Summing up- Overview and take home message on recent advances in Radiotherapy of carcinoma Cervix.

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Medanta the Medicity
Gurgaon.

Many of the following slides has been collected (with or without modifications) from other eminent presenter's on the subject. – gratefully acknowledged.
Radiotherapy - role in management of cervical cancers

• 1. Early stage cervical cancer
  - Post operative radiation

• 2. Locally advanced cervical cancer
  - External beam with concurrent chemo followed by brachytherapy.
Management of IB1: Radical Hysterectomy

- RCT of 469 IB or IIA cervical cancer patients, 87 months. 54% of IB1 & 84% of IB2 surgical pts had ART.
- Post-op Chemo-RT: SWOG 8797
  Peters et al. JCO 18:1606-13, 2000
Summary of post op RT

High risk features – includes
LVI,
Bulky tumor
Stromal invasion.
• LN +
• + Margins
• + Parametria.

Conclusions
After Sx, RT is required in 50% of patients.
Sx followed by SX +RT gives same result with significantly added toxicity including sub acute toxicity.
‘CONCURRENT CHEMORADIATION 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”
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<tr>
<th>Author</th>
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<td>RT+ Cisplatin</td>
<td>RT alone</td>
<td>Stage IB (≥ 4cm)</td>
<td>Combined with Surgery</td>
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<td>Peters 2000</td>
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<td>243</td>
<td>Surgery</td>
<td>Surgery</td>
<td>IA2, IB, IIA (with postop high risk)</td>
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<td>RT+Cisplatin+5FU</td>
<td>RT alone</td>
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<td>Morris &amp; Eifel</td>
<td>RTOG 9001</td>
<td>388</td>
<td>RT+Cisplatin+5FU</td>
<td>Extended -field RT</td>
<td>IB or IIA (≥5cmorPLN+)</td>
<td>Surgical staging for PALN</td>
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<td>1999 &amp;.2004</td>
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<td>IIB, III, IVA</td>
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<td>RT+ Hydroxyurea</td>
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<td>Rose 1999</td>
<td>GOG 120</td>
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<td>RT+ Hydroxyurea</td>
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<td>+Hydroxyurea</td>
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<td>Pearcey 2002</td>
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<td>RT alone</td>
<td>IB2, IIA (≥5cm), IIB, III, IVA</td>
<td>No surgical staging for PALN</td>
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</table>
Concurrent Chemoradiation  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 patients
- 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: 10%)
- Test for Heterogeneity: Positive
- No data on late toxicities

Chemoradiotherapy in Ca Cervix

- Green Metaanalysis Update, *Cochrane Database Syst Rev* ′05
- Lukka Metaanalysis, *Clin Oncol* ′02
- Green Metaanalysis, *The Lancet* ′01
- Pearcey, *Proc ASCO* ′00 [abst]
- NCI Clinical Announcement ′ 1999
- Tseng, Rose, Keys, Morris, Peters, Whitney
- Wong, *Gynecol Oncol* ′89
Cochrane Meta-analysis of Individual Patient Data (2010)- MRC (UK) group

• 18 RCTs (15 eligible), N=3452
• 5-yr OS improved by 6% (p<-0.001), DFS (8% improvement at 5 years) & local control (9% improvement at 5 years) also significantly improved. Similar benefit for platinum (10 trials) vs non-platinum
• Greater benefit for adjuvant chemotherapy (2 trials, 19% OS benefit at 5 years)
• Trend towards greater benefit of OS for early stage disease: 10% improvement for IB-IIA, 7% for IIB, 3% for III-IV. No such trend for DFS.
Summarizing CTRT Vs NACT in cancer cervix

Slide of Dr Sanjoy....Just see among other things the NACT person is actually not working at all.
Pitfalls

• Various ‘standard treatments’ in cntrl arm
  eg RT alone arm
  RT+HU arm
  EFRT arm

• Differences in exp arm
  eg CDDP alone arm
  CDDP+others
  Pre & Post-op RT
  Stage distribution

  Sig heterogeneity & difficulty in interpretation in metaanalysis
Summary: Evidence in favor of concurrent chemoradiation.

