LOCALLY ADVANCED CERVICAL CANCER

DR ROZITA ABDUL MALIK

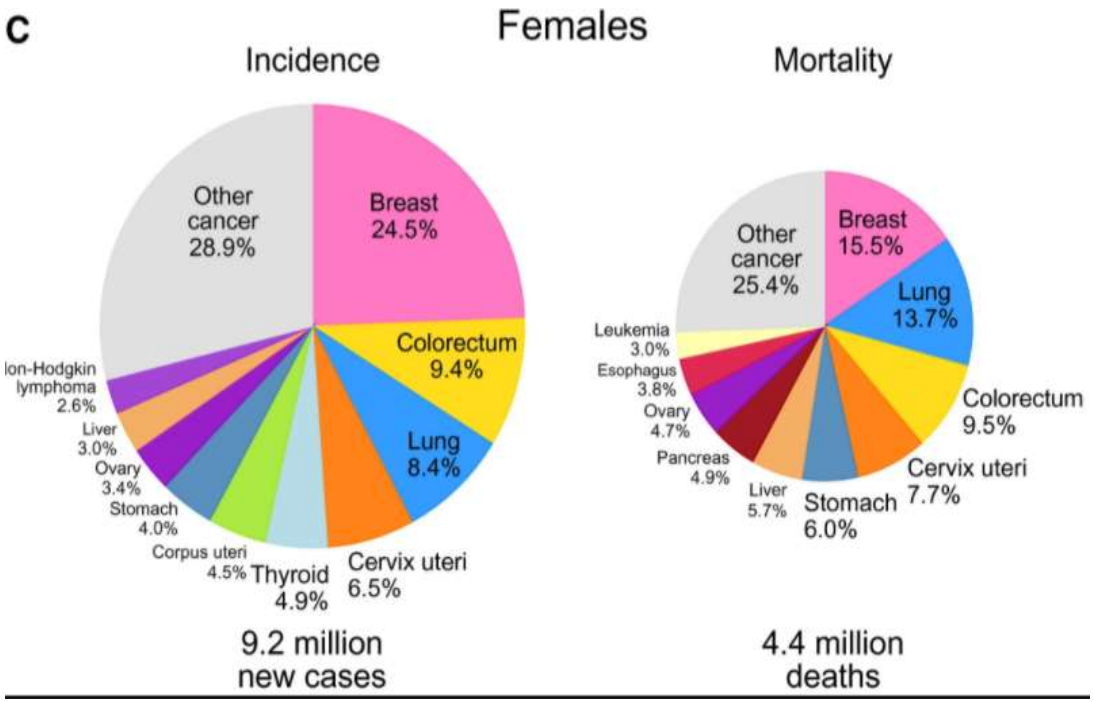
CLINICAL ONCOLOGY DEPARTMENT

UMMC

21/07/2021

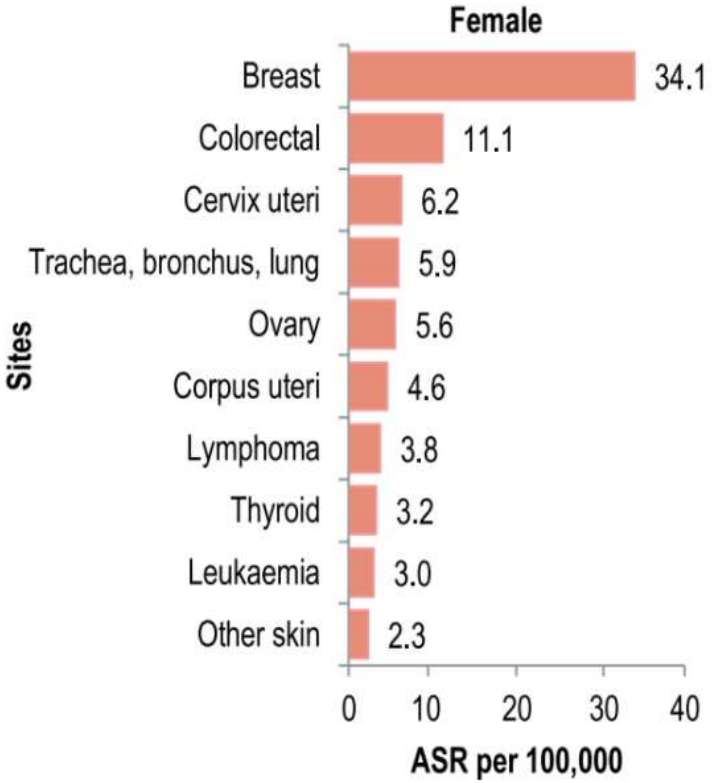
WORLDWIDE

- 4th most common cancer and 4th leading cause of cancer death in women worldwide
  - 604,127 new cases (6.5%) & 341,831 (7.7%) death in 2018 (*Globocan, 2020)*
- 75% occur in developing countries



MALAYSIA

- Among the 10 most common cancers
- 3rd most common cancers in women (3981 cases, 6.2%)



MALAYSIA NATIONAL CANCER REGISTRY REPORT, 2012-2016

WHAT IS LACC?

