"An Update and Challenges"

in

Treatment of GYN (Cervical) Cancers

A Radiation Oncologist's Perspective!

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&

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Executive Committee Member – Assoc. GYN Oncol of India (AGOI)

ANZGOG 2019 ANNUAL SCIENTIFIC MEETING : 20th – 23rd March 2019

NO RELEVANT DISCLOSURES TO DECLARE

TATA MEMORIAL CENTRE, MUMBAI, INDIA

TERTIARY CANCER CENTRE EXPERIENCE

ACTREC
&
Centre for Cancer Epidemiology

ADVANCED CENTRE FOR TREATMENT RESEARCH AND EDUCATION IN CANCER

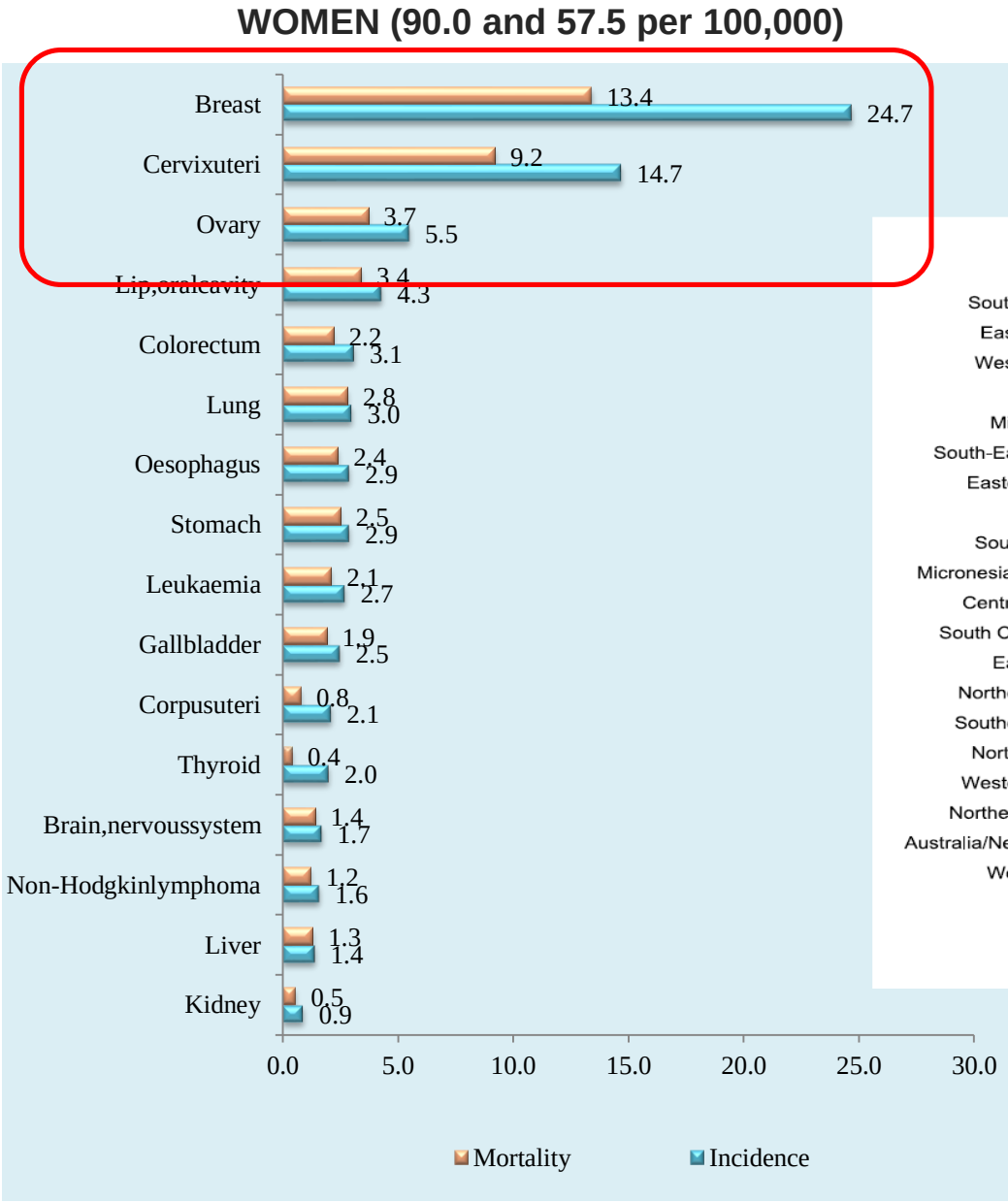
MISSION
Service
Research
Education

New Cases:
42,000 annually

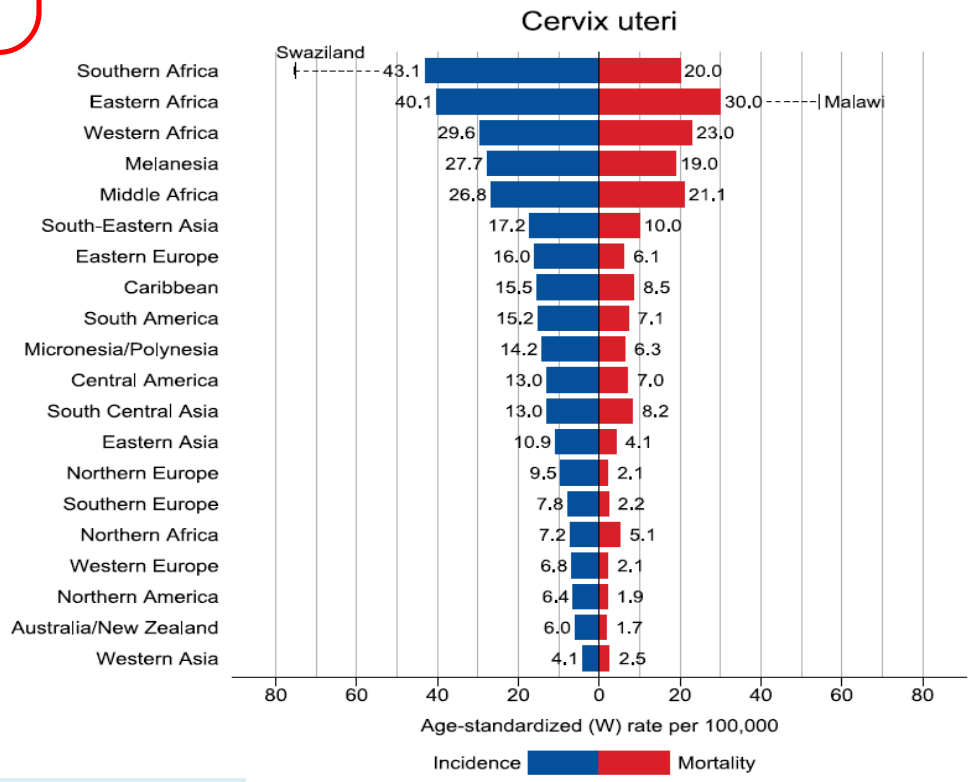
Radiotherapy for
all cancers
5500 annually

CERVCIAL CACNER : INDIAN SCENARIO - GLOBOCAN 2018

Estimated Incidence and Mortality Rates (ASR per 10^5)

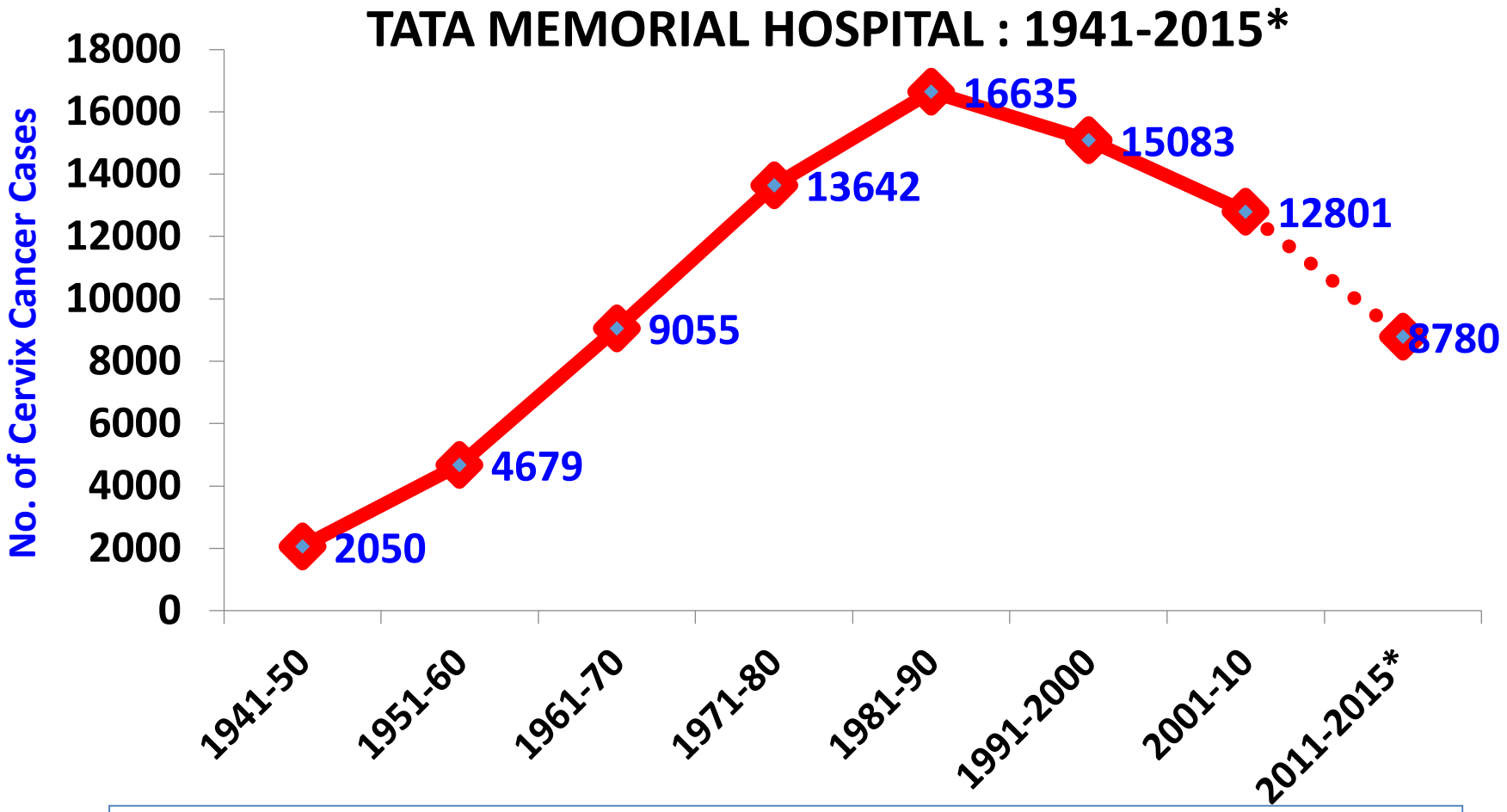


ASR for Cervical Cancer GLOBOCAN 2018



Advanced Disease in LMIC's/ LIC's

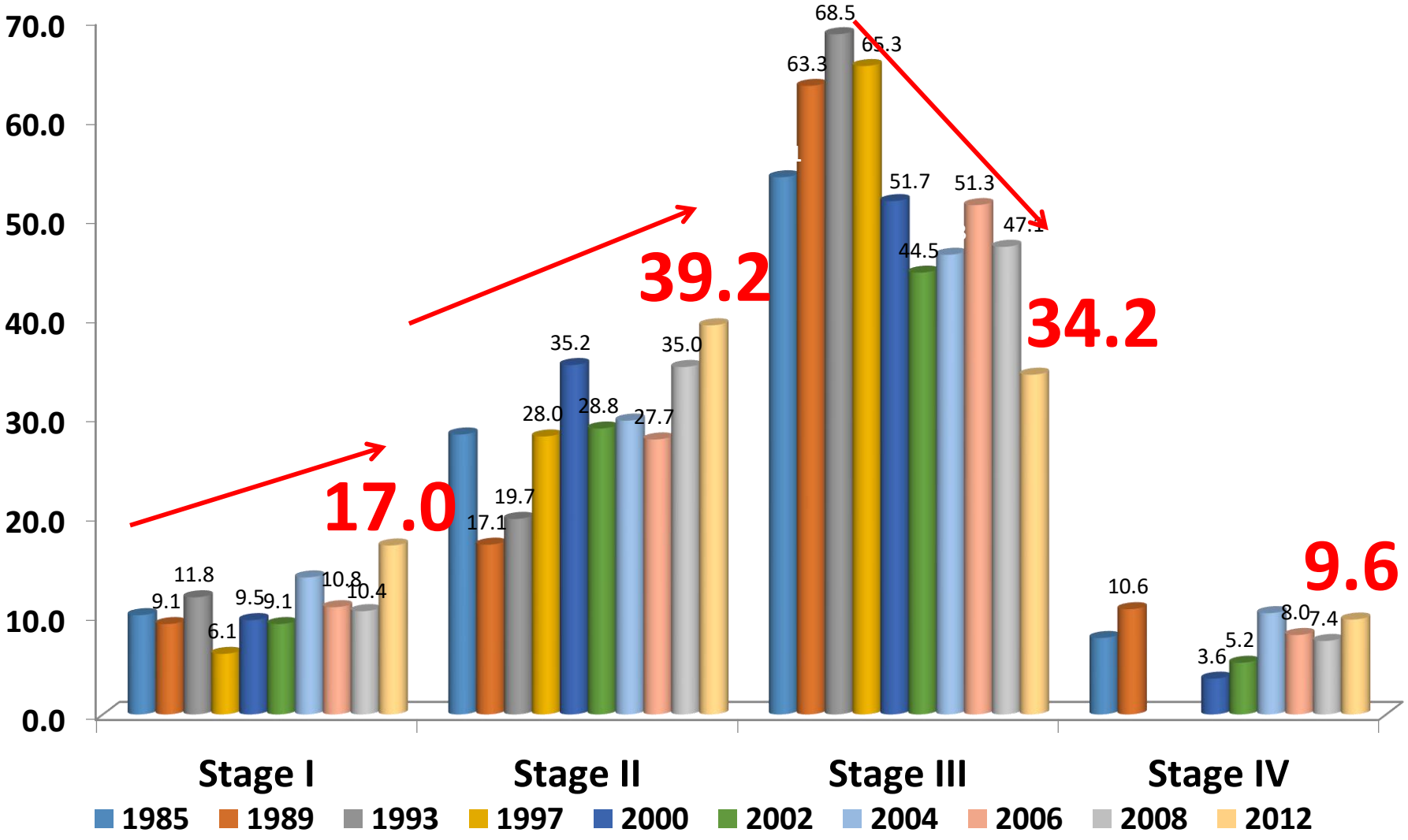
TRENDS OF CERVICAL CANCER



- **Radical RT +/- CT: 400 – 450 -500 pts annually**
- **Brachytherapy : Average 6 (3 - 9) pts Cx IC/ IC+IS daily**
  - 3 - 4 X-ray based; 2-3 CT based & 1 MR Based Planning
- **Template based : 1-2 pts Interstitial /wk (CT Based)**

Tata Memorial Hospital Cancer Registry (1985-2012)

Significant Down Staging!

