

# Radiation oncology perspectives in uterine cervix cancer

Coza Ovidiu Florin, MD, PhD

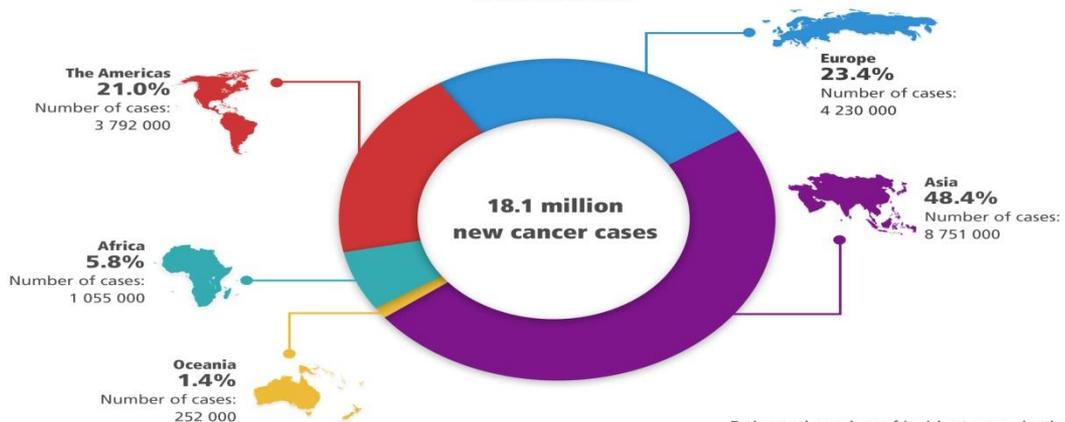
University of Medicine and Pharmacy “Iuliu Hațieganu”

The Oncology Institute “Ion Chiricuță”

Cluj-Napoca

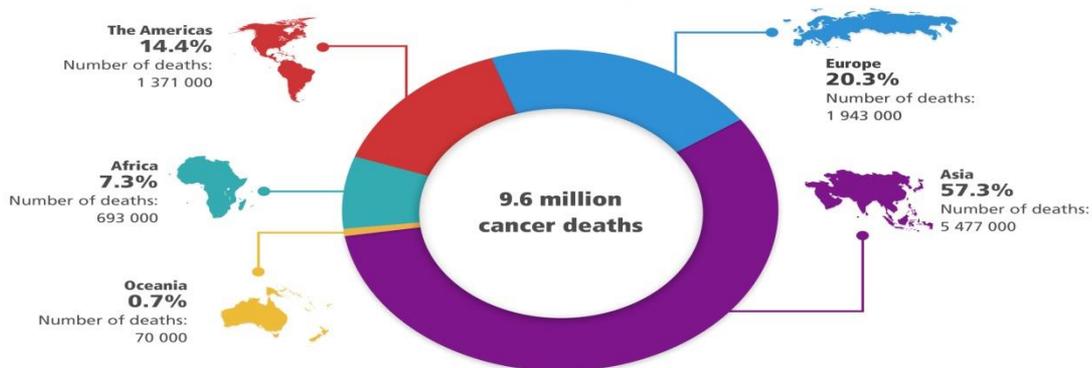
ROMANIA

## Global cancer incidence

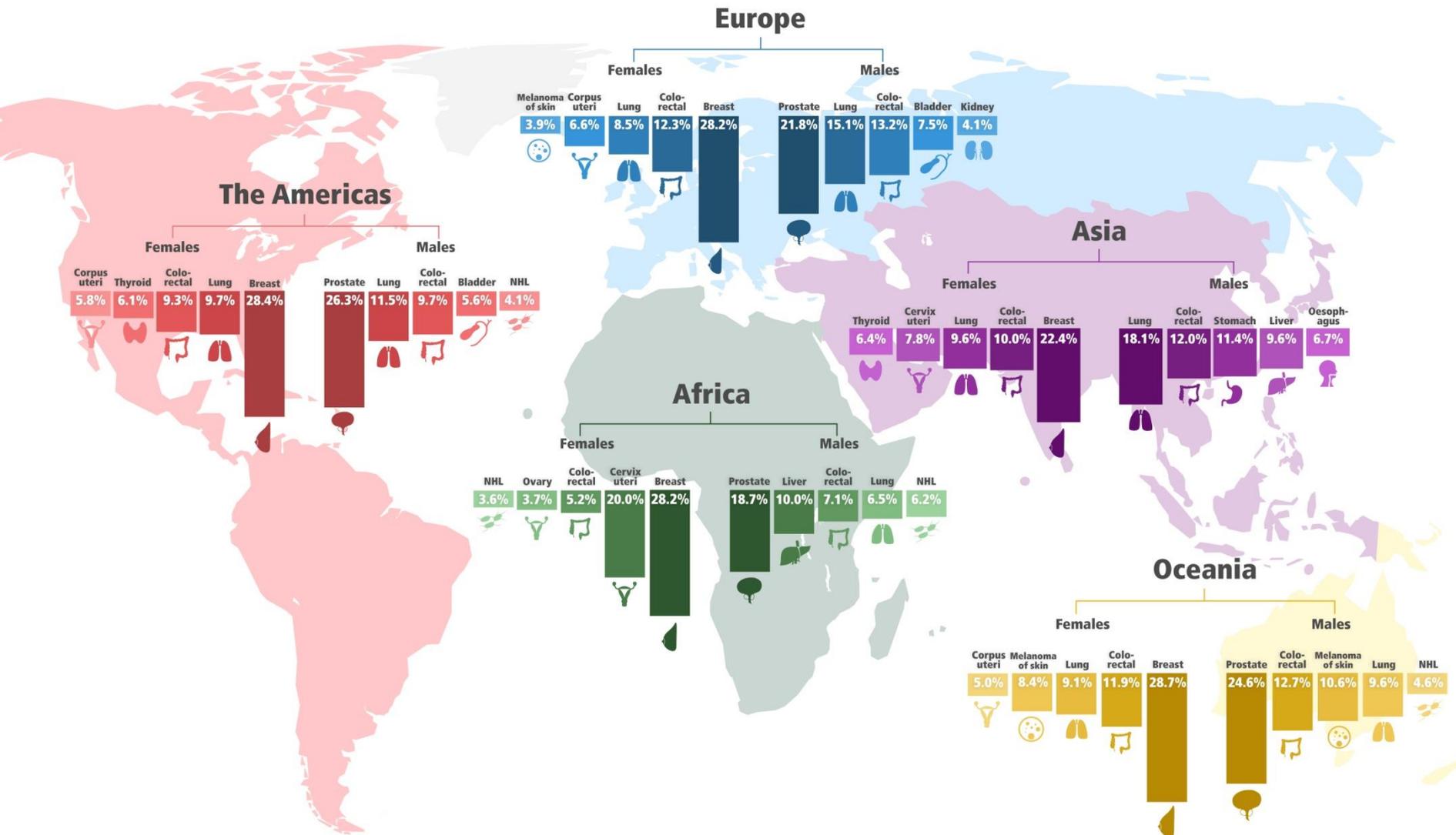


Estimated number of incident cases, both sexes, all cancers including non-melanoma skin cancer, for all ages, worldwide

## Global cancer mortality



Estimated number of deaths, both sexes, all cancers including non-melanoma skin cancer, for all ages, worldwide



Data source: GLOBOCAN 2018

Available at Global Cancer Observatory (<http://gco.iarc.fr/>)

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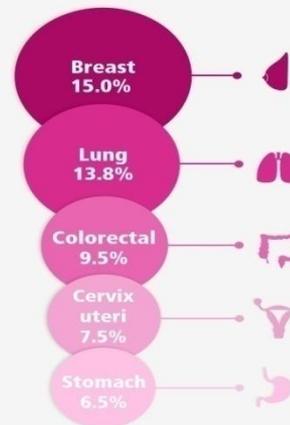
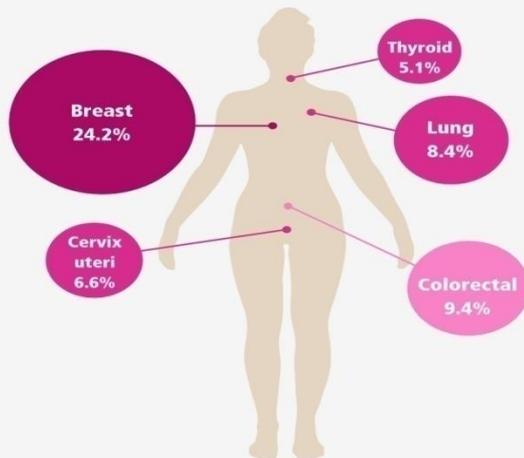
NHL = Non-Hodgkin lymphoma

Top five cancer sites among all ages, excluding non-melanoma skin cancer

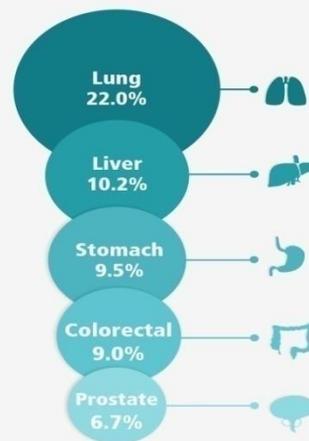
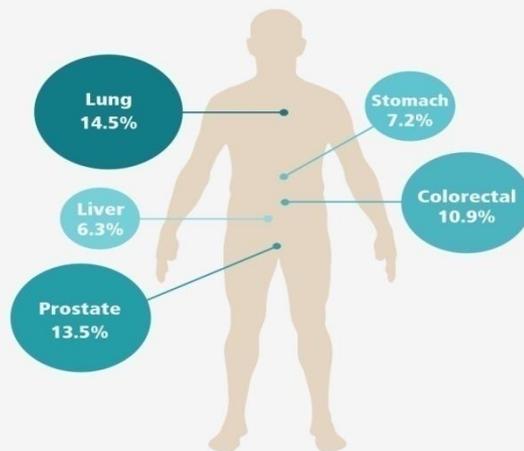
Global cancer incidence