- Green et al, The Lancet' 01
- Green et al metaanalysis on concurrent chemoradiation: update, Cochrane Database Syst Rev, 2005 Jul 20; (3)
- Rose et al, JCO' 02
- Lukka et al, Clin Oncol'02
- Cochrane Meta-analysis of Individual Patient Data (2010) - MRC (UK) group
- Meta-analysis: Green et al, 2017
- Datta et al, Gyn Oncol
Conventional vs Conformal technique in EBRT

- There is significant geographic miss superiorly (common iliac nodes) and laterally (external iliac nodes) in particular
- This correlates with the sites of intra-pelvic failures.
- Majority of failures are marginal. Of these most common is ABOVE the field.

Need for improvement in techniques of EBRT

• To lower toxicity both acute and late.
• Treating PA nodes.
• Boost to pelvic nodes.
• Decrease morbidity and to treat second primary/recurrent disease if required.
Advancements in use of radiotherapy in treatment of cancer cervix

• Advances in techniques.
  Diagnosis and Imaging.
  Contouring techniques and target volumes.
  Advancements in EBRT (3DRT/IMRt and now SBRT).
  Advancements in Brachytherapy (IGRT/interstitial).
• Advancement in outcomes with Radiotherapy.
Role of PET CT

- Primary Tumor Staging
- Lymph Nodal Staging: Early Vs Advance Stages
- Pre-treatment Prognostic Value
- Treatment Plan Optimization: Single modality.
- Post-therapy Surveillance
  - Local
  - Regional (Pelvic / Para-aortic)
  - Distant Metastasis
MRI is the gold standard for evaluation of cervical cancer

Indications for MRI in cervical cancer

• Diagnosis
• Local staging of disease
• Burden of nodal Disease: Pelvic and para-aortic
• Supplements in RT Planning (EBRT) and is of definitive use in IGBT.
• Evaluation of response to treatment
• Recurrent disease/ fibrosis
• Prediction of response to treatment
CT vs MRI vs PET-CT for determination of nodal disease: Meta-analysis

- 41 studies
- PET or PET-CT showed highest sensitivity (82%) and specificity (95%)
- CT sensitivity 50% and specificity 92%
- MRI sensitivity 56% and specificity 91%

Internal target motion


• 39 relevant studies
• Patient specific motion: 5-40mm
• Population based margins would be large (up to 40mm)

Uterine motion is greater than cervical.

Uterine motion is predominantly influenced by bladder filling, cervical motion by rectal filling.

Organ motion patterns are patient specific.

*Individualised PTV margins and adaptive IGRT strategies have also been recommended to ensure target volume coverage while increasing OAR sparing.*

Note-Uninvolved uterus is not the most critical target 15-20mm is common for CTV-T LR to PTV margin.
For nodes 5-7 mm margin is considered adequate.
EFRT – Landmark trials.

*RT versus RT and chemotherapy RTOG 90-01: 8 yr update J Clin Oncol 22(5):872-880, 2004*

IB1, IB2, IIA (N+ or >5cm); IIB-IVA; PAN neg

- Arm 1: Extended field RT (pelvic & PAN)
  - RT dose: 45Gy pelvis and PAN + 40 Gy point A
- Arm 2: RT+CDDP

OS with CTRT was significantly greater than with EFRT (67% vs 41% at 8 years; $P \, .0001$).

Overall reduction in the risk of disease recurrence of 51% (95% CI, 36% to 66%) for patients who received CTRT.

Serious late complications of treatment was similar.

Stage IB to IIB had better OS and DFS ($P \, .0001$).
Patterns of spread and prognostic parameters for nodal pelvic and para-aortic recurrences

- 47% of the patients had nodal metastases at the time of diagnosis, mainly located in the pelvis.
- Para-aortic failures contributed with 69% of all nodal failures, with the strongest predictor being nodal disease at the time of diagnosis.
- 78% of para-aortic failures in EMBRACE were in patients who did not receive para-aortic irradiation.
- PAN irradiation will be investigated in EMBRACE II.
- Location of nodes (common iliac), number of nodes (≥3) and also to some degree nodal size.
Taking a risk based approach- may be the next step

Conclusions
PA field irradiation seems to have positive results.
Toxicities are high and bothersome, specially can decrease CT cycles and increase total treatment time.

