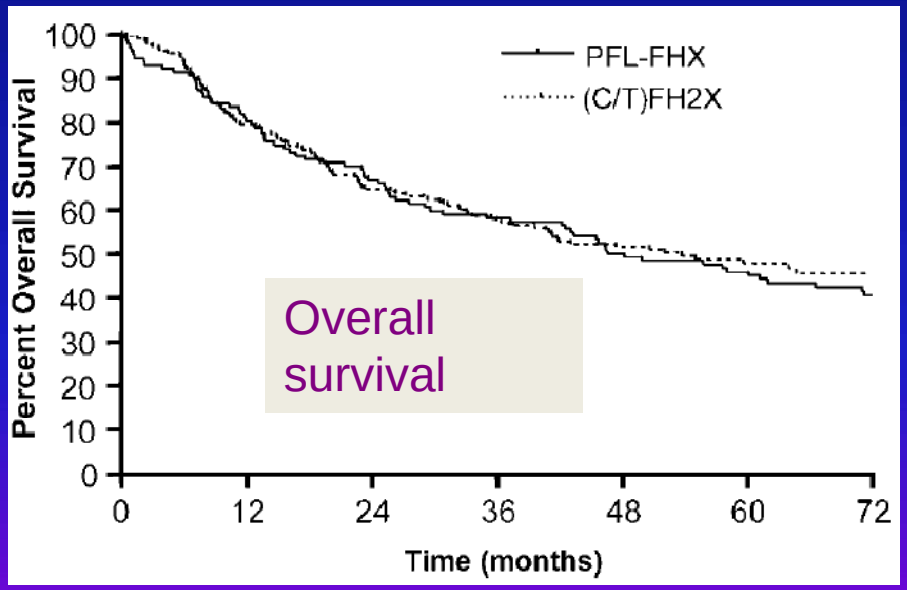
+

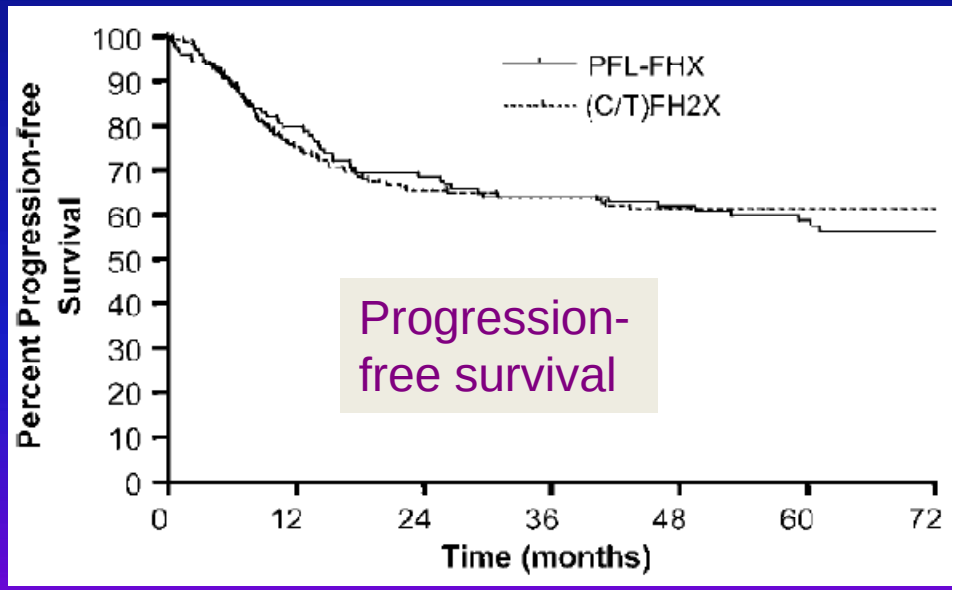
5FU 800mg/m2/d x 5/wk
Hydroxyurea 1000mg q12h, 11doses/wk
RT 6000cGy/30fx

J Clin Oncol. 1995; 13: 876-83
Annals of Oncology 2004; 15: 1179-1186









J Clin Oncol. 1995; 13: 876-83
Annals of Oncology 2004; 15: 1179-1186

Yale 6557 protocol

C/T: Cisplatin 20mg/m2/d x 4d
5FU 800mg/m2/d x 4d
LV 500mg/m2/d x 4d
q4w

CCRT:
RT: 70Gy/35fx
Cisplatin 100mg/m2, q3w

42 pts, HN cancer, stage III/IV resectable/unresectable → C/T x 2 → CCRT → Non-responder → operation