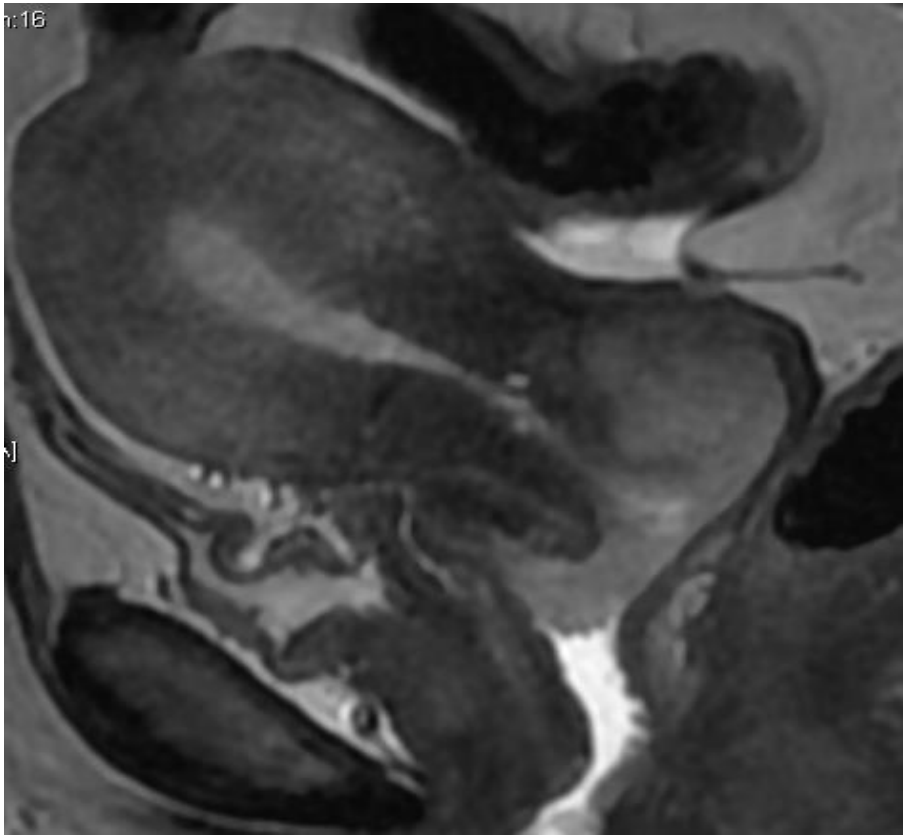


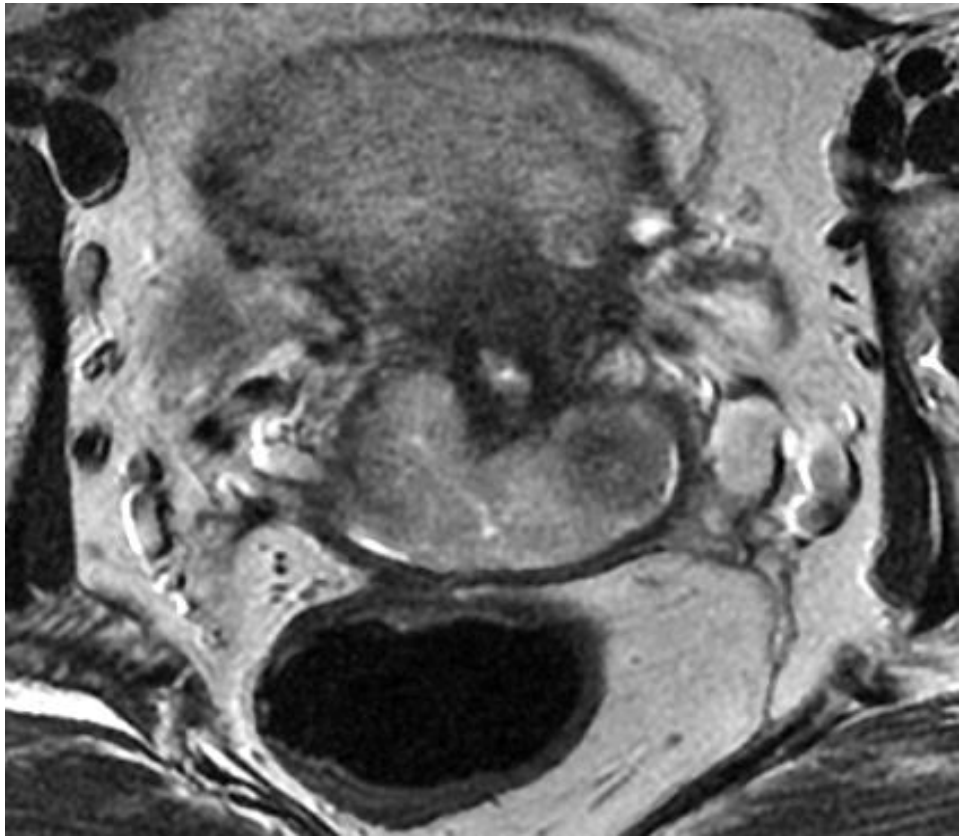
CHALLENGES & UPDATES : GYN Cancers

- High Disease Burden & Advanced Disease (cervix) in LMIC's & LIC's
- Radiotherapy Infrastructure, Accessibility & Logistics
- Combined Modality treatments :
  - Neo-adjuvant chemotherapy followed by Sx (IB2-IIB)
  - Concomitant Chemo-radiation in Adv. Disease (IIIB)
  - Neo-adjuvant CT / Adjuvant CT followed by CTRT (other sessions)
- Brachytherapy: Utilization & Advances
- Post treatment relapses, treatment & outcome

FIGO Stage Ib2-IIB: Neoadjuvant chemotherapy + Sx

A. Primary Tumor : T1b2
B. No significant pelvic or PA lymph nodes on CT Abd





Final Stage: FIGO Ib2 (2018) / T1b2N0(i)

Q: Which of the following treatment options would you offer and why? And how would you help patient in decision making?

- **Radical Chemo-radiation**
- **Radical Surgery + Radiation +/- chemotherapy**
- **Neo - adjuvant chemo + Surgery**
- **Any other ?**

Neo-adjuvant Chemotherapy + Surgery

Versus

Concurrent Chemo-radiation (STD)

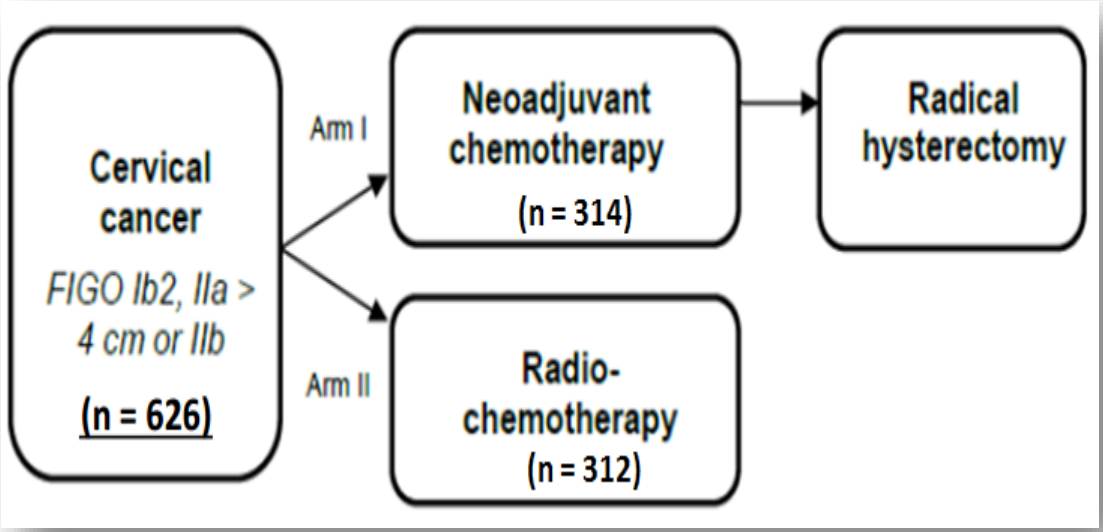
in Stage IB2 / IIB Squamous Carcinoma of Cervix

EORTC – 55994 STUDY

TMH NACT STUDY

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**

Final Analysis: 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

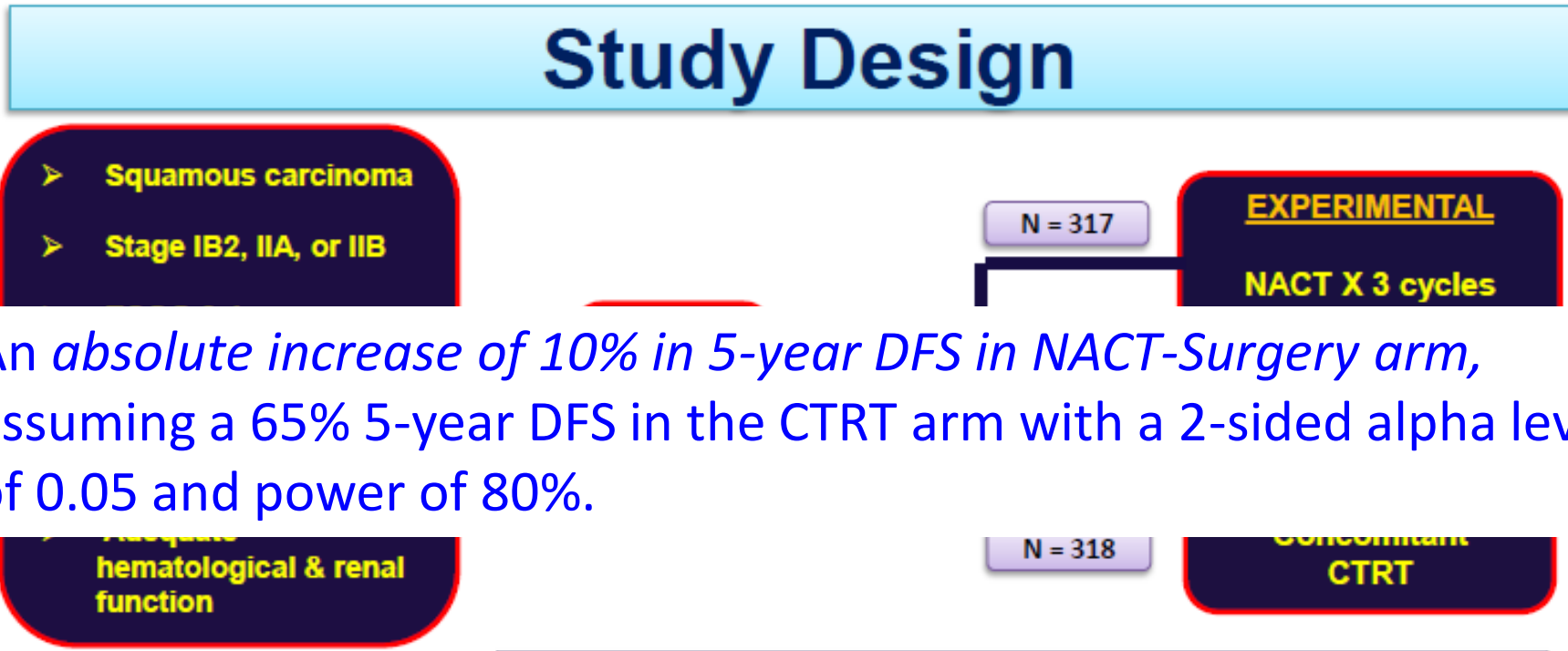
Funded by Tata Memorial Centre, Government of India

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%.

Study Design…

- **Planned cross-over from NACT-Surgery to CTRT**
  - ✓ No response or progression after 2nd or 3rd cycle NACT
  - ✓ Intraoperative unresectability of primary tumor or lymph node disease
- **Postoperative adjuvant RT**
  - ✓ T > 4 cm, LVSI +, deep cervical stromal invasion, (any two)
- **Postoperative adjuvant CTRT**
  - ✓ LN +, parametrium +, surgical margin +, (any one)

MADRID 2017 ESMO congress

END POINTS

- PRIMARY : DISEASE FREE SURVIVAL

- SECONDARY : OVERALL SURVIVAL & TOXICITIES

Patient Characteristics

Characteristic	NACT-Surgery (N=316)	CTRT (N=317)	All (N=633)
ECOG PS			
0	290 (91.8%)	293 (92.4%)	583 (92.1%)
1	26 (8.2%)	24 (7.6%)	50 (7.9%)
FIGO Stage			
IB2	57 (18.0%)	56 (17.7%)	113 (17.9%)
IIA	80 (25.3%)	78 (24.6%)	158 (25.0%)
IIB	179 (56.7%)	183 (57.7%)	362 (57.2%)
Radiological pelvic LN status			
Positive	46 (14.6%)	45 (14.2%)	91 (14.4%)
Negative	270 (85.4%)	272 (85.8%)	542. (85.6%)

Adjuvant RT / CTRT after NACT + Sx : 23%

Treatment in NACT-Surgery Arm

Radical Surgery	N (%)
Yes	227 (71.8%)
No	89 (28.2%)
Loco-regional treatment in NACT-surgery arm *	
Radical Surgery	227 (71.8%)
Definitive CTRT	68 (21.5%)
Adjuvant CTRT	42 (13.3%)
Adjuvant RT	31 (9.8%)

- Numbers are more than group total because some surgical patients received adjuvant RT or CTRT

Adjuvant RT / CTRT after NACT + Sx : 23%

Acute toxicity during treatment or within 42 days after treatment

Toxicity	NACT-Surgery (N=316)		CTRT (N=317)		p value grade 3-4
	Grade 1-2	Grade3-4	Grade 1-2	Grade 3-4	
HAEMATOLOGICAL					
Anemia	20 (6.3%)	8 (2.5%)	15 (4.7%)	2 (0.6%)	0.063
Thrombocytopenia	13 (4.1%)	11 (3.5%)	6 (1.9%)	1 (0.3%)	0.003
Neutropenia	17 (5.4%)	6 (1.9%)	12 (3.8%)	3 (0.9%)	0.340
NON-HAEMATOLOGICAL					
Abdominal pain	71 (22.5%)	6 (1.9%)	66 (20.8%)	1 (0.3%)	0.069
Vomiting	157 (49.7%)	6 (1.9%)	161 (50.8%)	3 (0.9%)	0.340
Diarrhea	63 (20%)	5 (1.6%)	104 (32.8%)	9 (2.8%)	0.419
Gastrointestinal bleeding	6 (1.9%)	0	3 (0.9%)	0	-

Acute grade ¾ hematological higher in study arm

Toxicity of any grade occurring or persisting more than 24 months after completion of treatment

Site	NACT-Surgery (N=316)	CTRT (N=317)	p value
Rectal	7 (2.2%)	11 (3.5%)	0.474
Bladder	5 (1.6%)	11 (3.5%)	0.204
Vaginal	38 (12.0%)	81 (25.6%)	<0.001
Other	17 (5.4%)	11 (3.5%)	0.334

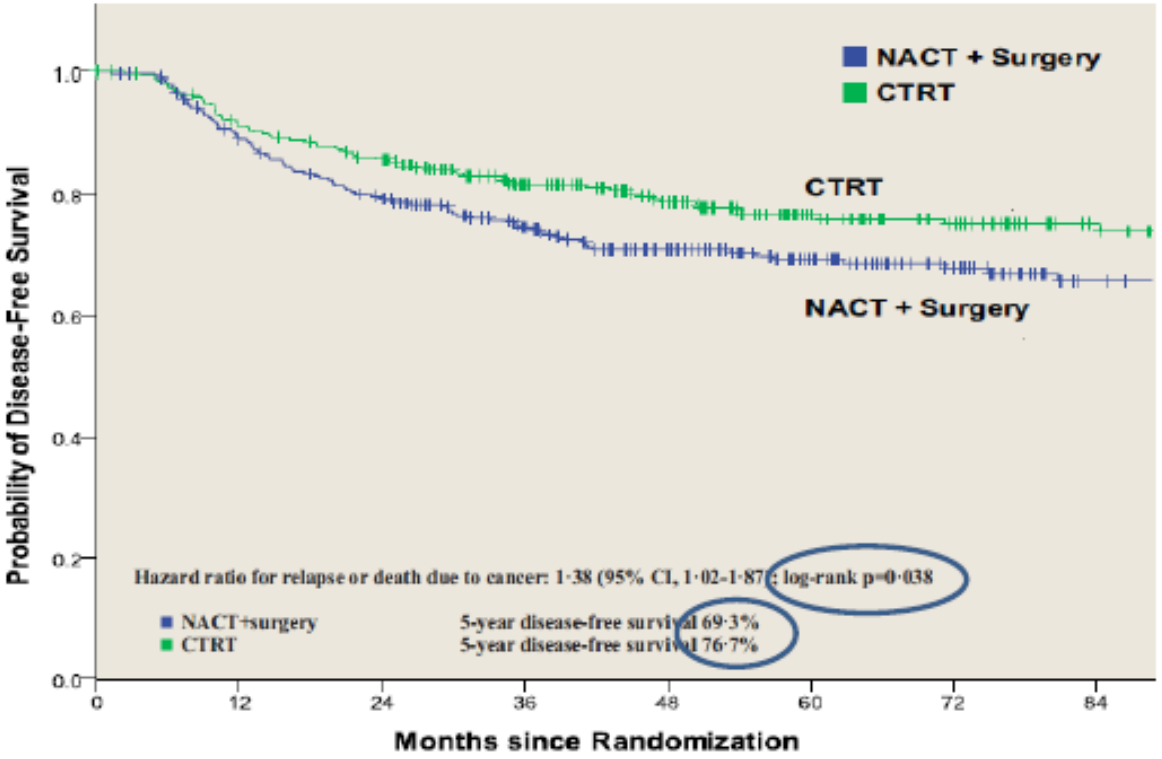
MADRID 2017 ESMO congress

Late vaginal toxicities : higher with CTRT

ESMO PLENARY PRESENTATION – 2017

TMH NACT STUDY

Disease-free survival in intention-to-treat population

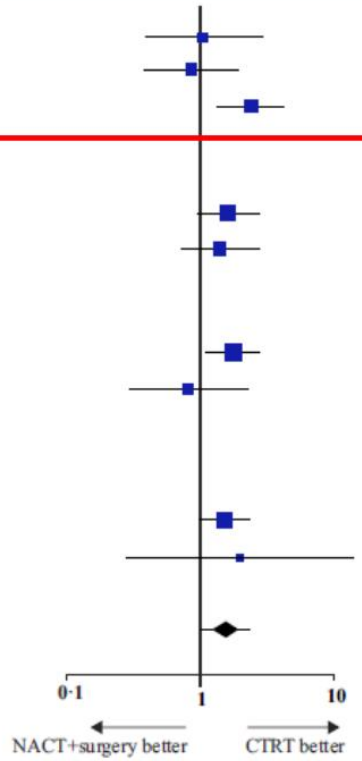


No. at Risk								
NACT+Surgery	316	266	233	192	152	114	84	54
CTRT	317	282	261	210	167	116	85	60