Risk based approach
• Limited PA irradiation.
• Classifying the high risk patients who have more chances of PA failure.
• Limited PA irradiation fields with concurrent chemotherapy.
• Using better techniques/IMRT/IGBT and
Risk categorization and EBRT portals in EMBRACE II.

Adopted from EMBRACE II protocol
Use of IGRT in cancer cervix

IGRT is seeing before hitting the target. Use of more conformal planning techniques (IMRT, VMAT, tomotherapy) has raised the importance of IGBT so that the target is not missed CONFORMALLY!

• When it’s a bony target or elective LN region- Simple EPID may be good enough.
• But to see bladder/rectum filling and the movement of uterus or cervix we need CBCT. Use of regular image guidance can reduce target margins causing less bowel irradiation.
Advanced IGRT

• **Basic IGRT** - standard margins from CTV-T to ITV-T are applied to compensate for internal target motion. Daily online position verification using CBCT, kV or EPID imaging.

• **Intermediate IGRT** - CTV-T to ITV-T margin is individualized based on multiple pre-treatment imaging series. ITV-T can become more representative in individual case. CBCT imaging is used for daily.

• **Advanced IGRT** - is based on individual library plans in which different plan specific ITV-T margins are applied. Daily CBCT is required to select the best treatment plan covers the CTV-T on that day.
## Dosimetric and toxicity summary from - Dr MG Janki

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Dosimetric Parameter</th>
<th>Reduction</th>
</tr>
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<tbody>
<tr>
<td>Bowel</td>
<td>V100</td>
<td>reduced by 50 %</td>
</tr>
<tr>
<td>Bladder</td>
<td>V100</td>
<td>reduced by 23 %</td>
</tr>
<tr>
<td>Rectum (as an IMRT Boost)</td>
<td>V66</td>
<td>reduced by 22%</td>
</tr>
<tr>
<td>Bladder (as an IMRT Boost)</td>
<td>V66</td>
<td>reduced by 19%</td>
</tr>
<tr>
<td>Bone marrow (BMS IMRT vs 3DCRT vs AP/PA)</td>
<td>V20</td>
<td>72 vs 97.8 vs 99 % (lesser gr 3 &amp; 4 toxicity)</td>
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</table>

<table>
<thead>
<tr>
<th>Tissue</th>
<th>IMRT vs 4 field</th>
<th>Reduced From</th>
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</thead>
<tbody>
<tr>
<td>GU gr II</td>
<td></td>
<td>91 to 60 %</td>
</tr>
<tr>
<td>Chronic GI</td>
<td></td>
<td>20 to 3 %</td>
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<tr>
<td>Hematological (gr III)</td>
<td></td>
<td>24 % for pelvic</td>
</tr>
<tr>
<td></td>
<td>IMRT vs 3 DCRT</td>
<td>28 % for para aortic (similar)</td>
</tr>
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</table>
IMRT studies with clinical results

- Gandhi AK al., 2013, IJROBP - WP-IMRT is associated with significantly less toxicity compared with WP-CRT and has a comparable clinical outcome. Further studies with larger sample sizes and longer follow-up times are warranted to justify its use in routine clinical practice.

- 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) 2017- MRT 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.
PARCER trial

2015 American Society for Radiation Oncology (ASTRO) 57th Annual Meeting
News Briefing, Monday, October 19, 2015, 10:30 a.m., Central time

Plenary Session: Monday, October 19, 2015, 2:15 – 3:15 p.m., CT, the Henry B. González Convention Center

8 Phase III RCT of Postoperative Adjuvant Conventional Radiation (3DCRT) Versus IGIMRT for Reducing Late Bowel Toxicity in Cervical Cancer (PARCER) (NCT01279135/CTRI2012/120349): Results of Interim Analyses

Author Block: S. Chopra1, R. Engineer2, U. M. Mahantshetty3, T. Dora4, S. Kannan1, R. Phurailatpam1, S. N. Paul1, J. Swamidis1, J. Ghosh1, S. Gupta1, T. Shylasree2, A. Maheshwari1, R. Kerkar3, and S. K. Shrivastava2;ACTREC/Tata Memorial Centre, Navi Mumbai, India; Tata Memorial Centre, Parel, Mumbai, India

Conclusion: There is no difference in late grade ≥2 late bowel toxicity with the use of IG-IMRT. However significant reduction is observed in incidence of late grade ≥3 toxicity with use of IG-IMRT. Final analyses will be conducted after completion of accrual and median follow up of 3 years.
Conventional vs IMRT/IGRT

Cheap and cost effective
Treatment of mass
Effective for the purpose and reliable.
Time tested
I just love my Maruti my first Car!!