Hypopharynx	24%
Larynx	38%
NPC	9.5%
Tongue base	19%
Tonsil	7.5%
Unknown	9%

- Induction C/T: RR 76%
- C/T→CCRT: 67% CR

5y PFS	5y OS	2y Local control	2yr Distant control
54%	52.4%	76.3%	79%

Journal of Clinical Oncology 2004; 22: 3061-3069

SWOG

C/T: Cisplatin 100mg/m2
5FU 1000mg/m2/d x 5d
q3w

CCRT:
RT: 72Gy/36fx
Cisplatin 100mg/m2, q3w

59 pts, HN cancer,
resectable stage III/IV → C/T x 2 → CCRT → operation

C/T x 2 → Non-responder → operation

CCRT → Non-responder → operation

Hypopharynx	22 pts
Tongue base	37 pts

- Induction C/T: RR 78%
- C/T→CCRT: 54% CR

3y PFS	3y OS	3y PFS with Organ preservation
57%	64%	52%

Journal of Clinical Oncology 2005; 23: 88-95

Post-op CCRT

Risk factors of post-op recurrence

- Primary tumor
  - Positive or close margin
- Neck
  - Multiple LN: >2
  - Extracapsular extension
  - Perineural invasion
  - Vascular embolism
- Both locoregional and distant

Annals of Oncology 2004; 15: 1179-1186
Head and Neck 2000; 22: 680-686

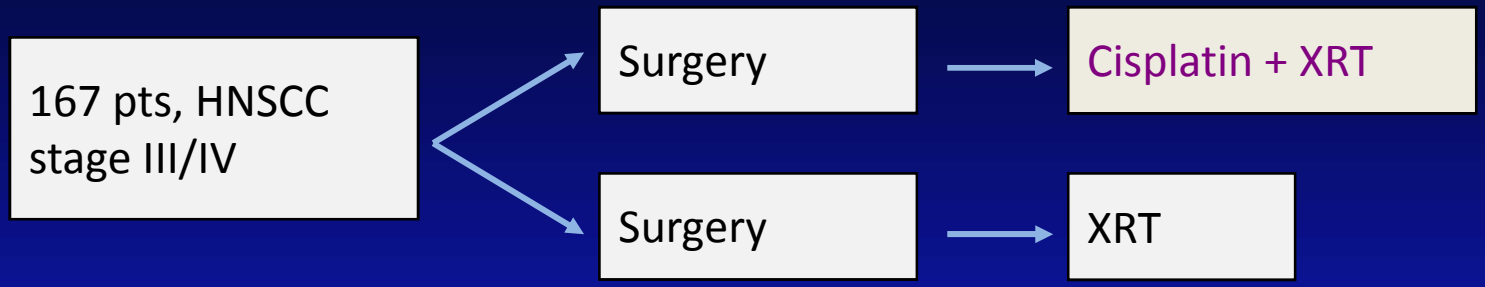
Adjuvant RT

- For possible residual disease
  - Positive margin or close margin
  - Multiple neck LN
- Attempt to decrease local failure
  - Decrease subsequent distant failure
- CCRT better than RT ?

Radiology 1970; 95: 185-188
Clinical Otolaryngology 1982; 7: 185-192
Head and Neck Surgery 1984; 6: 720-723
Head and Neck Surgery 1987; 10: 19-30

EORTC 22931

Cisplatin 100mg/m2, D1, D22, D43
XRT 54Gy/27fx, Boost 12Gy/6fx



pT3/T4 + any N
pT1/T2 + N2/N3
pT1/T2 + N0/N1 + unfavorable patho

	Margin	Perineural invasion	Extracapsular spread	Vascular embolism
Positive	28%	13%	57%	20%
Negative	71%	85%	43%	80%
Unknown	1%	2%		

