Role of chemotherapy in the treatment of Cervical Cancers

Umesh Mahantshetty

Professor,

Department of Radiation Oncology

&

GYN Disease Management Group Member

Tata Memorial Hospital, Mumbai, India

Objectives

- To understand the role of chemotherapy in the management of locally advanced cervical cancer

- To learn from the most important clinical series the real benefit of chmeotherapy

Chemotherapy Schemes

- **Neo - adjuvant Chemotherapy:**
  - **NACT followed by RT Vs RT**
  - **NACT followed by Sx Vs RT**
  - **NACT followed by Sx Vs Sx**
  - **NACT followed by Sx Vs Chemo-RT**
- **Concomitant Chemotherapy**
- **Concomitant followed Adjuvant Chemotherapy**
- **Palliative Chemotherapy in recent era**

PERGAMON

European Journal of Cancer 39 (2003) 2470–2486

European Journal of Cancer

www.ejconline.com

Neoadjuvant chemotherapy for locally advanced cervical cancer: a systematic review and meta-analysis of individual patient data from 21 randomised trials

Neoadjuvant Chemotherapy for Cervical Cancer Meta-analysis Collaboration*,1

- Individual patient data from 23 trials
- Two comparisons:
  - *Comparison 1* – NACT followed by RT Vs RT alone
  - *Comparison 2* – NACT followed by Sx Vs RT

Tierney J, et al.

Comparison 1

NACT followed by RT Vs RT

- 18 trials
- N = 2074
- 92% of patients from all eligible trials
- Survival data available from all trials
- Median FU – 5.7 years
- 70% pts had stage II or III disease
- Lymph node status unknown in 60%

Comparison 1

NACT followed by RT Vs RT

Table 3
All endpoints in comparison 1

Endpoint	Number of events/patients	Hazard ratio (95% CI), *P* value	Heterogeneity *P* value
Survival	1084/2074	1.05 (0.94–1.19), 0.393	0.0003
Disease-free survival	938/1724	1.00 (0.88–1.14), 1.000	0.001
Loco-regional disease-free survival	911/1724	1.03 (0.90–1.17), 0.654	0.0002
Metastases-free survival	899/1724	1.00 (0.88–1.14), 1.000	0.002

- Significant heterogeneity among the trials
- It may be inappropriate to combine the trials
- Trials divided in two ways:
  - Cycle interval (> 14 d Vs ≤ 14 d)
  - Cisplatin dose intensity (< 25 Vs ≥ 25 mg/m2/wk)

Overall survival (OS) by frequency of chemotherapy and cisplatin dose intensity in comparison 1 [6]

Variable	Trials	HR (95% CI)	*p* value	Heterogeneity *p* value	5-year OS
Frequency of chemotherapy					
>14 days	11	1.25 (1.07–1.46)	0.005	0.23	↓8%
≤14 days	6	0.76 (0.62–0.92)	0.005	0.19	↑7%
Cisplatin dose intensity					
<25 mg/m^2	7	1.35 (1.11–1.64)	0.002	0.74	↓11%
≥25 mg/m^2	11	0.91 (0.78–1.05)	0.2	0.001	↑3%

- Chemotherapy may select radio-resistant clones due to cross resistance
- Longer cycle duration may lead to accelerated re-growth between cycles
- Dose dense and intensity : better outcome

Comparison 2

NACT followed by Sx Vs RT

- 5 trials
- N = 872
- Planned cycle interval = 10 - 21 days
- Cumulative cisplatin dose = 100 – 300 mg/m2
- RT similar across trials (EBRT 45-60 Gy & ICRT 25-40 Gy)
- One third pts had stage IB & 1/3rd stage II

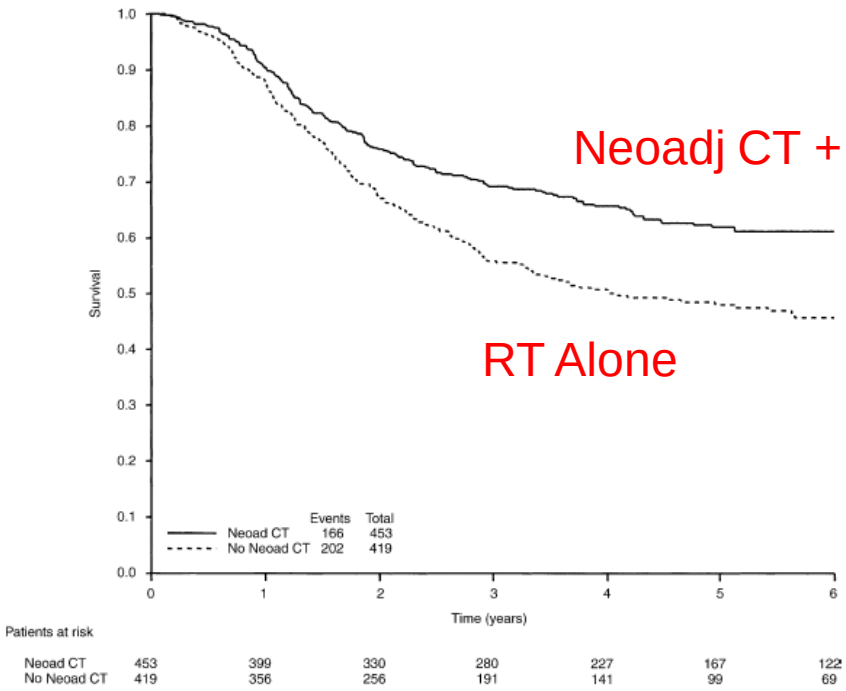


Fig. 5. Kaplan–Meier curves of overall survival in comparison 2. Neoad CT, neoadjuvant chemotherapy.

Neoadj CT + Sx +/ - RT

RT Alone

Caveats

- No of pts/events (872/368):small
- A large fraction of pts in the surgical group received RT
- The RT dose was suboptimal by current standards
- Chemo regimens were not ‘modern’
- There was lack of concurrent chemo in the RT group

NeoAdj CT + Sx Vs Sx alone

[Intervention Review]

Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer

Larysa Rydzewska[1], Jayne Tierney[1], Claire L Vale[1], Paul R Symonds[2]

[1]Meta-analysis Group, MRC Clinical Trials Unit, London, UK. [2]Department of Oncology, Leicester Royal Infirmary, Leicester, UK

Contact address: Larysa Rydzewska, Meta-analysis Group, MRC Clinical Trials Unit, 222 Euston Road, London, NW1 2DA, UK. lhr@ctu.mrc.ac.uk.

- 6 trials, 1072 pts
- PFS available in all trials (1036)
- OS, resection rates, path response available in 5 trials (909-938 pts)

Cochrane – NACT + Sx Vs Sx

- Use of post-op RT was balanced in the two arms
- 3 trials used high cisplatin dose intensity and 3 used lower intensity
- Chemotherapy drugs
  - Cisplatin
  - Bleomycin
  - Vincristine
  - 5-FU
  - Mitomycin

Cochrane – NACT + Sx Vs Sx

- NACT favorably impacted (or trended in that direction) on many outcome measures like resection rates, pathological characteristics and PFS
- There was a lack of convincing benefit in OS
- Chemotherapy may add benefit to surgery!

Furthermore, two ongoing randomised phase III trials (EORTC 55994, NCT00193739) are currently comparing neoadjuvant chemotherapy followed by surgery with concomitant chemoradiation and the results of these trials may also be important in determining whether neoadjuvant chemotherapy prior to surgery is a valid alternative to chemoradiation.

Neoadjuvant Chemotherapy + Surgery versus Concurrent Chemoradiation Therapy in Stage IB2 / IIB Squamous Carcinoma of Cervix

Rationale

- NACT prior to RT has not improved outcome Vs RT alone
- NACT followed by surgery has improved outcome over RT alone (some benefit)
- NACT followed by surgery has shown equivocal results Vs surgery alone
- The current standard Rx for IB & II is CT/RT
- There is theoretical lack of cross-resistance between surgery and CT/RT

Neo-adjuvant Chemotherapy + Surgery

Versus

Concurrent Chemo-radiation (STD)

in Stage IB2 / IIB Squamous Carcinoma of Cervix

EORTC – 55994 STUDY

TMH NACT STUDY

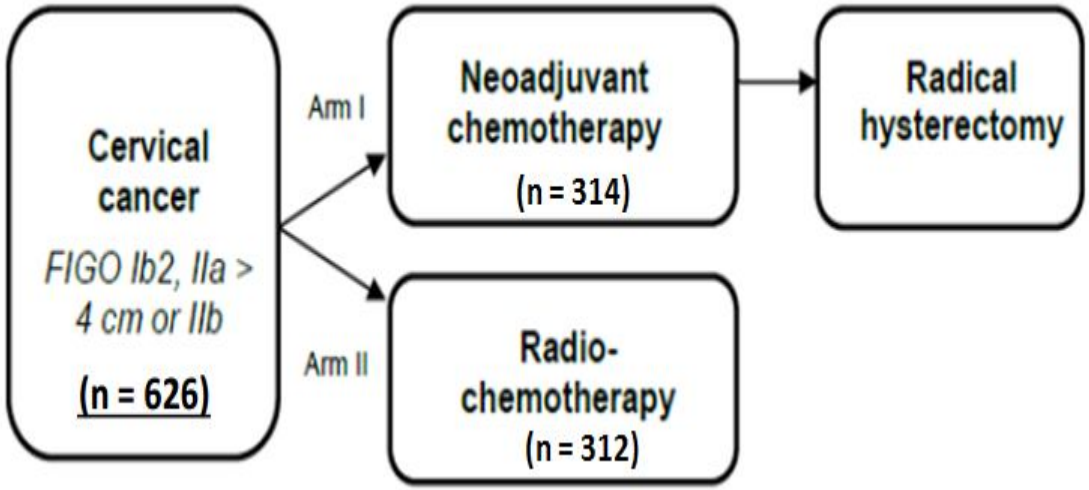
EORTC
European Organisation for Research and Treatment of Cancer

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

AGO-OVAR
ANZGOG
EORTC
GEICO
GINECO
GOG
JGOG
MRC/NCRI
NCI
NCIC CTG
NSGO
RTOG
SGCTG

EORTC Trial # 55994:
Randomized phase III study of neoadjuvant chemotherapy followed by surgery vs. concomitant radiotherapy and chemotherapy in FIGO Ib2, IIa > 4 cm or IIb cervical cancer.

- Largest multi-centric randomized trial in cervical cancer comparing NACT followed by radical hysterectomy directly with CCRT



Primary endpoint:
- Overall survival at five years

Secondary endpoints:
- Overall survival
- Progression free survival
- Toxicity
- Quality of life

Stratification: Institution; FIGO stage; age (18-50; 51-75); histological subtype (adenomatous vs non-adenomatous)

Completed recruitment in June 2014

Final Analysis: 2019

Short term toxicity & preliminary data on the surgical arm are out.

Results:

- **238 (76%)** patients underwent surgery in NACT arm.
- **54 patients** didn't undergo surgery after NACT due to
  - 23 patients (7.3%)- Treatment-related toxicity
  - 17 patients (5.4%)- Progressive disease
  - 14 patients (4.5%)- insufficient response to chemotherapy
- Pathological examination showed: parametrial invasion in 49 (20.6%), vascular invasion in 57 (23.9%), positive surgical margins in 32 (13.4%), peri-nodal spread in 19 (8.0%), pelvic lymph node metastases in 66 (27.7%), metastatic common iliac lymph nodes in 22 (9.2%) and para-aortic nodes in 7 (2,6%) patients.
- Pathological complete response was found in 53 patients (22.3%).

EORTC GCG 55994

Randomized phase III study of neoadjuvant CT followed by surgery vs. concomitant RTX+CT in FIGO stage Ib2, IIa > 4 cm or IIb cervical cancer.