Effective for purpose and reliable.
Comfortable journey (less acute toxicity) along with GPS (Image guidance).
Costly.
Better for long drive (EFRT)
I aspire to drive it one day.
Can SBRT/IMRT replace brachytherapy

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.

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

If you are waiting for proton – Don’t wait!

AROI ESTRo slide
Use of IGRT in Brachytherapy.....IGBT

• Advancements in IGRT

**IGBT is not**

Doing an MRI brachytherapy always.

Even simple USG/CT scan in ICA applications can improve outcome by making sure that the tandem is in the uterus.

Upto 10 % false passage is documented in literature even in best hands. (I doubt its an conservative estimation).

Doing an Simple USG TAUS/TRUS during USG will improve the success rate.

CT is now widely available and can be widely used to plan Brachytherapy.
Evolution of imaging in brachytherapy

Plain x ray
International standard until 2002

2002-2011, more and more centers in India are using CT based planning

After 2011
Use is increasing slowly
Upcoming use of USG in Gyn Brachytherapy

• Maximilian P. Schmid et al, Transrectal ultrasound for image-guided adaptive brachytherapy in cervix cancer – An alternative to MRI for target definition? Radiotherapy and oncology: 2016 - *TRUS is superior to CT as it yields systematically smaller deviations from MRI, with good to excellent image quality.* - meaningful for a resource starved country like India.

• Mahanshetty U - Trans-abdominal ultrasound (US) and magnetic resonance imaging (MRI) correlation for conformal intracavitary brachytherapy in carcinoma of the uterine cervix. *Radiother Oncol* 2012;

Use of ultrasound in image-guided high-dose-rate brachytherapy: enumerations and arguments

Susovan Banerjee, MD, Tejinder Kataria, MD, DNB, Deepak Gupta, MD, Shikha Goyal, MD, DNB, Shyam Singh Bisht, MD, Trinanjan Basu, MD, Ashu Abhishek, MD
Department of Radiation Oncology, Medanta - The Medicity, Gurugram, Haryana, India

Abstract

Inherently, brachytherapy is the most conformal radiotherapeutic technique. As an aid to brachytherapy, ultrasonography (USG) serves as a portable, inexpensive, and simple to use method allowing for accurate, reproducible, and adaptive treatments. Some newer brachytherapy planning systems have incorporated USG as the sole imaging modality. Ultrasonography has been successfully used to place applicator and dose planning for prostate, cervix, and anal canal cancers. It can guide placement of brachytherapy catheters for all other sites like breast, skin, and head and neck cancers. Traditional USG has a few limitations, but recent advances such as 3-dimensional (3D) USG and contrast USG have enhanced its potential as a dependable guide in high-dose-rate image-guided brachytherapy (HDR-IGBT). The authors in this review have attempted to enumerate various aspects of USG in brachytherapy, highlighting its use across various sites.

Key words: image guided brachytherapy, high-dose-rate, ultrasonography.
Indications of IC+IS/IS brachytherapy

- Extensive parametrial disease (More than 2.5 cm from OS)
- Lower vaginal involvement
- Distorted anatomy
- Central Recurrence/reradiation
- Unacceptable dose to normal tissue dose from IC applications.
Summarizing the volumes of CTVs of Brachytherapy

- **HRCTV** = Whole cervix + GTV/ Nodularity (from clinical assessment or MR) + Grey zones (MR).
  - Intent: 85 to 90 + Gy total dose (EQD2) to HRCTV in definitive radiotherapy.
  - Dose comparable with dose to point A
  - Most important of all the volumes
  - Reproducible - least interobserver variation.
  - Dose volumes of HRCTV predicts outcomes most consistently.