Oral cavity	26%
Oropharynx	30%
Hypopharynx	20%
Larynx	22%
Unknown	1%

N Eng J Med 2004; 350: 1945-1952

EORTC 22931

	C/T on time without delay
1st	88%
2nd	66%
3rd	49%

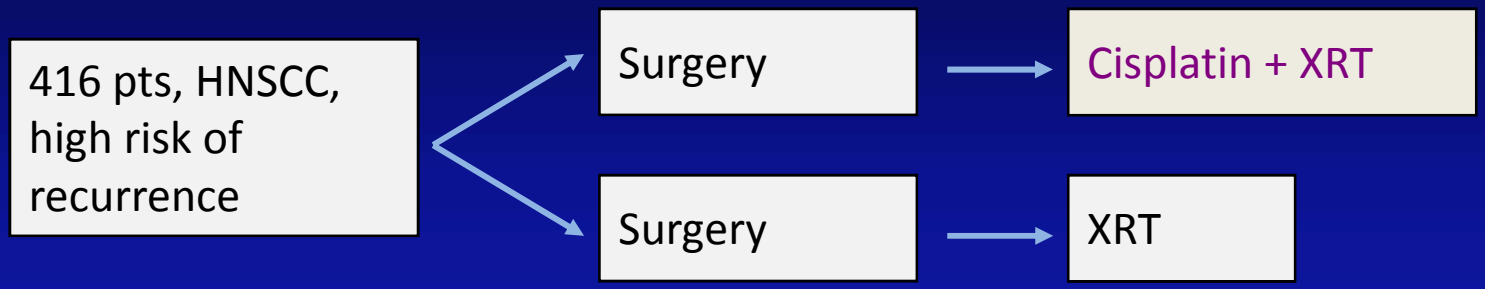
	5yr PFS	5yr OS	LRR	Dist Mets
CCRT	47%	53%	18%	21%
RT	36%	40%	31%	25%
p value	0.04	0.02	0.007	0.61

	Acute mucosa reaction	Mucosa fibrosis	Xerostomia	Severe leukopenia
CCRT	41%	10%	14%	16%
RT	21%	5%	20%	-
p value	0.001			

N Eng J Med 2004; 350: 1945-1952

RTOG 9501

Cisplatin 100mg/m2, D1, D22, D43
XRT 60Gy/30fx, Boost 6Gy/3fx



Positive margin	17%
LN>2 or extracapsular extension	83%

Oral cavity	27%
Oropharynx	42%
Hypopharynx	10%
Larynx	21%

N Eng J Med 2004; 350: 1937-1944

RTOG 9501

45.9 months follow-up time

	DFS	OS	LRR	Dist Mets as 1st event
CCRT	40%	52.5%	19%	23%
RT	30%	45%	30%	20%
p value	0.01	0.19	0.01	0.46

	Acute adverse effect	Late adverse effect
CCRT	77%	21%
RT	34%	17%
p value	0.001	0.29

hematological,
mucosa,
GI tract

N Eng J Med 2004; 350: 1937-1944

Post-op adjuvant CCRT

- Decrease locoregional recurrence
- Not affect distant metastasis
  - Though systemic side-effect
  - Insufficient dose delivery?
  - Single agent not enough?
- Actually improve survival
  - Locoregional recurrence dominant in HNSCC

