Clinical aspects and implications of Chemo-radiation

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Radiation Oncology

Radiation : Major treatment modality for loco-regional disease control in cancer

Rate of failure is still high due to –

a) Large tumour size

b) Advanced stage of disease

Advances in Radiation Oncology

A. Technical innovations

Introduction of conformal radiation e.g. 3DCRT.IMRT ,IGRT or SBRT can deliver higher doses of radiation to tumour and lower doses to the normal tissues thereby increasing therapeutic ratio but little effect on local control and survival however decease in radiation morbidity

B. Modulation of biological response –

a) Altered fractionation regimens.

b) Chemo-radiation

i) Combined modality treatment by chemical and biological agents.

ii) Targeting molecular processes and signally pathways

Chemo - radiation

1. Chemo-radiation perhaps has strongest impact on cancer radiation therapy practice.

2. Chemo-radiation has become common treatment option in many clinical settings which is particularly true of concurrent chemo-radiation.

3. Chemo-radiation is superior to radiation alone for local control of disease and also for improving survival.

Biological basis of Chemo-radiation

1. Chemotherapy drugs reduces number of tumour cells by their cytotoxic activity.

2.Renders tumor cells more susceptible to radiation therapy – Radio sensitization effect.

3. By virtue of systemic activity of chemotherapy drugs, may act on distant metastasis.

4. Chemo-radiation enhances radiation response which gives better control of local disease

Goals of Chemo-radiation

1. To improve survival by improving local control.
2. To decrease or eliminate distant metastasis.
3. To preserve organ & tissue integrity as well as function.
4. To have independent toxicity.
5. To enhance tumour radio response.

Combinations of Chemo-radiation

1. Sequential Chemo radiation
2. Concurrent Chemo radiation
3. Concurrent Chemo radiation and adjuvant chemotherapy
4. Induction or Neo-adjuvant chemotherapy and Concurrent Chemo-radiation

Advantages and disadvantages of different combinations

Strategy	Advantages	Disadvantages
1.Sequential Chemo-radiation	•Least toxic •Maximize systemic therapy •Smaller radiation fields if induction shrinks tumour	•Increased treatment time •Lack of local synergy
2.Concurrent Chemo-radiation	•Shorter treatment time •Radiation enhancement	•Compromise systemic therapy •Increases toxicity •No cytoreduction of tumour
3.Concurrent Chemo-radiation & Adjuvant Chemotherapy	•Maximize systemic therapy •Radiation enhancement •Both local and distant therapy delivered upfront	•Increased toxicity •Increased treatment time •Difficulty to complete chemotherapy after chemo-radiation
4.Induction or Neo-adjuvant chemotherapy and concurrent chemo-radiation	•Maximize systemic therapy •Radiation enhancement	•Increased toxicity •Increased treatment time •Difficult to complete chemo-radiation after induction chemotherapy

Indications for Chemo-radiation

1. Lung cancer-SCLC & NSCLC
2. Head & Neck cancer
3. Carcinoma Cervix
4. Carcinoma urinary bladder
5. Carcinoma Anal Canal
6. Carcinoma Oesophagus
7. Carcinoma Rectum
8. Glioblastoma Multiforme

Drugs for Chemo-radiation

1. Platinum based drugs:
    a) Cisplatin
    b) Carboplatin
2. Taxanes:
    a) Paclitaxel
    b) Docetaxel
3. Mitomycin C
4. Antimetabolites:
    a) 5 –Flurouracil
    b) Methotrexate
    c) Gemcitabine
5. Topoisomerase:
    a) Irinotecan
    b)Topotecan

HEAD AND NECK

CHEMORADIATION IN CA NASOPHARYNX

- NPC is highly radiosensitive and chemosensitive tumour.
- High rate of local-regional failure and distant dissemination in advanced disease.
- 5-year survival rate **~35% for stage III-IV** disease with radiation therapy alone.
- Main objective of using chemotherapy in locally advanced NPC is to potentially enhance the radiation therapy local control rate and reduce the incidence of distant failure in high-risk patients.

"Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized INTERGROUP STUDY 0099".

Concurrent chemo-Rt**: **Cisplatin (100mg/m2)** on day 1, 22, 43{3 weekly} in + **RT (70Gy/35#)

followed by

***Adjuvant chemotherapy**: **Cisplatin (80mg/m2)** and **5FU(1gm/m2)** on days 71 ,99 and 127{3 weekly}*

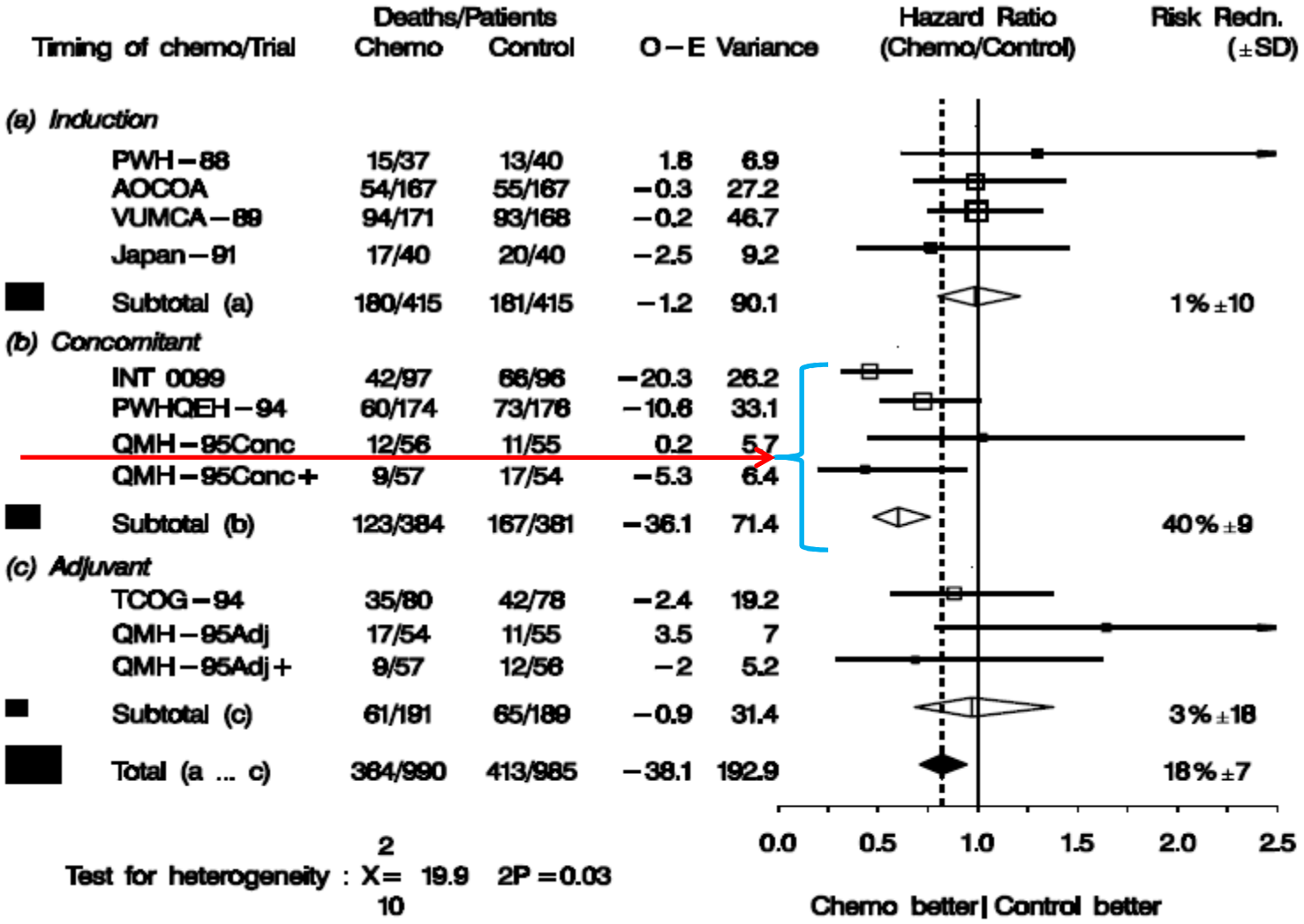
3-year survival rate for patients randomized to radiotherapy was 46%, and for the chemo-Rt group was 76% (P < .001)