Conclusions from preliminary data

- This is the largest randomized trial in cervical cancer comparing NACT followed by radical hysterectomy with CCRT
- Short term safety is acceptable, mainly due to CT in both arms
- Discontinuation of protocol is high (**20-30%**)
- Pathological complete/ optimal response in NACT - arm = **37%**
- Complete response based on imaging in arm 2 = **49%**
- Adjuvant therapy in arm 1 for patients who underwent surgery = **27%**
- Survival data will follow **mid 2019**

Abstract No. 3395 / 928O_PR

Neoadjuvant chemotherapy followed by surgery versus concomitant cisplatin and radiation therapy in patients with stage IB2, IIA or IIB squamous carcinoma of cervix: A randomized controlled trial

Sudeep Gupta, M.D., on behalf of

Pallavi Parab, Rajendra Kerkar, Umesh Mahantshetty, Amita Maheshwari, Supriya Sastri, Reena Engineer, Rohini Hawaldar, Jaya Ghosh, Seema Gulia, Swati Godbole, Neha Kumar, Malliga Jeyaraman, Renuka Dalvi, Yogesh Kembhavi, Madhuri Gaikar, Rohit Ranade, Hemant Tongaonkar, Rajendra Badwe and Shyam Shrivastava

Gynecologic Oncology Group, Tata Memorial Centre, Mumbai

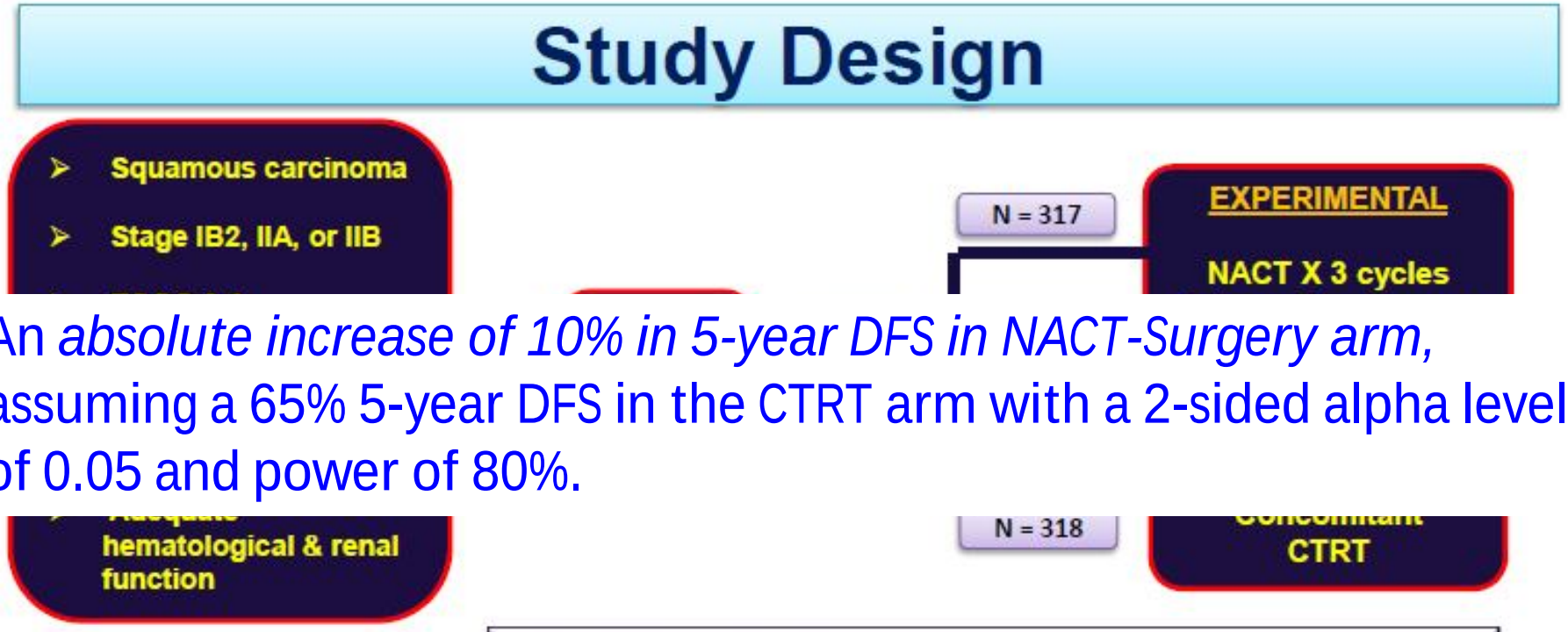
MADRID 2017 ESMO congress

Funded by Tata Memorial Centre, Government of India

ESMO PLENARY PRESENTATION - 2017

Gupta et al; JCO Feb 2018

ESMO PLENARY PRESENTATION – 2017
TMH NACT STUDY

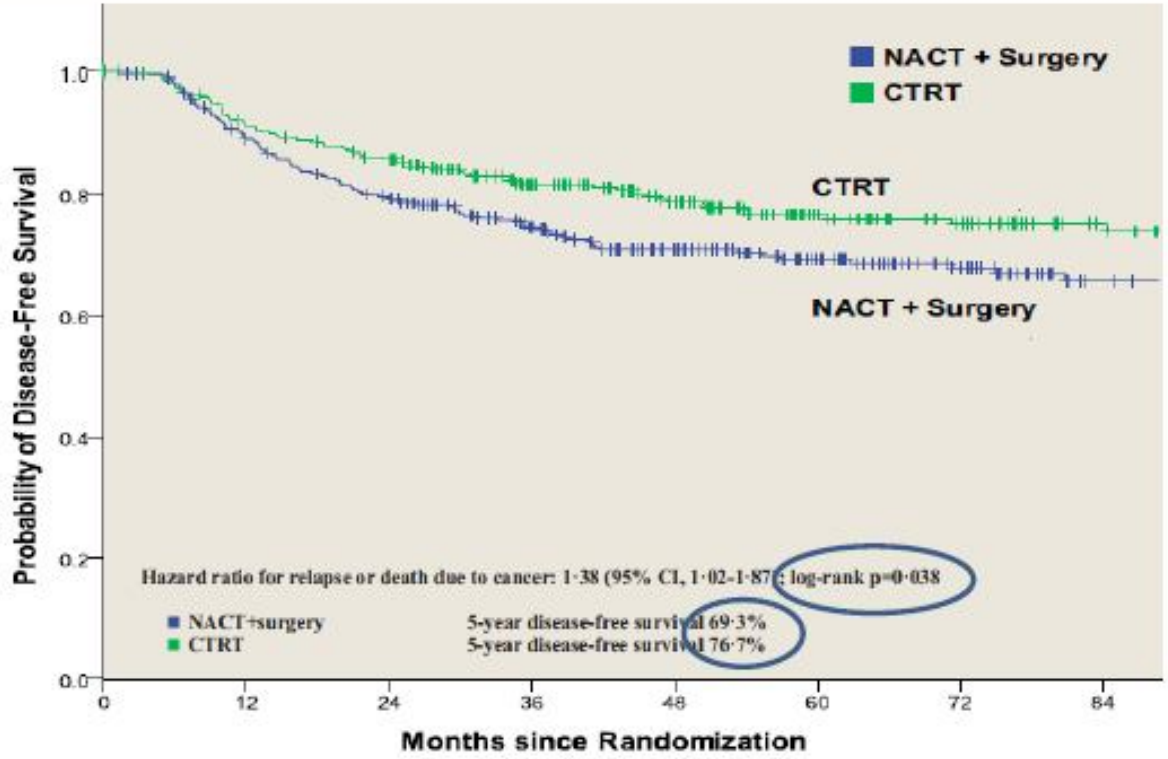


An *absolute increase of 10% in 5-year DFS in NACT-Surgery arm*, assuming a 65% 5-year DFS in the CTRT arm with a 2-sided alpha level of 0.05 and power of 80%.

MADRID 2017 ESMO congress

ESMO PLENARY PRESENTATION – 2017
TMH NACT STUDY

Disease-free survival in intention-to-treat population



No. at Risk								
NACT+Surgery	316	266	233	192	152	114	84	54
CTRT	317	282	261	210	167	116	85	60

Gupta et al; JCO Feb 2018

ESMO PLENARY PRESENTATION – 2017
TMH NACT STUDY

CONCLUSIONS

- Our hypothesis of improved outcomes with NACT-surgery was not proven.
- Concomitant chemoradiation with weekly cisplatin resulted in significantly higher DFS compared with neoadjuvant chemotherapy followed by radical surgery in patients with locally advanced squamous cervical cancer.
  - ✓ The main benefit of CTRT was in stage IIB patients

Gupta et al; JCO Feb 2018

ESMO PLENARY PRESENTATION – 2017
NACT STUDY - TMH

CONCLUSIONS...

- Neoadjuvant chemotherapy and surgery should not be routinely practiced.

- Concomitant chemoradiation should be the standard of care in locally advanced cervical cancer.

Gupta et al; JCO Feb 2018

RATIONALE FOR CONCURRENT CHEMO-RADIATION

- Increased tumor cell kill without delaying the course of RT or protracting the overall treatment time

- Synergistic action with RT
  - potentiates the sub-lethal damage
  - inhibits the DNA damage repair induced by RT

RADIOSENSITIZING CT AGENTS

- HYDROXYUREA
- 5 FLUROURACIL
- CISPLATIN
- CARBOPLATIN
- VINCRISTINE
- ETOPOSIDE
- BLEOMYCIN
- PACLITAXEL
- MITOMYCIN

New Generation CT agents: Gemcitabine, Capecitabine, Targetted therapy etc.

Cisplatin: CT in a dose of 40 - 50 mg/m2 or 50 - 70 mg/m2 three weekly

Phase III trials with concurrent chemo-radiotherapy in stage IB2-IVa CERVICAL CANCER:

Dose of Cisplatin/m2

- **GOG 85** : **Cisplatin 50 mg day 1, 29 + FU infusion**
- **GOG 120** : **Cisplatin 50 mg day 1, 29 + FU infusion +HU**
- **GOG 120** : **Cisplatin 40 mg weekly**
- **GOG 123** : **Cisplatin 40 mg weekly**
- **SWOG8797/GOG 109** : **Cisplatin 70 mg day 1, 22 + FU infusion**
- **RTOG 9001** : **Cisplatin 70 mg day 1, 22 + FU infusion**
- **NCIC** : **Cisplatin 40 mg, weekly**

RCT on Chemoradiation

Study group	No. of Pts	Overall survival (%) CCRT vs control	P-value	Follow-up
GOG 85	388	65 vs 51 (5y)	0.018	104mo
GOG 120	526	66 vs 50 (3y)	0.004	35mo
		67 vs 50 (3y)	0.002	
GOG 123	369	83 vs 74 (3y)	0.008	36mo
SWOG 8797	268	81 vs 71 (4y)	0.007	42mo
RTOG 9001	388	73 vs 52 (5y)	< 0.001	43mo
NCIC	253	62 vs 58 (5y)	0.53	82mo

(Whiteney et al, JCO, 1999. Rose et al, NEJM, 1999. Keys et al, NEJM, 1999. Peters et al, JCO, 2000. Morris et al, NEJM, 1999. Pearcy et al, JCO 2002)

Post Wertheim's Sx : C/M +, para + or nodes +

High Risk : Role of Adjuvant Therapy

Intergroup 0107 RCT Trial (Gynae Oncol 73 ;177-183: 1999)

Outcome	PORT N = 116	POSTOPCT+RT N = 127	p value
4yr RFS	63%	80%	0.01
4yr OAS	71%	81%	0.01
Pelvic rec	17%	6%	
Distant mets	11%	7%	
Pelvic+ distant	4%	3%	

ADJUVANT CHEMO-RADIATION SHOULD BE STANDARD OF CARE

NATIONAL CANCER INSTITUTE
CLINICAL ANNOUNCEMENT

'CONCURRENT CHEMO-RADIATION
FOR
CERVICAL CANCER'

in February 1999

"Five major randomized phase III trials show that platinum based chemo when given concurrently with RT prolongs survival in women with locally advanced cervical cancer stages Ib2 - IVa as well as in women with stage I / IIa found to have metastatic pelvic lymph nodes, positive parametrial disease and positive surgical margins at the time of primary surgery "

NCIC Trial : 6th RCT

Median follow-up: 82 months

Stage IB2 and IIA (5 cm in diameter), IIB, IIIB, IIIA, and IVA (< 5cm if LN + ve)			
Randomization		**CT+RT (CDDP) 127 pts**	**RT alone 126 pts**
OS	**3 yrs**	**69%**	**66%**
	5 yrs	**62%**	**58%**
	HR	**1.13 (95% CI 0.77 to 1.67)**	**P=0.42**

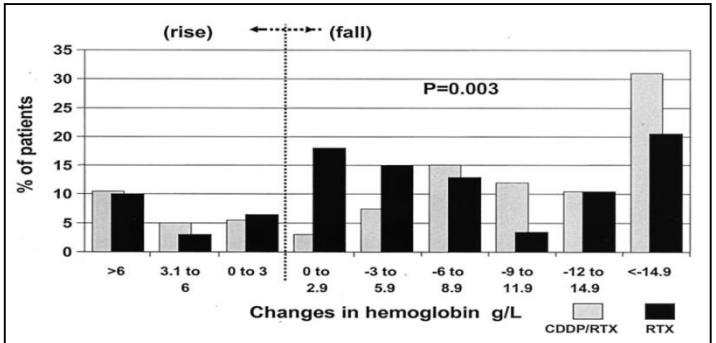


Fig 4. Changes in hemoglobin level during treatment (week 5 to baseline) by treatment arm.