Gupta et al; JCO Feb 2018

Subgroup Analysis for DFS

	Number of events/number of patients		Hazard ratio (95% CI)	p value for interaction
	NACT+surgery	CTRT		
Stage				
IB2	16/57	15/56		0·14
IIA	22/80	23/78		0·04
IIB	57/179	36/183		
Haemoglobin				0·78
>11	60/206	44/203		
≤11	35/110	30/114		
Pelvic lymph node status				0·15
Negative	82/270	58/272		
Positive	13/46	16/45		
ECOG performance status				0·79
0	90/290	71/293		
1	5/26	3/24		
All patients	95/316	74/317		



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
TMH NACT STUDY

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

VOLUME 26 · NUMBER 35 · DECEMBER 10 2008

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Reducing Uncertainties About the Effects of Chemoradiotherapy for Cervical Cancer: A Systematic Review and Meta-Analysis of Individual Patient Data From 18 Randomized Trials

Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration

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

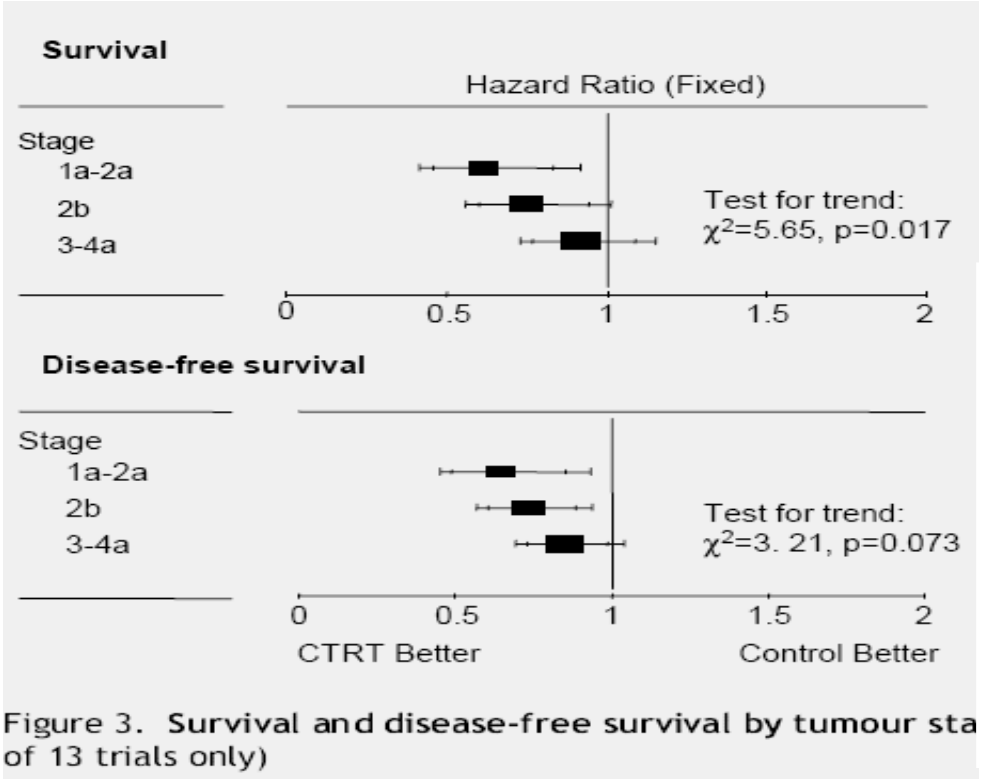
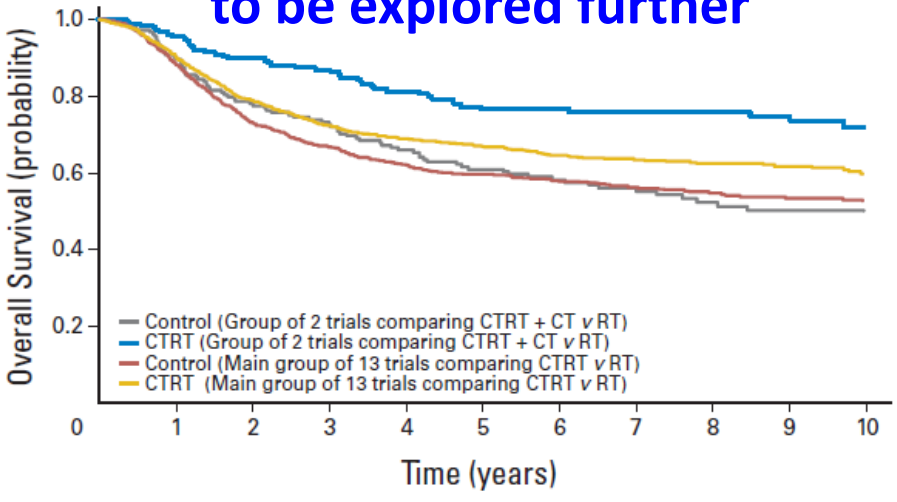


Figure 3. Survival and disease-free survival by tumour sta
of 13 trials only)

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

CRITICAL REVIEW OF EVIDENCE

Advanced Disease (IIIB) in LMIC's IIIB

- 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

PLENARY PRESENTATION
Abstract Number: ESGO- 7-1305

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

ESGO 20 INTERNATIONAL MEETING OF THE EUROPEAN SOCIETY OF GYNAECOLOGICAL ONCOLOGY (ESGO)
NOVEMBER 04-07, 2017 | VIENNA, AUSTRIA
European Gynaecological Oncology Congress 2017

STUDY DESIGN

Open label phase III randomized 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*

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*

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 completion	**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

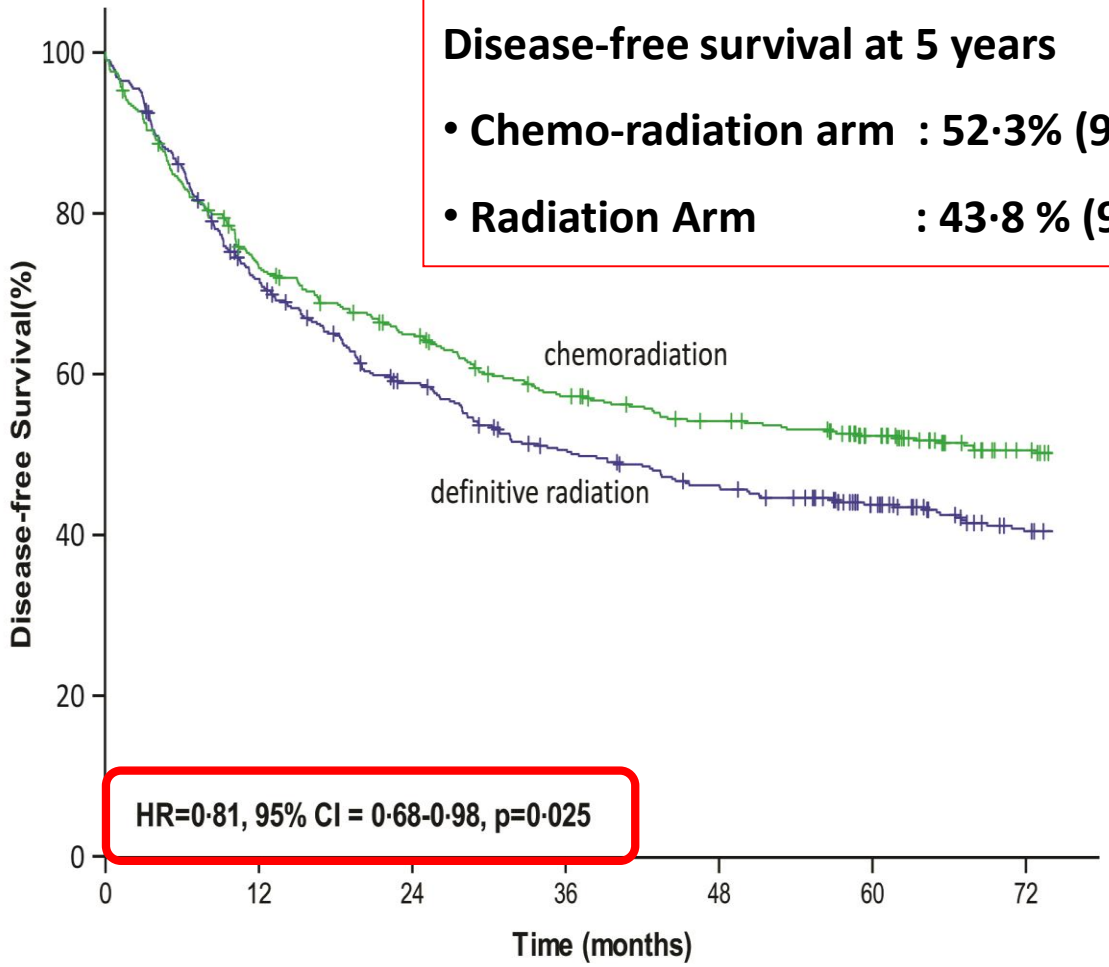
Acute & Late Toxicities by Arms

	CTRT ARM (N = 424)		RT 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 Telangiectasia / 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)**



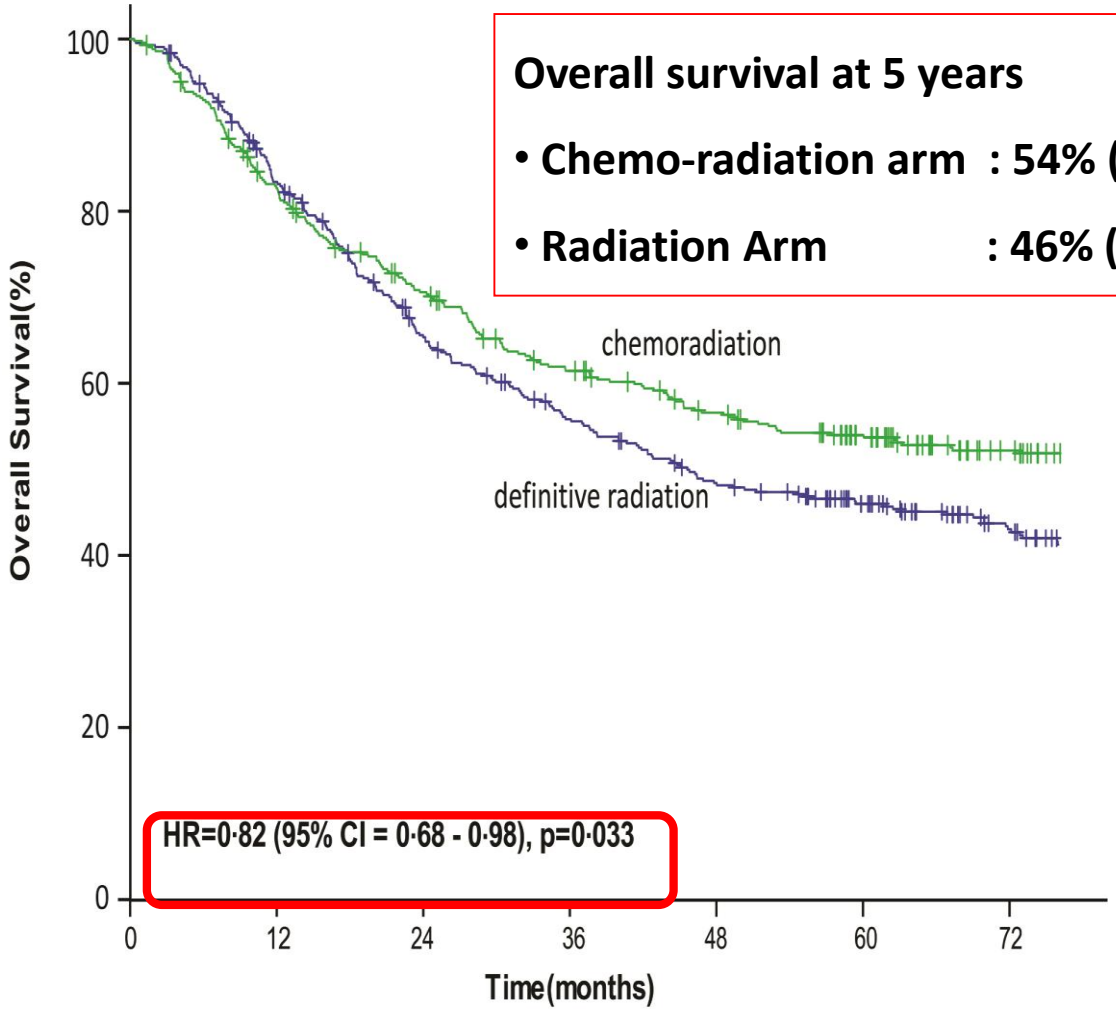
chemoradiation	424	305	265	228	208	188	157
definitive radiation	426	298	236	197	177	147	117

Mahantshetty et al : 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

Mahantshetty et al : JAMA Oncol. Feb 2018

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 (8.5%) & overall survivals (8%) in FIGO Stage III B (Squmaous cell carcinoma) Cervical Cancer
- 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

Mahantshetty et al : JAMA Oncol. Feb 2018

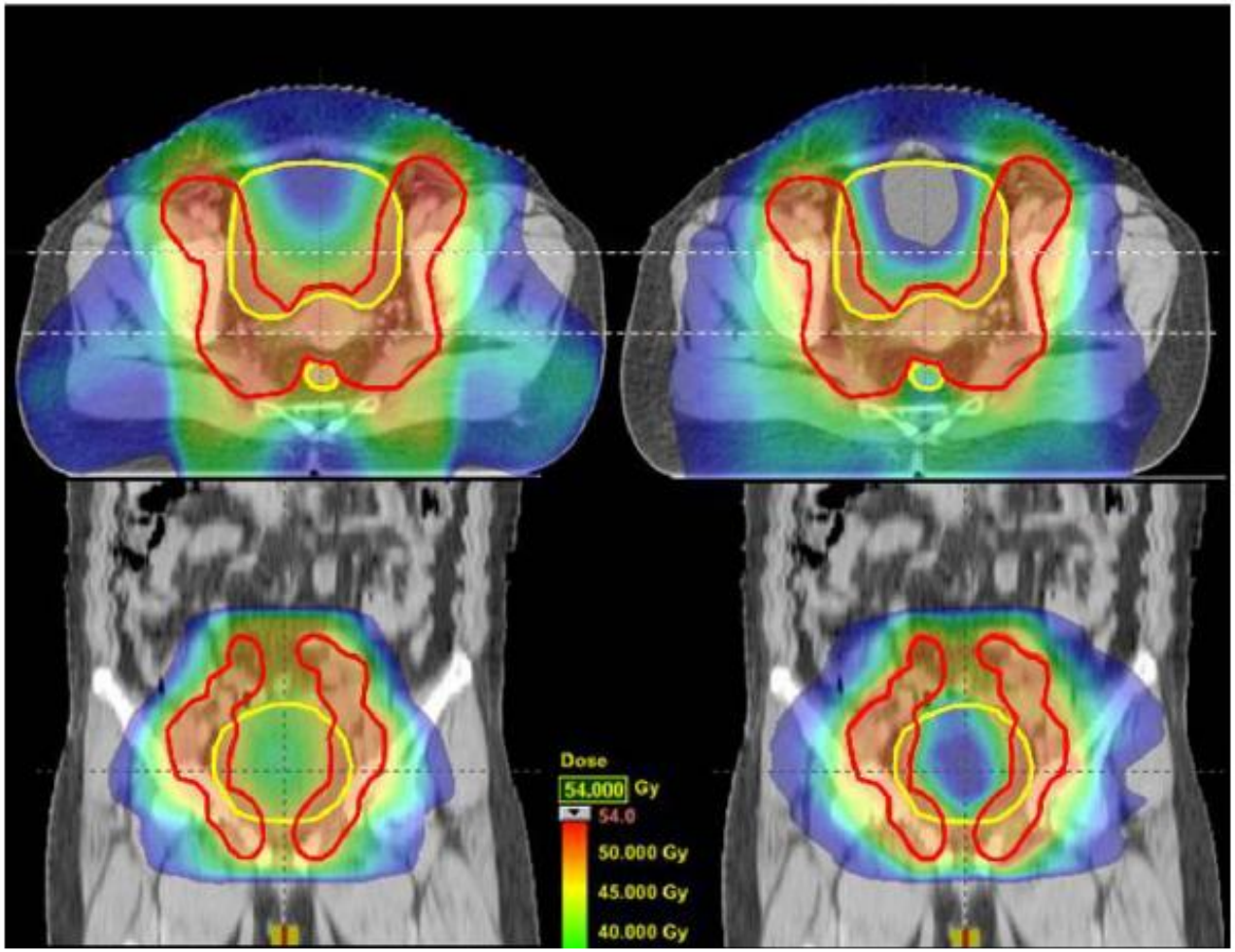
RT Techniques: IMRT Vs VMAT

8 patients with ca. cervix

IMRT

VMAT (Rapid Arc)