Results of Chem-oradiation in Ca.Nasopharynx

	IGS-099, 1998	Lin et.al 2003	Chan 2005	Kwong 2004	Wee 2005	NPC-9901 2005
Patients	193	284	350	222	221	348
RT	70 Gys	70-74 Gys	66 Gys	62-68 Gys	70Gys	68Gys
CT-Cisplatin	100mg x3 3wks	80mg-x2 4wks	40mgx6-8 weekly	Weekly 6-7	25mg d1-4 weekly	100mgx3 3wks
Adjuvant CT	3 cycles	-	-	3cycles	3 cycles	3 cycles
Local control-%	-	89 vs 73	NS	80 vs 72	87 vs 70	92 vs 82
D.F.S. -%	58 vs 29	72 vs 53	60 VS 52	69 vs 58	72 vs 53	72 vs 62
O.S.-%	67 vs 37	72 vs 53	70 vs 59	87 vs 77	80 vs 65	78 vs 78

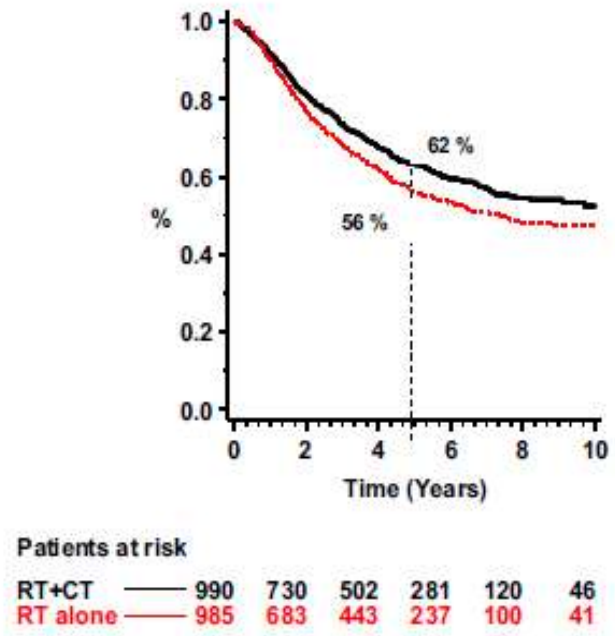
Meta analysis of chemotherapy with radiation in ca nasopharynx

Concurrent chemotherapy showed maximum benefit



❖Absolute survival benefit of 6% at 5 yrs.

❖Concomitant trials showed a better treatment effect than induction trials or adjuvant trials.



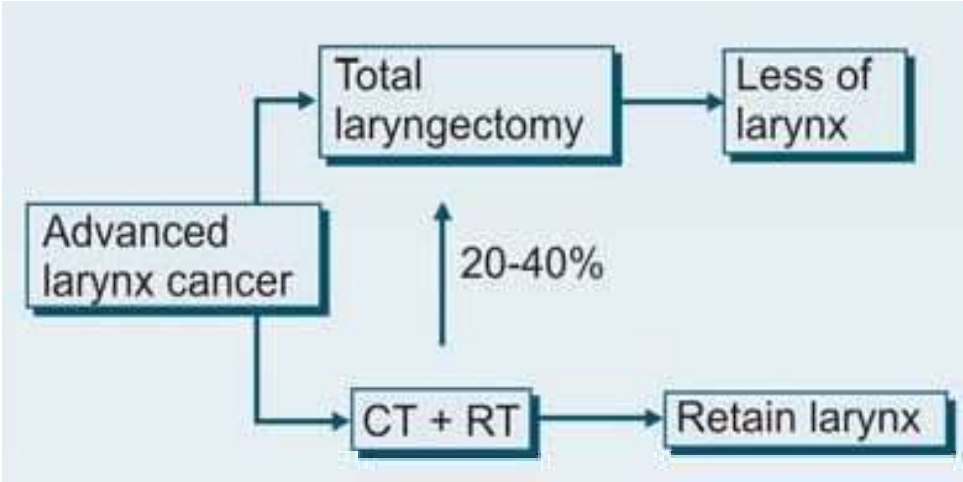
KAPLAN MEIER CURVES SHOWING OVERALL SURVIVAL

CONCLUSION:

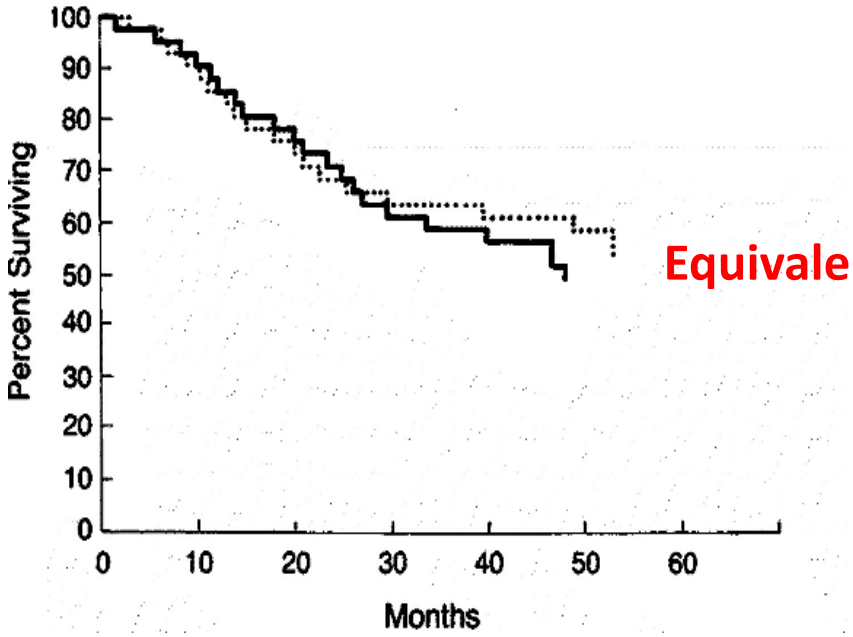
"The addition of chemotherapy to standard RT provides a small, but significant, survival benefit in patients with ca nasopharynx and hence chemoradiation is the standard of care."

Veterans Affairs Laryngeal Cancer Study Group (N Engl J Med. 1991)

n=332



64% retain larynx

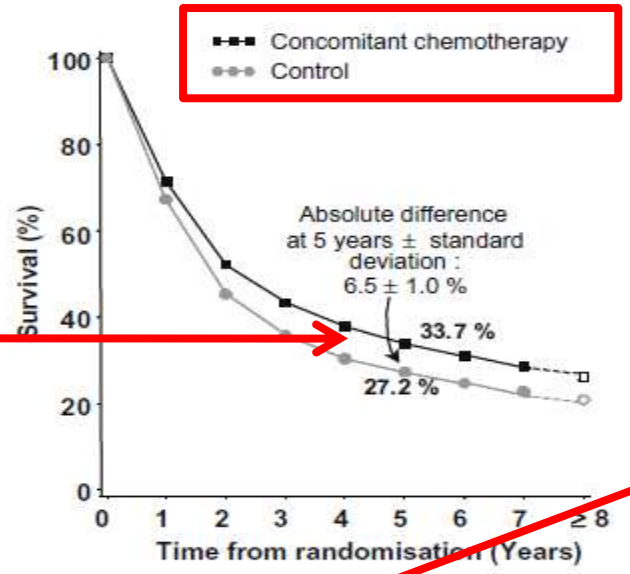


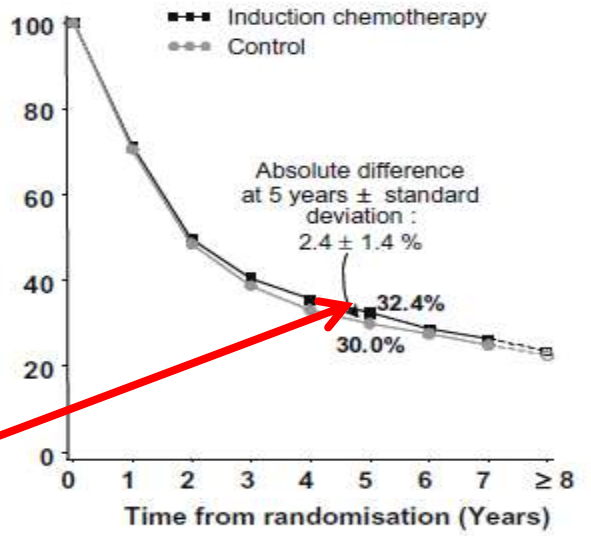
Equivalent survival for both groups

MACH-NC (Pignon et al; updated in 2009)