Global cancer mortality

Females

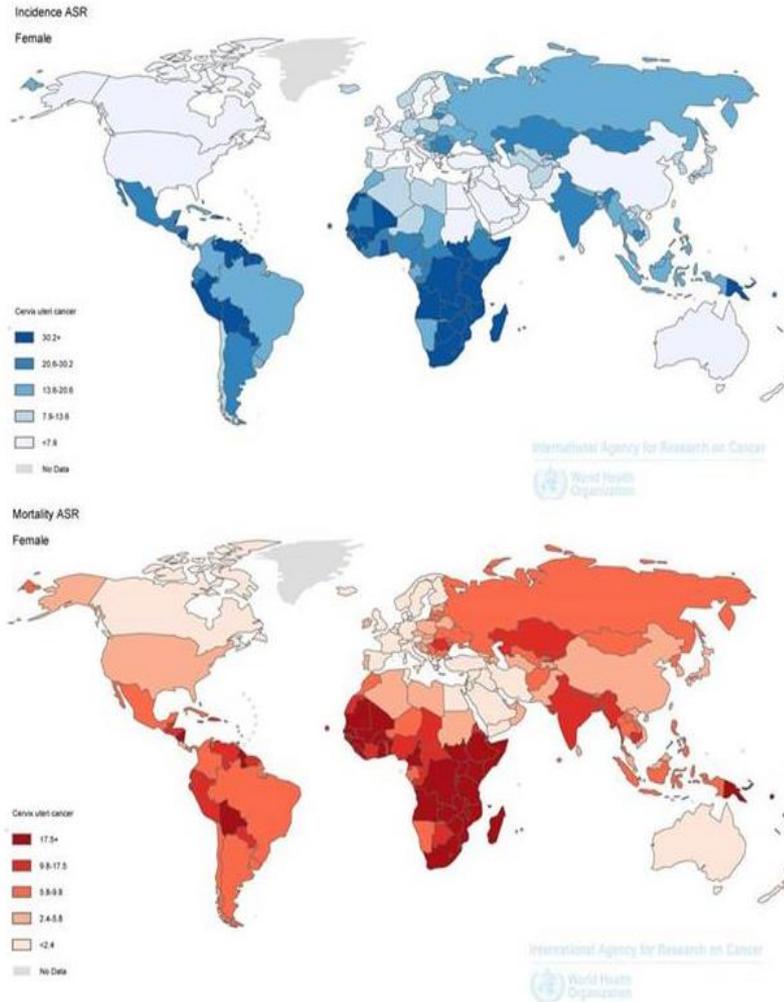


Males



Not depicted: non-melanoma skin cancer, 5.8% of incident cases

# Economic development and uterine cervix cancer incidence & mortality



Source: GLOBOCAN 2012 (IARC)

(Globocan,2012)

# Radiotherapy treatment for cervix cancer

Geographic area	RT units	population
North America	6	1 million
Europe	15	1 million
Africa	No RT 29/52 countries	198 million
Etiopia	1	40 million
Marocco	1	1 million

**total global shortage of 7000 RT units !**

**IAEA 2013**

# INCIDENCE & MORTALITY BY UTERINE CERVIX CANCER IN EUROPE

	Population of women at risk (15 y and more)	Incidence	Mortality	New cases per year	Deaths per year
Serbia	3.83 mil.	30.2	12.2	1501	609
Bosnia and Herzegovina	1.66 mil.	18.5	4.6	359	89
Bulgaria	3.18 mil.	32.8	11.4	1254	437
Croatia	1.89 mil.	14.3	6.2	325	140
Czech Republic	4.59 mil.	13.4	4.6	315	315
Hungary	4.47 mil.	17.3	4.6	461	461
Montenegro	0.26 mil.	17.3	4.6	26	26
Poland	17.13 mil.	17.7	9.4	3513	1858
Romania	8.59 mil.	39.4	17.3	4343	1909
Slovakia	2.4 mil.	21.6	8.2	607	232
Macedonia	0.87 mil.	16.6	7.9	171	81
Slovenia	0.89 mil.	13.4	6.1	139	64

**Incidence 13.4 – 39.4**  
**Mortality 4.6 – 17.3**

# ASCO resource-stratified clinical practice guidelines

- match the treatment with available resources:
  - **basic**
  - limited
  - enhanced
  - maximal
- Journal of Global Oncology, May 25, 2016
- the full ASCO Guideline methodology supplement can be found at:  
[www.asco.org/rs-cervical-cancer-treatment-guideline](http://www.asco.org/rs-cervical-cancer-treatment-guideline)

# ASCO resource-stratified clinical practice guidelines

- *general recommendations:*
  - combinations of surgery, chemotherapy, and radiation therapy (including **brachytherapy**) should be used for women with stage IB to IVA disease, depending on available resources
  - **pain control** is a vital component of palliative care
  - health care providers and health care system decision makers should be guided by the recommendations for the **highest stratum of resources available**
  - the guideline is intended to **complement but not replace** local guidelines

# Treatment by stage

Type of Disease	Setting			
	Basic	Limited	Enhanced	Maximal
IIB and IIIA	<p><b>NACT followed by extrafascial hysterectomy (modification as deemed necessary)</b></p> <p>Type of recommendation: consensus-based Evidence: insufficient Recommendation: weak</p>	<p><b>ChemoRT or RT<sup>6</sup> followed by extrafascial or modified hysterectomy ± PLND<sup>7</sup> ± PANB</b></p> <p><b>NACT followed by extrafascial or modified hysterectomy ± PLND<sup>7</sup> ± PANB<sup>6</sup></b></p> <p>Type of recommendation: consensus-based Evidence: low/intermediate Recommendation: weak/moderate</p>	<p><b>Pelvic RT plus concurrent low-dose platinum-based chemotherapy plus brachytherapy</b></p>	<p>Pelvic RT plus concurrent low-dose platinum-based chemotherapy plus brachytherapy</p>
	<p>Extrafascial hysterectomy when chemotherapy is not consistently available</p> <p>Type of recommendation: consensus-based Evidence: insufficient Recommendation: weak</p>	<p><b>Extrafascial or modified hysterectomy plus pelvic LND ± para-aortic LN sampling<sup>4</sup> plus adjuvant therapy</b></p> <p>Type of recommendation: consensus-based Evidence: insufficient Recommendation: weak</p>	<p><b>Adjuvant hysterectomy is an option only if residual disease after chemoRT</b></p> <p>Type of recommendation: evidence-based Evidence: high Recommendation: strong</p>	<p>Adjuvant hysterectomy is an option only if residual disease after chemoRT</p> <p>Type of recommendation: evidence-based Evidence: high Recommendation: strong</p>
	<p>Palliative care</p> <p>Type of recommendation: consensus-based Evidence: intermediate Recommendation: strong</p>			

# Treatment by stage

Type of Disease	Setting			
	Basic	Limited	Enhanced	Maximal
IIIB to IVA	<p>Palliative care</p> <p>Type of recommendation: evidence-based Evidence: intermediate Recommendation: strong</p>	<p><b>ChemoRT or RT<sup>6</sup> followed by extrafascial or radical hysterectomy (see Note) ± PLND<sup>7</sup> ± PANB</b></p> <p><b>NACT (followed by radical hysterectomy plus PLND<sup>7</sup> ± PANB may be an option] and/or palliative care</b></p> <p>Type of recommendation: consensus-based Evidence: low/intermediate Recommendation: weak/moderate</p>	<p><b>Pelvic RT plus brachytherapy plus concurrent low-dose platinum-based chemotherapy (in some cases extended-field RT)</b></p> <p>AND/OR palliative care</p> <p>Type of recommendation: evidence-based Evidence: high Recommendation: strong</p>	<p>Pelvic RT plus brachytherapy plus concurrent low-dose platinum-based chemotherapy (in some cases extended-field RT)</p> <p>AND/OR palliative care (Options before palliative care alone include: <b>RT boost, salvage surgery, or chemotherapy</b>)</p> <p>Type of recommendation: evidence and consensus-based Evidence: high Recommendation: strong</p>
	<p><b>NACT followed by extrafascial hysterectomy</b></p> <p>Type of recommendation: consensus-based Evidence: insufficient Recommendation: weak</p>	<p><b>RT ± concurrent low-dose platinum-based chemotherapy (may offer systemic adjuvant chemotherapy)</b></p> <p>Type of recommendation: evidence-based Evidence: intermediate Recommendation: moderate</p>	<p>RT + <b>brachytherapy</b> ± concurrent low-dose platinum-based chemotherapy (may offer systemic adjuvant chemotherapy)</p> <p>Type of recommendation: evidence-based Evidence: intermediate Recommendation: weak</p>	<p>RT + brachytherapy ± concurrent low-dose platinum-based chemotherapy (may offer systemic adjuvant chemotherapy)</p> <p>Type of recommendation: evidence-based Evidence: intermediate Recommendation: weak</p>
Note		<p>Wherever radical hysterectomy with concurrent chemoRT listed as a surgical option above, <b>extrafascial hysterectomy is preferred if there is residual disease or initial tumor &gt; 6 cm</b></p> <p>Type of recommendation: consensus-based Evidence: intermediate Recommendation: weak</p>		

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# The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology Guidelines for the Management of Patients With Cervical Cancer

*David Cibula, MD,\* Richard Pötter, MD,† François Planchamp, MSc,‡ Elisabeth Avall-Lundqvist, MD,§ Daniela Fischerova, MD,\* Christine Haie Meder, MD,|| Christhardt Köhler, MD,¶ Fabio Landoni, MD,# Sigurd Lax, MD,\*\* Jacob Christian Lindegaard, MD,†† Umesh Mahantshetty, MD,‡‡ Patrice Mathevet, MD,§§ W. Glenn McCluggage, MD,|||| Mary McCormack, MD,¶¶ Raj Naik, MD,## Remi Nout, MD,\*\*\* Sandro Pignata, MD,††† Jordi Ponce, MD,‡‡‡ Denis Querleu, MD,‡ Francesco Raspagliesi, MD,§§§ Alexandros Rodolakis, MD,||||| Karl Tamussino, MD,¶¶¶ Pauline Wimberger, MD,#### and Maria Rosaria Raspollini, MD\*\*\*\*\**

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**Background:** Despite significant advances in the screening, detection, and treatment of preinvasive cervical lesions, invasive cervical cancer is the fifth most common cancer in European women. There are large disparities in Europe and worldwide in the incidence, management, and mortality of cervical cancer.