five coplanar equally spaced fields, 6 MV



360° arc rotation, 10 beam angles 6 MV

Cozzi, Mahantshetty et al R&O 2008

Post Operative IMRT in GYN Cancers

I. J. Radiation Oncology ● Biology ● Physics Volume 52, Number 5, 2002

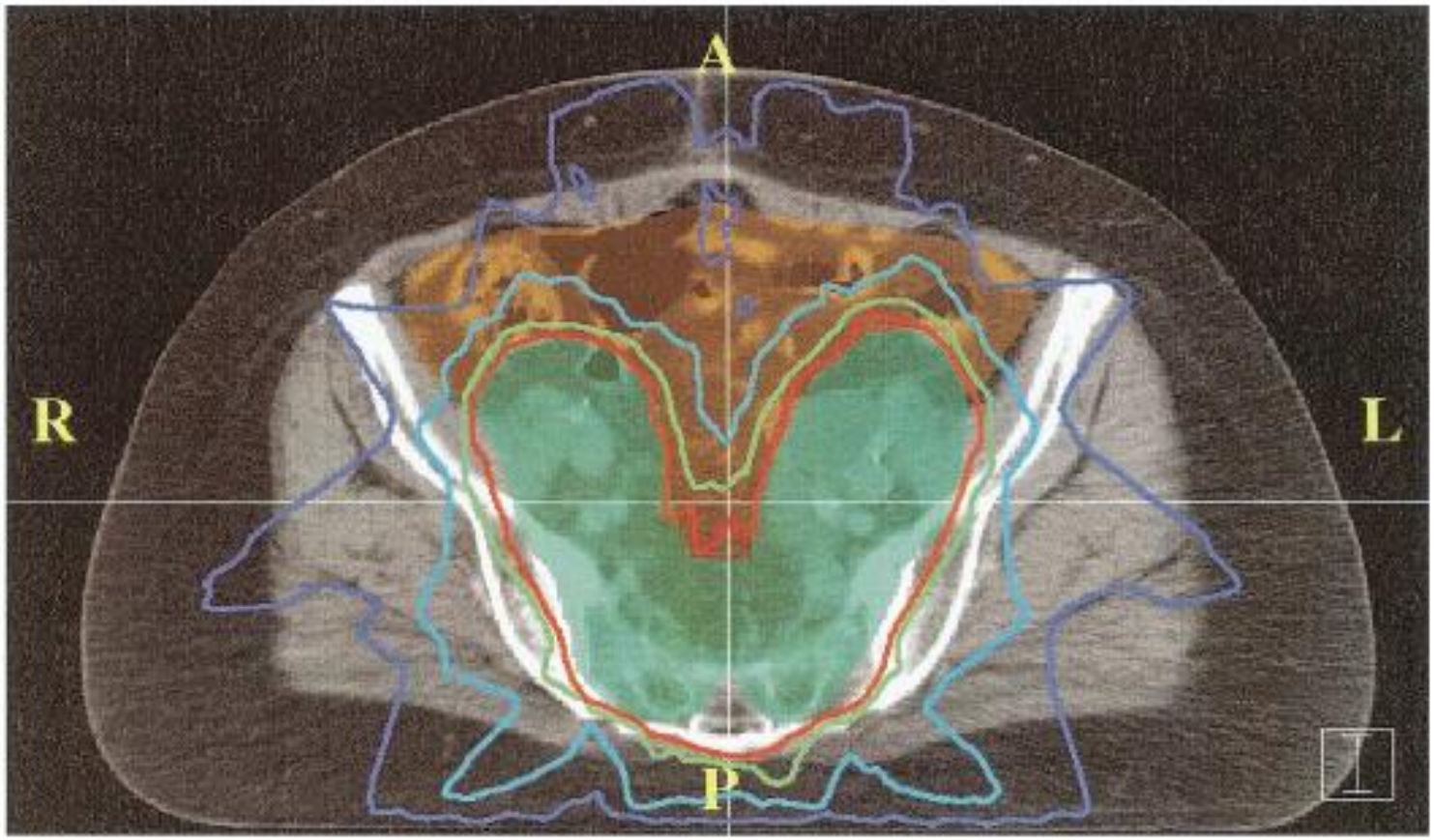
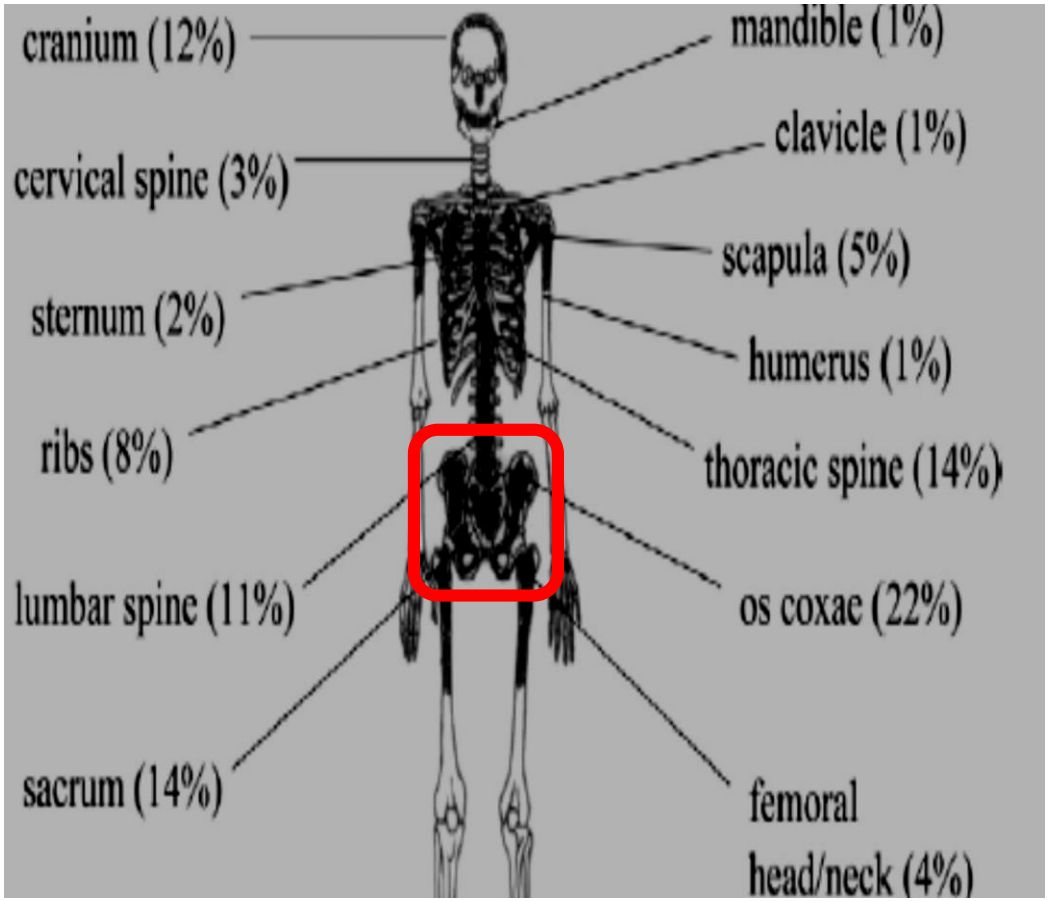


Fig. 2. Isodose curves from an IM-WPRT plan superimposed on an axial CT slice through the upper pelvis. The small bowel and PTV are shaded in orange and green, respectively. Highlighted are the 100% (red), 90% (green), 70% (light blue), and 50% (dark blue) isodose curves.

PET-CT Based Active Bone Marrow as a potential OAR

Bone marrow : Organ at risk for haematological toxicities

Adult: Haematopoietic Tissue Distribution



- **Approx. 45-50% of active marrow in pelvic field**
- **Constitutes critical mass for toxicities**

International Evaluation of Radiotherapy Technology Effectiveness in Cervical Cancer (INTERTECC): Phase II/III Trial of Intensity Modulated Radiotherapy

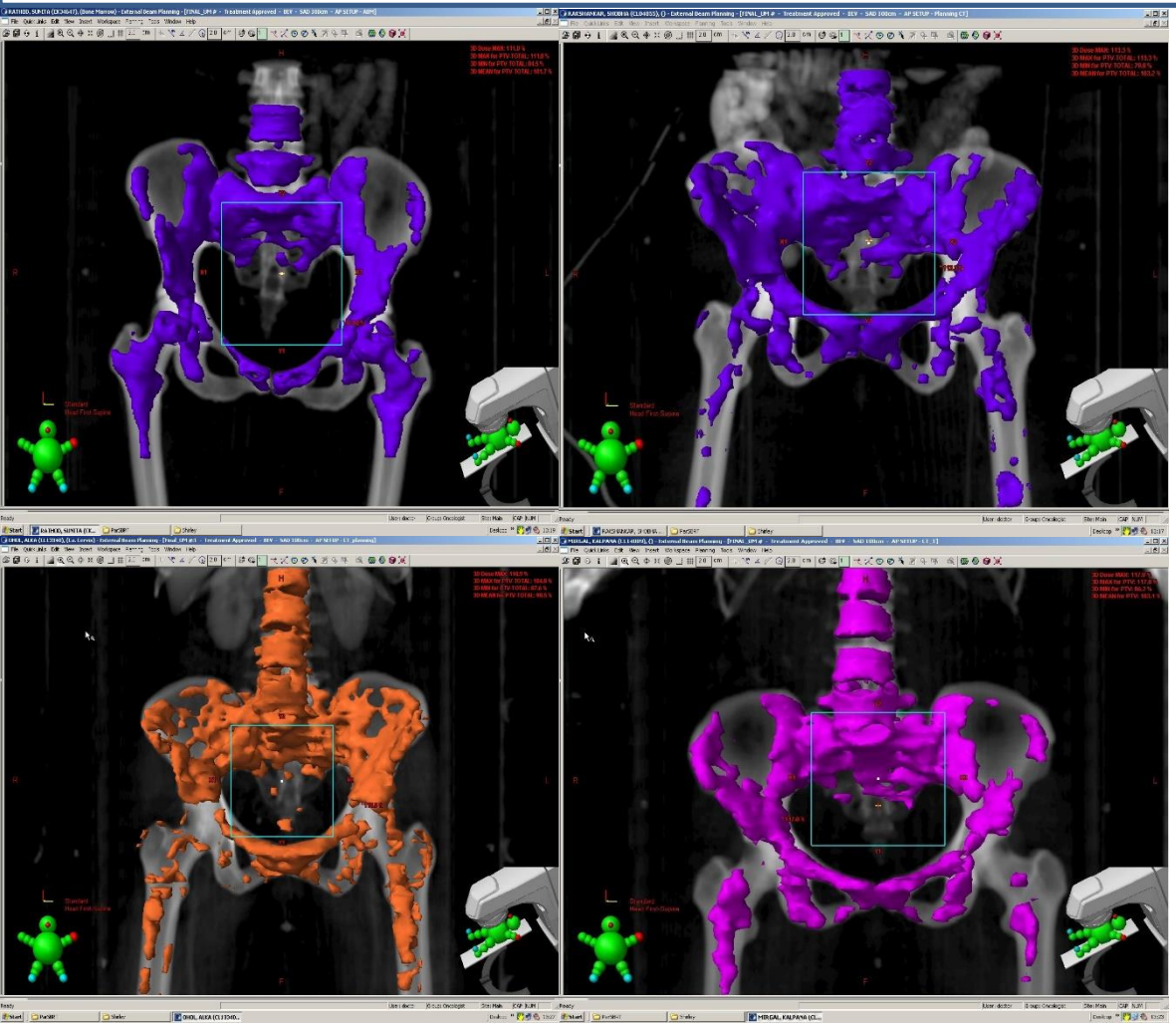
UC San Diego
RADIATION ONCOLOGY

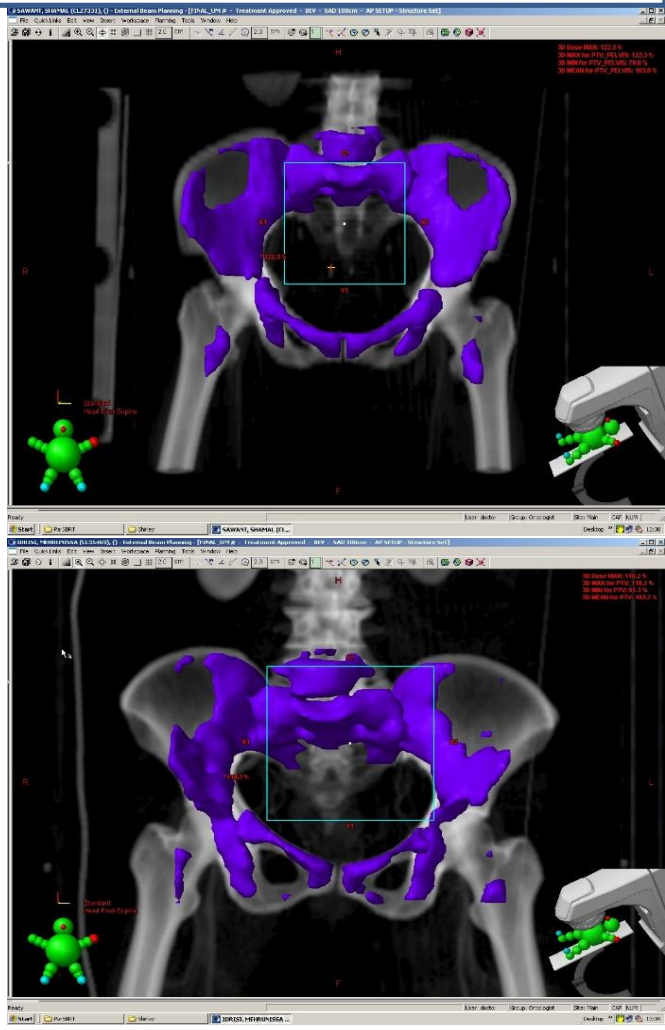
CART UCSD CENTER FOR ADVANCED RADIOTHERAPY TECHNOLOGIES

INTERTECC Trial: Multi-centric International Study

- Phase II/III Trial of IMRT (45-50.4 Gy) with Cisplatin CT
- Stage I-IVA, Post-op or Intact
- Primary Endpoint: Acute G3 Heme + G2 GI Toxicity
- Target Accrual: 91 (Phase II) + 334 (Phase III) = 425
- Phase II: Single Arm (Lead-In)
- Translational Sub-Studies:
  - Phase II Trial of Image-Guided BM-Sparing IMRT
  - Validation of High-Dimensional Model of BM Toxicity
  - Validation of Shape Model using Daily kV CBCT
- Phase III: Randomized Trial of BM sparing IMRT Vs. IMRT/ 3D CRT
- Central IMRT QA (MDA and Wash U.)

TMH Participation: 9 patients





FDG PET based contouring

FLT PET based contouring

TMH Experience : 9 pts recruited in phase II study

	Baseline	Wk 1	2	3	4	5	Vol of FBM (cc)	V10Gy (<90% -Mell et al)	V40Gy (< 40% - RTOG 0418)	Mean Dose FBM (<25Gy)
Pt 1	0	0	0	0	0	Gr 1	**425**	74.2 %	25.6 %	24.9 Gy
Pt 2	0	0	0	0	0	Gr 1	**482**	83.9 %	34.9 %	29.0 Gy
Pt 3	0	0	0	Gr 1	Gr 1	Gr 2	**446**	79.7 %	35.9 %	27.5 Gy
Pt 4	0	0	0	Gr 1	Gr 1	Gr 2	**702**	69.3 %	13.2 %	21.9 Gy
Pt 5	0	0	0	0	0	Gr 1	**409**	83.1 %	18.3 %	24.4 Gy
Pt 6	**0**	**0**	**Gr 4 ***	**Gr 2**	**0**	**0**	**272**	**95.3 %**	**28.9 %**	**28.8 Gy**

- **Baseline Active BM reserves were low**
- **Dose constraints not achieved**
- **Grade 4 HT toxicity**

Int J Radiat Oncol Biol Phys. 2017 Mar 1;97(3):536-545. doi: 10.1016/j.ijrobp.2016.11.027. Epub 2016 Nov 23.

Bone Marrow-sparing Intensity Modulated Radiation Therapy With Concurrent Cisplatin For Stage IB-IVA Cervical Cancer: An International Multicenter Phase II Clinical Trial (INTERTECC-2).

Mell LK[1], Sirák I[2], Wei L[3], Tarnawski R[4], Mahantshetty U[5], Yashar CM[6], McHale MT[7], Xu R[7], Honerkamp-Smith G[7], Carmona R[7], Wright M[7], Williamson CW[6], Kasaová L[2], Li N[6], Kry S[8], Michalski J[9], Bosch W[9], Straube W[9], Schwarz J[10], Lowenstein J[7], Jiang SB[7], Saenz CC[7], Plaxe S[7], Einck J[6], Khorprasert C[11], Koonings P[12], Harrison T[12], Shi M[3], Mundt AJ[6]; INTERTECC Study Group.

RESULTS:

- October 2011 to April 2015, (median follow-up was 26.0 months)
- 83 patients
- The incidence of any primary event was 26.5% (95% [CI] 18.2%-36.9%),

Significant reduction in acute grade 3 neutropenia with BM sparing IMRT

- Compared with patients treated without IG-IMRT (n=48), those treated with IG-IMRT (n=35) had a significantly lower incidence of grade ≥3 neutropenia (8.6% vs 27.1%; 2-sided χ^2P=.035) and nonsignificantly lower incidence of grade ≥3 leukopenia (25.7% vs 41.7%; P=.13) and any grade ≥3 hematologic toxicity (31.4% vs 43.8%; P=.25).

CONCLUSIONS:

IMRT reduces acute hematologic and GI toxicity compared with standard treatment, with promising therapeutic outcomes. Positron emission tomography IG-IMRT reduces the incidence of acute neutropenia.