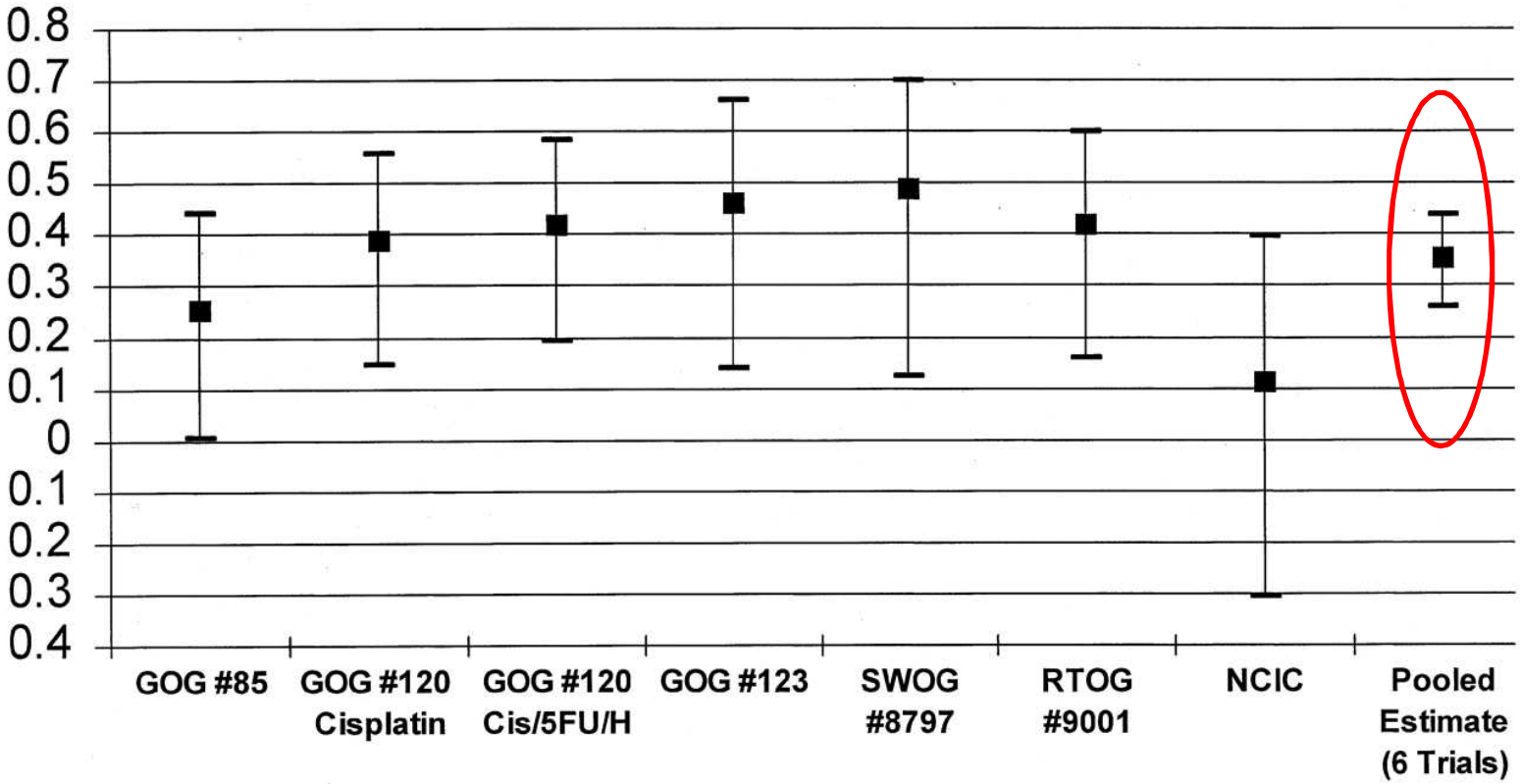
Conclusions:

The best results are certainly achieved by careful attention to RT details, including dose and overall delivery time, the use of ICBT whenever possible, and probably the addition of concurrent CDDP CRT

Approximately 53% of patients on the CRT regimen had decreases in their hemoglobin levels of 9 g/L or more.

Pearcey et al JCO 2002

Reduction in the risk (1 - relative risk) of death from six chemo-radiation clinical trials in cervix cancer



- Collectively, the six trials continue to support improvement in local control, progression-free survival, and survival with concurrent cisplatin-based CRT.
- Although the NCIC study alone fails to demonstrate significant differences in progression-free and overall survival, all outcomes slightly favored cisplatin CRT.

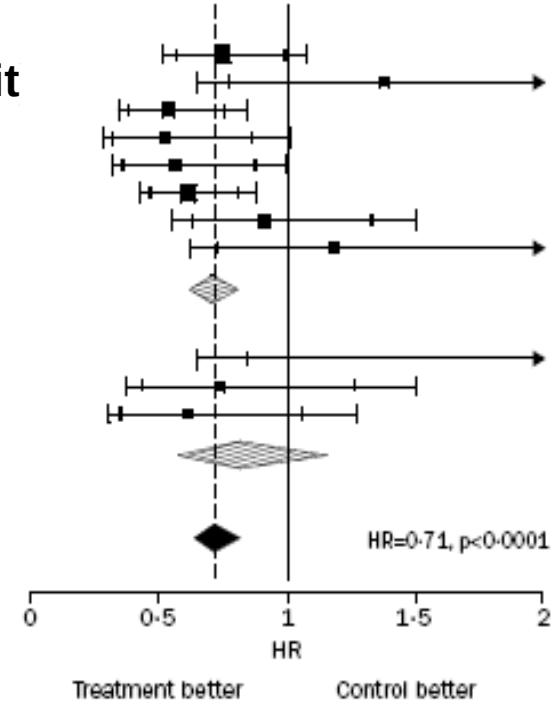
Editorial : Rose, P. G. et al. J Clin Oncol; 20:891-893 2002

Concurrent Chemo-radiation
Results of Meta-analyses

Cochrane Collaborative Group (19 Trials) (4580 patients)

Green JA et al Lancet 358;781 (Sept. 2001)

- 19 RCTs between 1981 and 2000 : 4580 randomized pts
- Increase in OAS by 12% & RFS by 16% (absolute benefit (p=0.0001)
- Greater benefit in patients in stages IB2 and IIB
- Decrease in local and systemic recurrence (p=0.0001)



Update in July 2005: 21 trials and 4921 pts

- **Similar findings (absolute benefit: OAS:10%; PFS: 13%)**
- **Test for Heterogeneity : Positive**
- **No data on late toxicities**

Cochrane Database Syst Rev. 2005 Jul 20;(3):CD002225.

Canadian Group (9 Trials) - 4 year survival data

Meta-analysis

- **Cisplatin based Concomitant Chemo-radiation**
- **Significant improvement in Overall Survival**

  - Advanced Stages (Only 30% tumors)

  - Bulky IB tumors (prior to surgery)

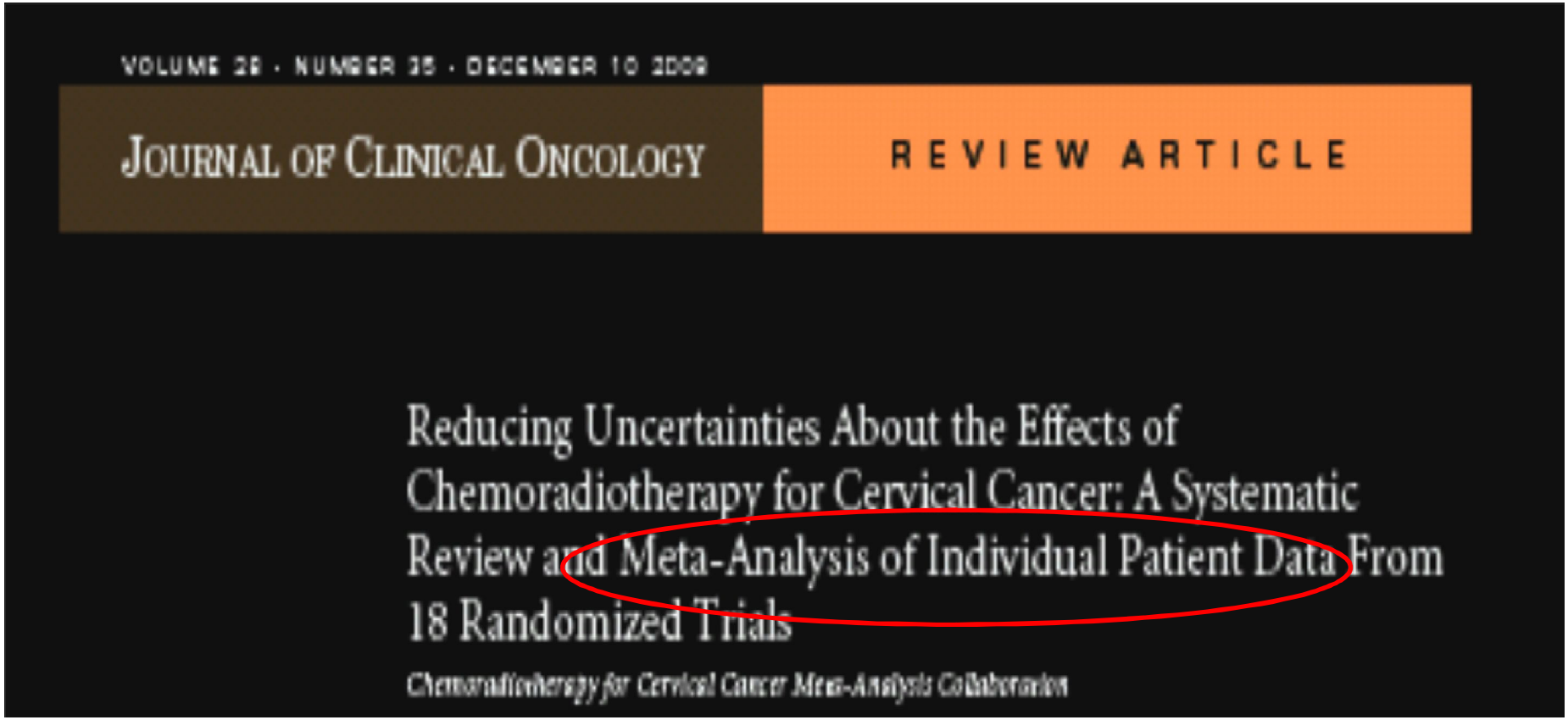
  - High risk early disease (post-surgery)

- **Toxicities** Acute Grade 3/4 Hematological and G.I significantly higher : all short lived

  2 deaths due to the toxicities

  No significant late toxicities seen

Lukka et al, Clinical Oncology 14;203 (June 2002)



THE CHEMORADIATION FOR CERVICAL CANCER META-ANALYSIS COLLABORATION- (CCCMAC)