- FIGO stage IB2, IIA2
- FIGO stage IIB to IVA
- FIGO Stage 2018
  - IB1 (<5mm depth of stromal invasion, ≤2cm)
  - IB2 (>2- <4cm)
  - **IB3** (≥4cm)
  - **FIGO 3C1**: pelvic nodes mets
  - **FIGO 3C2**: para-aortic LN with/without pelvic LN

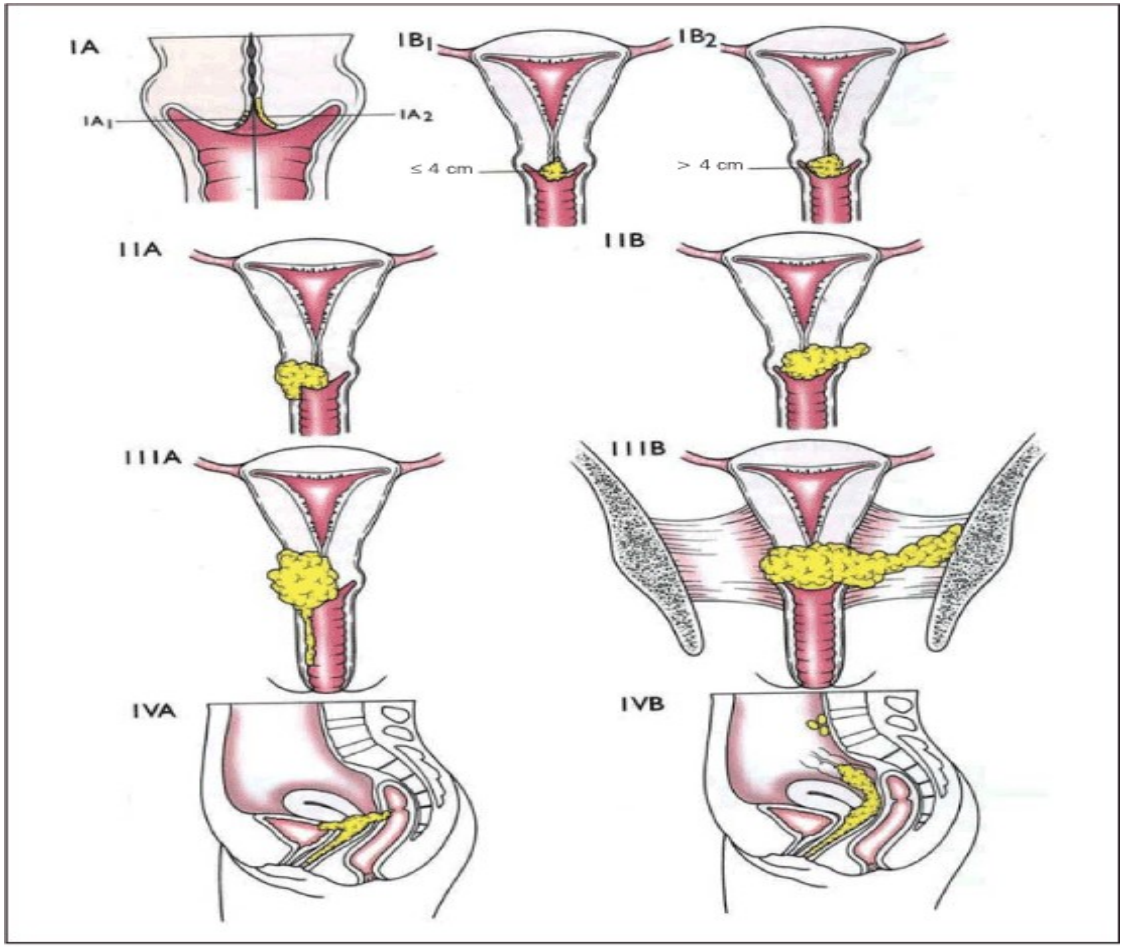


Figure 1. Staging of uterine cervix carcinoma according to FIGO[3].

RISK OF LN METASTASES

+ Lymph Node Metastases

- Most important prognostic factor is LN Status

Stage	% +Pelvic Nodes	% + Para-aortic Nodes
IA1	0	0
IA2 (3-5 mm)	4.8	<1.0
IB	16	2
IIA	25	11
III	45	30
IVA	55	40

Factors Affecting Survival & LC in LACC

- Large tumours (> 5cm)
- Young age (≤ 40 years)
- Non-squamous histology
- Positive nodes on MRI
- Advanced stage

- High risk:
  - 1.) tumour > 5cm & at least one other risk factor
  - 2.) tumour < 5cm & 3 other risk factors

Bae et al. Int J Gynecol Cancer 2016

HPV infection also affects LC & Survival

- A systematic review
  - Reported that HPV genotypes result in differential prognoses even after adjusting for staging, tumour size & tumour grade

Li P et al. Oncotarget, 2017

Negative Prognosticators

- Pre-treatment systemic markers (Patient treated with CCRT):
  - Anaemia
  - Thrombocytosis
  - Leucocytosis
  - Lymphopenia

Examination & Investigation for LACC

- Examinations recommended for staging:
  - V/E & Speculum: inspection, palpation
  - EUA – inspection, palpation, colposcopy,
    +/-cystoscopy, proctoscopy/sigmoidoscopy (suspicious on imaging)
  - CT/PET:
    - assess lymph nodes status
    - assess distant metastases
  - MRI (Pelvis): local extend of tumour
  - Surgical (laparascopic) - assess lymph nodes