Brachytherapy: Utilization & Advances

International Journal of
Radiation Oncology
biology • physics

www.redjournal.org

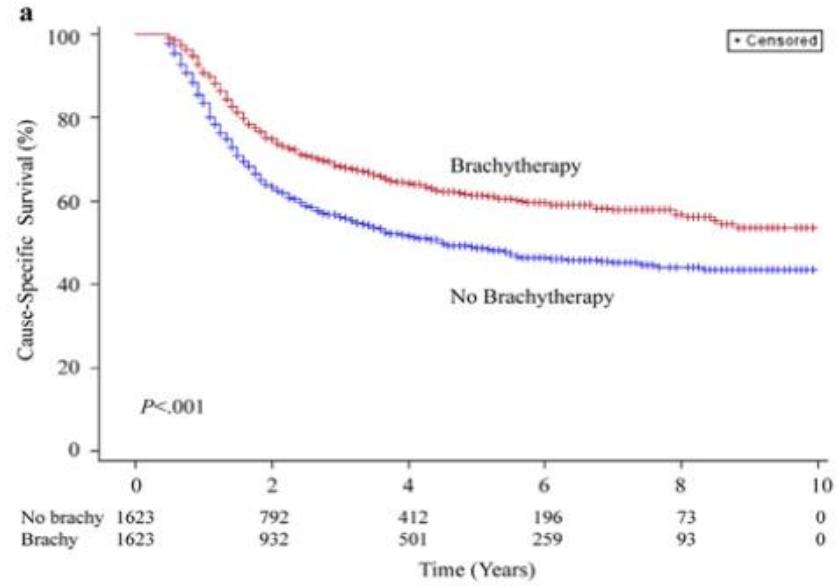
EDITORIAL

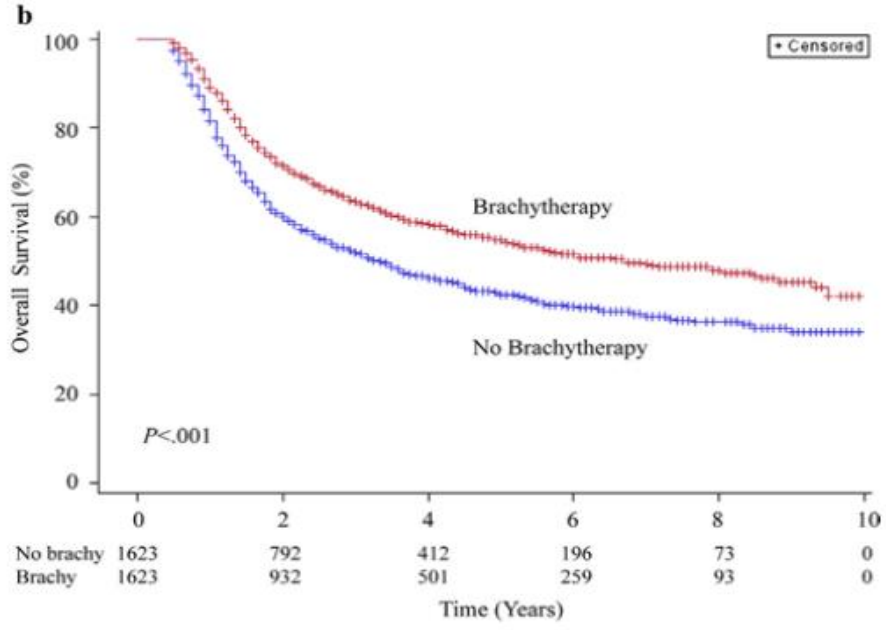
Curative Radiation Therapy for Locally Advanced Cervical Cancer: Brachytherapy Is NOT Optional

Kari Tanderup, PhD,*,† Patricia J. Eifel, MD,‡ Catheryn M. Yashar, MD,§
Richard Pötter, MD,‖ and Perry W. Grigsby, MD*

Int J Radiation Oncol Biol Phys 88:537-9;2014

Importance of brachytherapy +++





Clinical Investigation: Gynecologic Cancer

Trends in the Utilization of Brachytherapy in Cervical Cancer in the United States

Kathy Han, MD,* Michael Milosevic, MD,* Anthony Fyles, MD,* Melania Pintilie, MSc,† and Akila N. Viswanathan, MD, MPH‡

**Radiation Medicine Program, Princess Margaret Hospital, University Health Network, Toronto, Ontario, Canada; †Department of Biostatistics, Princess Margaret Hospital, Toronto, Ontario, Canada; and ‡Department of Radiation Oncology, Dana-Farber Cancer Institute/Brigham and Women's Hospital, Boston, Massachusetts*

Received Mar 24, 2013, and in revised form Apr 30, 2013. Accepted for publication May 20, 2013

A significant detriment in outcome if brachytherapy treatment was not given

EVIDENCE

Can High Tech XRT replace BT?

High Tech XRT

Vs

BT (Conventional)

Clinical Investigation

National Cancer Data Base Analysis of Radiation Therapy Consolidation Modality for Cervical Cancer: The Impact of New Technological Advancements

Beant S. Gill, MD,* Jeff F. Lin, MD,† Thomas C. Krivak, MD,‡ Paniti Sukumvanich, MD,† Robin A. Laskey, MD,† Malcolm S. Ross, MD,† Jamie L. Lesnock, MD,† and Sushil Beriwal, MD*

*Departments of *Radiation Oncology and †Gynecologic Oncology, Magee-Womens Hospital of University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; and ‡Department of Gynecologic Oncology, Western Pennsylvania Hospital, Pittsburgh, Pennsylvania*

Int J Radiation Oncol Biol Phys, Vol. 90, No. 5, pp. 1083–1090, 2014

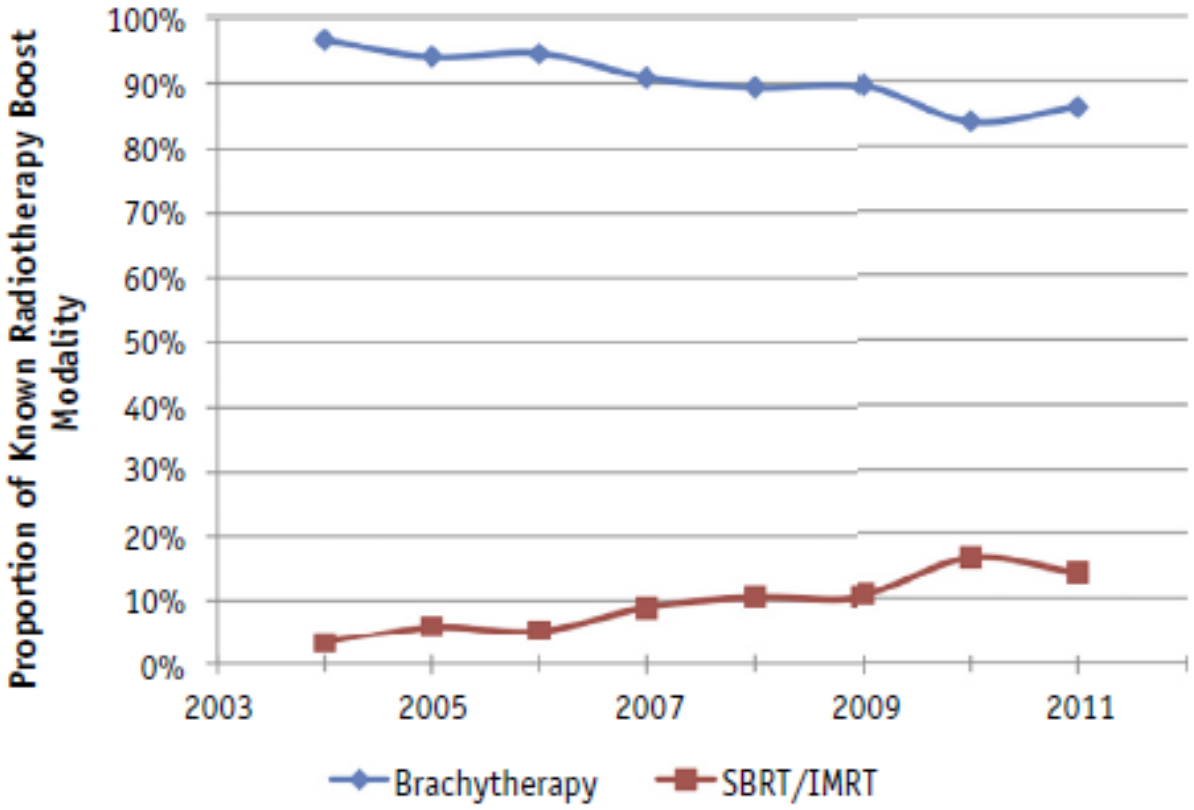


Fig. 1. Changes in radiation therapy boost modality utilization over time from 2004 to 2011. IMRT = intensity modulated radiation therapy; SBRT = stereotactic body radiation therapy.

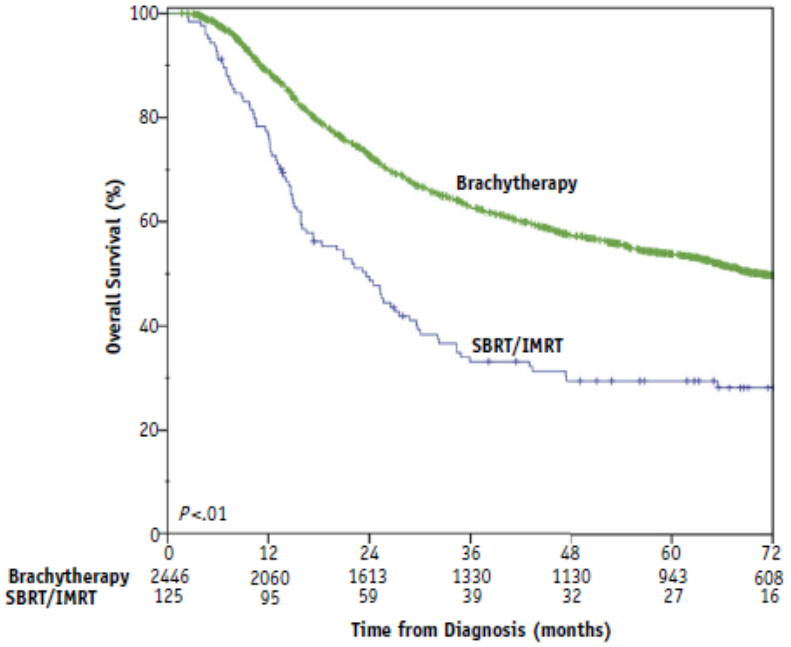


Fig. 2. Kaplan-Meier overall survival estimate stratified by boost modality. IMRT = intensity modulated radiation therapy; SBRT = stereotactic body radiation therapy.

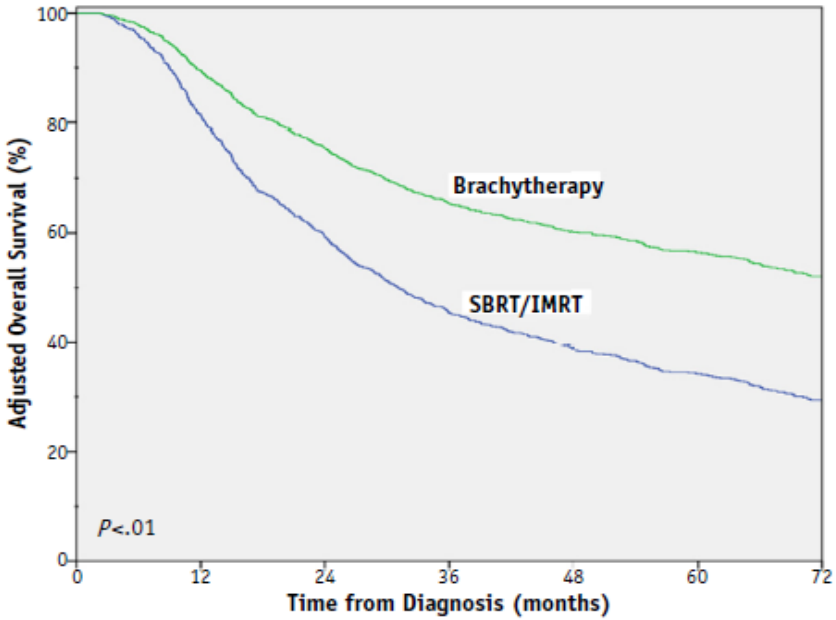
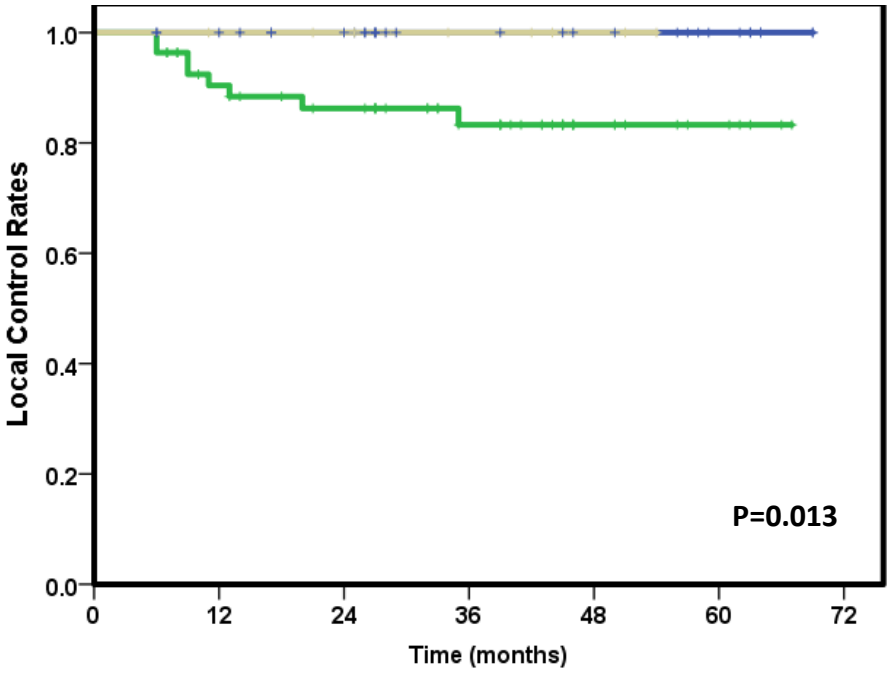


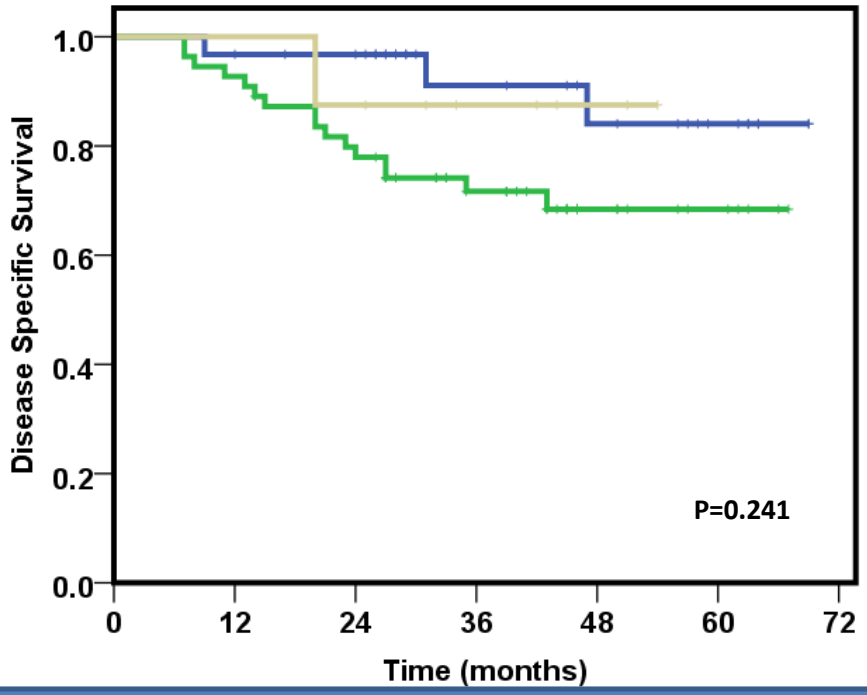
Fig. 3. Adjusted overall survival estimate, stratified by boost modality and corrected for significant variables on multivariable Cox proportional hazard model analysis (age, Charlson/Deyo score, stage, and chemotherapy utilization). IMRT = intensity modulated radiation therapy; SBRT = stereotactic body radiation therapy.