MEDICAL RESEARCH COUNCIL CLINICAL TRIALS UNIT- UK

JCO December 2008

REDUCING UNCERTAINTIES ABOUT THE EFFECTS OF CHEMORADIATION FOR CERVICAL CANCERS: SYSTEMATIC REVIEW AND META-ANALYSIS

OVERALL SURVIVAL AND DISEASE FREE SURVIVAL

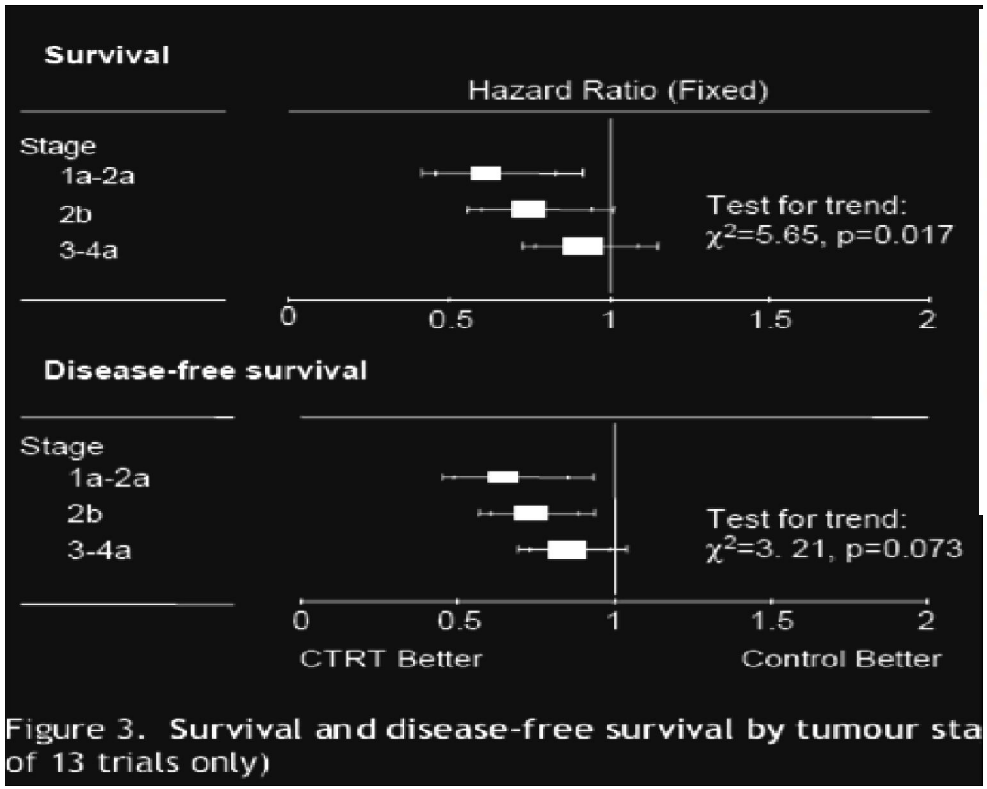
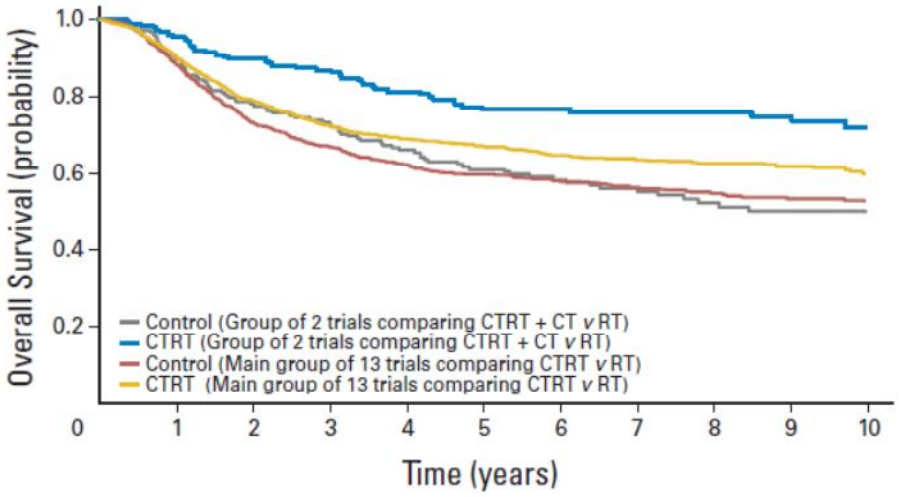


Figure 3. Survival and disease-free survival by tumour sta
of 13 trials only)



Adjuvant CT after CRT needs to be explored further

There was however the suggestion of a decreasing relative effect of chemo-radiation on survival with increasing tumor stage, with estimated absolute survival benefits of 10% (stage1a-2a), 7% (stage 2b) and

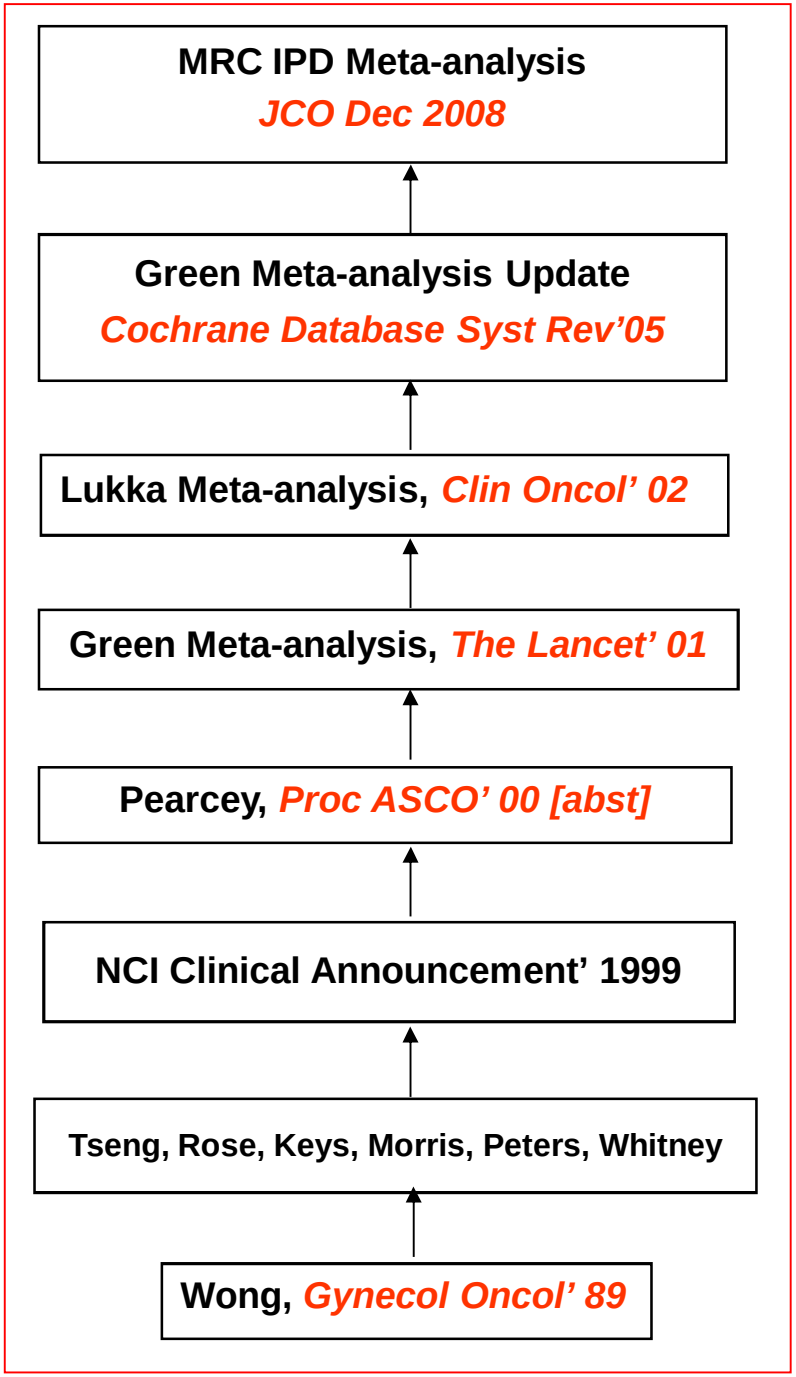
3% (stage 3-4a) at 5-years

JCO Dec '08

A Systematic Review and Meta-analysis
J. A Green - Confessions

- In our review, 68% of patients overall were stage I and II;
- Although an overall reduction in the risk of death with chemo-radiotherapy was shown, ***Gillian Thomas*** advised

"*caution in extrapolation of the results to advanced stages.* Our exploratory analysis *shows less benefit* and *more heterogeneity* in studies with a high proportion of advanced-stage patients than in those with a low proportion of such patients"



CRITICAL REVIEW OF EVIDENCE

- Heterogenous patient data
- Suboptimal Radiotherapy Schedules Used
- Non-uniform use of CT drugs and Sequencing
- QOL issues : Unknown
- Cost effectiveness in India including developing countries ? due to
  - Advance Disease at presentation
  - Poor nutritional status (anemia) & low compliance rates
  - inadequate supportive therapy & financial constraints
- Sparse literature from developing countries

**Shrivastava SK et al: JCRT 2013*
***Five randomized trial & NCI Alert:1999*
*** Green JA et al Lancet :2001*
*** Lukka et al, Clinical Oncology 2002*

LENARY PRESENTATION

Abstract Number: ESGO7-1305

Cisplatin Chemo-radiation Versus Radiation in FIGO Stage IIIB Squamous Cell Carcinoma of the Uterine Cervix - A Phase III Randomized Trial (CRACx Trial: NCT00193791)

U. Mahantshetty, *Professor in Radiation Oncology*

SK Shrivastava, R. Engineer, S. Chopra, R. Havaldar, V. Hande, R. Kerkar, A. Maheshwari, T. Shylasree, J. Ghosh, J. Bajpai, L. Naidu, S. Gulia, S. Gupta

on behalf of

Gynecologic Oncology Disease Management Group, Tata Memorial Centre, India

Funded by Tata Memorial Centre, Government of India

ESGO20 INTERNATIONAL MEETING OF THE EUROPEAN SOCIETY OF GYNAECOLOGICAL ONCOLOGY (ESGO)
NOVEMBER 04-07, 2017 | VIENNA, AUSTRIA
European Gynaecological Oncology Congress 2017

STUDY HYPOTHESIS

Concurrent Cisplatin chemotherapy with radiation will improve the outcome compared to radiation alone in FIGO Stage IIIB Squamous Cell Cervical Cancer by virtue of radio-sensitizing effect on tumor cells

STUDY DESIGN

Open label phase randomized III Trial

INCLUSION CRITERIA

- ✓ FIGO Stage IIIB
- ✓ SQ CA histology
- ✓ Age > 18 years & < 65 years
- ✓ WHO perf. Status : 0 or 1
- ✓ Hemoglobin ≥ 10 gm %
- ✓ Normal blood counts
- ✓ Normal renal functions

Exclusion Criteria

- ✓ Bilateral HN
- ✓ HIV positive
- ✓ Medical Renal Disease
- ✓ Gross PA nodes on Imaging

1 : 1 randomization

N = 424 → **STUDY ARM**

Concomitant Chemo-radiation (Cisplatin weekly 40 mg/m2 for 5 cycles atleast)

N = 426 → **STANDARD ARM**

Definitive Radiation

Definitive Radiation:

- External Beam : 50 Gy / 25 # (MLB at 40 Gy when ever feasible)

- Brachytherapy : LDR (25- 30 Gy to point 'A' 1#) or HDR (7 Gy to point 'A' x 3# once weekly)

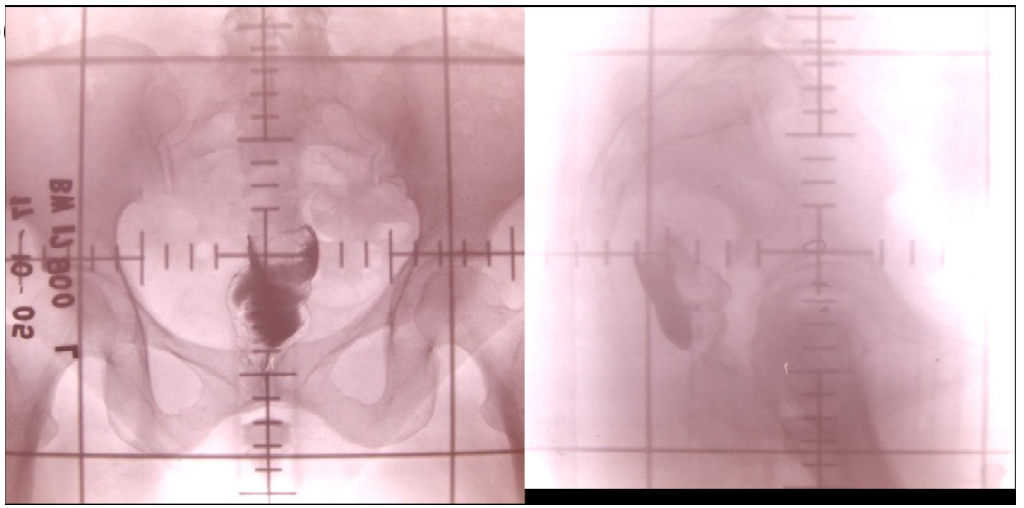
- Total RT (Physical) Doses : 76 Gy – 81 Gy (LDR Equivalent) to Point 'A' *