**Objective:** The European Society of Gynaecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP) jointly develop clinically relevant and evidence-based guidelines in order to improve the quality of care for women with cervical cancer across Europe and worldwide.

**Methods:** The ESGO/ESTRO/ESP nominated an international multidisciplinary development group consisting of practicing clinicians and researchers who have demonstrated

# LACC: T1b2, T2a2, cN0 (imaging)

## Grade

*of recommendation*

- **Treatment strategy:** to avoid comb.radical surgery and postop. external RT (morbidity+, survival~) **C**
- **Preferred treatment: concomitant chemo-radiotherapy (cis-Platin) and brachytherapy** **A**
- PALND may be considered (CTV for RT), no PLND **C**
- Radical surgery is an **alternative option** (neg. risk factors) **ea**
- Neoadjuvant chemotherapy and surgery **controversial** **C**

# LACC: T2b, T3b, T3a, T4a, N0/N1

**Grade**

*of recommendation*

- **Recommended treatment: concomitant chemo-radiotherapy (cis-Platin) and brachytherapy** **A**  
(plus **boost** to involved pelvic lymph nodes  
± **paraaortic** RT in case of increased risk)
- PALND may be considered (target for RT), PLND not, debulking of suspicious LN may be considered **ea**
- Option for **pelvic exenteration** in selected T4a, N0, M0 **ea**

# Limited Distant Metastatic Disease (at presentation)

**Grade**  
*of recommendation*

- **Paraaortic nodal disease only**  
**treatment with curative intent** **D**  
extended field chemoradiotherapy + brachytherapy,  
maybe additional chemotherapy, surgical LN debulking
- **Supraclavicular nodal disease only**  
**treatment with curative intent** **ea**  
treatment analogue paraaortic nodal disease

# Distant Metastatic Disease

(at presentation)  
various issues

**Grade**  
*of recommendation*

- **Adjuvant chemotherapy**

may be considered in case of **high risk of recurrence**  
e.g. positive margins, positive lymph nodes, LVSI

**C**

- **Radiotherapy for **palliation****

must be considered e.g. for bleeding, pain

**ea**

# Radiotherapy

principles: definitive chemoradiotherapy

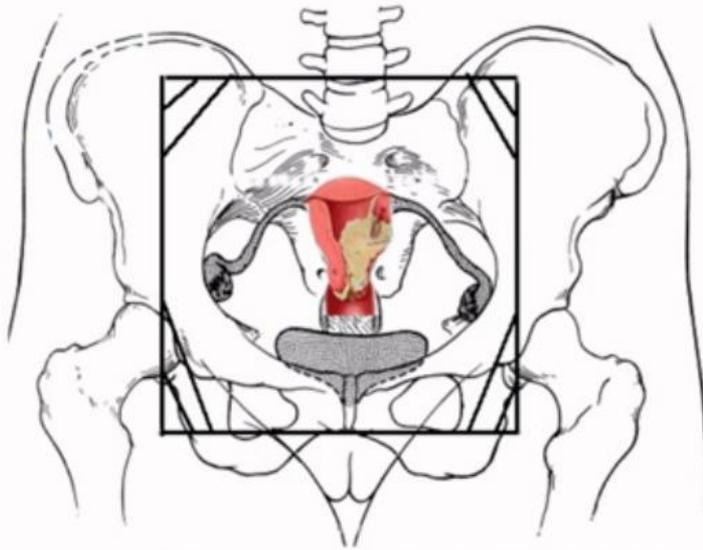
- **EBRT: Pelvic intensity modulated radiotherapy (IMRT)**  
45-50 Gy in 5 weeks (+ conc. cis Platin)
- **Image guided Radiotherapy (IGRT) recommended**
- **Targets: tumor and pelvic LNs related**  
± paraaortic LNs in case of increased risk
- **Boost involved LNs: preferably simultaneous**  
55-60 Gy in 5 weeks
- **Overall treatment time (EBRT): 5-6 weeks**

# Radiotherapy

principles: definitive brachytherapy

- **Image guided adaptive brachytherapy (IGABT)**  
using MRI and gyn exam (other options US and CT)  
**40-45 Gy in 3-4 fractions (HDR) or 1-2 (PDR)**
- **Target: based on tumor response after CCRT (CTV<sub>HR</sub>)**  
residual gross tumor and adjacent cervix/parametria
- **Overall target (CTV<sub>HR</sub>) dose EBRT+BT:  $\geq 85-90$  Gy**
- **Dose constraints for organs at risk**
- **Intracavitary and combined intracavitary/interstitial**
- **Overall treatment time: 1-2 weeks**

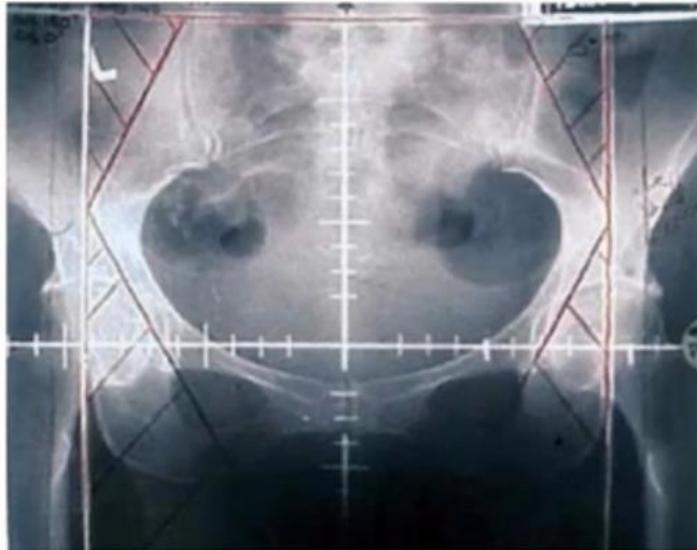
# From 2D to 3D: role CT & MRI



CT

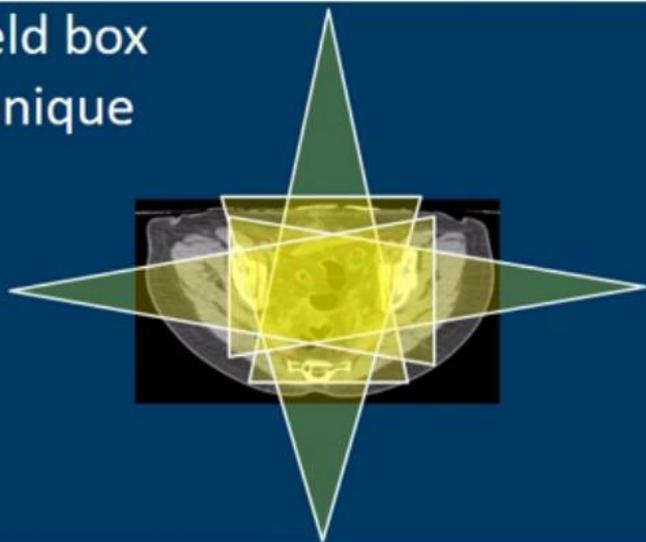


MRI

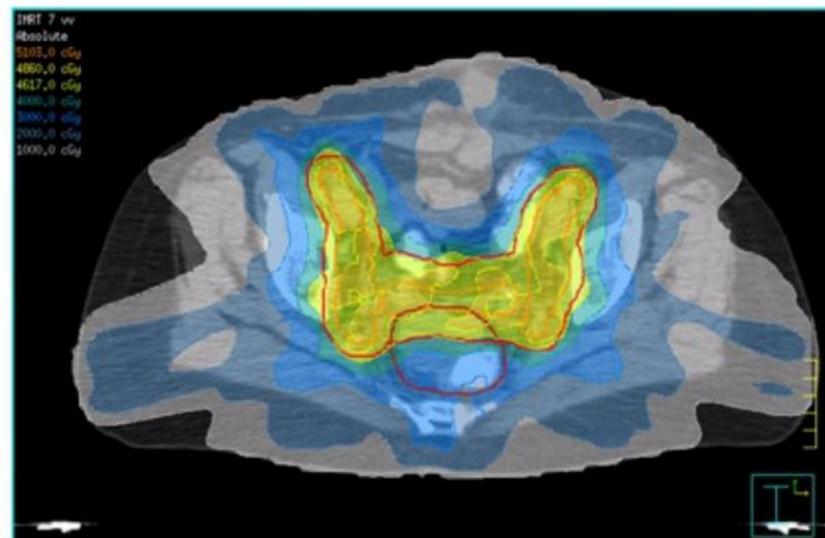
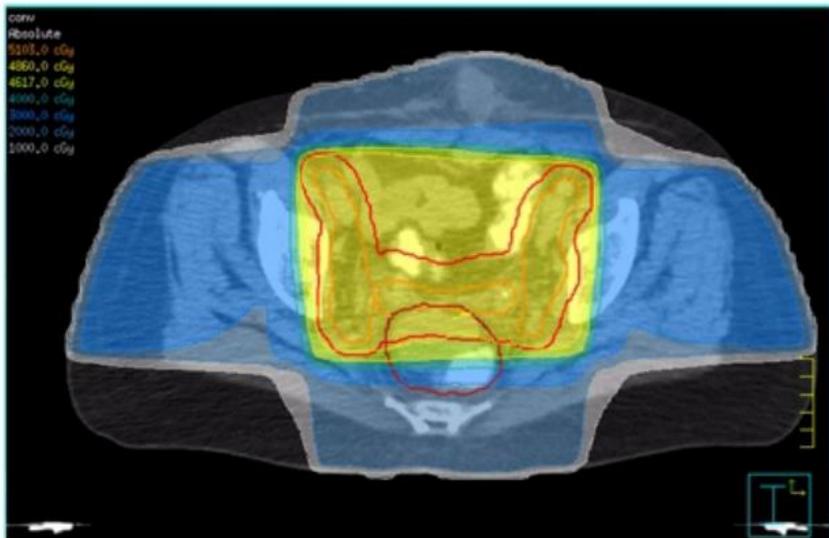
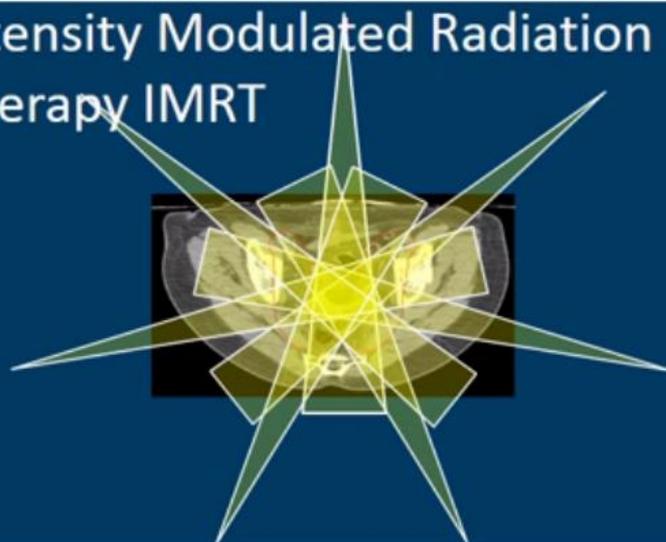