Organ preservation

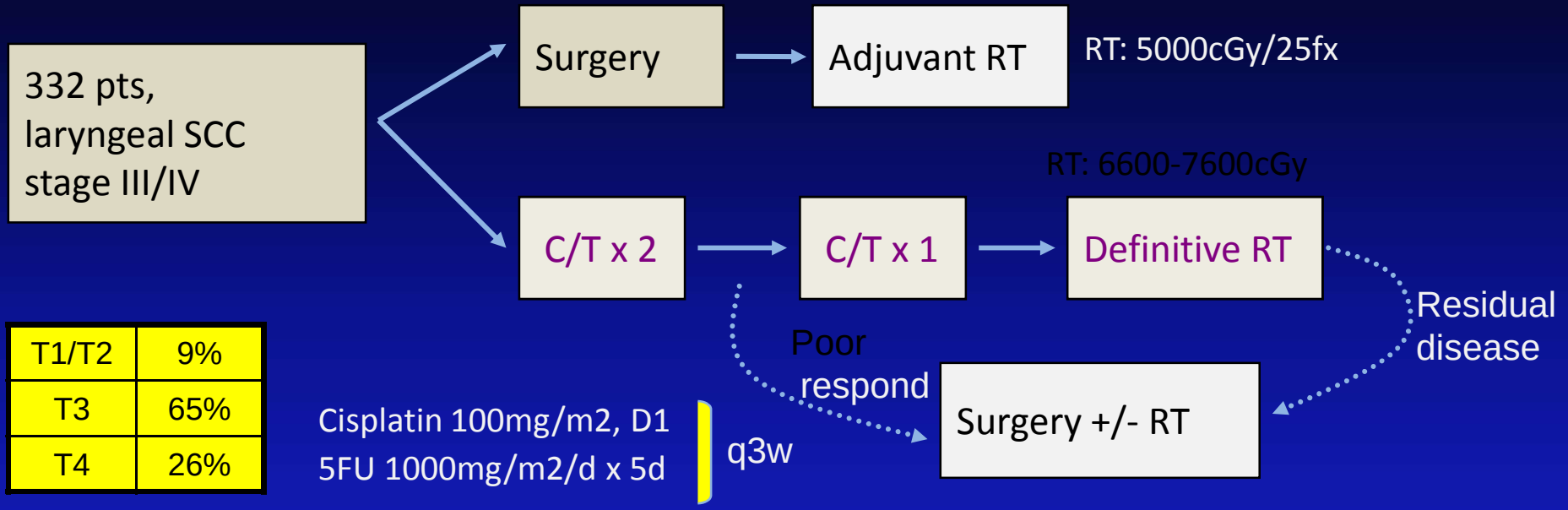
Organ Preservation

- Laryngeal cancer as an example
  - Supraglottic
  - Subglottic
    - T1: limited, not extend to glottis
    - T2: extend to glottis, but normal cord mobility
    - T3/T4: cord fixation, invade adjacent tissue
  - Glottic
    - T1a/b: limited to one/both sides, no cord fixation
    - T2: impair cord motility, to supra- or subglottis
    - T3/T4: cord fixation, invade adjacent tissue/organ

Laryngeal cancer

- Historically
  - Early: T1, T2
    - RT alone, surgical salvage, or
    - Surgical → adjuvant RT
    - Larynx usually preserved
  - Advance: T3, T4
    - RT alone not sufficient
    - Surgical resection, usually total laryngectomy