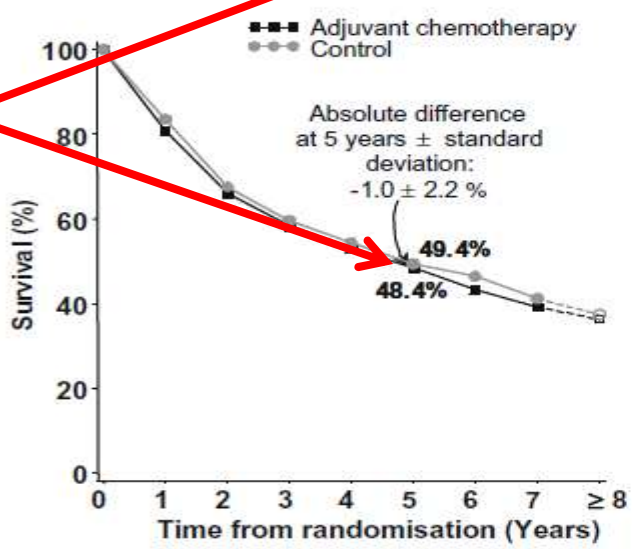
Concurrent chemoradiation showed maximum benefit

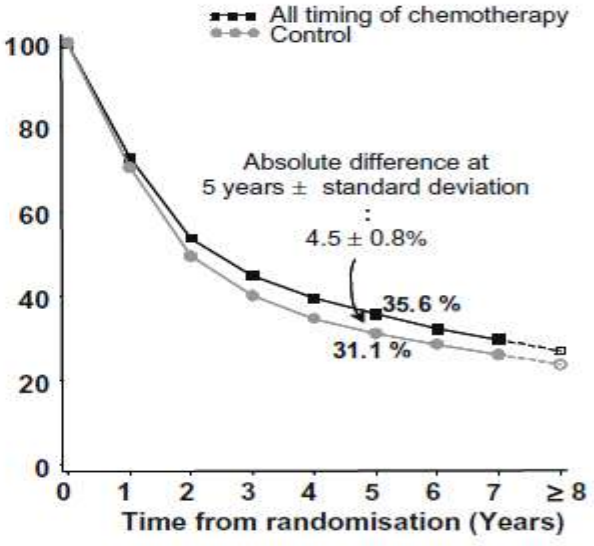
6.5% at 5 yrs



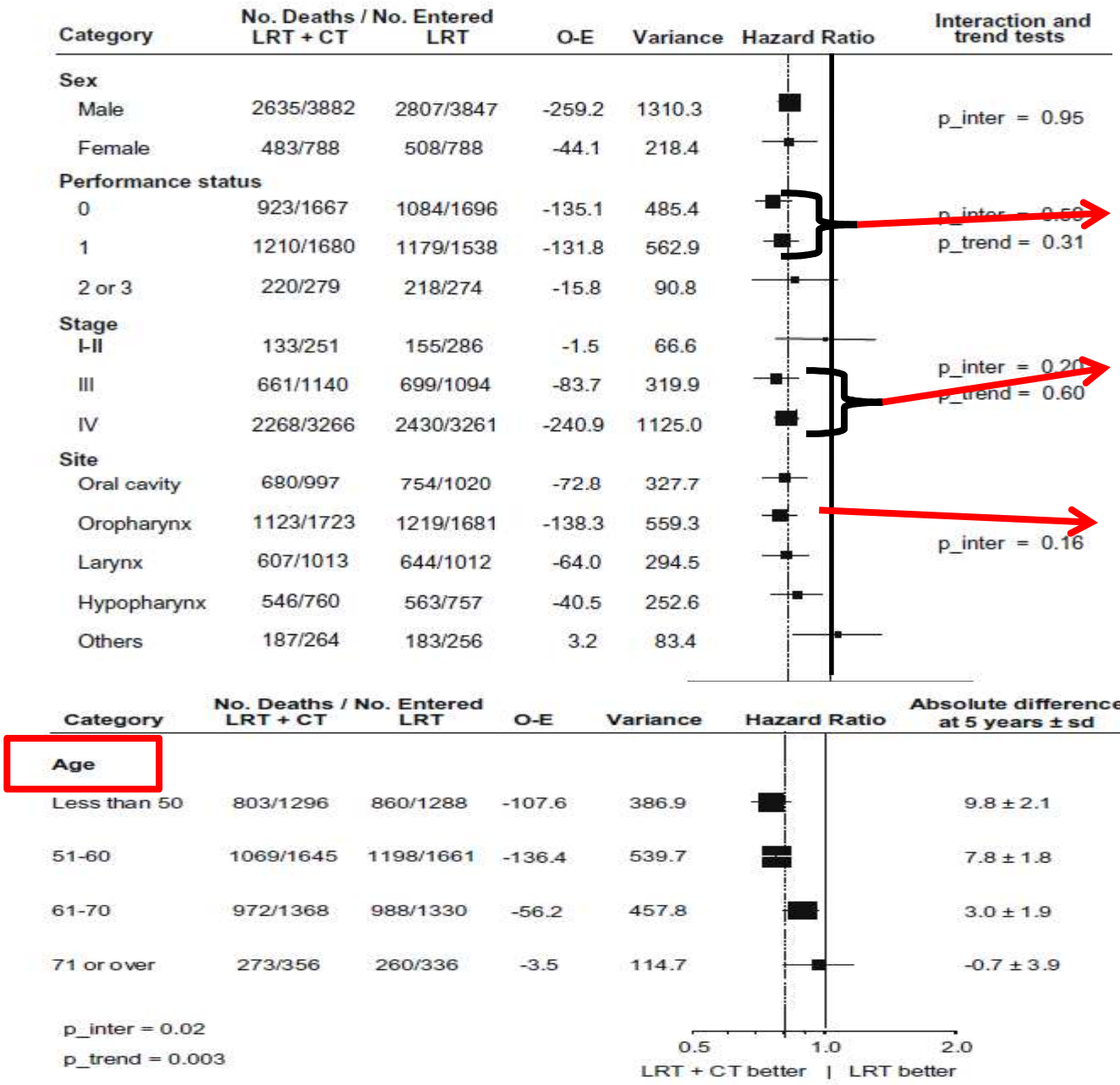


No major benefit from induction and adjuvant chemotherapy





Benefit of chemotherapy based on patient characteristics



Category	No. Deaths / No. Entered LRT + CT	LRT	O-E	Variance	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 = 0.50
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	
III	661/1140	699/1094	-83.7	319.9	p_inter = 0.20
IV	2268/3266	2430/3261	-240.9	1125.0	p_trend = 0.60
Site					
Oral cavity	680/997	754/1020	-72.8	327.7	
Oropharynx	1123/1723	1219/1681	-138.3	559.3	p_inter = 0.16
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	

Category	No. Deaths / No. Entered LRT + CT	LRT	O-E	Variance	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