# Advances in treatment planning

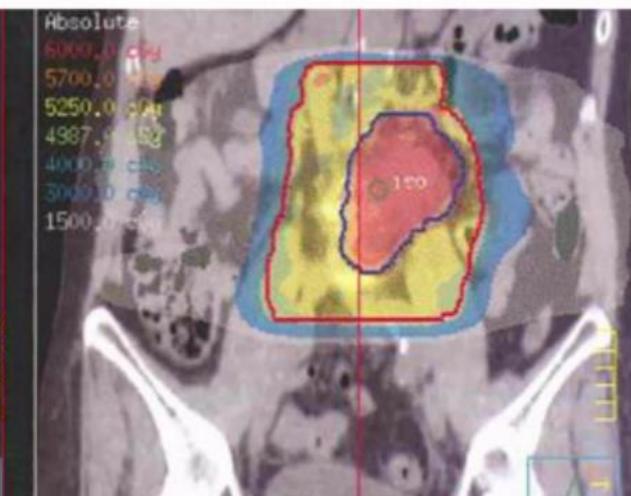
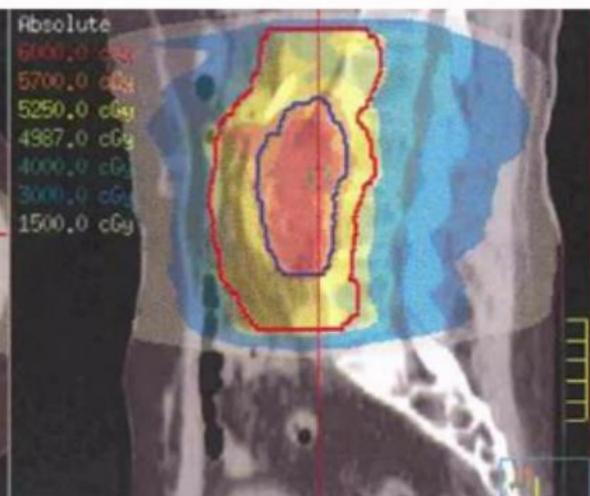
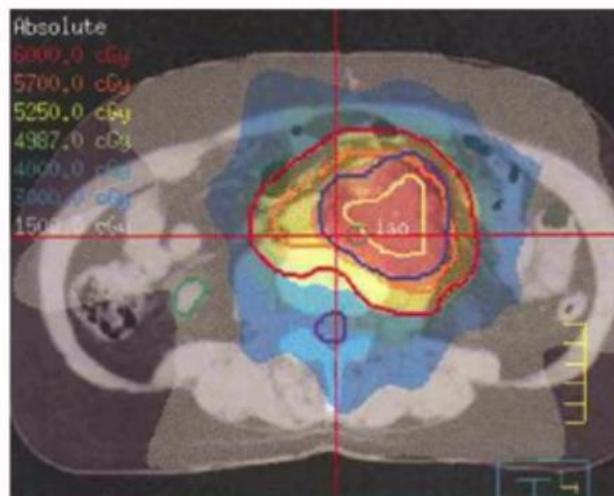
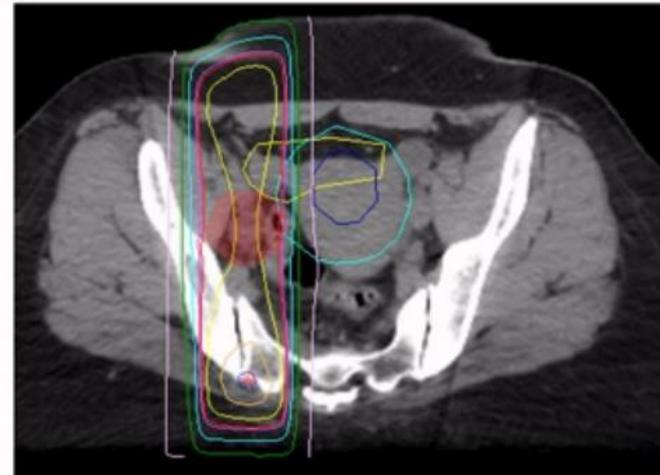
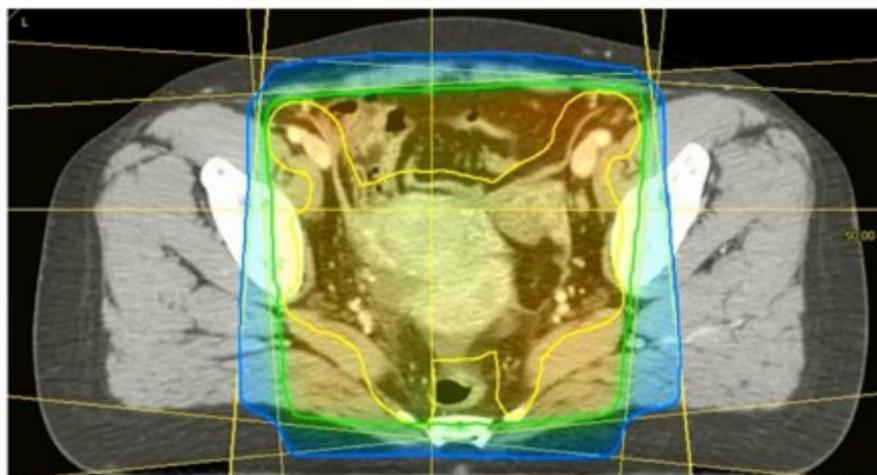
## 4-field box technique



## Intensity Modulated Radiation Therapy IMRT

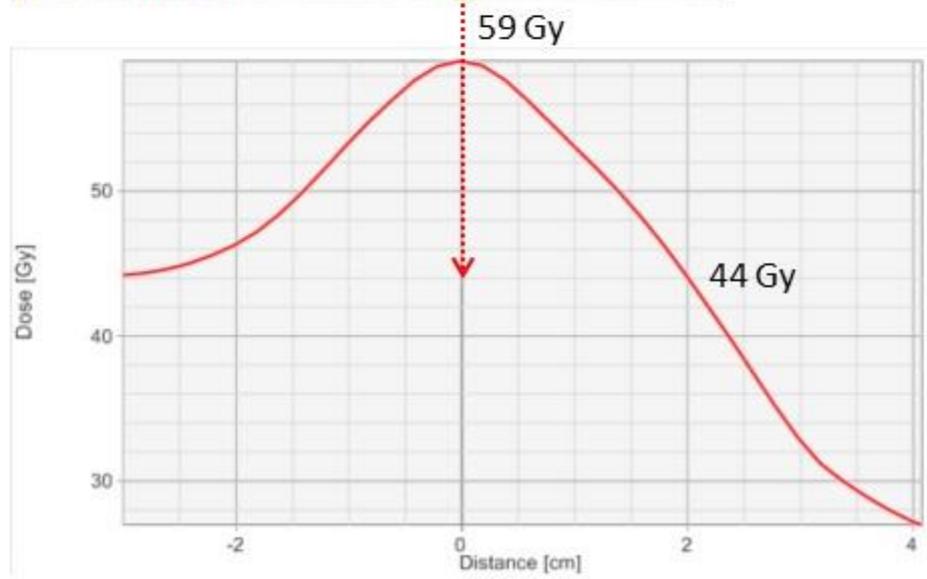
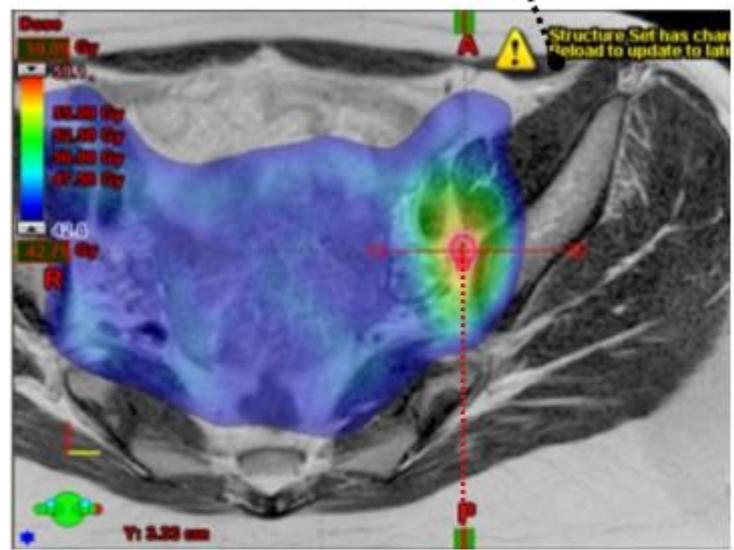