A significant detriment in outcome with newer external beam techniques as compared to conventional BT

Int J Radiation Oncol Biol Phys, Vol. 90, No. 5, pp. 1083–1090, 2014

KM Curves for Cervical cancer
Local control & Disease Specific Survival

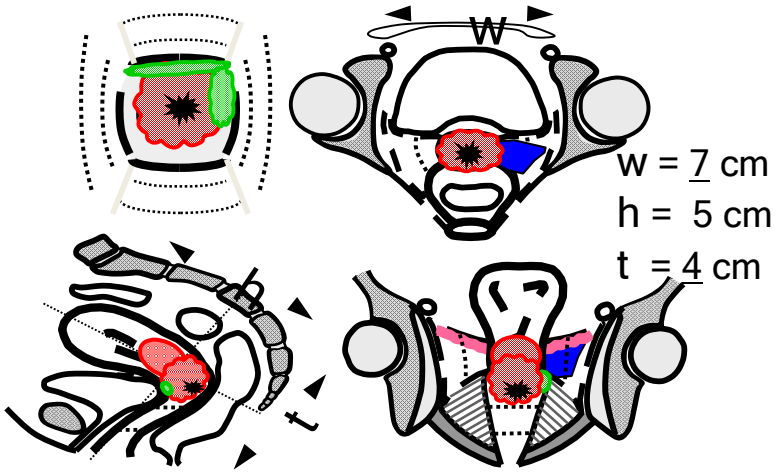




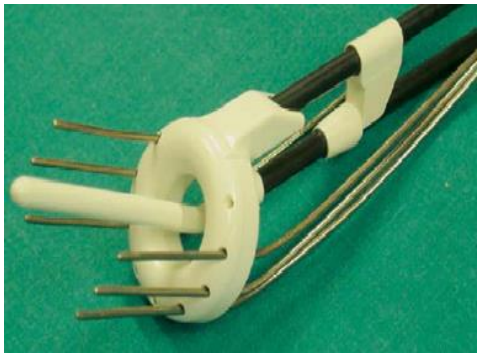
Appears like
“ Outcome of Sx for early stage”

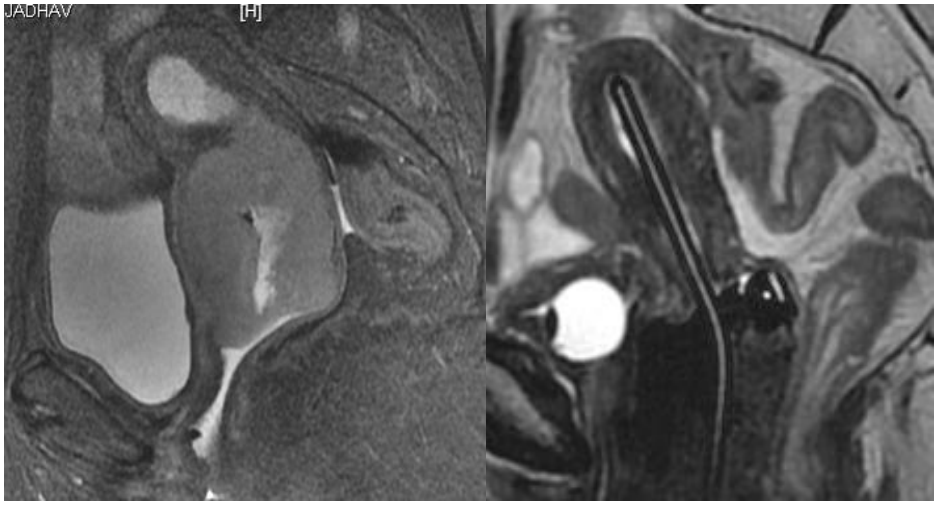
Mahantshetty et al, IJROBP 2017

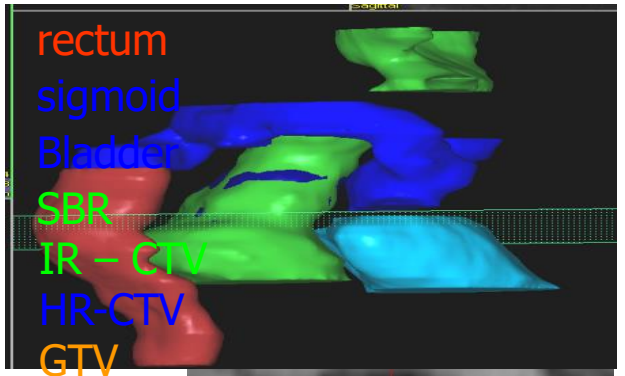
Image guided Brachytherapy for Cervical Cancers

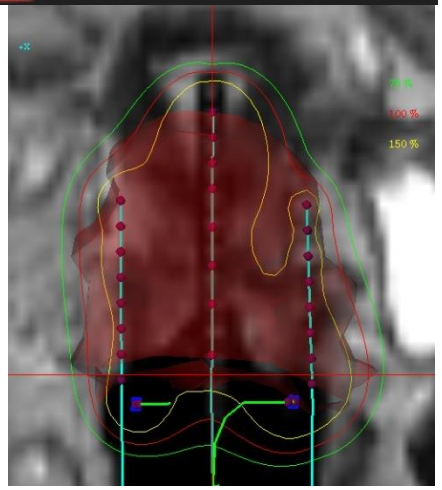


"GOLD STANDARD APPROACH : MR IGABT"









- Clinical Examination
- MR imaging at Diagnosis and at BT
- Target definition on MR
- Treatment Planning on MR Based Target

Tata Memorial Hospital Participation in International Multicentric Studies

- Refine treatment standards

- GYN GEC-ESTRO Research Network

A European study on MRI-guided brachytherapy
in locally advanced cervical cancer

EMBRACE

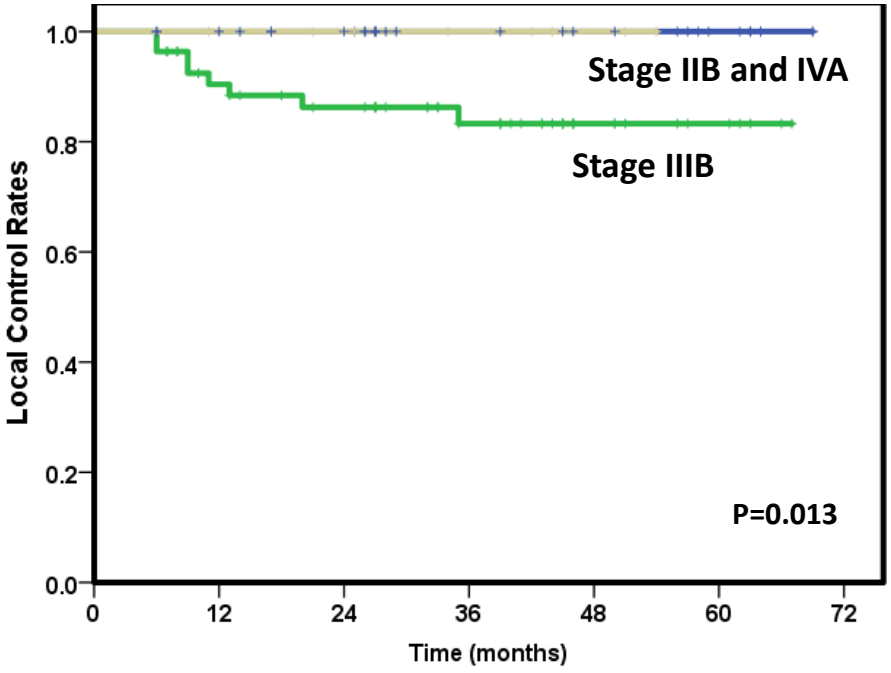
(ENDORSED BY GEC ESTRO)

2009 ONWARDS

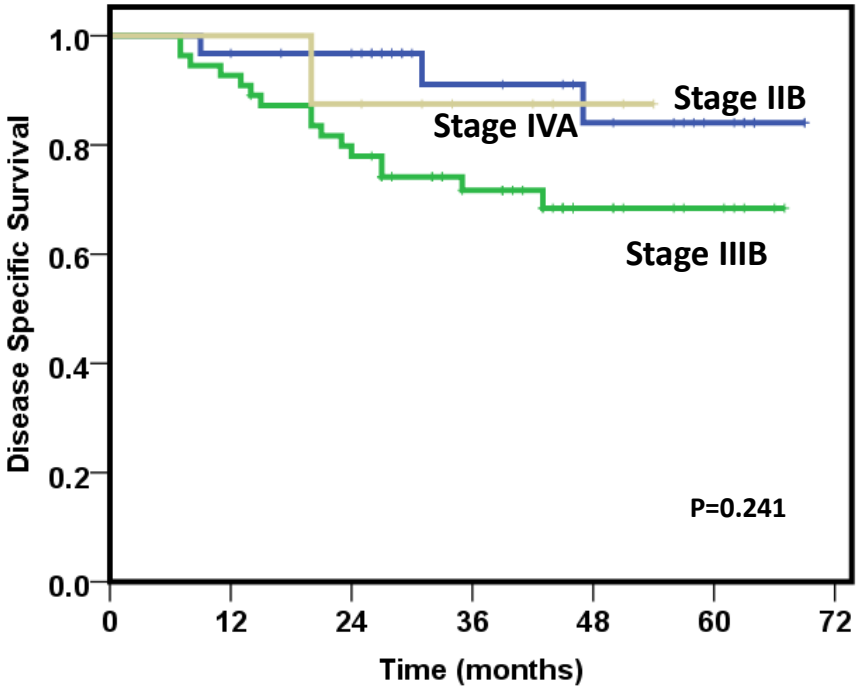
TATA HOSPITAL CONTRIBUTION TO EMBRACE

100 patients (IIB-IVA)

MR IMAGE BASED BRACHYTHERAPY
EMBRACE STUDY : 1419 PATIENTS
TMH ACCRUAL: 94 PATIENTS



IIB	31	28	24	15	12	07	01
IIIB	55	45	39	27	10	05	01
IVA	08	07	06	04	02	00	00

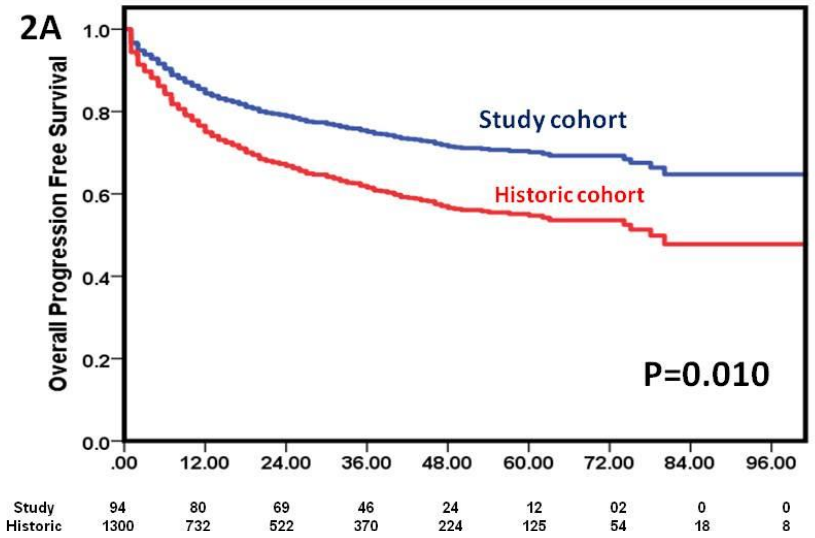


IIB	31	29	26	16	12	07	01
IIIB	55	51	43	28	10	05	01
IVA	08	08	07	04	02	00	00

EXCELLENT LOCAL CONTROL RATES FOR ALL STAGES

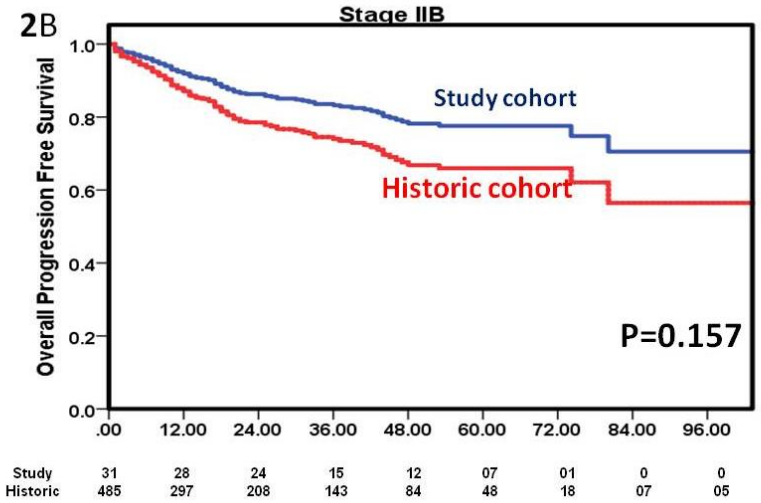
Mahantshetty et al, IJROBP 2017

COMAPRISON OF HISTORICAL CONTROLS Vs MR BT EXPERIENCE: TMH



HISTORIC COHORT B: CONVENTIONAL BT SERIES (1979-94)

STUDY COHORT : MR IGABT APPROACH



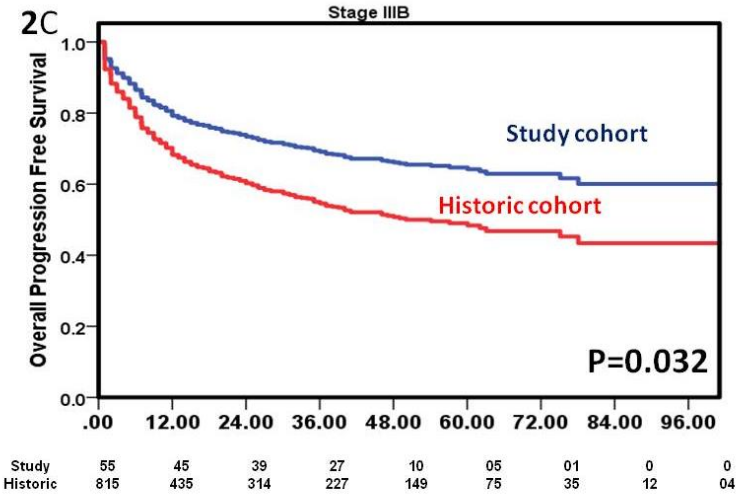


Figure 2: Comparison of overall progression free survival using log rank test for study cohort and historic cohort [21] for, all patients (A), stage IIB (B), and stage IIIB (C).

Mahantshetty et al, IJROBP 2017

Clinical Evidence in IGABT Cervix Cancer

- Mono-institutional cohorts (publications since 2007)
- Multi-center cohorts with retrospective evaluation

  RetroEMBRACE (Sturdza, Fokdal 2016 …)

- **Prospective Trials**

  STIC: comparative 2D vs. 3D (Charra-Brunaud 2012)

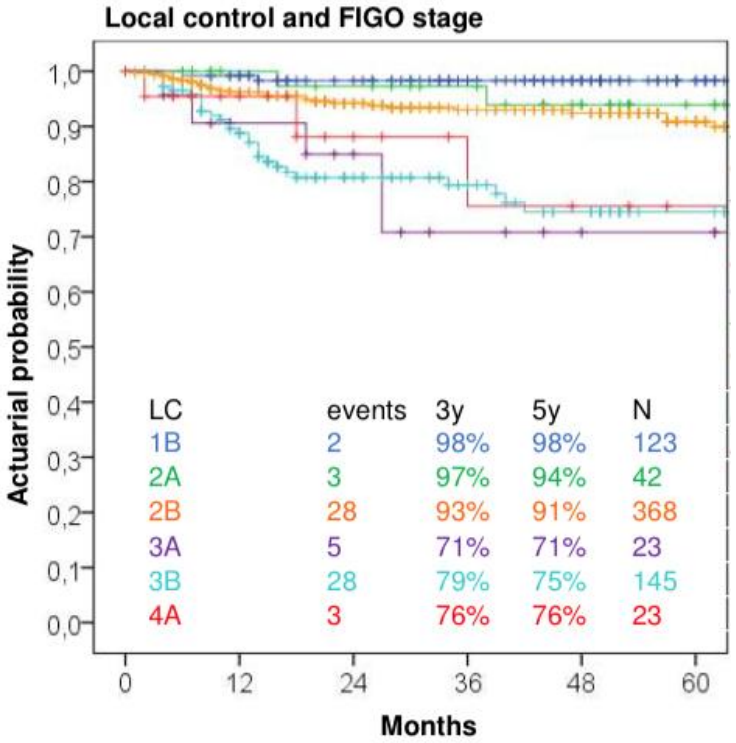
  EMBRACE I: observational, 08/2008 - 12/2015