0.5 1.0 2.0
LRT + CT better | LRT better

Better P.S - **Better results**

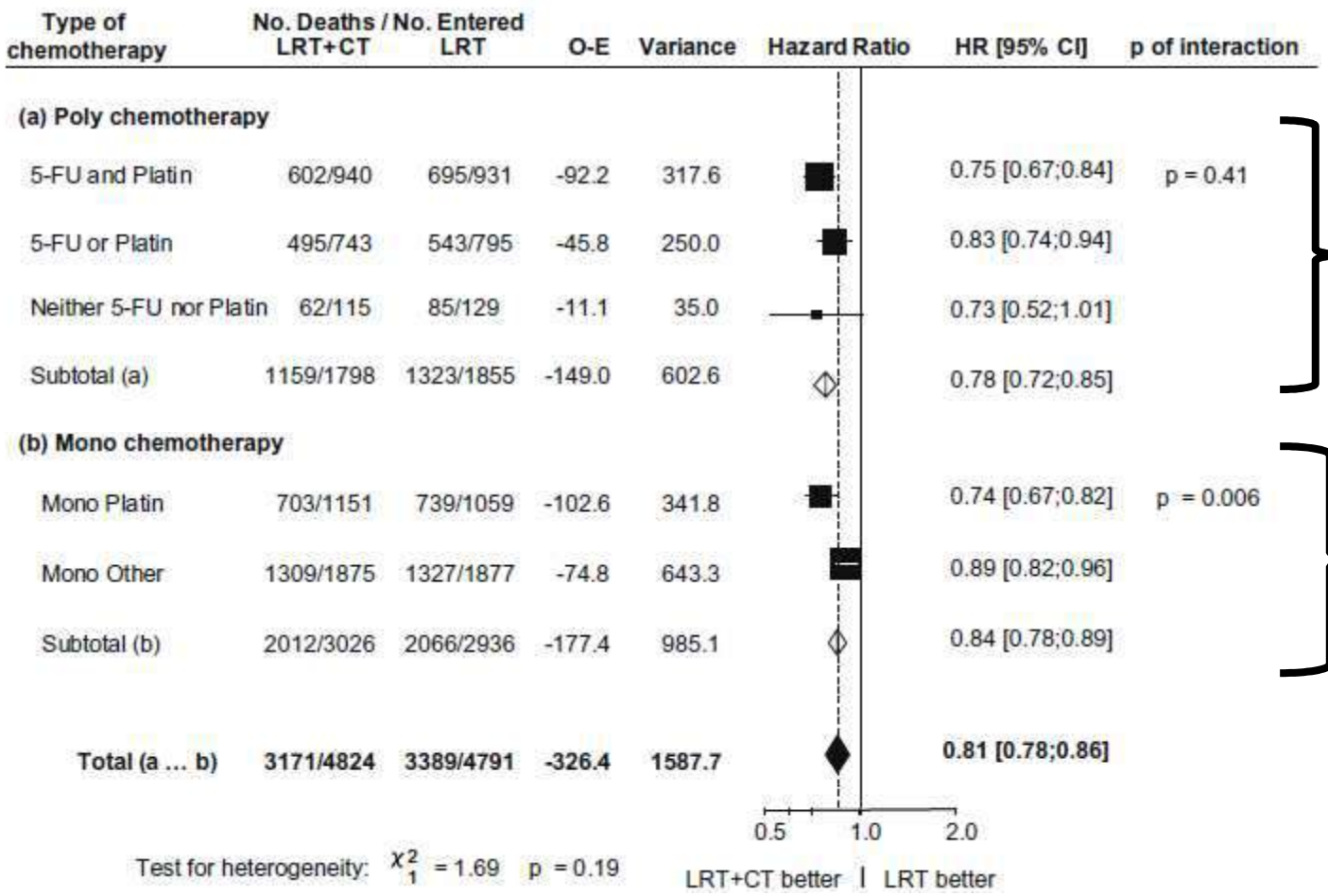
Locally advanced cancers
Better results

Best results with
Ca Oropharynx

Most significant factor was 'Age'

Decreasing benefit of chemotherapy on survival with **Increasing age.**

Benefit of chemotherapy based on chemotherapeutic agent



PLATINUM BASED COMBINATIONS SHOWED MAXIMUM BENEFIT

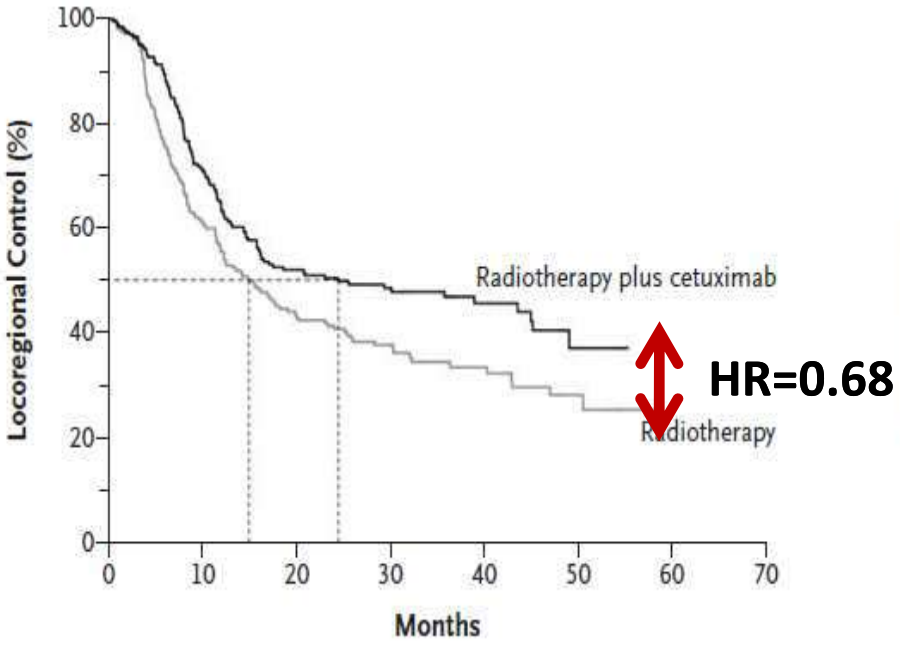
CISPLATIN AS SINGLE AGENT SHOWED MAXIMUM BENEFIT

Radiotherapy plus Cetuximab for Squamous-Cell Carcinoma of the Head and Neck

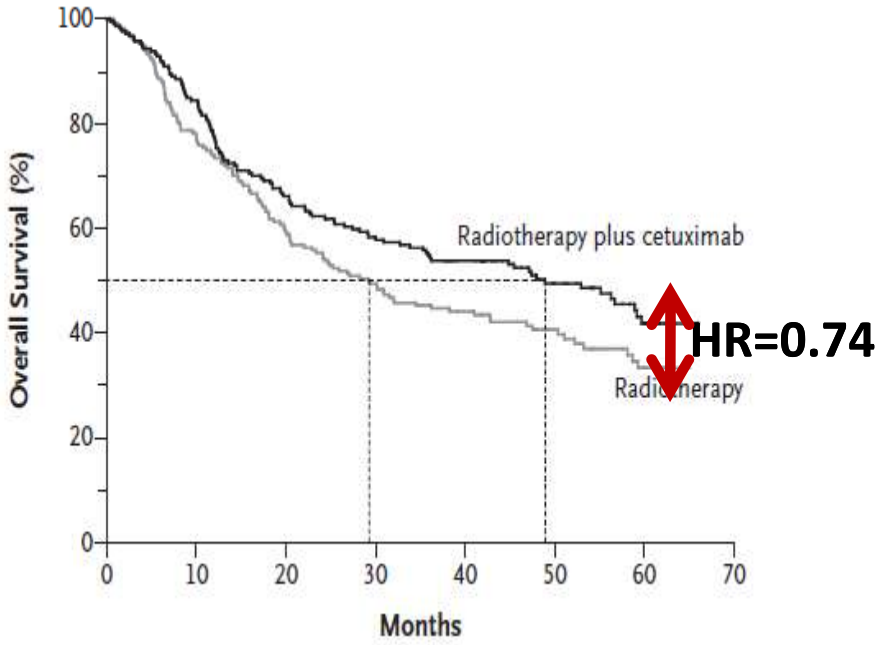
James A. Bonner, M.D., Paul M. Harari, M.D., Jordi Giralt, M.D.,

N Engl J Med. 2006 Feb 9;354(6):567-78.