# Sequential or simultaneous integrated boost

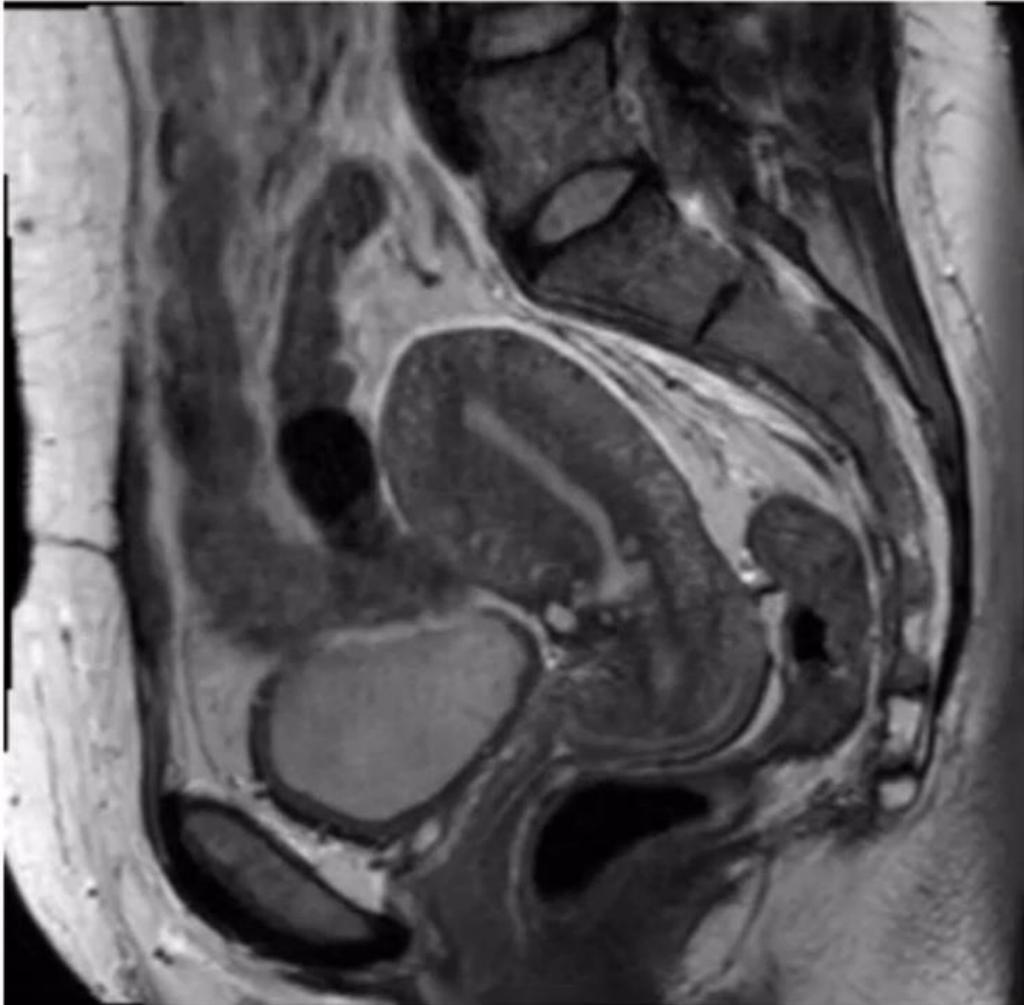


# Simultaneous Integrated Boost (CoP) for lymph node boost: Clinical example

- Cervix cancer IIB
  - PET pos node < 1 cm
  - IMRT dose & fractionation
    - PTV-E: 45 Gy/25 fx
    - CTV-N: 55 Gy/25 fx
      - 56 Gy<sub>EQD2</sub> EBRT
      - 4 Gy<sub>EQD2</sub> BT
- 
- 60Gy<sub>EQD2</sub> total

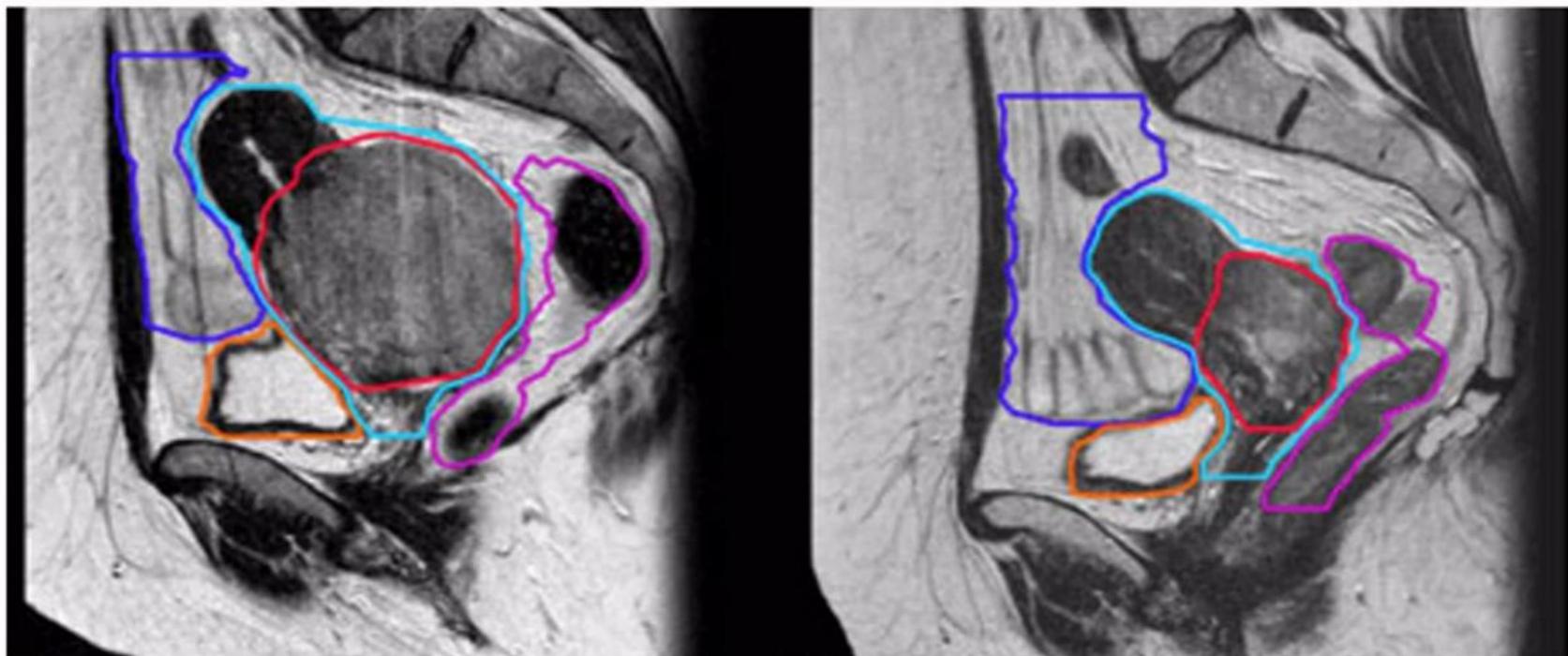


## Pelvic organ movement: 4 dimensional MRI



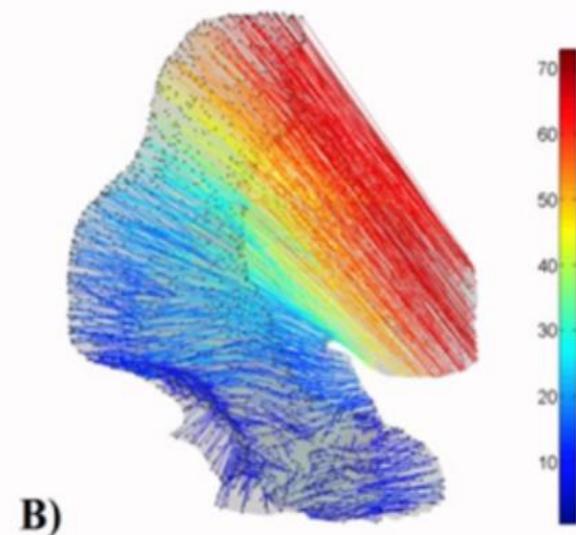
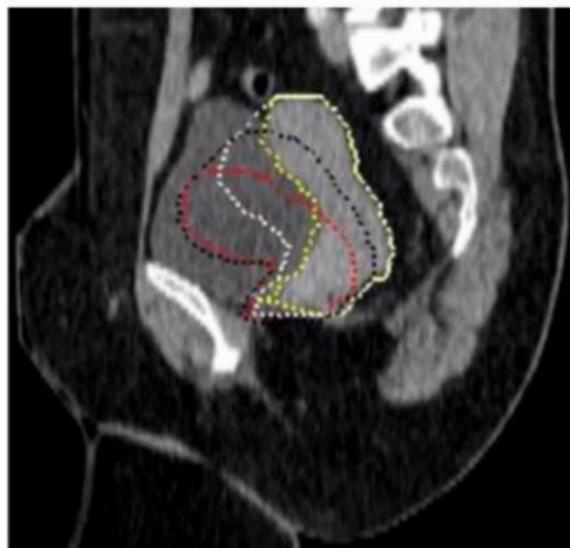
- Innovation in diagnostic imaging: CT & MRI
- Increased understanding of 3- and 4-dimensional individual anatomy
- MRI: functional information