MANAGEMENT OF LACC

FIGO IB2 & IIA2

FIGO IIB - IVA

FIGO IB2 & IIA2

- Treatment aimed to avoid combining surgery and RT/CCRT as it will increase morbidity
- CCRT is preferred as these are bulky tumours & tend to have pelvic LN involvement
- CCRT is needed post surgery if:
  - Positive pelvic LN
  - Positive/close margin
  - Surgical stage IIB or greater
    - GOG 109 *(Peters WA et al., 2000)*
      - RT vs CCRT in high-risk early stage cervical cancer
      - Addition of cisplatin significantly improved PFS & OS

CCRT is Better Than RT Alone (FIGO IIB – IVA)

- No curative surgical options
- Standard treatment is CCRT with brachytherapy
- Traditionally RT alone
- 1991, NCI recommended "strong consideration for adding platinum based chemotherapy"
  - Based on 5 RCT
  - Later confirmed by meta-analysis (13RCTs)
- DFS HR: 0.78, OS HR:0.81 → absolute improvement DFS: 8%, OS: 6%
- Relative effect of CCRT by stage:
  - Decreasing benefit with increasing stage (I/II: 10%, III/IVA: 3%)
- Higher toxicity (esp. haematological & GI toxicities)

Definitive Chemoradiotherapy

- Concurrent chemoradiation (EBRT) & Intracavitary Brachytherapy (ICBT)
- Chemotherapy (platinum based) – preferably cisplatin 40mg/m2 weekly
- Overall treatment time, ideally 7 weeks & not exceeding 8 weeks
- Delay of treatment/interruptions should be avoided
- Anaemia should be corrected

EBRT

- EBRT to pelvis +/- PAN,
- Techniques:
  - 3D
  - IMRT
- Dose:
  - Pelvis: 45Gy – 50.4Gy/ 25-28#
  - Para-aortic: 45Gy/25#
  - Lymph node boost (total dose): 55-60Gy (SIB within IMRT or sequential boost)
- Target volume:
  - Primary cervical tumour, adjacent tissues such as parametria, uterus, upper vagina
  - Pelvic LN (upper pre-sacral, obturator, internal & external iliac +/- common iliac)

ICBT (Intracavitary Brachytherapy)

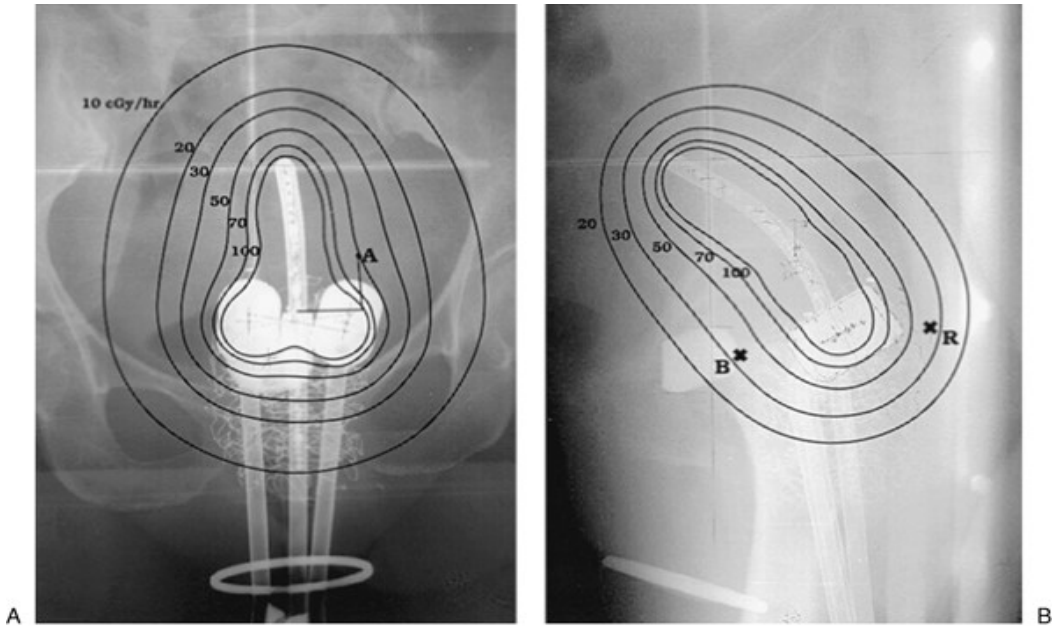
- Major role in delivering a **substantial dose** of radiation to the **tumour** in the central pelvis while **sparing** the surrounding **organs at risk**
- 2D (**point-based** prescription) to 3D (**volumetric –based** prescription)
- IGABT (Image-guided adaptive brachytherapy) is recommended
  - MRI preferred, CT or US may be used
- Dose to HRCTV D90: 80-90Gy (EBRT + ICBT)