- Cetuximab:-initial dose of **400 mg/m²** followed by **250mg/m²** weekly with radiotherapy



LOCOREGIONAL CONTROL



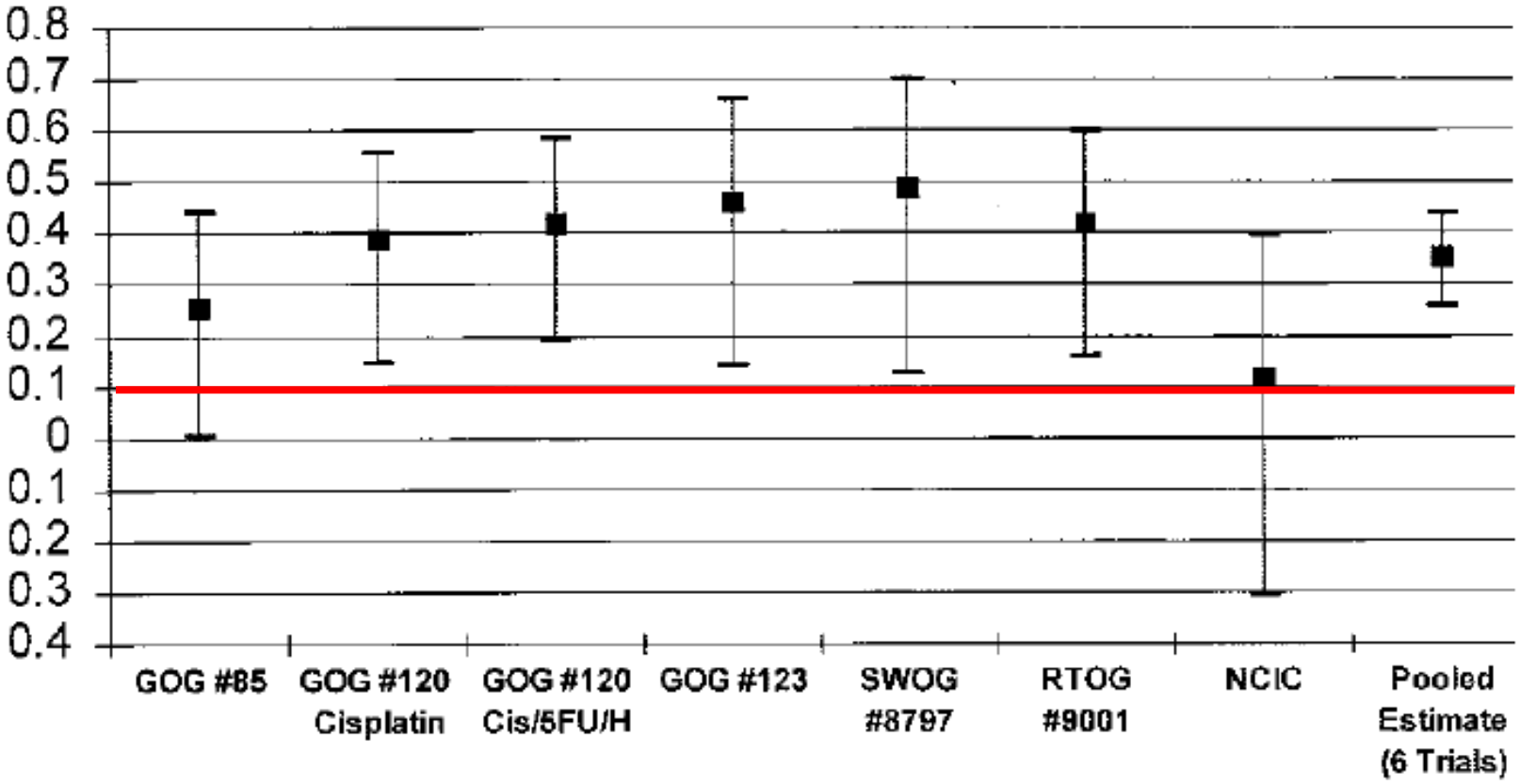
OVERALL SURVIVAL

CANCER CERVIX

Major clinical trials-basis for NCI alert.

Author	Trial	No.	Investigational Arm	Control Arm	Tumor	Comment
Keys 1999	GOG 123	369	RT+ Cisplatin Surgery	RT alone Surgery	Stage IB (≥ 4cm)	Combined with Surgery
Peters 2000	SWOG 8797	243	Surgery RT+Cisplatin+5FU	Surgery RT alone	IA2, IB, IIA (with postop high risk)	Combined with Surgery
Morris & Eifel 1999 &.2004	RTOG 9001	388	RT+Cisplatin+5FU	Extended - field RT	IB or IIA (≥5cmorPLN+) IIB, III, IVA	Surgical staging for PALN
Whitney 1999	GOG 85	368	RT+Cisplatin+5FU	RT+ Hydroxyurea	IIB, III, IVA	Surgical staging for PALN
Rose 1999	GOG 120	526	RT+Cisplatin RT+Cisplatin + 5FU +Hydroxyurea	RT+ Hydroxyurea	IIB, III, IVA	Surgical staging for PALN
Pearcey 2002	NCIC	253	RT+Cisplatin	RT alone	IB2, IIA(≥5cm), IIB, III, IVA	No surgical staging for PALN

Reduction in the risk of death from six chemoradiation clinical trials in cervix cancer



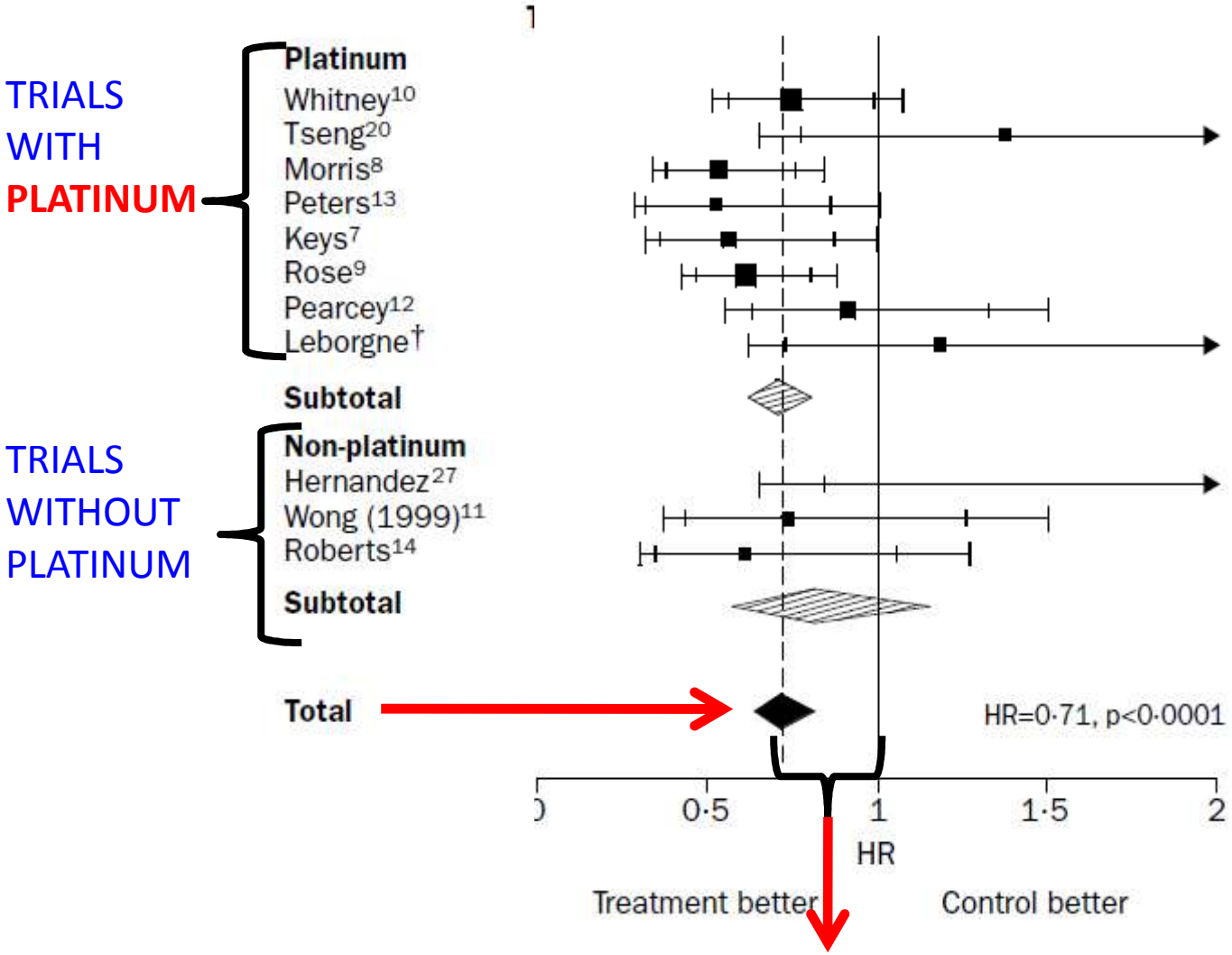
NCI Clinical alert February 23, 1999.