## Tumour regression during treatment

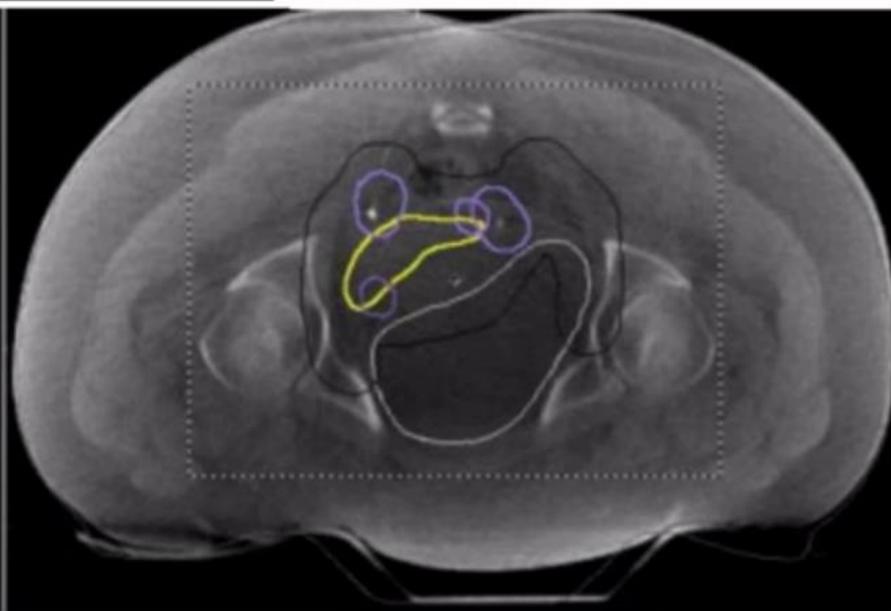
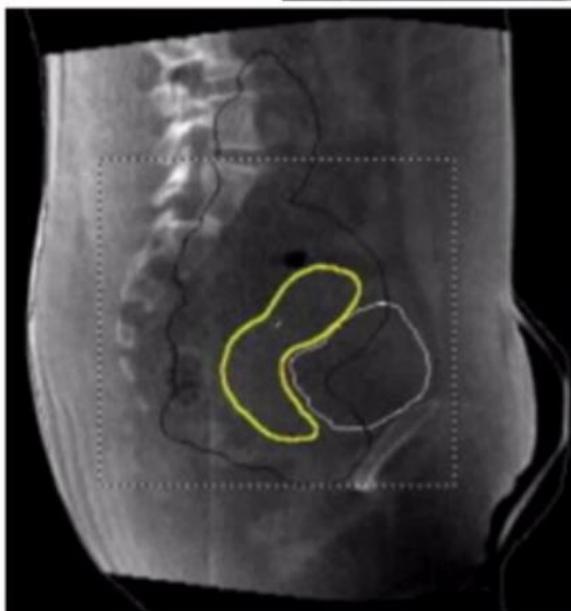


## From 3D to 4D: adaptive radiotherapy

Reduction of margins using 'Plan library':  
2-3 treatment plans for different bladder filling

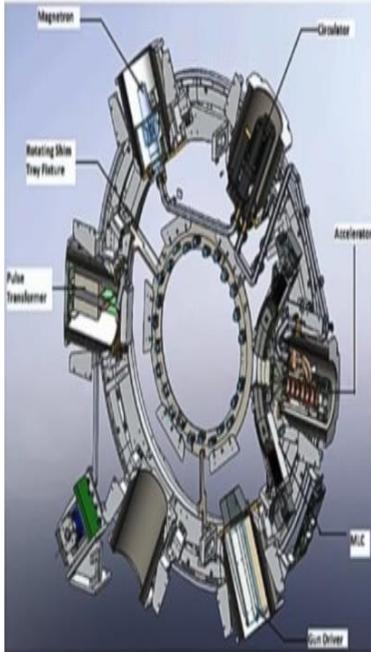


- Cone beam CT to choose 'plan of the day'



# MRI integrated LINAC

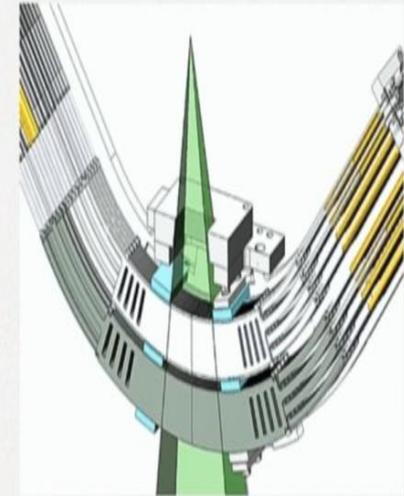
## MR-Linac Design



- Split bore 0.35T MRI
- 6XFFF magnetron powered linac
- No bending magnet
- 4,000 lbs (mostly steel sleeves)
- Components separated & shielded
  - ✓ RF interference
  - ✓ Impact of magnet on beam

## Double Stack MLC + Beam Specs

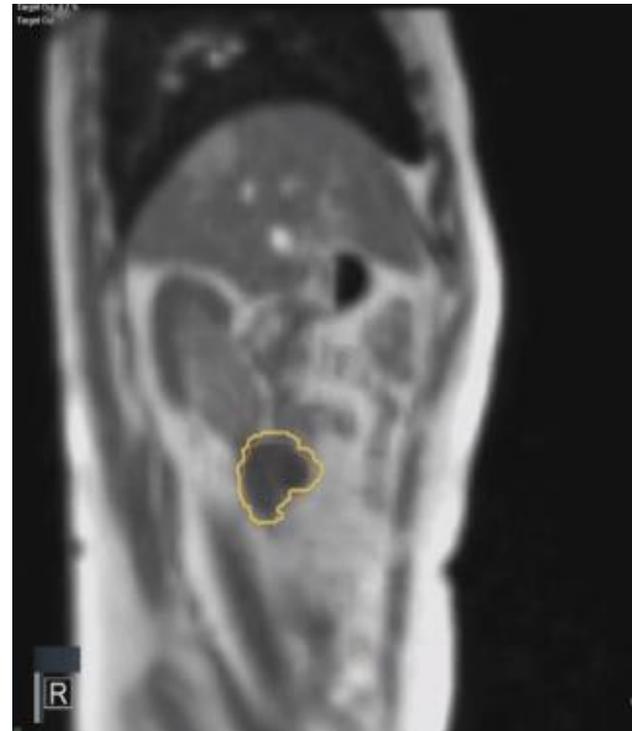
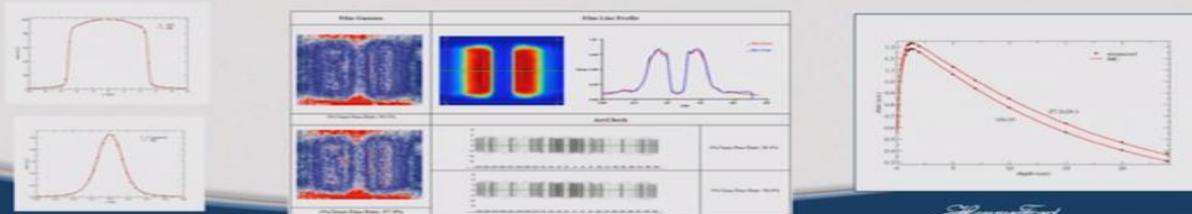
- Double Focused Leaves
  - ~8 mm leaf width
  - SAD – 90cm
  - Leaves traverse entire distance across field
  - Lower stack is offset by 4mm
    - No Tongue and Groove
- Nominal dose rate ~645 MU/min
- Step & Shoot IMRT
- Field Size:
  - Minimum: 0.2 cm by ~0.4 cm
  - Maximum: 27.4cm x 24.1 cm



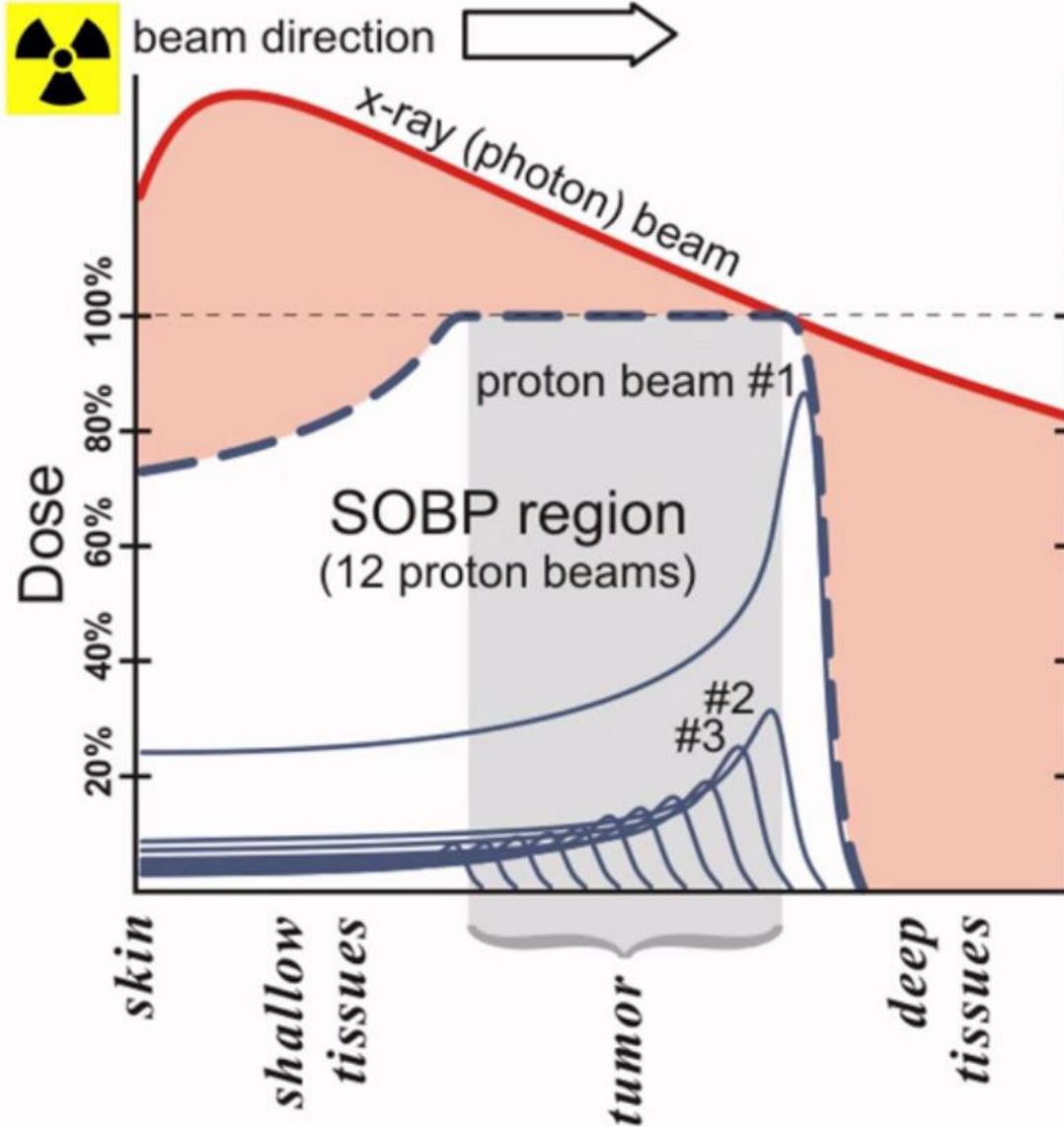
# ADVANTAGES MRI - LINAC

## MRIdian™ Installation/Commissioning Timeline

- 02/27/17: MRI-Linac FDA Approved
- Feb-May: System installation, powering, validation
- June-July: Functional/Acceptance testing, Commissioning (3 wks!)