OVERVIEW OF IGBT

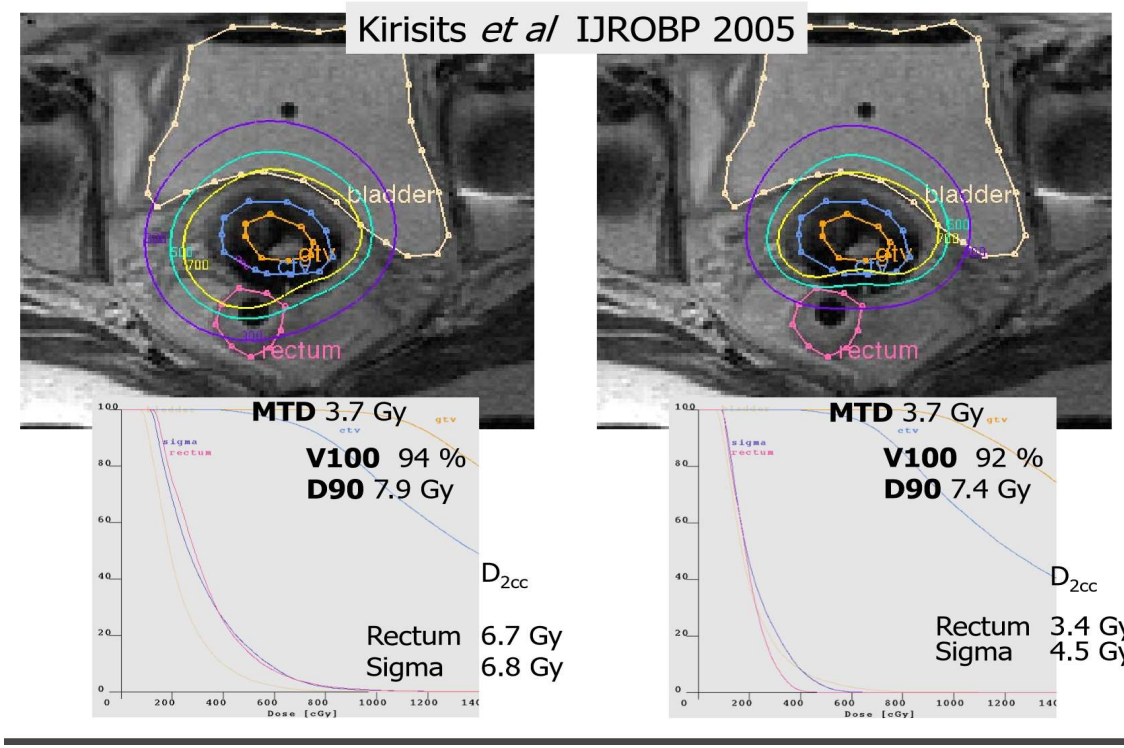
- In 2005, the European society of brachytherapy, GEC-ESTRO published the recommendation for the use of IGBT and later was endorsed by both GEC-ESTRO and ABS (American brachytherapy society) as the **new international standard of brachytherapy** for cervical cancer
- The **GEC-ESTRO guidelines (I-IV)** – universally accepted as the new international standard of brachytherapy for cervical cancer
- Advantage: Possibility to **conform the dose** to the **target** while **reducing doses to organs at risk**. This would allow escalation of dose to the target which has been shown to improved local control and hence may be expected to translate into improvements in overall survival.

Brachytherapy Prescription

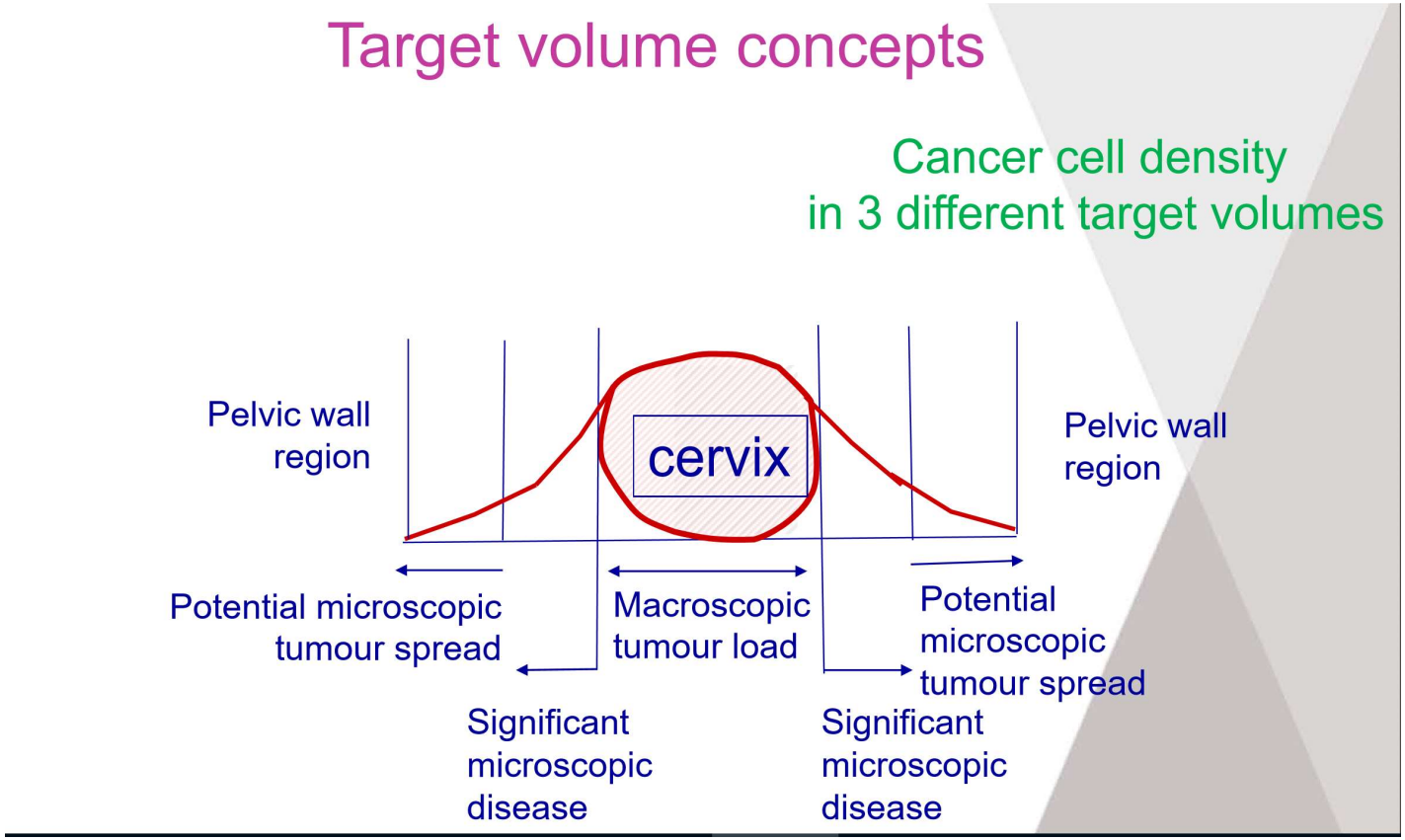
- 2D era: dose prescription based on ‘systems’
  - to Point A
  - or to a reference volume