"based on significant improvement in both progression-free survival and overall survival when cisplatin-based chemotherapy was given concurrently with radiotherapy"

". . . strong consideration should be given to the incorporation of concurrent cisplatin-based chemotherapy with radiation therapy in women who require radiation therapy for treatment of cervical cancer."

META-ANALYSIS OF THE RANDOMISED TRIALS

Green JA, et al Lancet. 2001 Sep 8;358

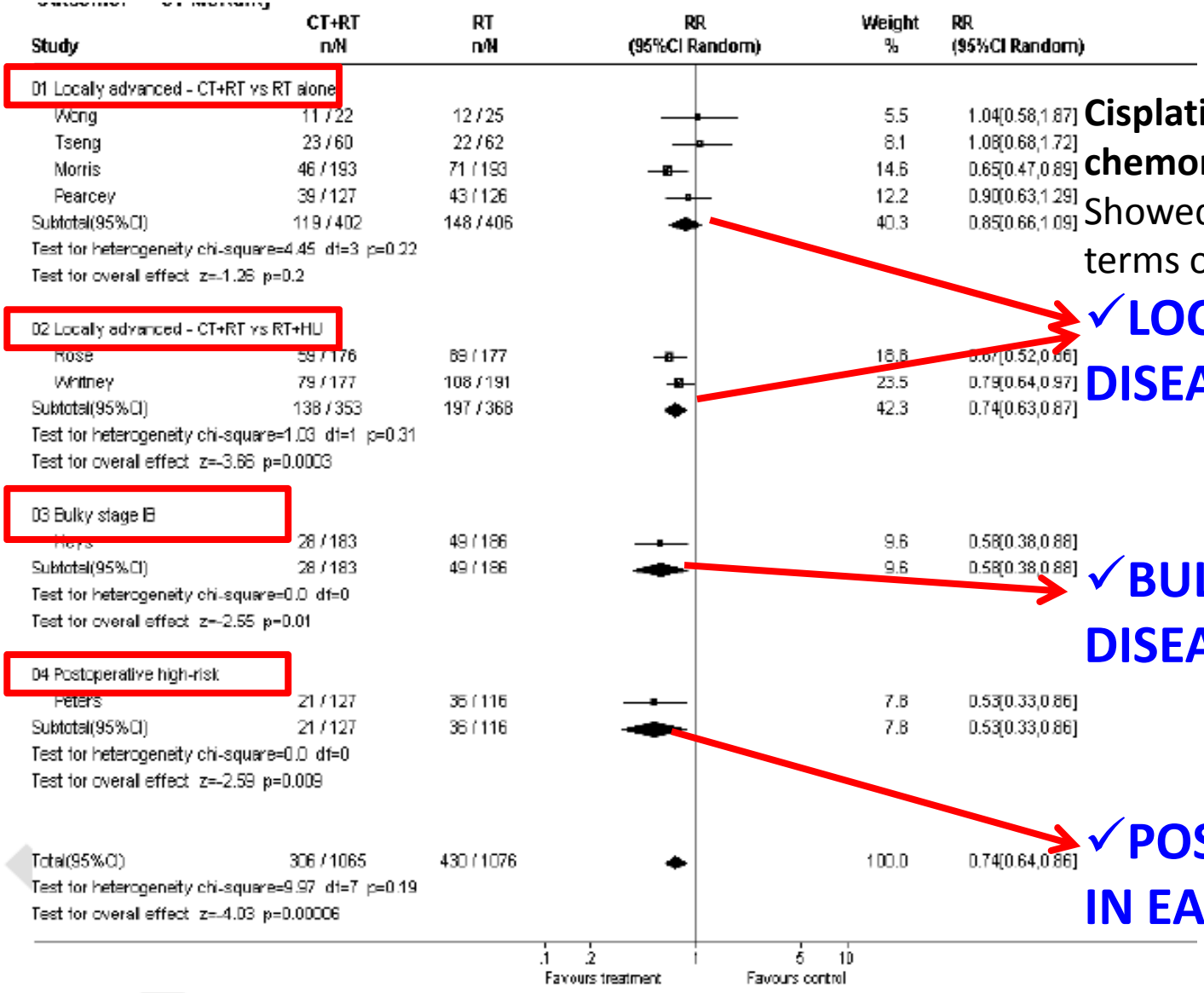


Chemoradiation improves overall survival

(**Hazard Ratio 0·71**, p<0·0001)

Canadian Group(9 Trials) meta-analysis

Lukka et al, *Clinical Oncology 14;203;June 2002*



Cisplatin based concurrent chemoradiation Showed improvement in terms of :

✓**LOCALLY ADVANCED DISEASE**

✓**BULKY STAGE IB DISEASE**

✓**POST-OP HIGH RISK IN EARLY STAGES**

META-ANALYSIS OF THE RANDOMISE TRIALS

Green JA, et al Lancet. 2001 Sep 8;358

- Absolute **survival benefit of 12%**
- Absolute increase **in P.F.S by 13%**
- Significant impact **on both local and distant recurrences**
- **Greater benefit** in trials with **early stage** patients (**IB2 and IIB)**
- Most striking finding was **highly significant reduction of distant metastasis** in the chemo-radiation group.

In conclusion chemo-radiation is Standard of Care in all stages of Carcinoma Cervix at present

CARCINOMA ANAL CANAL

Combined Therapy for Cancer of the Anal Canal:

A Preliminary Report*

NORMAN D. NIGRO, M.D.,† V. K. VAITKEVICIUS, M.D.,‡ BASIL CONSIDINE, JR., M.D.§

From Wayne State University, School of Medicine, Detroit, Michigan

Report of Three Cases

Pre-op **30 Gy @ 1.8 Gy / #** + **5 FU and mitomycin**

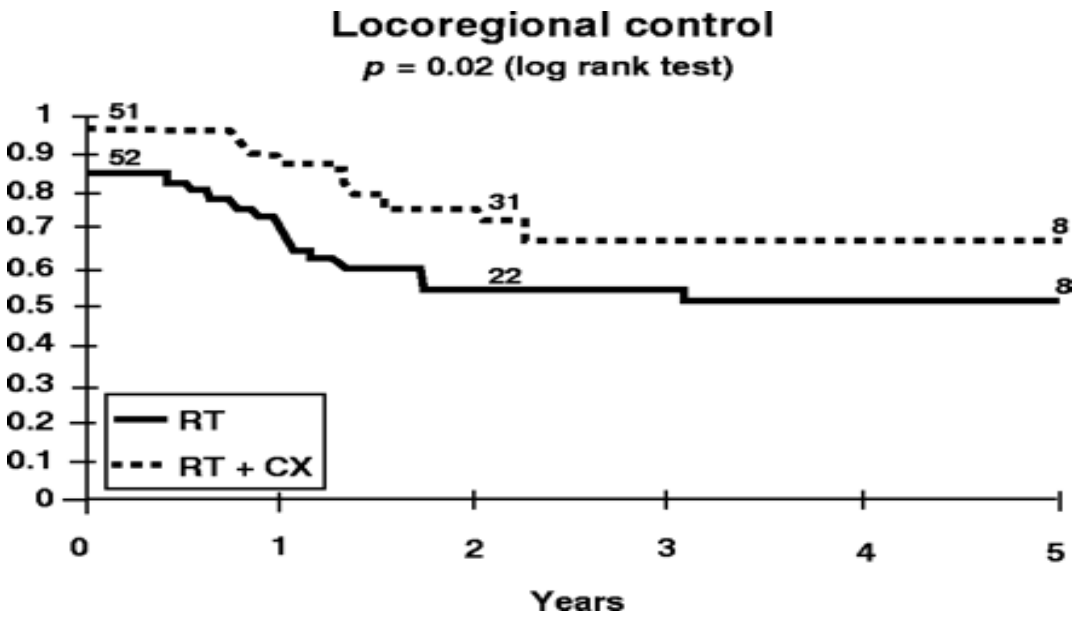
The lesions in all three patients reported here disappeared following the preoperative therapy

“complete histological remission led to a treatment strategy of definitive radiochemotherapy, reserving surgery as a salvage procedure for patients with persistent or relapsing tumors”