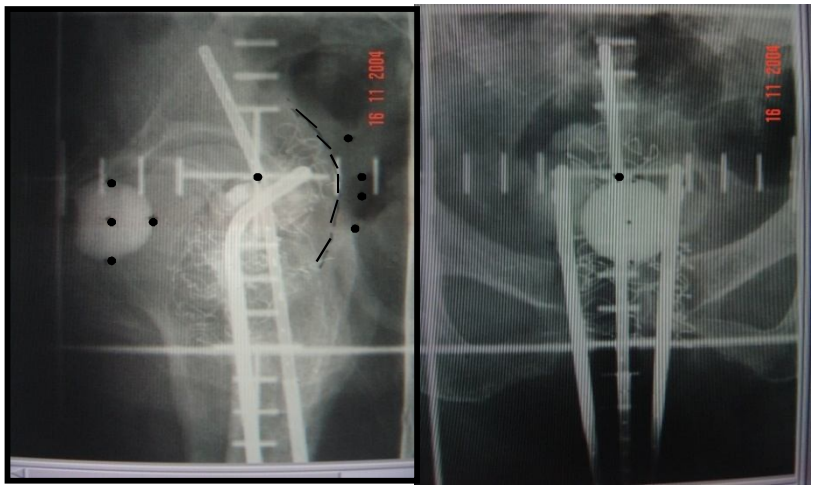
* *Orton et al ; Int J Radiat Oncol Biol Phys. 1991*

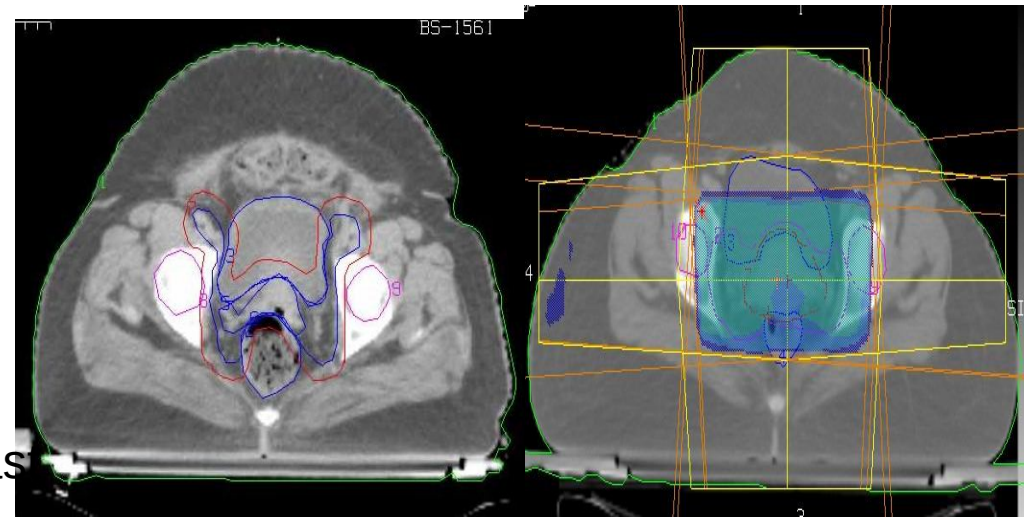
TREATMENT PROTOCOL

- **External RT :** Whole Pelvis with four field box technique or AP/PA
- **Dose:** 50 Gy / 25 # / 5 Weeks (40 Gy open + 10 Gy with MLB)
- **Brachytherapy: (X-ray / CT base**

LDR : 30 Gy X 1 # to pt A
Or
HDR : 7 Gy X 3 # to pt A







- **Chemotherapy**

Cisplatin 40 mg/m2 wkly X 5 cycles atleas

STUDY END POINTS

- **Primary Endpoint: Disease free Survival (DFS)**
  - *Definition of Event: Cervical cancer recurrence (any) or death whichever was earlier*
- **Secondary End Points:**
  - *Overall Survival and Toxicities*

Baseline Characteristics

Patient factors	Chemo-radiation ARM (N = 424)	Radiation Alone ARM (N = 426)
Mean Age (± SD) in years	49.4 (± 7.9)	49.3 (± 7.9)
Clinical Tumor dimension (in cm)		
≤ 4 cm	194 (51·2%)	185 (48·8%)
> 4 cm	**230 (48·8%)**	**241 (51·2%)**
Parametrium Invasion		
Unilateral	176 (41·5%)	150 (35·2%)
Bilateral	**248 (58·5%)**	**276 (64·8%)**
Pre treatment Hemoglobin (in g/dl)		
Median (IQR)	11(10·3 – 12)	11(10·2 – 11·9)

The two arms are well balanced with respect to baseline characteristics

Treatment Characteristics

Patient factors		Chemo-radiation ARM (N = 424)	Radiation Alone ARM (N = 426)
External RT Doses Median (Range)		50 (4 – 66)	50 (2 - 66)
	≥ 45 Gy	398 (94%)	402 (94·4%)
Brachytherapy	LDR	62 (14·5%)	68 (16%)
	HDR	333 (79%)	337 (79%)
	Defaulted	29 (6·8%)	21 (5%)
Point A Doses in EQD2	Median (IQR)	69·7(69·7 – 69.8)	69·7(69·7 – 69.8)
Radiation therapy	**Complete**	**395 (93%)**	**407 (95·5%)**
Overall treatment time	Median (IQR)	44 (41- 49)	44 (40 - 48)
Chemotherapy	Median (IQR)	5·0 (4 - 5)	--
	< 5 cycles	132 (31%)	--
	≥ 5 cycles	**293 (69%)**	--

Overall treatment compliance was > 90% approx. in the two arms

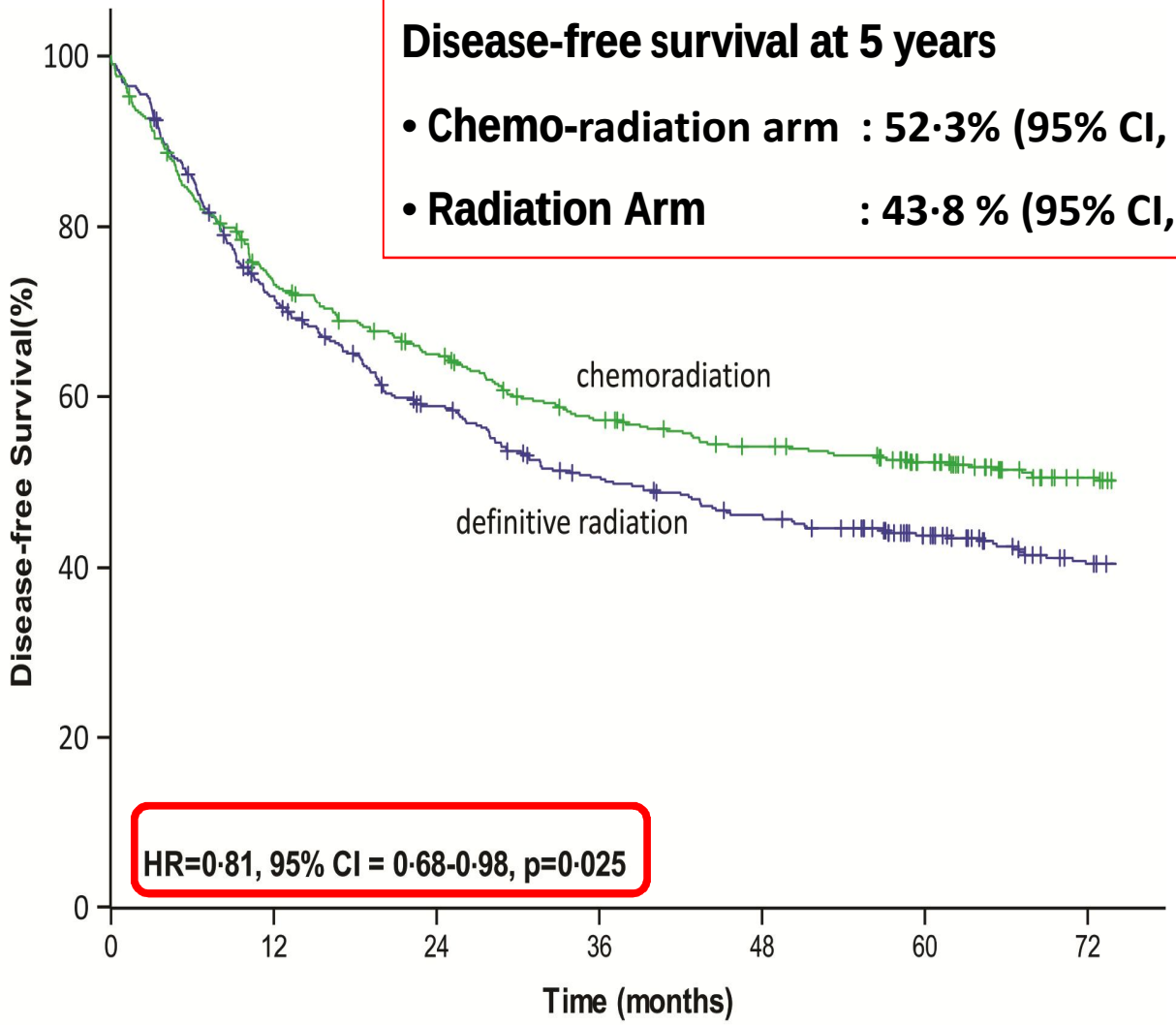
Acute & Late Toxicities by Arms

	Chemo-radiation ARM (N = 424)		Radiation Alone ARM (N = 426)	
Acute Toxicities	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Gastro-intestinal	-	37(8·7%)	-	24 (5·6%)
Genito-urinary	-	124(29%)	-	119 (27·9%)
Skin	-	141(33·2%)	-	149(35%)
Hematological				
Anemia	351 (82·7%)	24 (5·7%)	341 (80%)	22 (5·5%)
Leucopenia	214 (50·4%)	**19 (4·5%)**	75 (17·6%)	**03 (0·7%)**
Neutropenia	80 (18·8%)	**6 (1·5%)**	23 (5·4%)	**01 (0·2%)**
Thrombocytopenia	108 (25·4%)	04 (0·9%)	46 (10·8%)	02 (0·5%)
Deranged serum creatinine levels	143 (33·7%)	05 (1·2%)	94 (22·1%)	04 (1%)
Late toxicities				
Recto-sigmoid Bleeding proctitis/ Ulceration / Stricture /Fistula	-	**29 (6·8%)** 21 / 05 / 02 / 01	-	**19 (4·4%)** 09 / 07 / 01 / 02
Bladder **T**elangiectasia / Vesico-vaginal fistula	-	**08 (2%)** 08 / 00	-	**12 (2·8%)** 11 / 01 (due to recurrence)

Disease free Survival by Arms: ITT Analysis

Disease-free survival at 5 years

- **Chemo-radiation arm : 52·3% (95% CI, 52.25 – 52.35)**
- **Radiation Arm : 43·8 % (95% CI, 43.75 – 43.85)**