- **IRCTV** - Pre EBRT disease (Always includes HR-CTV with safety margins).
  - Intent: 60 + Gy total dose to CTV,
  - Comparable with dose to the 60Gy isodose (ICRU recommendations).
Points to volumes- summary of correlations

• Point A provides an estimate of the average CTVHR D90 % for a large patient population with a balanced disease-stage distribution. Point A is a good representation of “an average position” of the tumor. Helps in introducing / check for major dose escalation or reduction for such patient

• ICRU rectal reference point correlates with the D2cc dose of the organ rectum

• ICRU bladder reference point, does not correlate well with bladder complications (ICRU 38 bladder point underestimates the bladder dose)
Importance of advanced IC/IS technique

Increased dose resulted in improved local control in patient cohorts where application of IC/IS was performed in at least 20% of the patients.

Adopted from EMBRACE II protocol
Urinary morbidity and bladder D2cm³

- 680 pts from EMBRACE, 95 events of ≥G2 morbidity occurred (ureter stenosis excluded).
- The dominating events were frequency, urgency and cystitis.
- A significant dose relationship - dose beyond 80Gy EQD² there is a clinically significant increase in ≥G2 morbidity.

Actuarial incidence of G≥2 urinary morbidity (all endpoints except ureter stenosis) grouped according to D2cm³ dose levels (Tanderup K. et al. 2014,
Rectal bleeding and rectum D2cm3

- 701 patients from EMBRACE - Rectal bleeding (50 events)
- The dose response was shallow below 70Gy, and it is unclear how much clinical impact dose de-escalation below 70Gy could have.
- However, for doses above 70-75Gy there is a steep increase in risk of rectal bleeding.

Adopted from EMBRACE II protocol
Principles for dose de-escalation and dose escalation in EMBRACE II

- We are actually treating small volume diseases to a high dose the dose can be de-escalated.
- While at the same time patients with high volume disease needs some dose escalation as the LC can be better that we currently see.
- Improved IC/IS techniques are required to achieve this and is currently being evaluated in EMBRACE II trial.
Advancement in manpower and logistics

ICRO courses and classrooms being held throughout the country. Rapid increment in trained workforce by governmental policy of increasing post graduate radiotherapy training program.
Improvement of results after IGBT

- The improvement in OS and CSS by 10% and 14%, respectively, for the Retro EMBRACE cohort compared to the historic cohorts.
- The benefit of IGBT on CSS was maintained over time (5-year differences 21%, 9%, and 5%, respectively for IB, IIB and IIIB disease.)
Achievement in treatment of Cervix radiotherapy

BJR, Vol 5, Issue 55, 1932, A study on 811 cases, 5 years FU.

TABLE I

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of Cases</th>
<th>1/yr %</th>
<th>1 yr %</th>
<th>1½ yr %</th>
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<th>3 yr %</th>
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<td>Mean</td>
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TABLE II

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<tr>
<th>FIGO stage</th>
<th>Number of patients at 3/5 years</th>
<th>Actuarial local control at 3/5 years</th>
<th>Actuarial pelvic control at 3/5 years</th>
<th>Actuarial overall survival at 3/5 years</th>
<th>Actuarial cancer specific survival at 3/5 years</th>
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<tr>
<td>1A</td>
<td>2</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
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<tr>
<td>1B</td>
<td>123</td>
<td>98.9%</td>
<td>96.9%</td>
<td>88.8%</td>
<td>93.9%</td>
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<tr>
<td>2A</td>
<td>42</td>
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<td>95.9%</td>
<td>83%</td>
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<td>2B</td>
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<td>71.7%</td>
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<td>145</td>
<td>79.7%</td>
<td>73.6%</td>
<td>56.4%</td>
<td>65.5%</td>
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Schematic workflow for contouring primary target and nodal target and OARs

Adopted from EMBRACE II protocol
Summary and take home message

• Radiotherapy along with CT is the definitive cure.
• Technological advancements (both EBRT and brachytherapy) will lead to better dose escalation and sparing of normal tissues.
• IMRT seems to be promising due to its dosimetric superiority and evolving clinical data suggests its immediate and late benefits.
• IGRT will probably reduce irradiated volume.
• In order to chase the PA disease or boost pathological nodes with conc CTRT IMRT may be a necessity.
• Individualization of radiotherapy treatment and portals for cancer cervix (depending on disease burden) seems to be better approach.
• All technological and treatment advancements should be verified and we should wait for mature data before we move from current gold standards to next step.
Thank you all