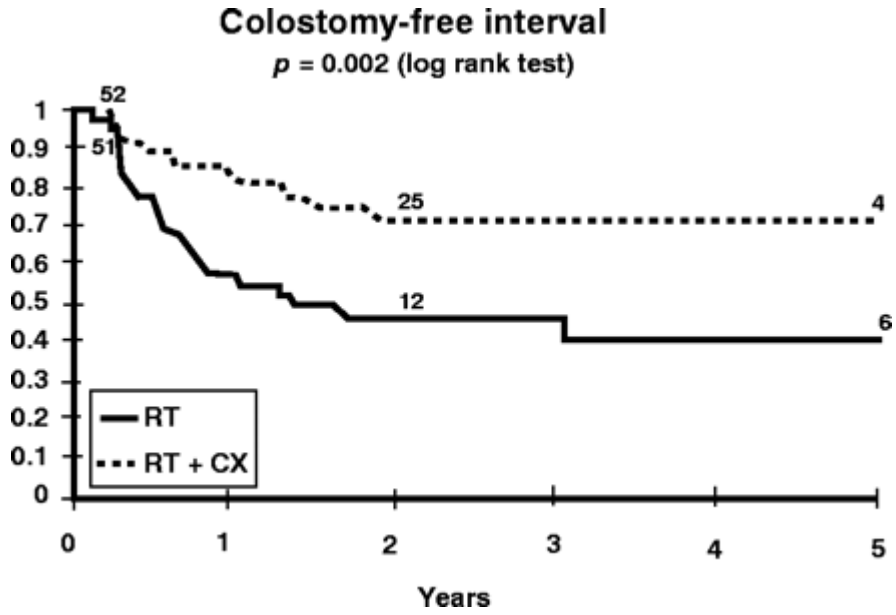
Three randomised trials showing benefit of chemo-RT

EORTC	Radiotherapy	Radiotherapy + 5-FU + MMC
Eligible patients	52	51
T1-T2 N0	0%	0%
T1-T2 N+	15%	16%
T3-T4 N0	48%	45%
T3-T4 N+	32%	39%
UKCCCR	**Radiotherapy**	**Radiotherapy + 5-FU + MMC**
Eligible patients	218	213
T1	15%	12%
T2	33%	29%
T3	40%	41%
T4	11%	15%
N+	17%	23%
RTOG/ECOG	**Radiotherapy + 5-FU**	**Radiotherapy + 5-FU + MMC**
Eligible patients	145	146
T1	15%	15%
T2	35%	42%
T3	42%	33%
T4	8%	10%
N0	82%	83%
N+	17%	17%

EORTC TRIAL

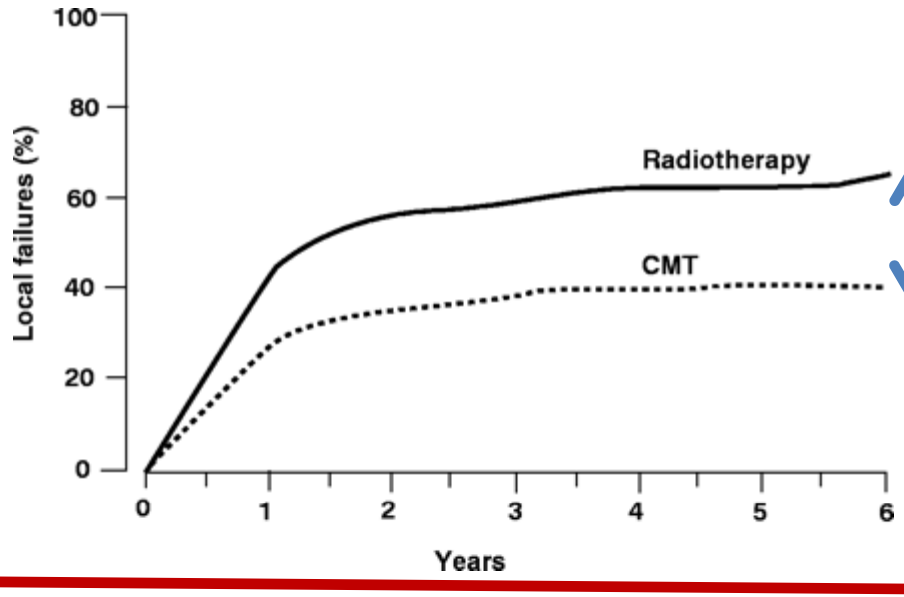


18% **better local control** at 5 yrs (p=0.02)

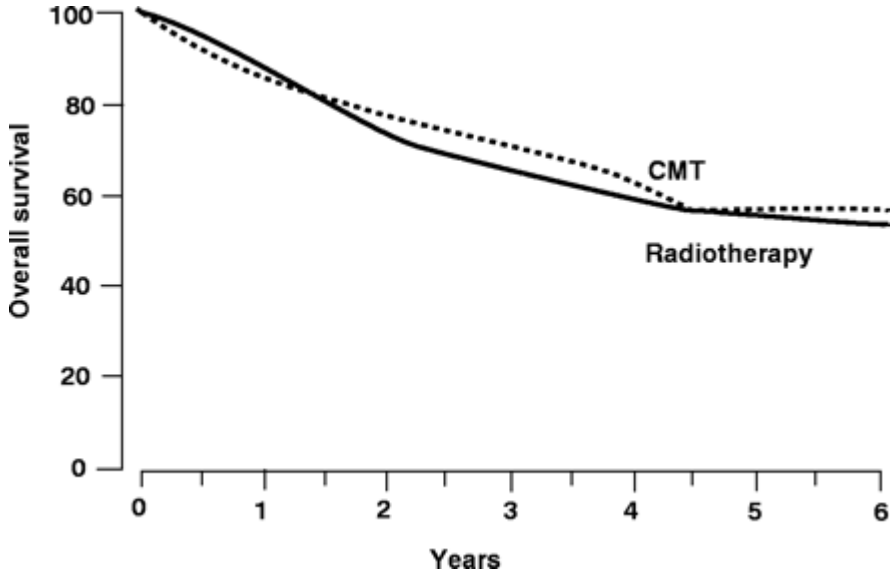


36% **increased colostomy free survival** at 5 yrs (p=0.002)

UKCCR TRIAL

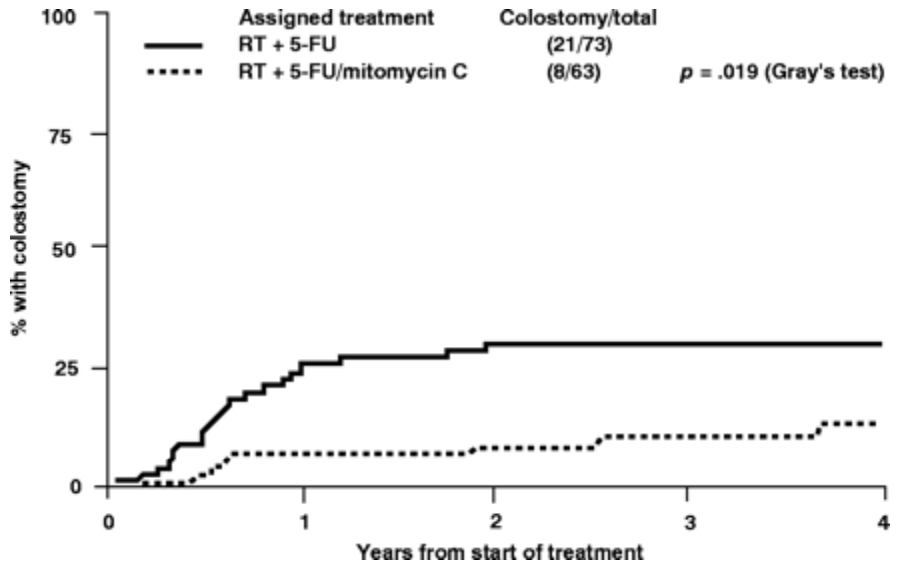


DECREASED LOCAL FAILURE FROM 61 % TO 39 % IN CMT ARM.