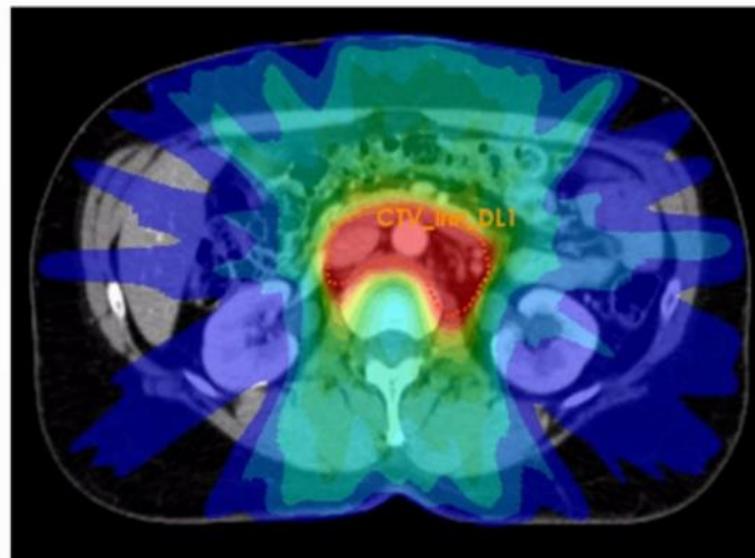
# Proton therapy



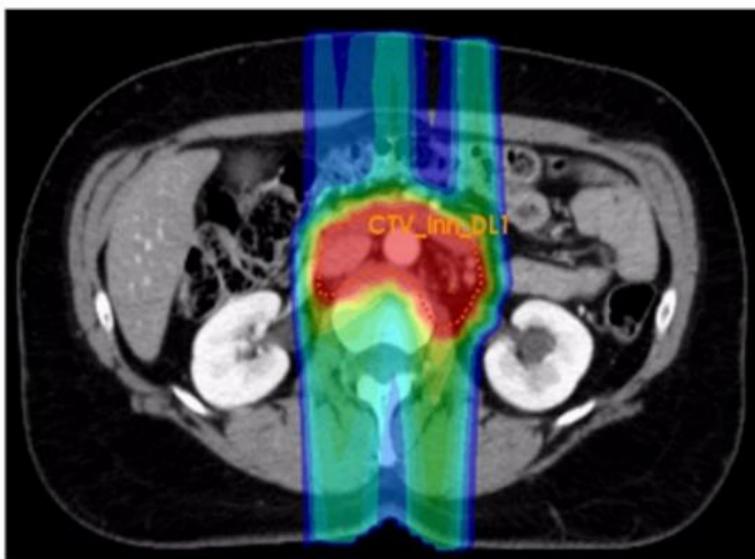
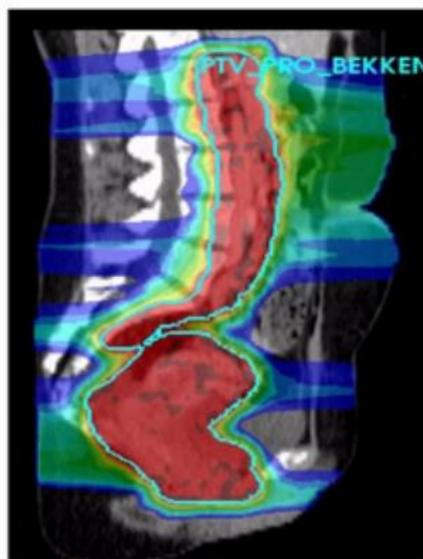
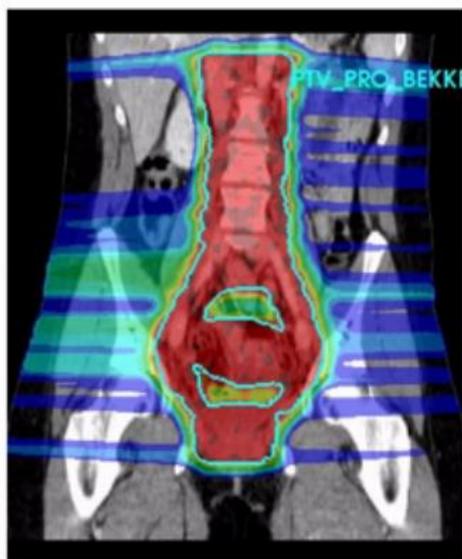
- Protons: particle therapy
- Spread Out Bragg Peak
- Protons more sensitive for differences in tissue density (bone, air, muscle)

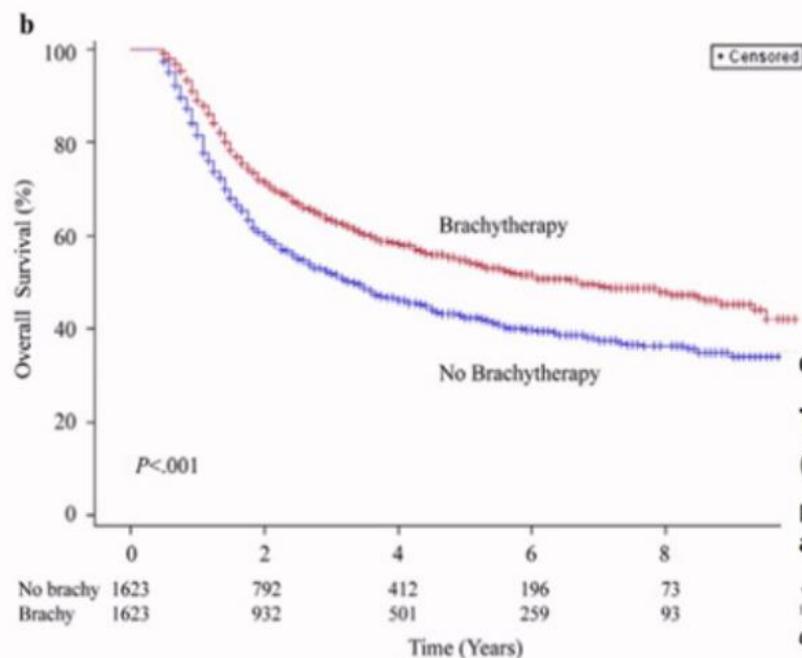
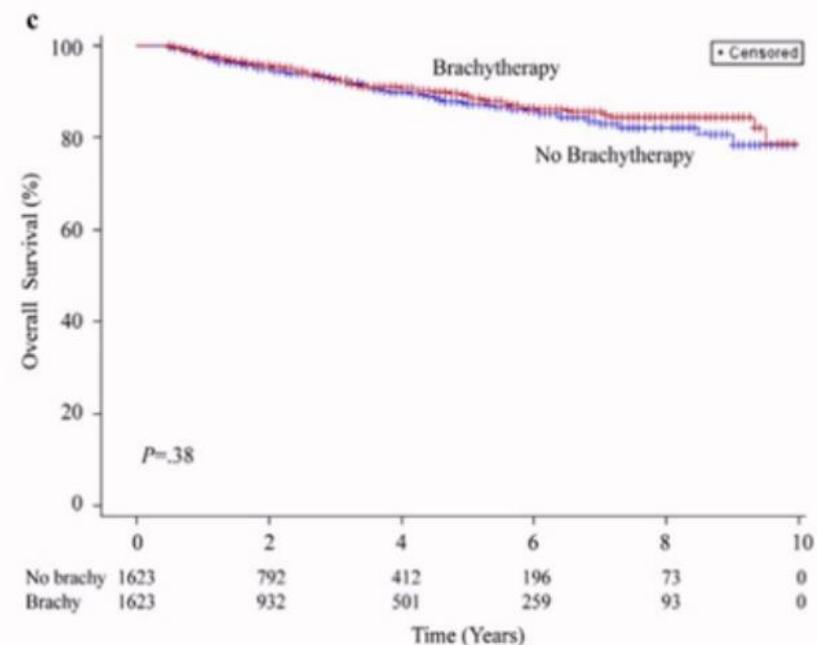
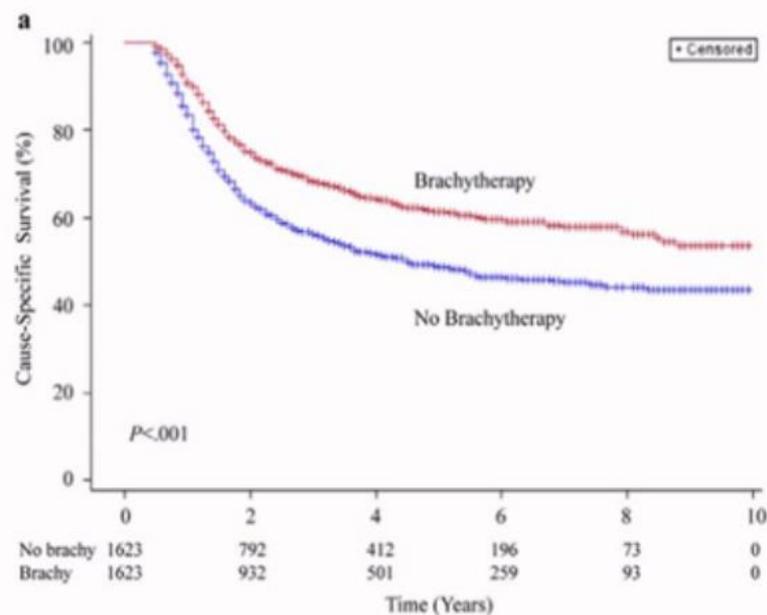
# Photons versus protons

Photons



Protons





**Fig. 2.** Survival by brachytherapy use for matched cohort between 2000 and 2009. (a) Cause-specific survival; (b) overall survival, and (c) non-cancer-related survival.