- 3D era:
  - Prescription to a target volume, ie HRCTV D90



TARGET VOLUME CONCEPTS



C. Haie-Meder et al; Radiotherapy and Oncology, 2005

TARGET VOLUME CONCEPTS
TARGET DEFINITION
2 CTVs

HIGH RISK CTV (HRCTV)

- A first target related to the extent of GTV **at time of BT**:

Taking into account tumour extent at diagnosis, with high dose prescribed to this target (80-90Gy)

- No safety margins
- Aim: Dose high enough to sterilize macroscopic tumour
- Dose comparable with dose to Point A

INTERMEDIATE RISK CTV (IRCTV)

- A second target related to the extent of **GTV at diagnosis**:

With an intermediate dose prescribed to this target (60Gy)

- Includes safety margins with regard to GTV initial size
- Aim: To sterilize microscopic disease
- Dose comparable with dose to the 60Gy isodose (ICRU recommendation)

RetroEMBRACE – improvement in outcome

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Radiotherapy and Oncology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Image guided brachytherapy in locally advanced cervical cancer: Improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study

Alina Sturdza [a], Richard Pötter [a,*], Lars Ulrik Fokdal [b], Christine Haie-Meder [c], Li Tee Tan [d], Renaud Mazeron [c], Primoz Petric [e], Barbara Šegedin [e], Ina Maria Jurgenliemk-Schulz [f], Christel Nomden [f], Charles Gillham [g], Orla McArdle [g], Erik Van Limbergen [h], Hilde Janssen [h], Peter Hoskin [i], Gerry Lowe [i], Ekkasit Tharavichitkul [j], Elena Villafranca [k], Umesh Mahantshetty [l], Petra Georg [a], Kathrin Kirchheiner [a], Christian Kirisits [a], Kari Tanderup [b], Jacob Christian Lindegaard [b]

[a] *Medical University of Vienna, Comprehensive Cancer Center, Department of Radiation Oncology, Austria;* [b] *Aarhus University Hospital, Department of Oncology, Denmark;* [c] *Gustave Roussy Cancer Campus Grand Paris, Department of Radiation Oncology, Villejuif, France;* [d] *Cambridge University Addenbrooke's Hospital, Department of Radiotherapy, United Kingdom;* [e] *Institute of Oncology Ljubljana, Division of Radiotherapy, Slovenia;* [f] *University Medical Center Utrecht, Department of Radiotherapy, The Netherlands;* [g] *St Luke's Hospital, Dublin, Ireland;* [h] *Department of Radiotherapy, University Hospital Gasthuisberg, Leuven, Belgium;* [i] *Mount Vernon Hospital, Department of Radiotherapy, London, United Kingdom;* [j] *Faculty of Medicine, Chiang Mai University, Thailand; and* [k] *University of Navarra, Department of Oncology, Pamplona, Spain;* [l] *Tata Memorial Hospital, Mumbai, India*

RetroEMBRACE

- First comprehensive report on clinical outcome in a large multi-institutional cohort (12 institutions worldwide- prior to participation in EMBRACE)
- Retrospective observational study (collection of data on 3D IGBT – locally advanced cervical cancer)
- Data collection: Oct 2010 – Sep 2013
- Inclusion criteria:
  - Histological confirmed cervical cancer
  - Treatment with curative intent by definitive EBRT (+CCRT), followed by IGBT MRI/CT guidance, treatment outcome outside EMBRACE
  - Para-aortic nodal disease also eligible

RetroEMBRACE

Table 1
Patient and tumour characteristics.