NO DIFFERENCE IN OVERALL SURVIVAL
58% RT vs 65% CMT

RTOG STUDY

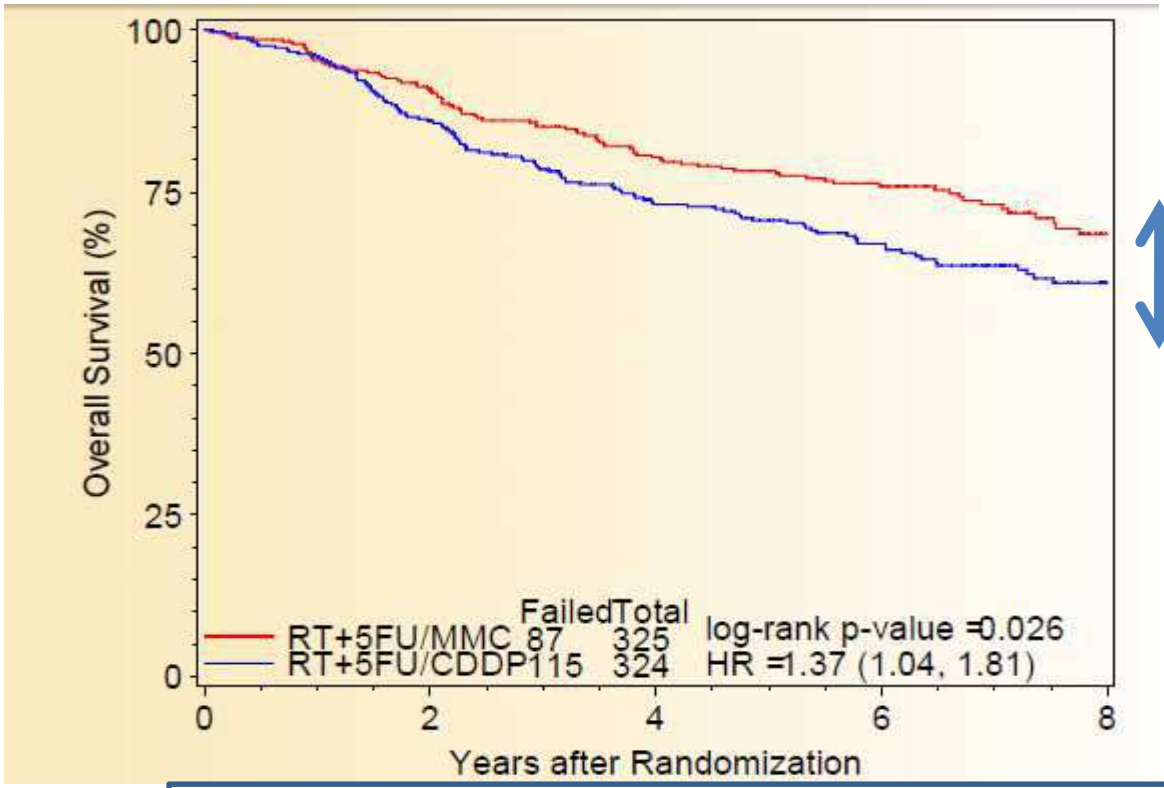


BETTER COLOSTOMY FREE SURVIVAL WITH MITOMYCIN

- Importance of mitomycin C within the chemotherapy regimen
- Difference in local control more pronounced for T3/T4 tumors
- Hematologic toxicity, **'neutropenic sepsis' deaths** in mitomycin C arm.

U.S. GI Intergroup RTOG 9811

Evaluated the role of **cisplatin** in chemoradiation regime



RT+5FU/MMC has better DFS & OS than RT+5FU/CDDP

Hence chemo-radiation is standard of care in Carcinoma Anal Canal

Carcinoma Oesophagus

Treatment Options in Ca. Esophagus

	Modality	L. C.	Survival
1.	Surgery alone	-	26 – 40 % 2 Yrs.
2.	Radiation alone	-	11 – 21 % 2 Yrs.
3.	Post operative Radiation	Improved	Effect unclear
4.	Pre-operative radiation plus Surgery	-	10 – 35 % 5 Yrs.
5.	Pre-operative Chemotherapy plus Surgery	-	No benefit
6.	Neo-adjuvant Chemotherapy plus Radiation	-	No benefit
7.	Chemo-radiation alone	Improved	Improved
8.	Chemo-radiation plus Surgery	Improved	Unclear but increased toxicity

Chemo-radiation in Ca. Esophagus

RTOG Phase III Trial in Locally Advanced Ca. Esophagus

Chemo-radiation vs Radiation alone

(Al-sarraf,M et.al,1997)

Regiemen: RT – 50 Gys in 25 Fractions or 64 Gys in 32 Fractions

CT : 5-F.U. 1000mg/M2 in 96 hrs.

Inj Cisplatin : 75mg/m2 day 1

Chemo every 4 wks during RT and every 3 wks afterwards

RESULTS : 5 Years Overall Survival - 26% vs 0%

Local Failure - 45% vs 68%

Grade 4 toxicity - 20% in CRT arm including death

Standard of care for locally advanced carcinoma Esophagus

Pre-operative Chemo-radiation vs Surgery alone in Ca. Esophagus

Author	Regimen	No. of Patients	Path CR	Median F.U. (Yrs.)	3 Yrs Survival
Urb,2001	5-FU +CP +45GYS.	50 50	28% -	8.2	30% 16%
Bosset,1997	CP + 37 Gys.	143 138	20% -	4.6	33% 36%
Walsh.1996	5-F.U.+ CP+40 Gys.	58 55	22% -	1.5	32% 6%
Burmeister, 2005	5-F.U.+ CP+35Gys.	128 128	16% -	5.4	35% 31%
Tepper,2006	5-F.U.+ CP+50 Gys.	30 26	40% -	6.0	39% 16%

Chemo-Radiation plus Surgery in Ca. Esophagus

French study by Bedenne.I et al.,2007

Total Patients

445 (Scc or Adeno)

Regimen: 5-F.U. +CP + RT 46 Gys in4.5 wks or30 Gys in 2wks

259 patient with PR –Randomized to Surgery or further Chemoradiation to a total dose of 66 Gys.

Results :

1. 2 years survival - 34% vs 40%
2. Death rate – 9% vs 1%
3. Patients with surgery had worst quality of life.

In conclusion addition of surgery does not enhances survival and complication rate is high.

Chemo-Radiation plus Surgery in Ca. Esophagus

German Study by Stahl M. et.al.,2005

Total patients – 172

Induction CT- 5FU=Etoposide+CP x 3 cycles followed by Concurrent CP+Etoposide+ 40 Gys.

Randomized to either Surgery or further Chemoradiation up to total dose of 60-65 Gys.

Results :

1. Local control –64% vs 41%
2. 2 years survival – 31% vs 24%
3. 3 years survival – 18% vs 9%
4. Hospital mortality -11% vs 0%
5. Over all Mortality – 13% vs 3.5%

Increased local control but no significant effect on survival

Neo-adjuvant Chemo-radiation in Resectable Carcinoma Esophagus

Limitations of Studies

1. All the studies were under powered
2. Used unconventional radiation regimens
3. Unbalanced treatment arms
4. Results were conflicting

Do not accept pre-operative chemo-radiation out side the clinical trials

Contra-indications for Chemo-radiation

1. Low general condition
2. Elderly person
3. Deranged renal functions
4. Affordability

CONCLUSIONS

1.Chemoradiation has become standard of care in many cancers more so if locally advanced with emphasis on concurrent chemoradiation

2.Increased tumour control have been achieved in most of cancers so treated but survival has also increased in some with agents e.g. Cisplatin and 5 F.U.

3.Cure rates of majority of tumors still remain poor however addition of chemotherapy is frequently associated with significant normal tissue toxicity.

4.There is a considerable room for improvement however, selection of drugs or optimal treatment approach remains a significant challenge.

Future Directions

1.Use of drugs which interfere with one or more radioresistance mechanism e.g. Taxanes,nucleosides analogues and topomerases.

2.Those drugs that have high potential for increasing therapeutic effectiveness of radiation and need evaluation.

3.Studies of mechanism of chemotherapy-radiation interaction at the level of genetic-molecular,cellular and tumor or normal tissue microenvironmental levels need to be done for obtaining clear insight into the remodulating the potential of chemotherapeutic agents and their ability to increase radio-therapeutic effect.

4.Recent advances in molecular biology has exposed many potential targets e.g. EGFR.COX-2 angiogenic molecules and various components of signal transduction pathways that these molecules initiate.

4.It is possible to intervene in these molecular pathways to improve therapeutic ratio. And hence molecular targeting strategies can be introduced in chemo-radiation for better control of different cancers.

THANK YOU