Veterans Affairs Laryngeal Cancer Study Group



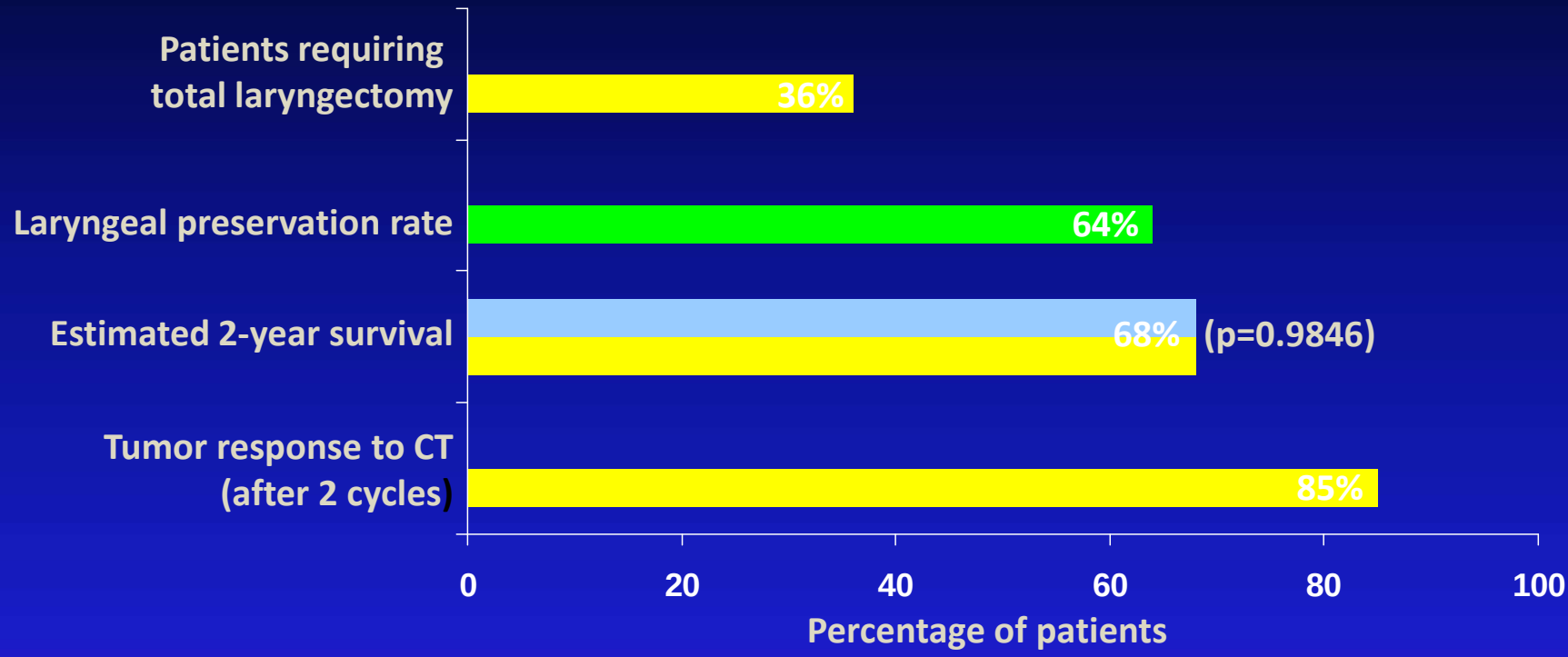
T1/T2	9%
T3	65%
T4	26%

Glottis	37%
Supraglottis	63%

2yr	DFS	OS	Recur at primary	Recur at regional	Distant mets	Laryngectomy-free survival
Surgery	75%	68%	2%	5%	17%	
C/T →RT	65%	68%	12%	8%	11%	39%
p value	0.12	0.98	0.001	NS	0.001	

New England Journal of Medicine 1991; 324: 1685-1690

VALSG study



- 2-year and 10-year follow up show significant difference in survival
- More local recurrences (p=0.0005) but fewer distant metastases (p=0.0016) in experimental arm

The Department of Veterans Affairs Laryngeal Cancer Study Group. N Engl J Med 1991;324:1685–1690

VALSG study

- **Laryngeal preservation achieved in 64% of patients in the CT arm**
- **Fewer distant metastases in the CT arm**
- **Overall survival rates for the two groups were similar, suggesting that chemotherapy could be used effectively for organ preservation without compromising overall survival.**

QOL assessment

- Veterans Affairs Laryngeal Cancer Study Group

- C/T → RT vs. Surgery → RT
  - "pain", "mental health", "bother "
- Laryngectomy vs. Laryngeal preserve
  - "pain", "mental health", "bother"
  - "role physical", "social function", "emotion", "response"
- No difference in speech and eating

Arch Otolaryngol Head Neck Srug 1998; 124: 964-971

EORTC

194 pts, hypopharynx SCC stage II/III/IV

Surgery → Adjuvant RT

RT: 5000cGy/25fx

C/T x 2 → C/T x 1 → Definitive RT

RT: 7000cGy

Residual disease

Poor respond → Surgery +/- RT

T2	20%
T3	75%
T4	5%

Cisplatin 100mg/m2, D1
5FU 1000mg/m2/d x 5d
q3w

Pyriform sinus	78%
Aryepiglottic fold	22%

5yr	DFS	OS	Recur at local	Recur at regional	Distant mets	Laryngectomy-free survival
Surgery	32%	35%	17%	23%	36%	
C/T →RT	25%	30%	12%	19%	25%	35%
p value	NS	NS	NS	NS	0.041	

Journal of National Cancer Institute 1996; 8: 890-899

GETTEC, French

68 pts,
laryngeal SCC
all T3

Surgery → Adjuvant RT — RT: 5000cGy/25fx

C/T x 3 → Definitive RT — RT: 7000cGy

Cisplatin 100mg/m2, D1
5FU 1000mg/m2/d x 5d
} q3w

Supraglottis	31%
Glottis	41%
Unknown	28%

	2yr DFS	2yr OS	8yr Laryngectomy-free survival
Surgery	78%	84%	
C/T →RT	62%	69%	42%
p value	0.02	0.006	

Inferior outcome !!

Oral Oncology 1998; 34: 224-228

RTOG 91-11

518 pts,
laryngeal SCC
III/IV

RT alone

CCRT

CCRT:
RT 7000cGy/35fx
Cisplatin 100mg/m2, q3w

C/T x 2 → C/T x 1 → RT

Residual disease

Cisplatin 100mg/m2, D1
5FU 1000mg/m2/d x 5d
q3w

Poor respond

Surgery +/- RT

T2	12%
T3	78%
T4	10%

Supraglottis	69%
Glottis	31%

0.02(C v A) 0.006(B v A)	NS	0.005(B v C) 0.001(B v A)	0.004(B v C) 0.001(B v A)	0.03(B v A)	Distant mets
A: RT	27%	56%	70%	56%	22%
B: CCRT	36%	54%	88%	78%	12%
C: C/T→RT	38%	55%	75%	61%	15%
p					