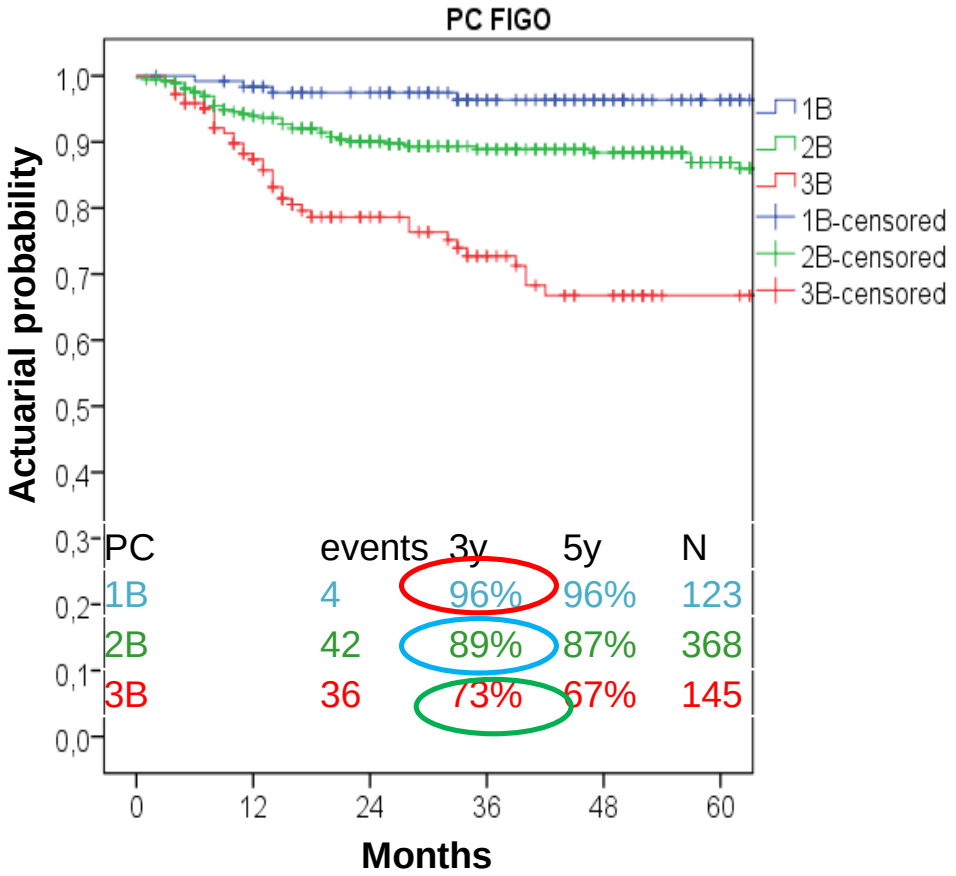
  EMBRACE II: interventional, start 01/2016

RETRO-EMBRACE STUDY (780 pts)

IGABT for Cervical Cancers

Local and Pelvic control and FIGO stage

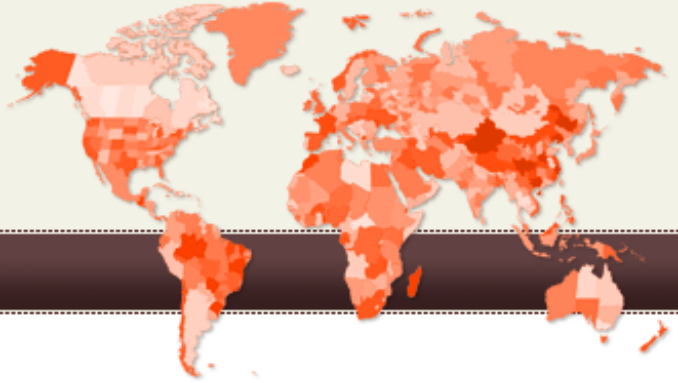




RetroEMBRACE Outcome Sturdza et al. 2016, Radioth Oncol

EMBRACE

An intErnational study
on MRI-guided BRachytherapy
in locally Advanced CErvical cancer

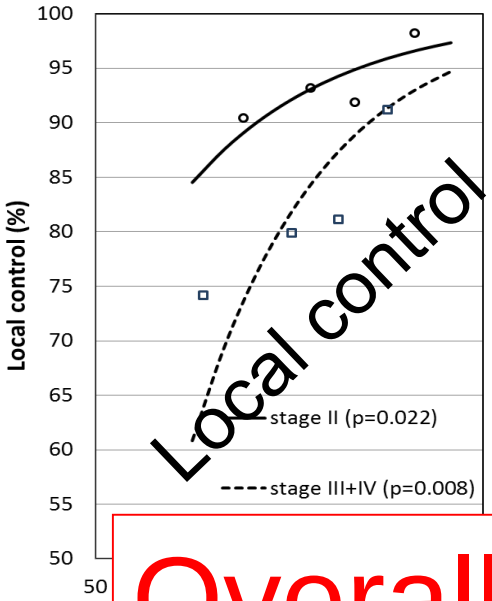


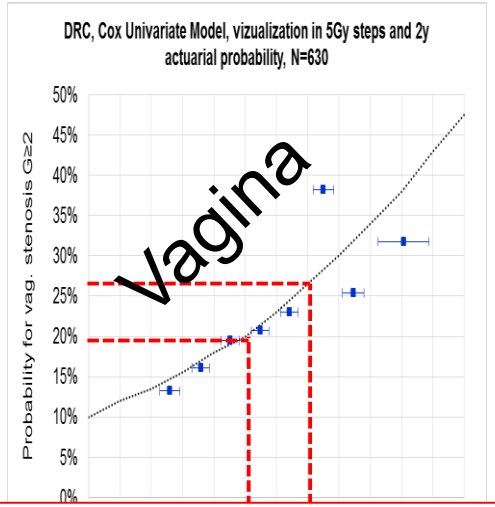
About Embrace | Contacts | Participation | Login

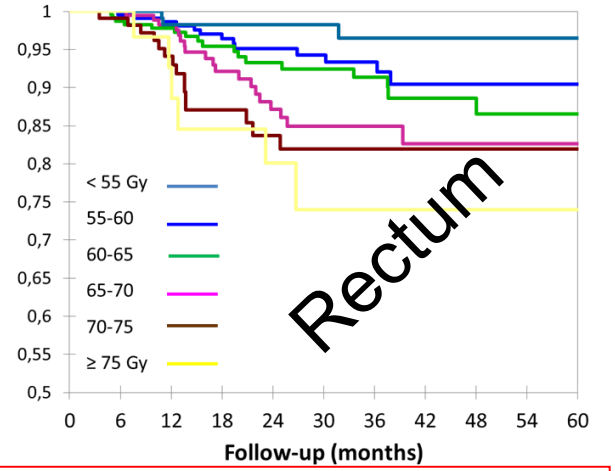
- EMBRACE - International study on MRI-based 3D brachytherapy in locally advanced cervical cancer
- A prospective observational multi-centre trial
- Contouring and reporting according to GEC ESTRO recommendations
- Fractionation, planning and prescription according to institutional practice
- Enrollment of patients in 2008-2015, 1419 pts accrued

Nucletron
Improving patient care

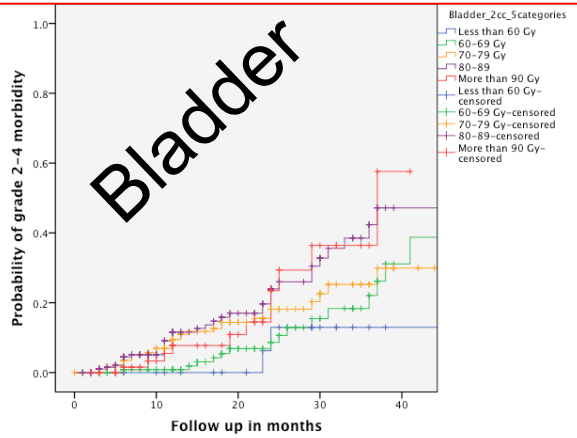
Evidence of dose and effect

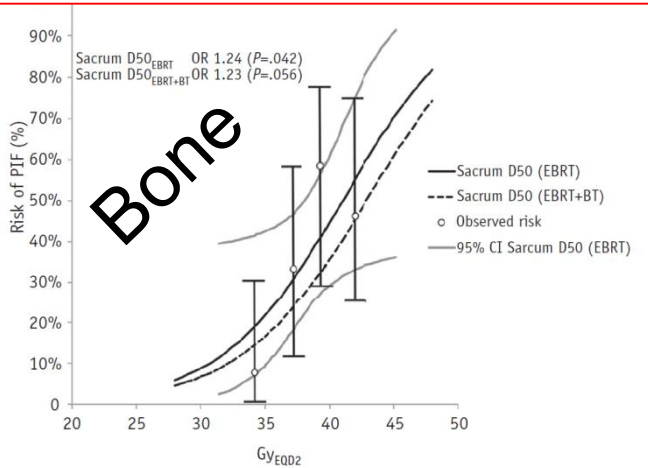






Overall outcome analysis: 2020





ELSEVIER

Brachytherapy ■ (2014) ■

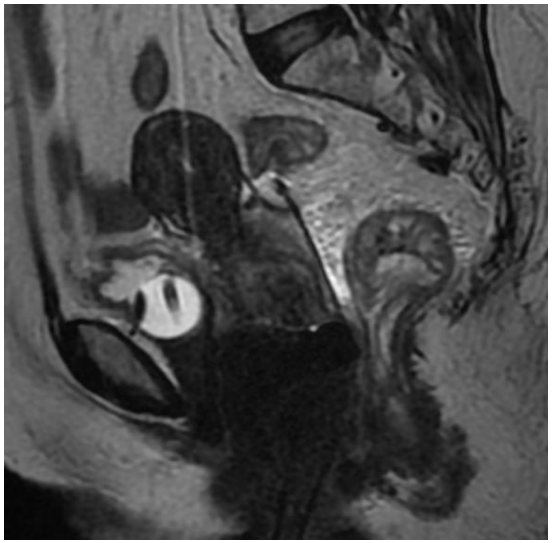
BRACHYTHERAPY

Reirradiation using high-dose-rate brachytherapy in recurrent carcinoma of uterine cervix

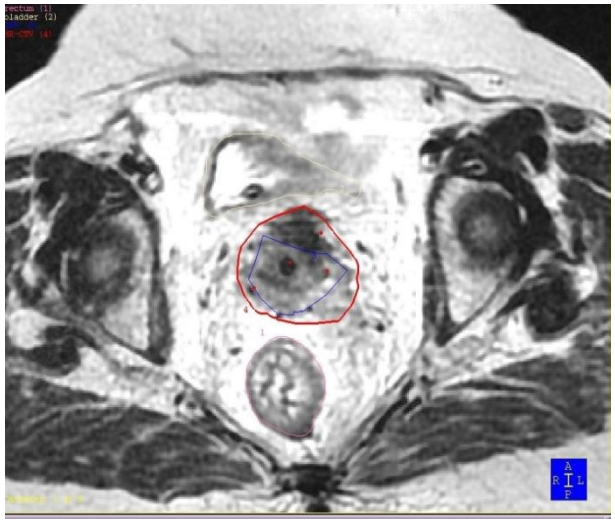
Umesh Mahantshetty*, Nikhil Kalyani, Reena Engineer, Supriya Chopra, Swamidas Jamema, Yogesh Ghadi, Deepak Deshpande, Shyamkishore Shrivastava

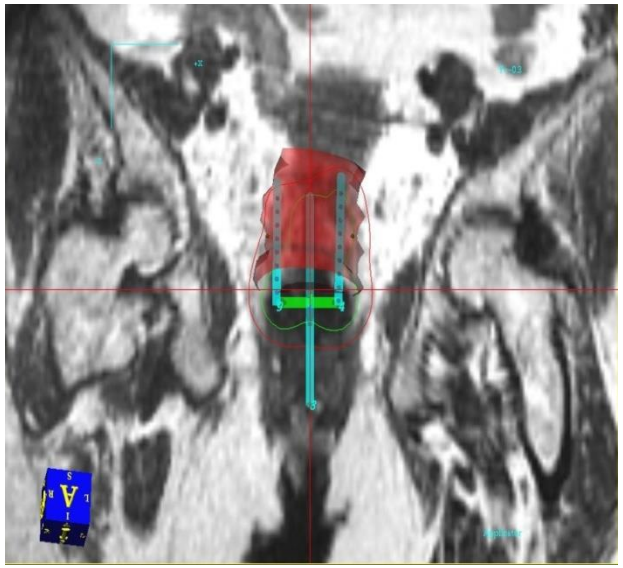
Department of Radiation Oncology and Medical Physics, Tata Memorial Centre, Mumbai, India

Baseline

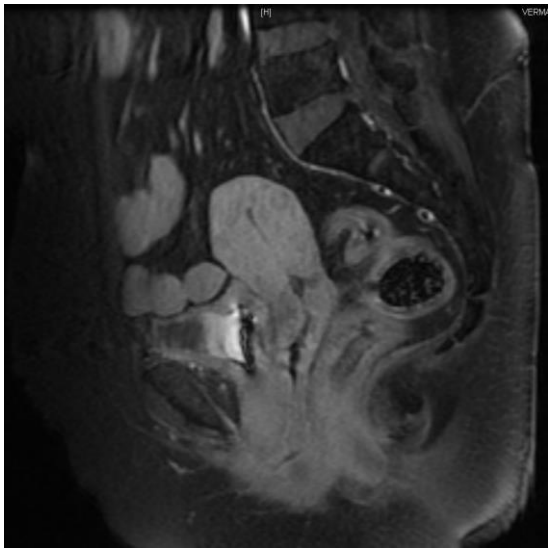


BT Planning





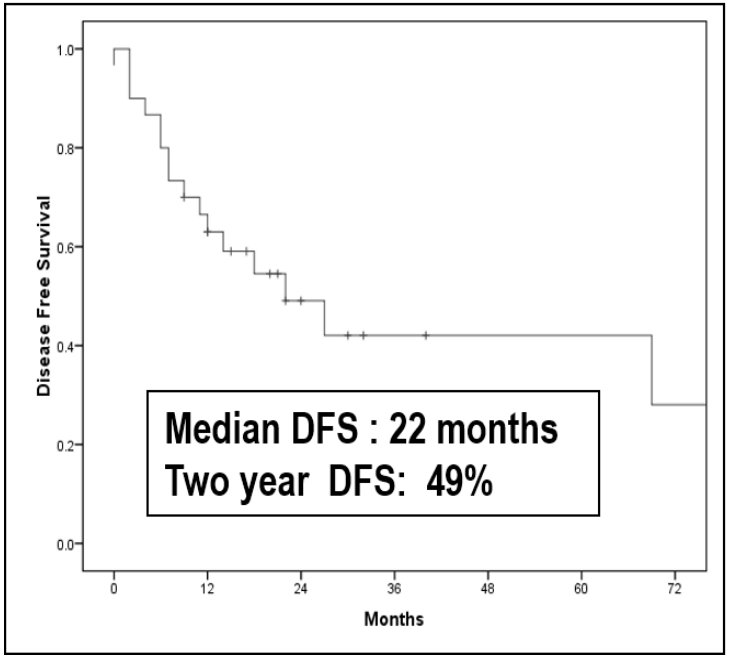
3 Months Post RT



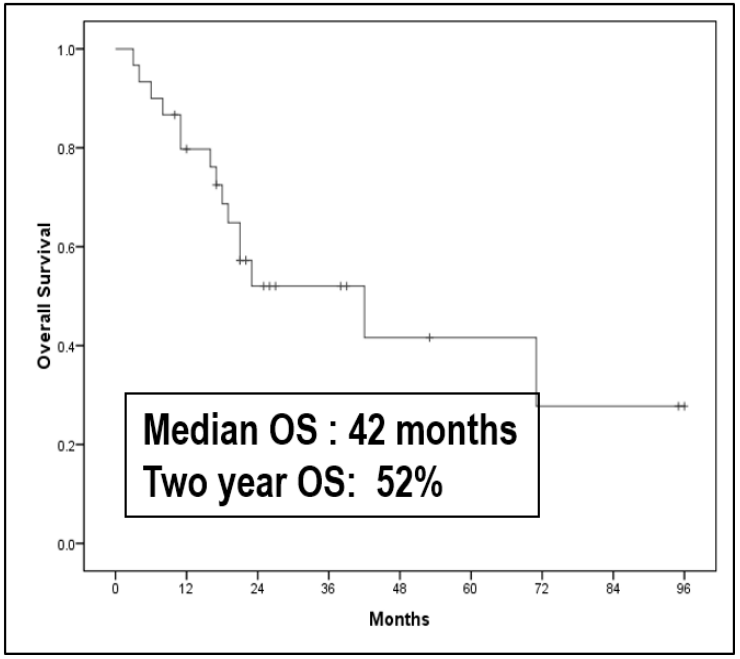
A Treated Patient

Results: Survival

Disease Free Survival



Overall Survival



CHALLENGES : GYN Cancers

- **Cervical Cancers :**

  - Ongoing clinical studies

- **Endometrial Cancers :**

  - PORTEC Studies (Other sessions)

- **Vulval Cancers (21st & 23rd March Sessions)**

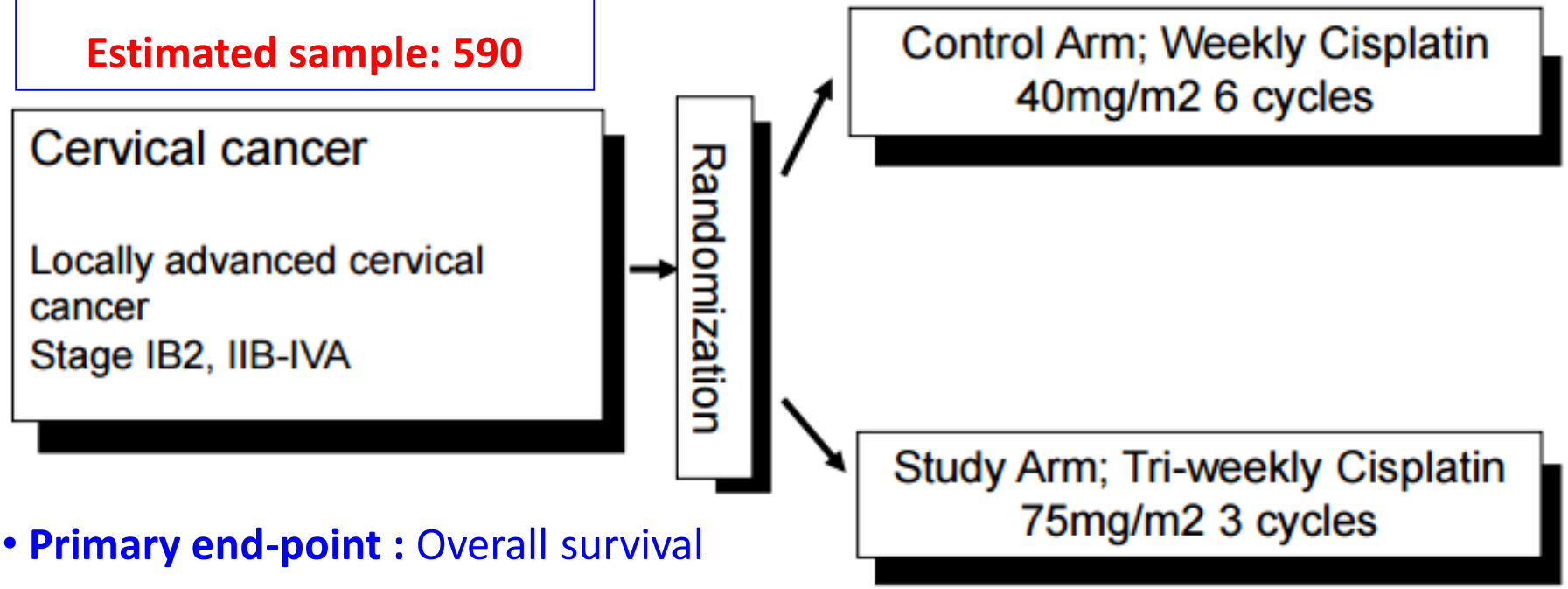
NCT01561586: A Phase III Randomized Trial
Korean GOG study

TACO

(Tri-weekly Administration of Cisplatin in LOcally Advanced Cervical Cancer)

Stage : 1B2 - IVA

Estimated sample: 590



- **Primary end-point :** Overall survival
- **Secondary end-points:** PFS, Toxicity, Compliance to radiation protocol, QOL.