Variable		No of patients *n*/%
Median age (years)	53 (23–91)	731
FIGO stage	1B	123 (16.8%)
	2A	42 (5.6%)
	2B	368 (50.3%)
	3A	23 (3.1%)
	3B	145 (19.8%)
	4A	23 (3.1%)
Histology	Squamous cell Ca	591 (84.7%)
	Adenocarcinoma	9.3%
	Others	6%
Median tumour width at diagnosis	Clinically: 50 mm	MRT: 46 mm
Nodal status	N+	40%
	N–	60%
CHT	Yes: 566 (76.5%)	No: 165 (22.5%)

RetroEMBRACE

- Results:
  - Median follow-up: 43 months
  - At 3/5 years:
    - LC 91%/89%
    - PC 87%/84%
    - CSS 79%/73%
    - OS 74%/65%
  - Mean EBRT dose was 46±2.5Gy; 77.4% received concurrent chemotherapy. Mean D90 HRCTV was **87±15Gy** ($EQD2_{10}$), mean D2cc was: bladder 81±22Gy, rectum 64±9Gy, sigmoid 66±10Gy and bowel 64±9Gy (all $EQD2_3$).
- Improvement in outcomes of about 10% (in agreement with mono-institutional reports)
- Limited severe morbidity

EMBRACE – late rectal toxicity

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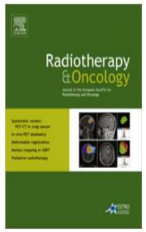


Original article

Dose–volume effect relationships for late rectal morbidity in patients treated with chemoradiation and MRI-guided adaptive brachytherapy for locally advanced cervical cancer: Results from the prospective multicenter EMBRACE study ☆

Renaud Mazeron [a,*], Lars U. Fokdal [b], Kathrin Kirchheiner [c], Petra Georg [c], Noha Jastaniyah [c], Barbara Šegedin [d], Umesh Mahantshetty [e], Peter Hoskin [f], Ina Jürgenliemk-Schulz [g], Christian Kirisists [c], Jacob C. Lindegaard [b], Wolfgang Dörr [c], Christine Haie-Meder [a], Kari Tanderup [b], Richard Pötter [c], on behalf of the EMBRACE collaborative group[1]

[a] *Department of Radiotherapy, Gustave Roussy, University of Paris-Saclay, Villejuif, France;* [b] *Department of Oncology, Aarhus University Hospital, Denmark;* [c] *Department of Radiation Oncology, Comprehensive Cancer Center, Medical University of Vienna/General Hospital of Vienna, Austria;* [d] *Department of Radiotherapy, Institute of Oncology, Ljubljana, Slovenia;* [e] *Department of Radiation Oncology, Tata Memorial Hospital, Mumbai, India;* [f] *Department of Radiotherapy, Mount Vernon Cancer Centre, United Kingdom; and* [g] *Department of Radiotherapy, University Medical Center Utrecht, The Netherlands*

$D2cm^3 \leq 65Gy$: minor/less frequent morbidity

$D2cm^3 \geq 75Gy$: major/more frequent morbidity

EMERGING USE OF IMRT

- IMRT is a newer method of delivering radiation to target structures
- The basis of IMRT is the use of intensity-modulated beams that can provide two or more intensity levels
- Able to generate concave dose distributions and dose gradients with narrower margins
- Therefore, suitable for treating complex treatment volumes and avoiding close proximity organs at risk (OAR) that may be dose limiting
- Theoretically may provide benefits in terms of increased tumour control through escalated dose and reduced normal tissue complications through OAR sparing.
- The main benefit expected with IMRT is **reduction in toxicities**