Speech/swallow : similar

New England Journal of Medicine 2003; 349: 2091-2098

Laryngeal preservation

- Chemoradiotherapy becomes standard
  - No negative survival impact, at most series
- Organ preserved, but function?
  - Fibrosis, choking, difficult speech
  - Reconstructed organ followed by rehabilitation
    - Function may be better
    - Loss of organ, psychological stress
- ASCO guideline
  - CRT for T3/T4 to preserve larynx (Aug. 2006)

CCRT, H&N, SJH*

PROTOCOL

• Arm I (Control)	Radiotherapy alone
• Arm II	RT+CDDP 70mg/m^2 D1&21
• Arm III	RT+CDDP 100mg/m^2 D1&21
• Arm IV	RT+CDDP 30mg/m^2 D1,8,15,21,28
• Arm V	RT+CDDP 70mg/m^2 D1&21
	+5FU 1000mg/m^2 D1,2,3 &21,22,23

*Kumar T Bhowmik, N Das, Rajiv Sharma, JS Bhatia, Daulat Singh, Shantanu Sharma, Vikas Madholia, Surbhi Gupta, A Safaya, VP Venkatachalam, Jyotsna Pandey et. al. 2000

PROTOCOL

- **Radiotherapy**
  - Cobalt 60, 80 cm SSD
  - Tumor dose 60-65Gy in 30-32 #
  - Portals reduced at 44Gy
- **Chemotherapy**
  - Cisplatin after adequate hydration and antiemetic therapy
  - 5FU in a 4hour infusion

CCRT, H&N, SJH

PATIENT CHARACTERISTICS

	CONTROL	RT+CDDP70 D1,21	RT+CDDP100 D1,21	RT+CDDP30 D1,8,15,21,28	RT+CDDP +5FU
ENROLLED	1800	749	350	498	528
EVALUABLE	1640	528	276	369	425
MALE	1476	475	248	332	386
FEMALE	164	53	28	67	39
MEAN AGE	52	54	51	53	52

CCRT, H&N, SJH

SITE OF LESION

	CONTROL	RT+CDDP70 D1,21	RT+CDDP100 D1,21	RT+CDDP30 D1,8,15,21,28	RT+CDDP +5FU
ORAL CAVITY	391	186	89	96	122
OROPHARYNX	429	197	104	162	171
LARYNX	436	195	106	159	158
HYPOPHARYNX	384	171	51	81	77

CCRT, H&N, SJH

RESULTS

	CONTROL	RT+CDDP70 D1,21	RT+CDDP100 D1,21	RT+CDDP30 D1,8,15,21,28	RT+CDDP +5FU
No.	1640	528	276	369	425
C.R.	161(10%)	132(25%)	71(26%)	114(31%)	127(30%)
P.R.	246(15%)	153(29%)	93(34%)	132(36%)	148(35%)
N.C.	230(14%)	105(20%)	55(20%)	55(15%)	63(15%)
P.D.	1003(61%)	138(26%)	57(20%)	68(18%)	87(20%)

CCRT, H&N, SJH

RESULTS Contd.

	CONTROL	RT+CDDP70 D1,21	RT+CDDP100 D1,21	RT+CDDP30 D1,8,15,21,28	RT+CDDP +5FU
Locoregional Control(%) (at 1 year)	42	55 P=0.05	62 P=0.01	73 P=0.005	77 P=0.001
Progression Free Survival(mo)	8.2	11.6 P=0.01	13.4 P=0.01	18.3 P=0.005	21.8 P=0.001
Actuarial Survival (2 years)	25%	40% P=0.01	45% P=0.005	60% P=0.001	62% P=0.001

CCRT, H&N, SJH

TOXICITIES (Grade III & IV)

	CONTROL	RT+CDDP70 D1,21	RT+CDDP100 D1,21	RT+CDDP30 D1,8,15,21,28	RT+CDDP +5FU
MUCOSITIS	820(50%)	316(60%)	179(65%)	258(70%)	297(70%)
NEUTROPENIA	33(2%)	53(10%)	41(15%)	73(20%)	106(25%)
NEPHRO-TOXICITY	0(0%)	0(0%)	0(0%)	18(5%)	42(10%)
TRT.INTURRPT. 0-7 DAYS 8-14 DAYS	 156(9%) 82(5%)	 26(5%) 11(2%)	 14(5%) 5(2%)	 37(10%) 55(15%)	 64(15%) 65(15%)

Conclusions

- Carcinoma of larynx has a very good control rates
- Both radiotherapy and surgery gives good results in early stages
- Combined modality treatment gives optimum results in advanced stages
- Presently the focus is on use of modalities with best cure rates and organ preservation

Thank You