Actual Study Start Date : March 2012
Estimated Primary Completion Date : March 2020
Estimated Study Completion Date : March 2023

Induction Chemotherapy followed by Concomitant Chemo-Radiation in Advanced Stage Carcinoma Cervix: A Phase III Randomized Trial *(INTERLACE Study - NCT01566240)*

Carcinoma Cervix Stage FIGO Ib2-IVA

Based on Phase II Study which evaluated the feasibility of delivering dose dense & dose intense CT (Pacli + Carbo weekly)

385 patients

Concomitant chemo radiotherapy

weekly Cisplatin (40 mg/m2 x 4 - 5 #)

385 patients

Induction chemotherapy with weekly x 6weeks Paclitaxel (80 mg/m2) + Carboplatin (AUC2)

Concomitant chemoradiotherapy

weekly Cisplatin (40 mg/m2 x 4 - 5 #) &

Outcomes:

Primary: Overall Survival

Secondary: Progression free Survival

Acute toxicities

Late Toxicities

Initiated in 2012

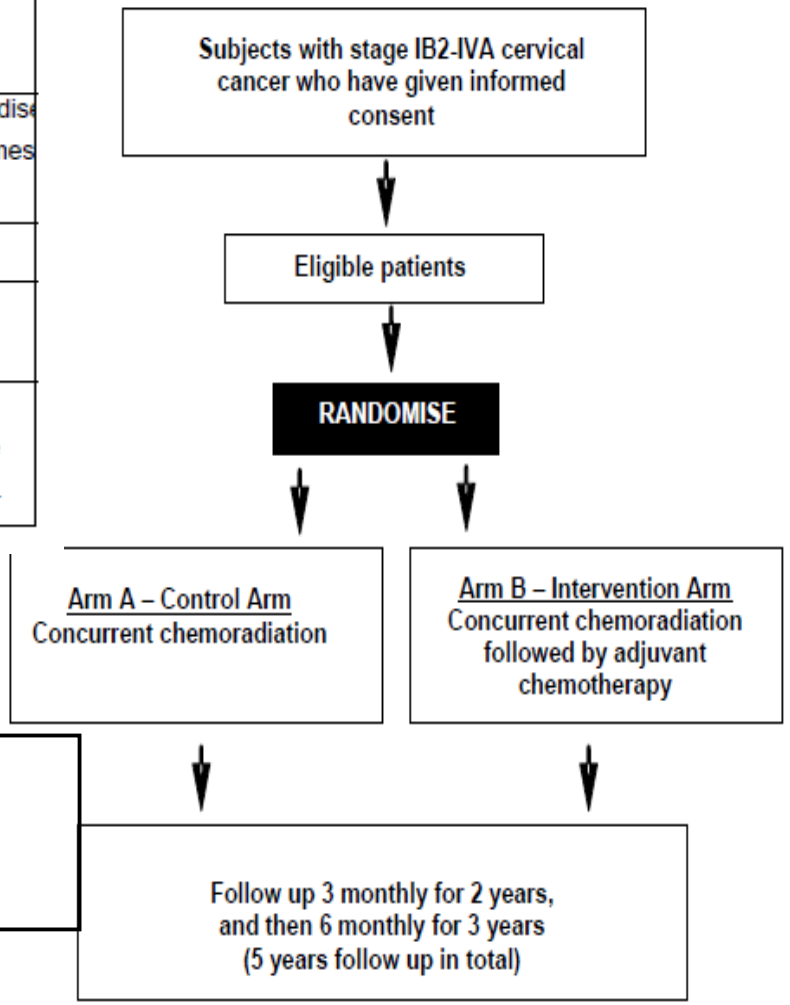
Accrual period: 4 years

Completion: 2021

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 dise 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

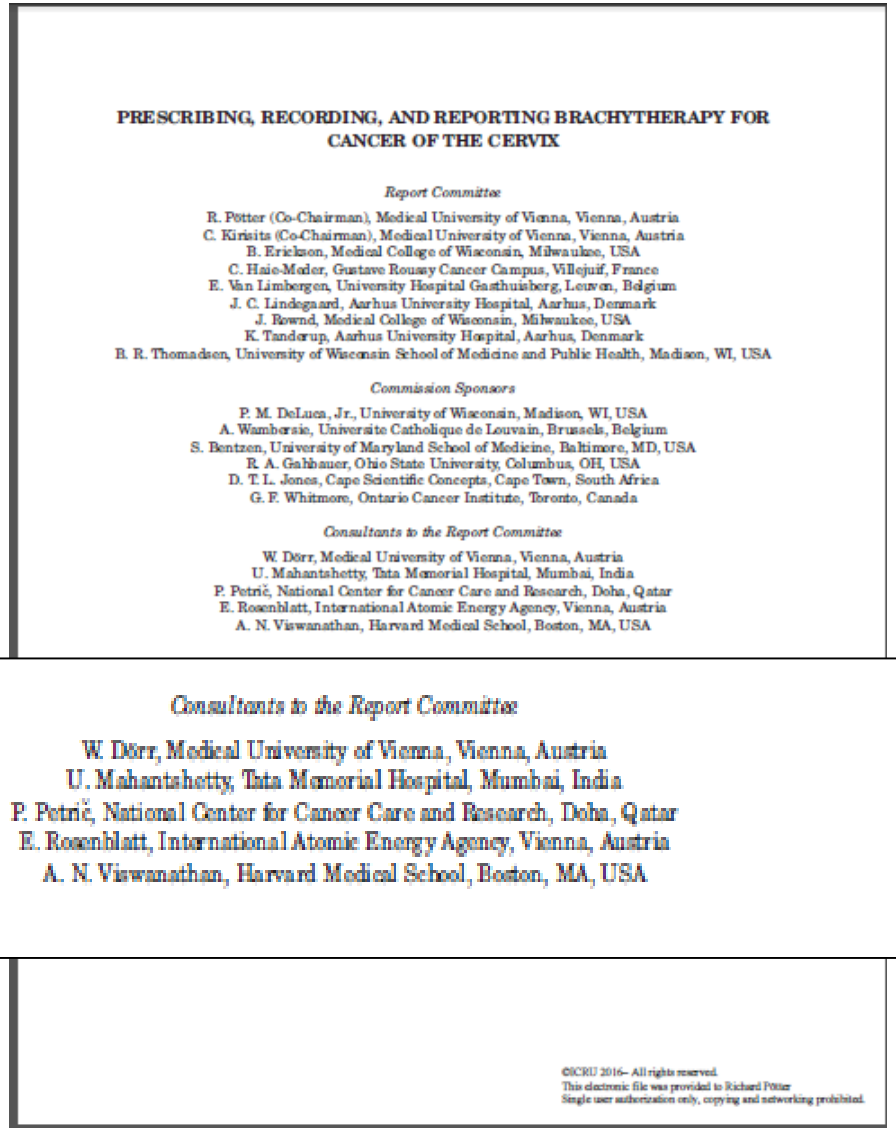
Recruited : Ongoing

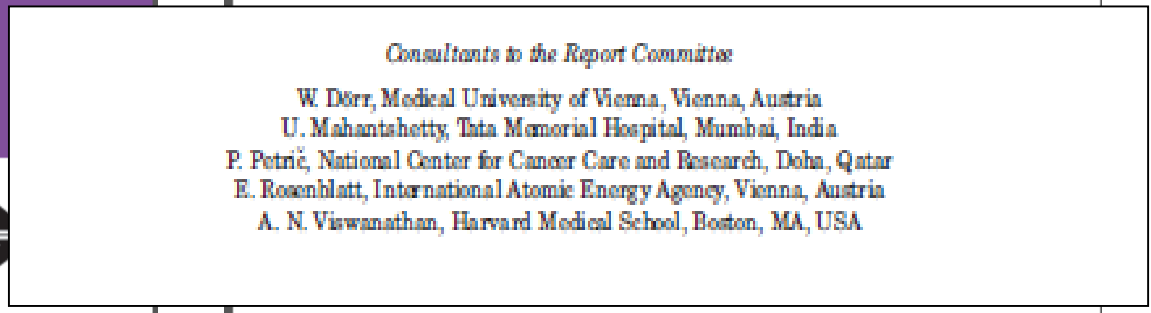
International Evaluation of Radiotherapy Technology Effectiveness in Cervical Cancer (INTERTECC): Phase II/III Trial of Intensity Modulated Radiotherapy

UC San Diego
RADIATION ONCOLOGY

CART UCSD CENTER FOR ADVANCED RADIOTHERAPY TECHNOLOGIES

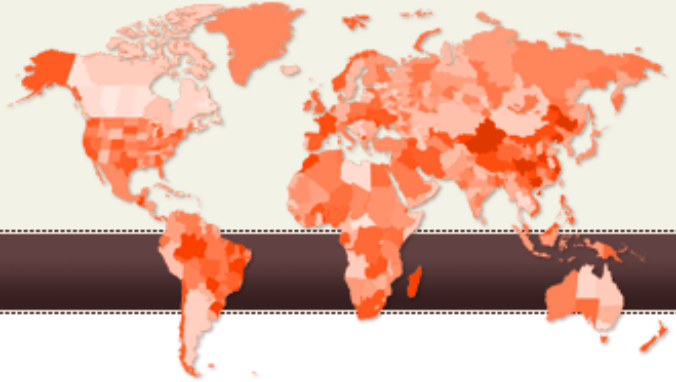
Brachytherapy in Cervical Cancers
Implementation of ICRU 89

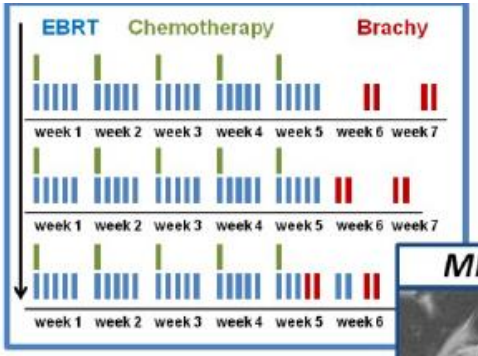


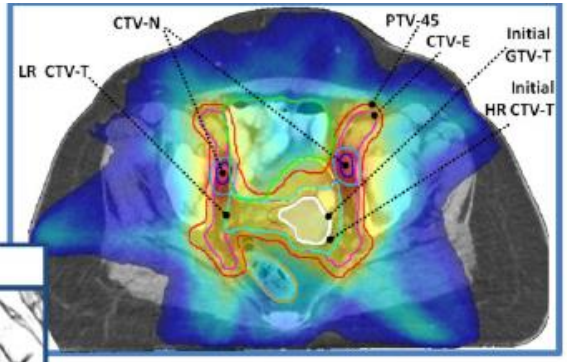


EMBRACE II

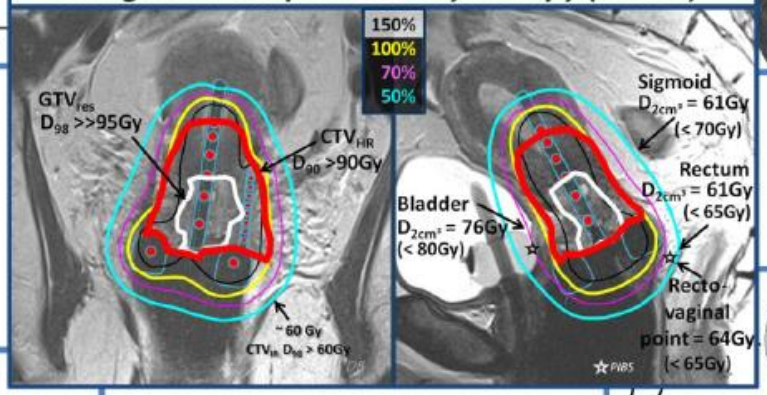
An intErnational study
on MRI-guided BRachytherapy
in locally Advanced CErvical cancer

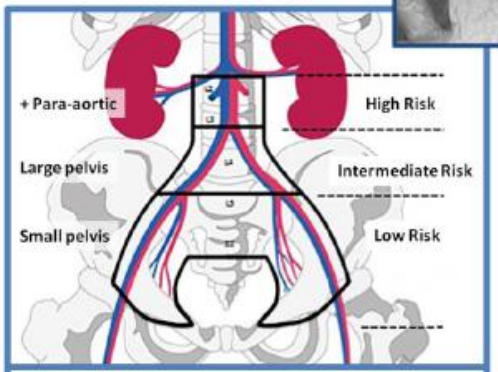




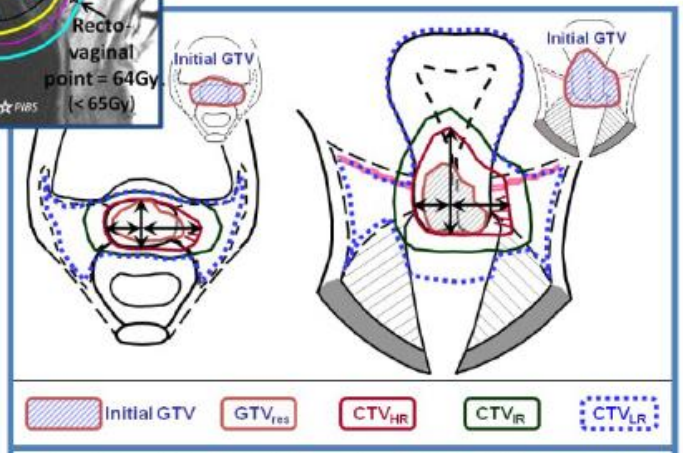


MRI guided adaptive brachytherapy (IGABT)





Nodal CTV-E based on Risk Group



Residual GTV-T, Adaptive HR CTV-T, IR CTV-T

Ongoing evidence for improving treatment planning – EMBRACE II

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Review Article

The EMBRACE II study: The outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies

Richard Pötter [a,1], Kari Tanderup [b,1,*], Christian Kirisits [a], Astrid de Leeuw [c], Kathrin Kirchheiner [a], Remi Nout [d], Li Tee Tan [e], Christine Haie-Meder [f], Umesh Mahantshetty [g], Barbara Segedin [h], Peter Hoskin [i], Kjersti Bruheim [j], Bhavana Rai [k], Fleur Huang [l], Erik Van Limbergen [m], Max Schmid [a], Nicole Nesvacil [a], Alina Sturdza [a], Lars Fokdal [b], Nina Boje Kibsgaard Jensen [b], Dietmar Georg [a], Marianne Assenholt [b], Yvette Seppenwoolde [a], Christel Nomden [c], Israel Fortin [a,o], Supriya Chopra [g], Uulke van der Heide [n], Tamara Rumpold [a], Jacob Christian Lindegaard [b], Ina Jürgenliemk-Schulz [c], the EMBRACE Collaborative Group [2]

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- Initiative EMBRACE study group within GEC-ESTRO
- Start inclusion 2016, 1000 patients intended
- Aims for **EBRT and brachytherapy**
- Exclusive IMRT
- SIB boosting for lymph node metastases
- Extension elective field based on defined risk profile

SUMMARY
Management of Cervical Cancers – An Update

- **Neo-adjuvant CT + Sx : Should not be routinely practiced**
- **Concomitant Chemotherapy : STD of Care for LACC**
- **Brachytherapy :**

  - IGABT improves control rates

  - Reirradiation with BT feasible

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- *Tata Memorial Centre*
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  - *Rad Oncol & Med Phy*
  - *Residents / fellows*
- *ESTRO Faculty*
- *Patients*

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