IMRT vs 3D conformal vs 2D conventional

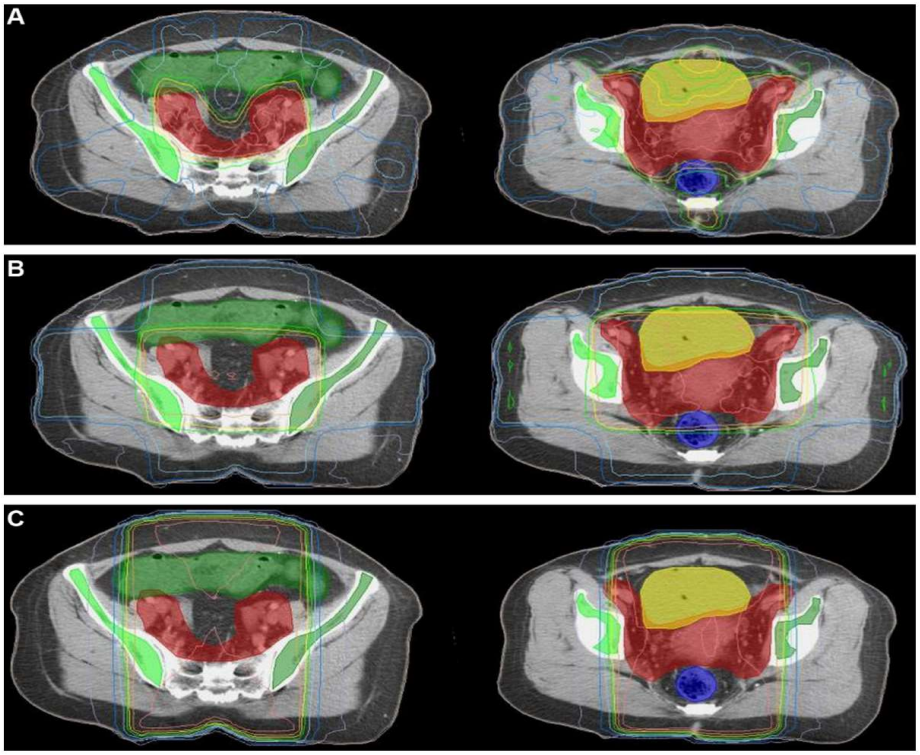
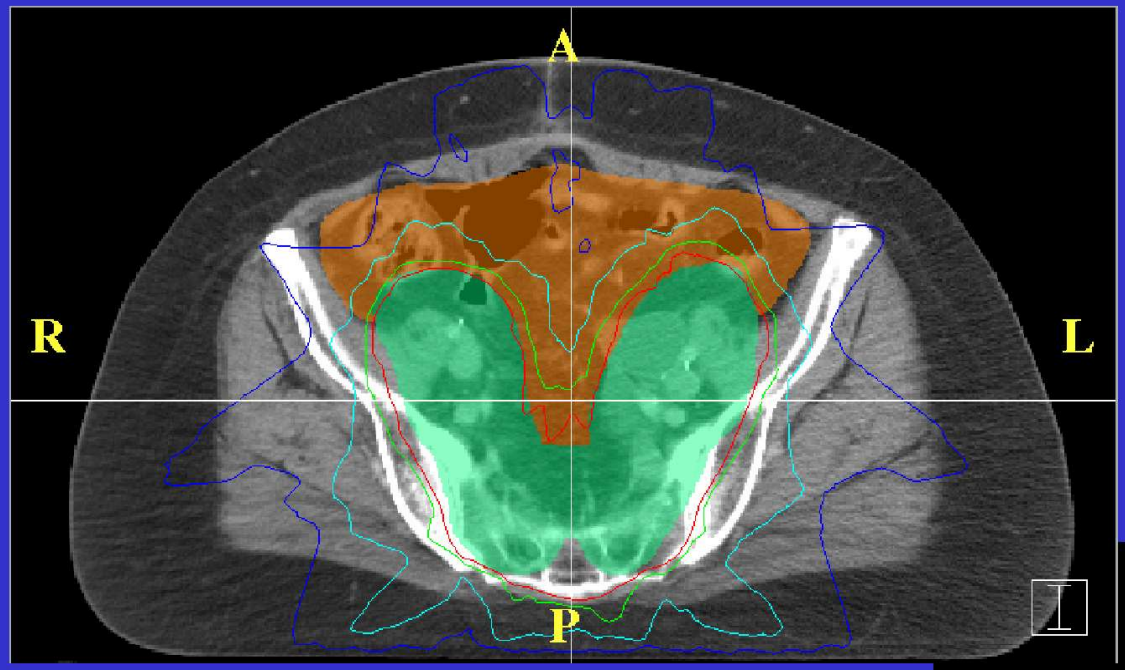
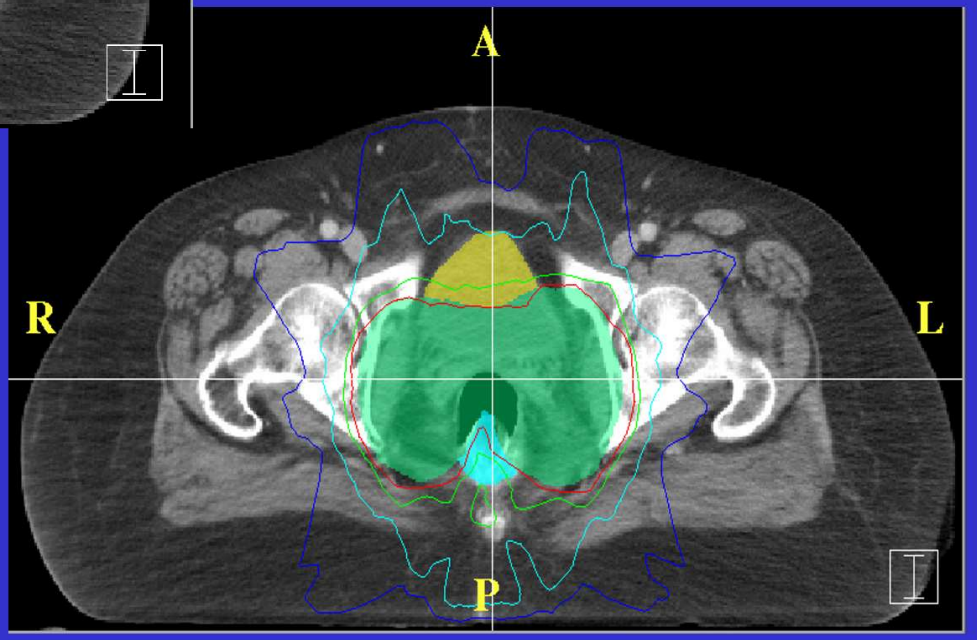


Fig. 1. Axial views of isodose distribution in radiotherapy for cervical cancer. A. Intensity-modulated radiotherapy. B. 3D conformal radiotherapy. C. Conventional radiotherapy.
Isodoses de radiothérapie du cancer du col utérin. A. Radiothérapie conformationnelle avec modulation d'intensité. B. Radiothérapie conformationnelle tridimensionnelle. C. Radiothérapie classique.