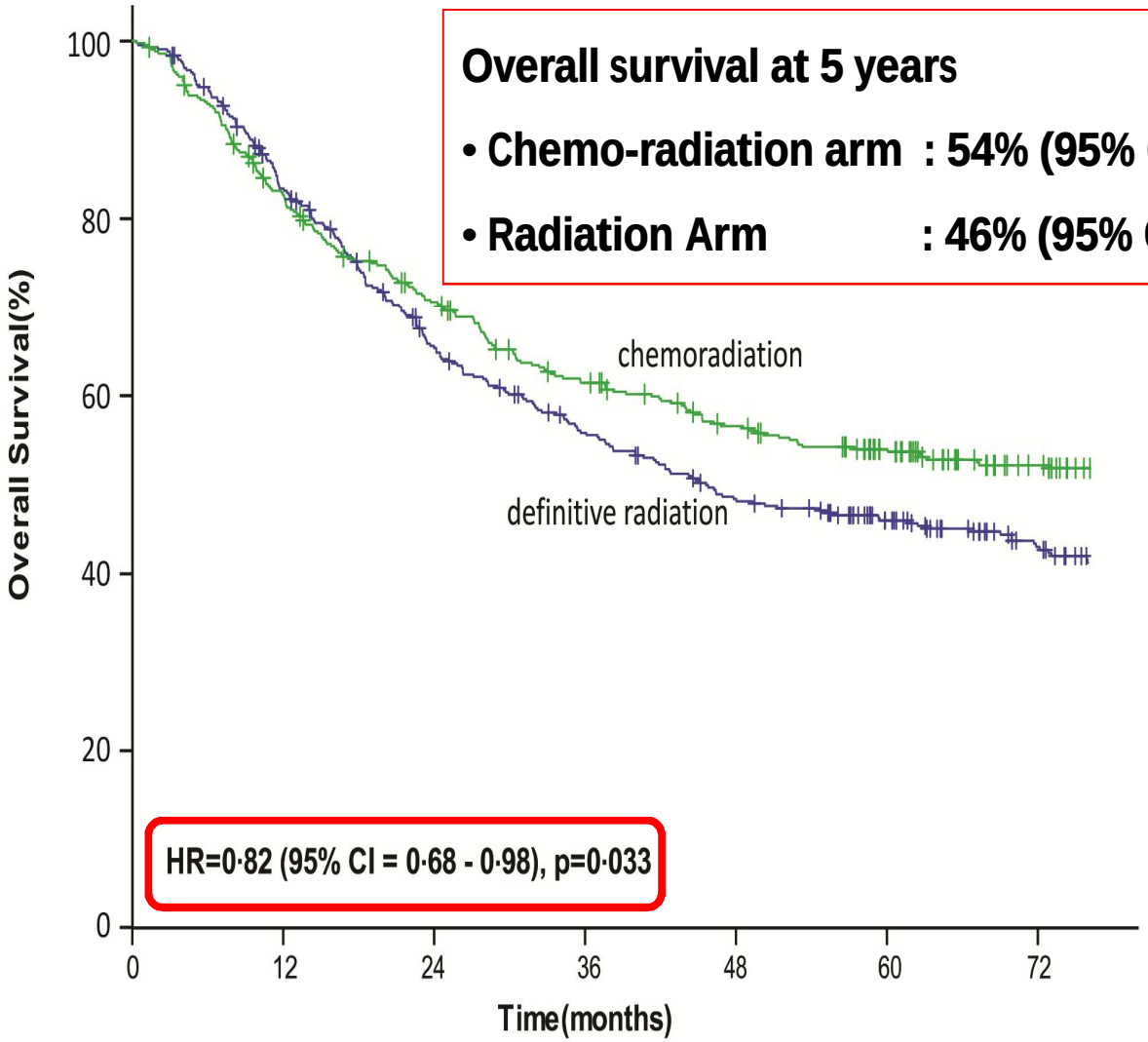
chemoradiation	424	305	265	228	208	188	157
definitive radiation	426	298	236	197	177	147	117

JAMA Oncol. Feb 2018

Overall Survival by Arms: ITT Analysis

Overall survival at 5 years

- **Chemo-radiation arm : 54% (95% CI, 53.95 – 54.05)**
- **Radiation Arm : 46% (95% CI, 45.95 – 46.05)**



chemoradiation	424	345	289	246	219	194	161
definitive radiation	426	347	264	220	187	157	125

JAMA Oncol. Feb 2018

PATTERNS OF FIRST FAILURE BY TWO ARMS

	Chemo-radiation ARM (N = 424)	Radiation Alone ARM (N = 426)
Overall Loco-regional	**90 (21·2%)**	**94 (22·1%)**
Local Only	66	68
Regional Only	16	18
Loco-regional	08	08
Distant only	**58 (13·7%)**	**69 (16·2%)**
Para-aortic	12	13
Lung only	16	18
Liver only	08	08
Bone	06	12
Left Supralavicular node	04	06
Combined /others like brain	12	12
Overall Loco-regional + Distant metastases	**31 (7·3%)**	**43 (10·1%)**
local +distant metastasis	09	14
Regional + distant metastasis	15	20
Loco-regional + distant	07	09
Secondary malignancy	01 (0·2%)	01 (0·2%)

Overall loco-regional and distant metastasis were lower by 5-6% in Chemo-radiation Arm

CONCLUSIONS

- **Our hypothesis of benefit of cisplatin based concomitant chemo-radiation in FIGO Stage IIIB is proven**
- **Concomitant cisplatin based chemo-radiation resulted in signficantly improved disease free & overall survivals with an absolute benefit of 8.5 % and 8% respectively in FIGO Stage III B (Squmaous cell carcinoma) Cervical Cancer**

JAMA Oncol. Feb 2018

CONCLUSIONS contd..

- **Our study is the largest trial in a homogenous group of advanced stage (IIIB) cervical cancer to prove the benefit of relatively simple and well tolerated concomitant cisplatin chemotherapy regimen over adequately delivered radiation therapy.**

Our study confirms that concomitant weekly ciplatin based chemo-radiation should be the standard of care in FIGO Stage IIIB Squamous Cell Cervical Cancer

JAMA Oncol. Feb 2018

Brachytherapy with Concurrent chemotherapy

Pilot study of 36 patients with LA Ca Cx

Hypothesis – BT + CT

Down-staging, Operable, Improve the prognosis.

2 Selectron MDR applications
1 week apart 20-25 Gy at pt A

+

continuous infusion
cisplatin (50 mg m2)
carboplatin (300 mg m-2)

Overall, 83% were disease free at 2.8 years mean follow-up.

Concerning late effects,

Rectovaginal fistula -1
Vesicovaginal fistula -1
Fistula associated with tumor recc - 3

E Koumantakis, BJR

OTHER RADIO-SENSITIZERS

- **CARBOPLATIN**

Higgins et al. Gynecol Oncol 2003

  - Fewer GI, renal and neuropathy than Cisplatin
  - Phase I/II studies - different schedules; wkly AUC 2 safe & active
  - Not compared in a phase III study with Cisplatin

- **PACLITAXEL**

Lee et al. Gynecol Oncol 2007

  - Phase II trial of paclitaxel / carbo with concurrent RT - 33 stage IB to IVB patients
  - RT + P (135 mg/m2) + Carboplatin (AUC 4.5) X 2/3 cycles, 4 wkly.

	Stage I-IIA	IIB	III	IV
3 yr DFS	**67%**	**91%**	**88%**	**50%**
3 yr OS	**89%**	**91%**	**88%**	**50%**

OTHER RADIO-SENSITIZERS

CAPECITABINE

CAPECITABINE + RT Phase II results

TREATMENT SCHEDULE

• RADIOTHERAPY 45Gy and HDR 25 Gy VBT: 8 weeks

• CAPECITABINE(C) 825mg/m2; Monday-Friday, weeks1-8 + *Adjuvant CT (C) x 6 cycles1000mg/m2 bid D1-14

** In patients achieving response or stable disease after Chemo-radiotherapy*

- **N=60 Patients were treated (Median Follow/up: 18.3 months)**
- **Stage at diagnoses IIB: 58%;IIIA: 2%;IIIB: 40%**
- **Overall Responses Rates: 88.3% (95% CI:77.4-95.2)**
  - – Complete Response: 80%
  - – Partial Response: 8.3%
- **Percentage of patients without progression was:**
  - – 86% (95% CI:77-95) at 12 months
  - – 76% (95% CI:65-88) at 23 months

Domingo et al, J Clin Oncol 26, 2008(abst# 5513)

OTHER RADIO-SENSITIZERS

Topotecan

- sabotage repair of sublethal cell injury
- prevent HIF-regulated hypoxic cell survival.

- Dunton and coworkers (2002) maximal tolerance dose (MTD) with RT
  - 1 mg/m^2 daily for 5 days on days 1–5 and 22–26 concomitantly
  - Grade III anemia in one case
  - Grade II leukopenia in two cases
  - Dose limiting toxicity was not reached.
- Bell and associates (2001) Brachy with topiotecan
  - 0.5 mg/m^2.

- Ongoing: Weekly IV Topotecan and Cisplatin With Radiation in Cervical Carcinoma NCT00257816
  - University of california
  - 2004-9

OTHER RADIO-SENSITIZERS

GEMCITABINE

- **Phase I study: 19 patients. MTD not determined.**

Low toxicity profile and highly active (90% CR +PR)

(ASCO 2005, abstr 5142)

- **Randomized phase II: 65 patients stage IIB-IIIB**
  - RT and weekly cisplatin 35 mg/m2 or weekly gemcitabine 150 mg/m2.
  - Similar overall response rate and toxicity
  - Higher CR rate with gemcitabine

(ASCO 2007, abstr 16012)

- ***prompted for further trials especially with concurrent and adjuvant gemcitabine.***

Adjuvant Chemotherapy after Chemo-radiation

- Disease progression after radical radio-chemotherapy:35%
- Distant relapses are major in locally advanced cervical cancer after radical Rx
- Adjuvant CT was part of few trials of Chemo-radiation
- No proper large study evaluating Adj. CT

VOLUME 29 · NUMBER 13 · MAY 1 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III, Open-Label, Randomized Study Comparing Concurrent Gemcitabine Plus Cisplatin and Radiation Followed by Adjuvant Gemcitabine and Cisplatin Versus Concurrent Cisplatin and Radiation in Patients With Stage IIB to IVA Carcinoma of the Cervix

Alfonso Dueñas-González, Juan J. Zarbá, Firuza Patel, Juan C. Alcedo, Semir Beslija, Luis Casanova,

Women with Ca Cervix IIB – IV A with KPS >70% with no evidence of PA LN

Arm A (n= 259 pts)

CCRT + Brachytherapy + Adj. CT

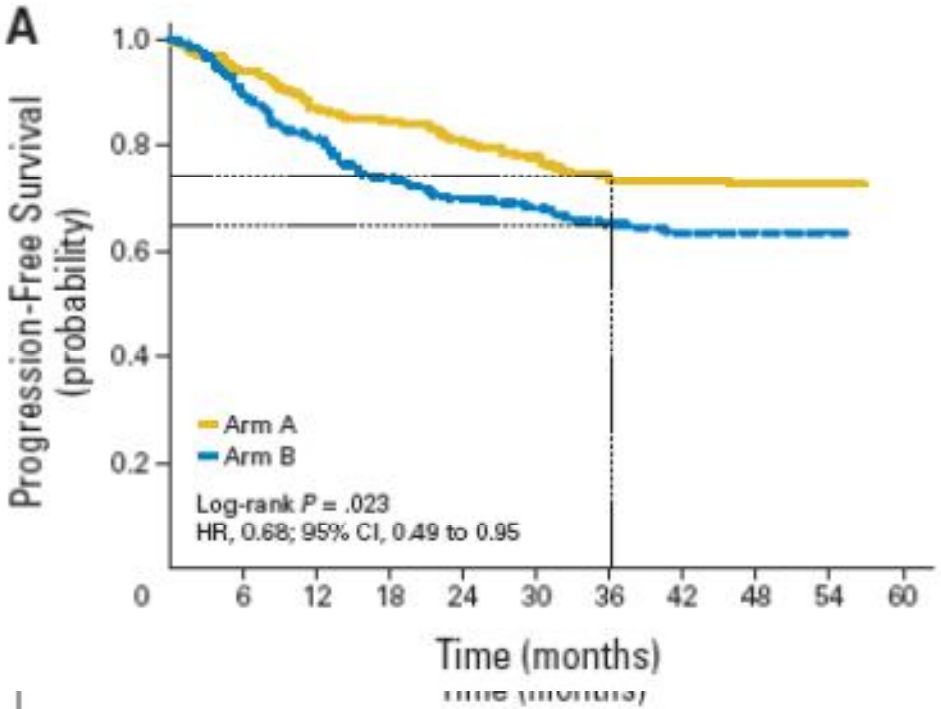
Concurrent Chemo - Weekly Cis 40 mg/m2
+ Gemcitabine 125mg/m2
Adjuvant chemo -2 weeks after brachy
Cisplatin and Gemcitabine 2 cycles

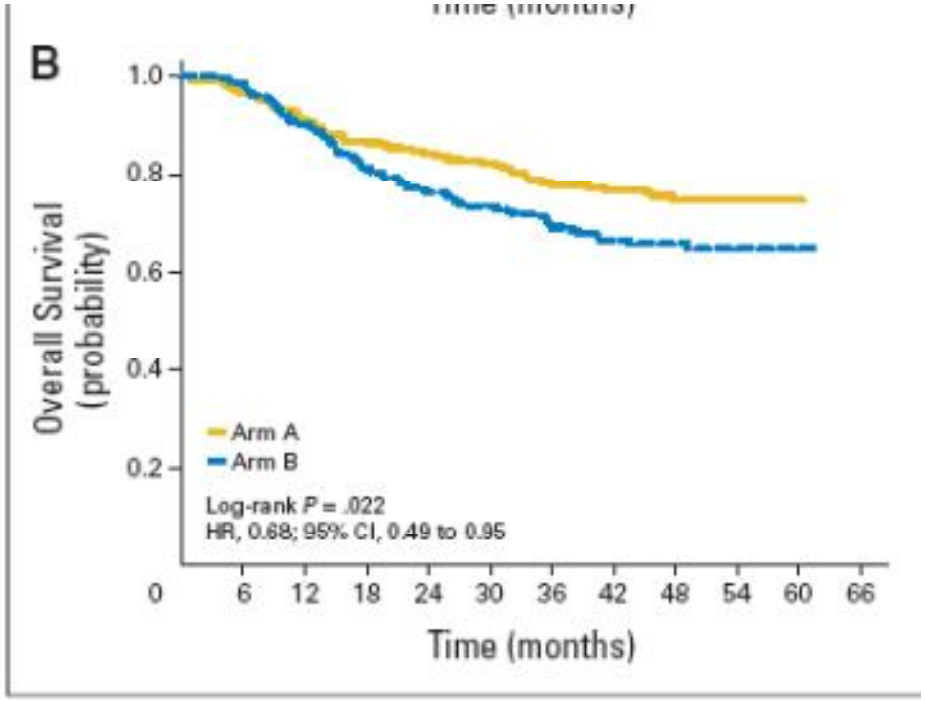
ARM B (n= 256 pts)

CCRT+ BRT
with
Weekly Cis 40mg/m2

Adverse Effects

- Arm A - More Grade 3-4 toxicities (p<0.001)
- Haematologic Toxicity
  - **Grade 3-4 ; 71.9% Vs 23.9 %**
- Non haematologic toxicities
  - Vomiting & diarrhea more in arm A (p=0.002)
- Hospitalization during treatment
  - Arm A -30 pts & Arm B -11 pts (p=0.02)
  - 3 deaths in arm A – 2 due to sepsis and bowel perforation & 1 due to acute encephalopathy
- Late toxicities slightly higher in Arm A
  - Grade 4 GI : 2.3 % Vs 0%





Results

- 3 Y PFS 74.4% Vs 69% (p=0.029)
- Median PFS- HR 0.68
- Statistically significant improvement in median PFS

Conclusion: Gemcitabine + cisplatin CRT followed by Brachy & adjuvant gem/cis CT improved survival outcomes with increased but clinically manageable toxicity compared to standard Rx

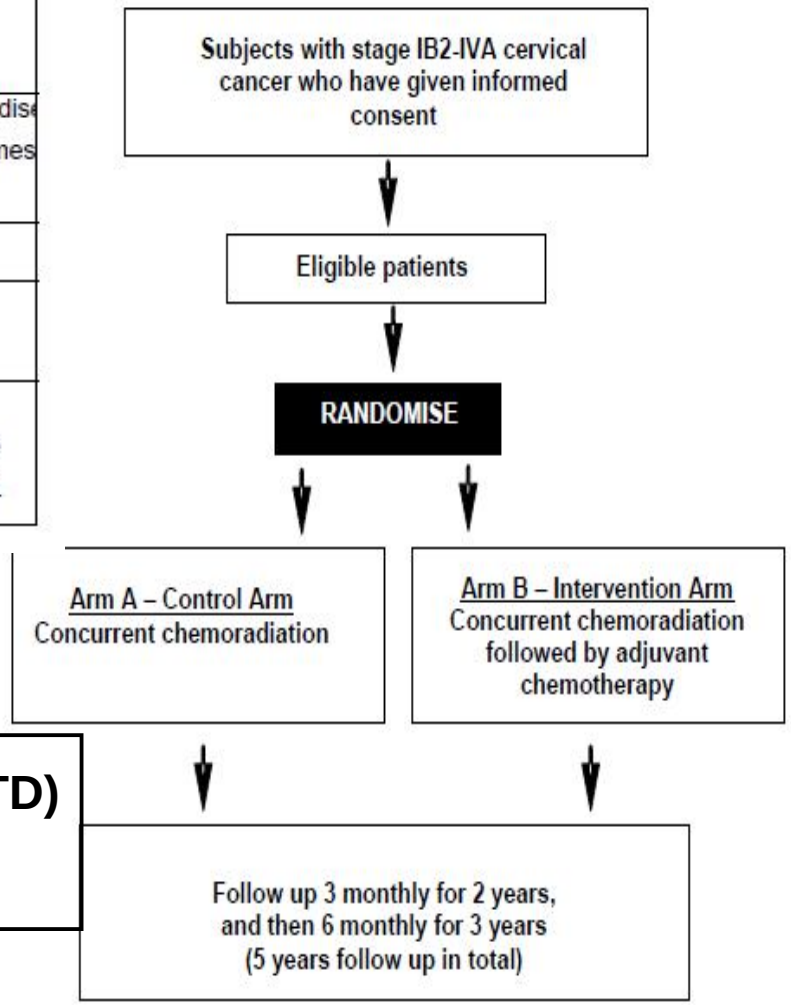
Concurrent CTRT + Adjuvant CT

- Challenges
  - Acute and chronic toxicity
    - Mainly
      - Hematological Toxicity
      - GI toxicity
- Options
  - Non overlapping toxicity drugs
  - Targeted agents
  - Improved radiotherapy techniques to avoid synergistic toxicity

OUTBACK TRIAL

MULTICENTRIC PHASE III STUDY

Primary Objectives:	To determine if the addition of adjuvant chemotherapy to standard cisplatin-based chemo-radiation improves progression-free survival.
Secondary objectives	To determine: overall survival rates, acute and long-term toxicities, patterns of dis recurrence, the association between radiation protocol compliance and outcomes patient quality of life, including psycho-sexual health.
# patients	780
Planned duration	4 years recruitment and a maximum of 5 years follow-up
Statistics	A sample size of 780 provides 80% power to detect an increase in the proportions who are both alive and progression free at 3 years from 55% in the control arm to 65.5% in the experimental arm with a 2-sided type 1 error of 5%.



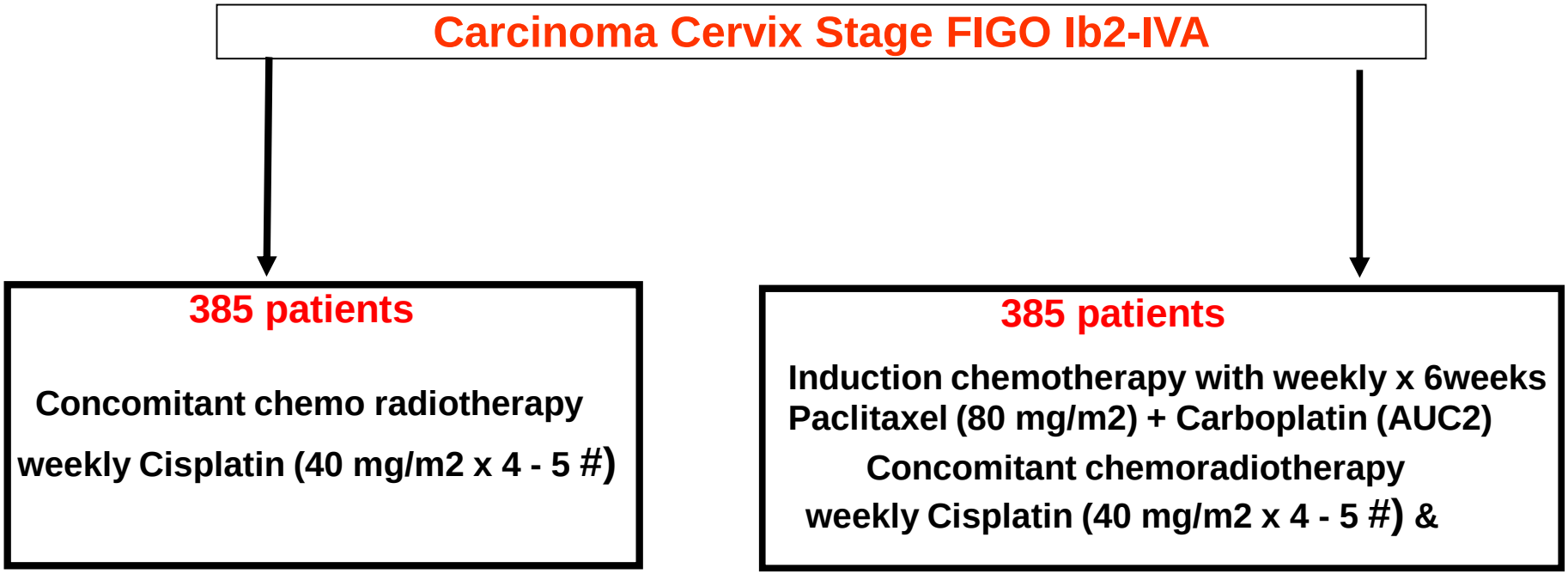
Cisplatin based concurrent chemo-radiation (STD)

Vs CCRT followed by Pacli + Carbo x 3 cycles

Recruited : 600 pts approx.

Induction Chemotherapy followed by Concomitant Chemo-Radiation in Advanced Stage Carcinoma Cervix:

A Phase III Randomized Trial *(INTERLACE Study - NCT01566240)*



Outcomes:

Primary: Overall Survival

Secondary: Progression free Survival

Acute toxicities

Late Toxicities

Initiated in 2012

Accrual period: 4 years

Completion: 2021

BIOLOGIC AGENTS

CELECOXIB

Phase I/II RTOG C-0128
COX-2 inhibitor, Celecoxib, chemoradiation
Locally advanced cervical cancer

- 78 patients
- Celecoxib daily for 12 months (400 mg orally BD)
- CRT -Cisplatin 75 mg/m2 on days 1, 22, and 43

  -5-FU 1 g/m2/d X 4 days – Bolus/cont inf Days 2–5, 23–26 and 44-47.

- At 2 years estimated DFS and OS was 69% and 83%.
- **Problematic loco- regional control**

Gaffney et al. Int J Radiat Biol Oncol Phys, 2007

CRT AND BIOLOGIC AGENTS

VEGF IN CERVICAL CANCER

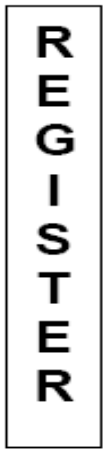
- Intratumoral protein levels of VEGF are increased in patients with cervical cancer when compared to normal cervical tissue (1)
- Increasing intratumoral levels of VEGF correlated with (1):
  - higher stage
  - increased risk of LVI
  - increased risk of lymph nodes metastasis
- Higher VEGF expression was an independent prognostic factor for poor disease-free and overall survival (2)

(1)Cheng et al. Obstet Gynecol 2000;96:721-6

(2)Loncaster et al. Br J Cancer 2000;83(5):620-5

BIOLOGIC AGENTS - BEVACIZUMAB

Phase II study of Bevacizumab in combination with definitive radiotherapy and cisplatin in locally advanced cervical carcinoma (RTOG 0417)



Pelvic RT:

45 Gy given in 25 once-daily fractions (1.8 Gy/fraction) Monday-Friday over 5 weeks

↓

LDR x 2 or HDR x 5

↓

Parametrial boost (if indicated)

Bevacizumab (Avastin®): IV Q2 weeks (Days 1, 15 and 29, total of 3 doses) during chemoradiation, given before cisplatin, on the same day as cisplatin

Cisplatin: Weekly infusion x 6 weeks

- 60 patients from 25 institutions were enrolled between 2006 and 2009
- 49 patients evaluable.
- Median follow-up of 10 months (Mostly IIB 63%, squamous-80%) no treatment-related SAEs.
- There were 15 (31%) protocol specified treatment-related AEs, most common were hematologic (12/15 =80%)

2010 ASCO Annual Meeting : J Clin Oncol 28:15s, 2010 (suppl; abstr 5006)

GOG 240
Schema

Eligibility:

1. Primary stage IVB or Recurrent/persistent carcinoma of the cervix

2. Measureable disease

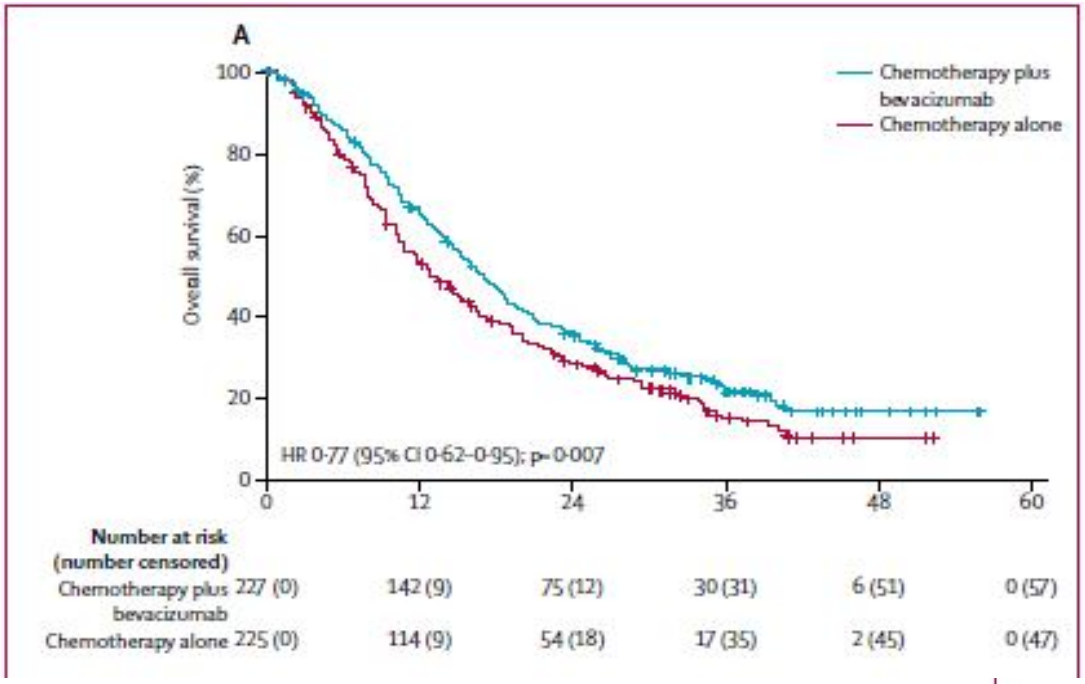
3. GOG PS 0-1

Regimen I
Paclitaxel 135 mg/m^2 IV d1 (24h)
Cisplatin 50 mg/m^2 IV d2
Q21d to progression/toxicity

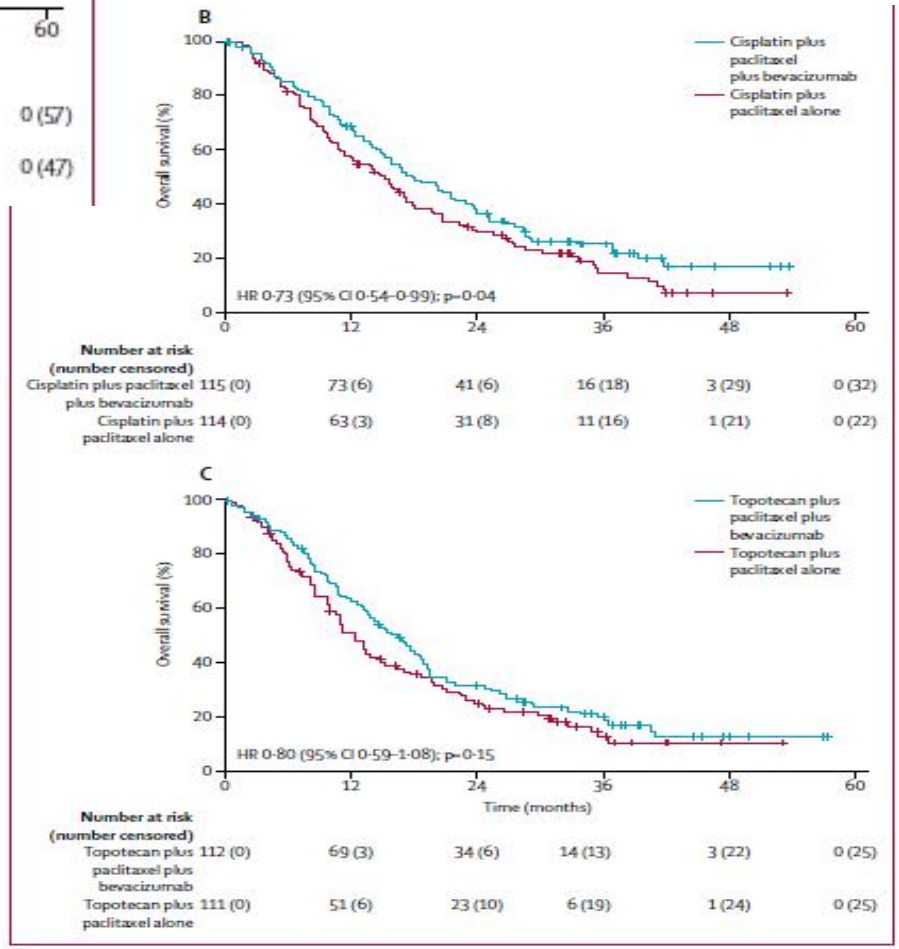
Regimen II
Paclitaxel 135 mg/m^2 IV d1 (24h)
Cisplatin 50 mg/m^2 IV d2
Bevacizumab 15 mg/kg IV d2
Q21d to progression/toxicity

Regimen III
Paclitaxel 175 mg/m^2 IV d1 (3h)
Topotecan 0.75 mg/m^2 d1-3 (30m)
Q21d to progression/toxicity

Regimen IV
Paclitaxel 175 mg/m^2 IV d1 (3h)
Topotecan 0.75 mg/m^2 d1-3 (30m)
Bevacizumab 15 mg/kg IV d1
Q21d to progression/toxicity



Number at risk (number censored)						
Chemotherapy plus bevacizumab	227 (0)	142 (9)	75 (12)	30 (31)	6 (51)	0 (57)
Chemotherapy alone	225 (0)	114 (9)	54 (18)	17 (35)	2 (45)	0 (47)



Number at risk (number censored)						
Cisplatin plus paclitaxel plus bevacizumab	115 (0)	73 (6)	41 (6)	16 (18)	3 (29)	0 (32)
Cisplatin plus paclitaxel alone	114 (0)	63 (3)	31 (8)	11 (16)	1 (21)	0 (22)
Topotecan plus paclitaxel plus bevacizumab	112 (0)	69 (3)	34 (6)	14 (13)	3 (22)	0 (25)
Topotecan plus paclitaxel alone	111 (0)	51 (6)	23 (10)	6 (19)	1 (24)	0 (25)

	Cisplatin plus paclitaxel (n=114)	Cisplatin plus paclitaxel plus bevacizumab (n=115)	Topotecan plus paclitaxel (n=111)	Topotecan plus paclitaxel plus bevacizumab (n=112)	Total (n=452)
Complete response	11 (10%)	18 (16%)	6 (5%)	13 (12%)	48 (11%)
Partial response	41 (36%)	40 (35%)	22 (20%)	41 (37%)	144 (32%)
Stable disease	45 (39%)	42 (37%)	54 (49%)	43 (38%)	184 (41%)
Progressive disease	12 (11%)	7 (6%)	21 (19%)	6 (5%)	46 (10%)
Indeterminate	5 (4%)	8 (7%)	8 (7%)	9 (8%)	30 (7%)

Data are n (%).

Table 2: Tumour response

	Chemotherapy alone (n=220)	Chemotherapy plus bevacizumab (n=220)	Risk ratio	p value
Grade 2 genitourinary fistula	1 (<1%)	8 (4%)	8·00 (1·01–63·43)	0·04
Grade 3 genitorurinary fistula	1 (<1%)	6 (3%)	6·00 (0·73–49·43)	0·12
Grade 2 GI fistula	1 (<1%)	11 (5%)	11·00 (1·43–84·48)	0·006
Grade 3 GI fistula	0	7 (3%)	NA	0·02
Grade 2 or higher hypertension	4 (2%)	55 (25%)	13·75 (5·07–37·29)	0·001
Grade 4 or higher neutropenia	58 (26%)	80 (36%)	1·37 (1·04–1·83)	0·03
Grade 3 or higher febrile neutropenia	12 (5%)	12 (5%)	1·00 (0·46–2·18)	1
Grade 3 or higher GI bleeding	1 (<1%)	4 (2%)	4·00 (0·45–35·50)	0·37
Grade 3 or higher proteinuria	0	5 (2%)	NA	0·06
Grade 3 or higher thrombosis or embolism	4 (2%)	18 (8%)	4·50 (1·55–13·08)	0·004
Grade 2 or higher pain	63 (29%)	72 (33%)	1·14 (0·86–1·51)	0·41

Data are n (%) or risk ratio (95% CI). GI=gastrointestinal. NA=not applicable.

Table 3: Adverse events

GOG 240: Conclusions

- Bevacizumab plus chemotherapy significantly improves OS in stage IVB, recurrent or persistent cervical carcinoma
  - Nearly 4-month improvement in OS is clinically significant
  - Increase in median PFS and ORR are also demonstrated
  - Cisplatin + paclitaxel arm is current standard of care and did not underperform
  - Benefit seen even when recurrent disease is in irradiated pelvis
- Bevacizumab treatment is associated with a higher rate of AEs
  - 3–8% rate of known bevacizumab-related AEs
- The improvement in OS with bevacizumab treatment was not accompanied by a decrease in HRQoL
- First targeted agent to improve OS in a gynecologic cancer

ASCO Plenary Session 2013
Lancet 2017

Safety Study of Nelfinavir + Cisplatin + Pelvic Radiation Therapy to Rx Cervical Ca

NCT01485731
Phase I target 24 patients January 2012: recruiting

Study of Nimotuzumab, Radiation Therapy and Cisplatin Versus Radiation Therapy and Cisplatin for Treatment of Stage IB e IVA UCC(CORUS)

Phase II NCT01301612; February 21, 2011; yet to open

Panitumumab, Cisplatin, and Pelvic Radiation Therapy in Treating Patients With Stage IB, Stage II, or Stage III Cervical Cancer

Phase II; CDR0000675699
MUI-AGO-20, EUDRACT-2009-012453-38, EU-21043, NCT01158248
recruiting 2009-2013

Cidofovir in Treating Patients With Stage IB, Stage II, Stage III, or Stage IVA Cervical Cancer Who Are Receiving Chemotherapy and Radiation Therapy

NCT00811408; 2008, status unknown

Erlotinib, Cisplatin, and Radiation Therapy in Treating Patients With Stage IB-Stage IVA Cervical Cancer
This study has been terminated. (Withdrawn due to lack of accrual)
Mansonic Cancer Centre; University of Minnesota

Cetuximab, Cisplatin, and Radiation Therapy in Treating Patients With Stage IB, Stage II, Stage III, or Stage IVA Cervical Cancer
This study is currently recruiting participants. GOG-NCI; Last Updated: February 10, 2011

Cetuximab, Cisplatin, and Radiotherapy in Women With Locally Advanced Cervical Carcinoma
This study is currently recruiting participants University of Virginia
Bristol-Myers Squibb

Radiation Therapy and Cisplatin With or Without Cetuximab in Treating Patients With Stage IB, Stage II, or Stage IIIB Cervical Cancer
This study is currently recruiting participants. Institute Curie NCI

SUMMARY
Chemotherapy IN Cervical Cancers

- **Neo - adjuvant Chemotherapy:**
  - **NACT followed by RT Vs RT: No Benefit**
  - **NACT followed by Sx Vs RT:** Some Benefit but has major limitations
  - **NACT followed by Sx Vs Sx: CR better but no survival benefit**
  - **NACT followed by Sx Vs Chemo-RT: Chemo-radiation STD of Care**
- **Concomitant Chemotherapy : STD of Care**
- **Concomitant followed Adjuvant CT : Still Investigational**
- **Palliative CT in recent era : Bevacizumab some benefit**

SUMMARY AND CONCLUSIONS

- ***Radical Radiation Therapy : Established treatment modality***
- ***Neo-adjuvant CT approaches: Investigational***
- ***CRT with Cisplatin extensively tested for cervical cancer***
- ***Concomitant Chemo-radiation with wkly cisplatin (40 mg/m2) : STD of Care***
  - ***CRT with weekly cisplatin recommended for FIGO Stage I B2 - IIB***
  - ***Post Wertheim's high risk Patients : CRT***
  - ***CRT for FIGO Stage III-IVA: to be established further (CRACx study)***
- ***Role of concomitant chemo-brachytherapy is not clearly established***
- ***Alternatives to Cisplatin: No much progress including biological agents***
- ***Adjuvant CT after CRT & Induction CT: Phase III studies ongoing***
- ***Targeted therapy / biological agents: Bevasizumab***

ACKNOWLEDGEMENTS

Tata Memorial Centre

IAEA & Teaching Material

ESTRO Teaching Material

ESTRO Faculty

Patients

mahantshettyum@tmc.gov.in