←In the upper pelvis, spares the small bowel

In the lower pelvis→ spares the bladder and rectum



Roeske et al. (2000)

Is there benefit associated with IMRT compared to 3D conformal RT (3DCRT)?

- Adjuvant post-op treatment with/without chemotherapy
- When EBRT as primary treatment with/without chemotherapy
- When additional dose is required to boost residual disease (IMRT vs 3DCRT or brachytherapy)

IMRT- Post-hysterectomy (adjuvant)

- First clinical series by *Mundt et al.* 2001/2002, whole pelvis IMRT
  - 40 patients with 24 patients: posthysterectomy
  - Compared with 35 historic controls (conventional fields)
    - Acute grade 2 GI toxicity was less common with IMRT (60% vs 91%, P=.002)
    - Acute haematological toxicity was reduced with IMRT in patients treated with CCRT
    - Chronic GI toxicity at 1 year was also decreased with IMRT (*Mundt et al*. 2003)

Extended Field IMRT

- Overall, studies have shown dosimetric & suggested clinical benefits
- Reduced acute GI & haematological toxicities
- Reduced chronic GI toxicity
- Furthermore, several patient series have shown the feasibility of IMRT in achieving tolerable dose escalation to involved para-aortic lymph nodes.

Salama et al; Int J Radiat Oncol Biol Phys 2006

Beriwal S et al; Int J Radiat Oncol Biol Phys 2007

Gerszten K et al; Gynecol Oncol 2006

IMRT – Definitive RT

- Role of IMRT in treating intact cervical cancer remains unclear
- Target mobility and tumour deformation/regression during a course of radiotherapy are of greater concern
- A preliminary attempt at target volume consensus in intact cervical cancer (based on a single case study) was published

(*Lim K et al; Int J Radiat Oncol Biol Phys, 2011*)

IMRT – Definitive RT

- Dynamic environment of pelvis – complexity of planning & treatment
  - Patient movement
  - Cancer target movement
  - Normal structure movement
  - Tumour shrinkage during treatment
- Planning appropriate target margins given internal target motion and variability is a challenge
- Image-guided radiation therapy (IGRT), regular use of cone-beam CT, may help improve and verify localization and positioning

IMRT for Cervical Cancer

- Offers distinct dosimetric advantages over traditional 2-D and 3-D planning techniques with regard to sparing normal tissues adjacent to cancer targets.
- Clear applicability in cervical cancer, particularly in the post-hysterectomy setting.
- Allows dose escalation to para-aortic lymph nodes and bulky sidewall disease, and may be useful in re-irradiation cases.
- May also be considered as a boost to primary disease in patients who are not brachytherapy candidates, however, should not be accepted as a routine substitute for brachytherapy

Is There Role of Adjuvant CT in LACC

- Further investigations are needed to clarify role of CT especially in high risk patients

- Randomised study: *Duenas – Gonzalez A et al., 2009*
  - 515 pts, IIB -IVA
  - cisp/gem-CCRT + 2 cycles post CCRT vs standard CCRT –cisp
  - Significant better PFS & OS (Both HR:0.68)
  - Significantly higher G3/4 toxicities (86.5% vs 46.3%, $p<0.001$), but manageable
  - Only 76.5% manage to complete the adjuvant treatment

- OUTBACK Trial – ongoing RCT (CCRT + 4 cycles of carbo/pacli vs CCRT alone)

Role of Neoadjuvant CT (Prior to RT/CCRT) vs CCRT

- Still investigational
- Risk-benefit of adding neoadjuvant CT to conventional CCRT remains inconclusive despite several positive reports
- INTERLACE study (UK) – weekly induction CT (carbo/pacli) followed by standard CCRT vs standard CCRT alone

Role of Neoadjuvant CT (Prior to Surgery) vs CCRT

- CCRT is superior to NACT followed by radical surgery (IB2-II) in terms of PFS: Based on 2 recent RCTs:

Study	Gupta et al. (2017)	EORTC 55994 (2019)
No of patients	635	626
Stage	IB2-II (SCC)	IB2-IIB (SCC, AdenoCa, AdenoSq)
Study arm	3x Carbo/pacli -> Sx **vs** CCRT (cisp)	Cisp-based chemo (cumulative min 225mg/m2) -> Sx **vs** CCRT (cisp)
5years DFS/PFS 5 years OS	69.3% vs 76.7% **(p=0.038)** 75.4% vs 74.7% (p=0.87)	56.9% vs 65.6% **(p=0.021)** 61.8% vs 67.7% (p=0.154)
Subgroup Analyses	Detrimental (IIB) DFS: HR 1.90	NACT better (IB2) OS, HR 0.89 NACT worse (IIA2, IIB) OS, HR 1.21, 1.32

SUMMARY

- Standard treatment for LACC is **CCRT**
- Overall treatment time should **not exceed 8 weeks**
- **Anaemia** has to be corrected
- Advances in RT techniques have improved outcomes in treatment of LACC
- IMRT **reduces toxicity** and has advantages in **allowing dose escalation** to para-aortic LN and pelvic nodes, however it possess challenges in definitive RT due to the dynamic environment of the pelvis
- IGBT allows **escalation of dose** to the target while **sparing the surrounding organs at risk**

THANK YOU