Clinical Investigation: Gynecologic Cancer

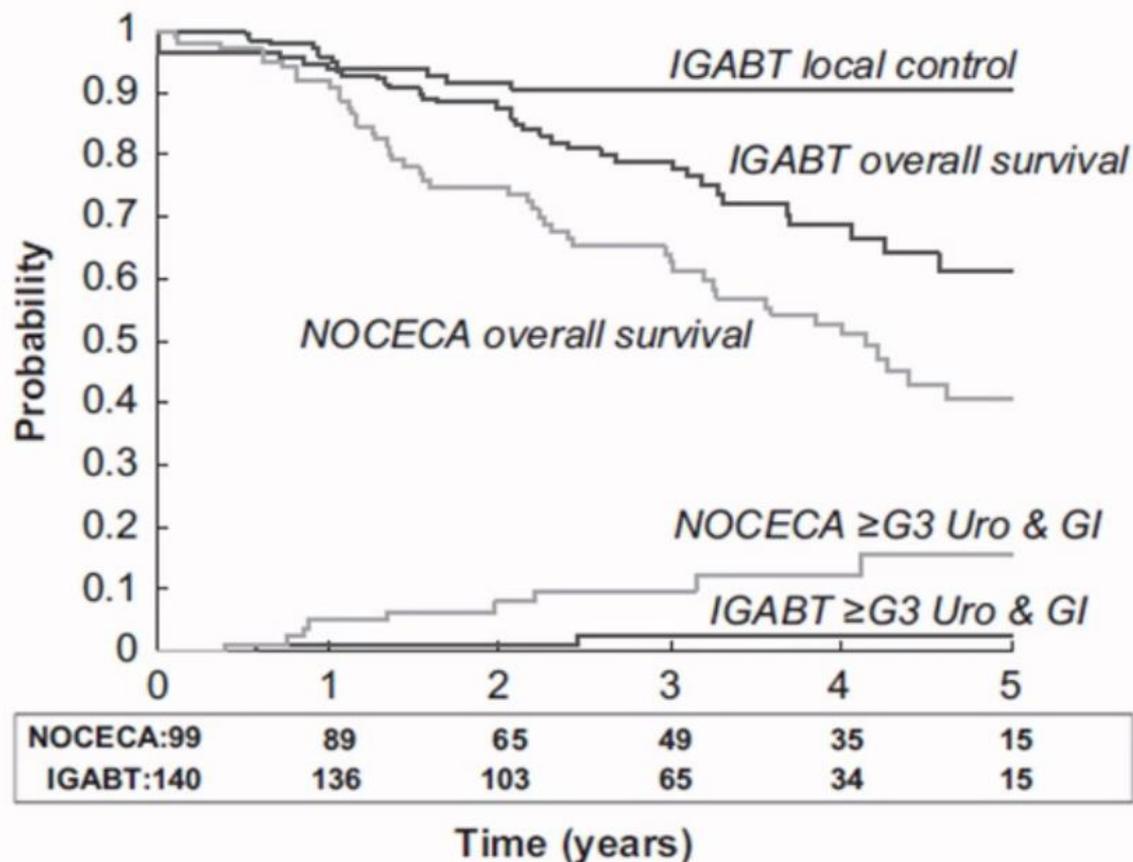
## Trends in the Utilization of Brachytherapy in Cervical Cancer in the United States

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

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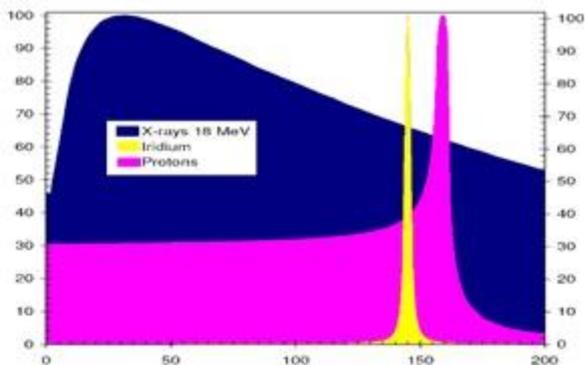
<sup>†</sup>Department of Biostatistics, Princess Margaret Hospital, Toronto, Ontario, Canada; and <sup>‡</sup>Department of Radiation Oncology, Dana-Farber Cancer Institute/Brigham and Women's Hospital, Boston, Massachusetts

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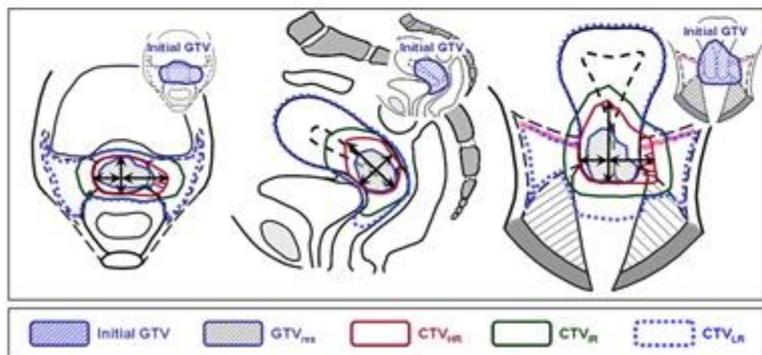
**LC 3 y: 90%**  
**OS 3 y:**  
**IGABT: 79%**  
**NOCECA: 63%**  
**morbidity 3y ≥G3:**  
**IGABT: 3%**  
**NOCECA: 10%**

Figure 3. Actuarial local control, overall survival and  $\geq$  grade 3 combined urological-gastrointestinal morbidity in 140 patients treated with IGABT (black lines). For comparison the curves for overall survival and morbidity in 99 patients treated with 2D x-ray-based brachytherapy (NOCECA) are indicated (grey lines). Patient number at risk for overall survival is indicated below the x-axis.

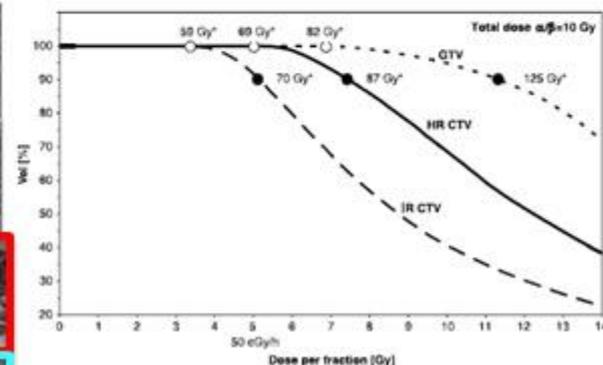
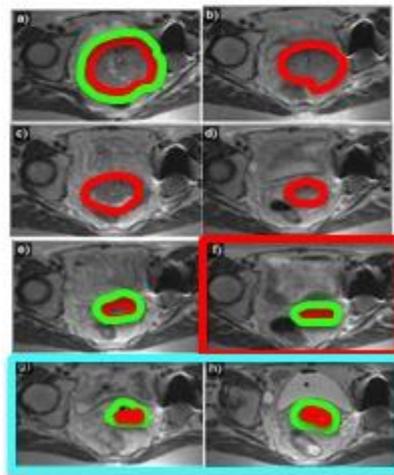


# The New Paradigm: individual Doses in adaptive Volumes (Vienna data 1998-2008)

LR CTV-T	~ 300 cm <sup>3</sup>	≥ 45 Gy EQD2
IR CTV-T	~ 85 cm <sup>3</sup>	~ 66 Gy EQD2
HR CTV-T	~ 39 cm <sup>3</sup>	~ 89 Gy EQD2
Res. GTV	~ 9 cm <sup>3</sup>	~ 119 Gy EQD2



ICRU GEC ESTRO Rep 89, 2016  
Kirisits et al. IJROBP 2005/2006;



GEC ESTRec II, 2006  
Schmid et al. StrOnk 2013



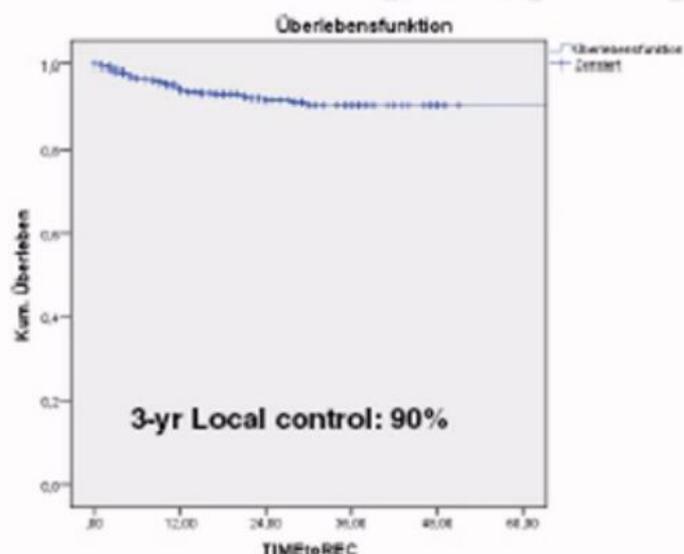
# EMBRACE

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



About Embrace | Contacts | Participation | Data entry | Tools | Members info | Logout

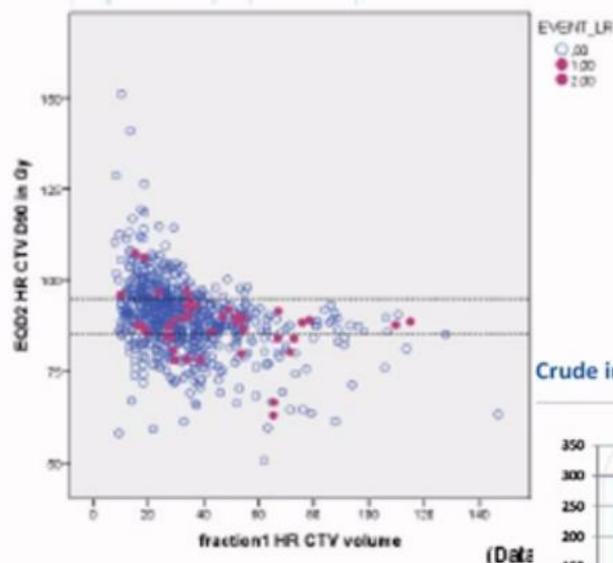
## Local Recurrences - overall



N = 714

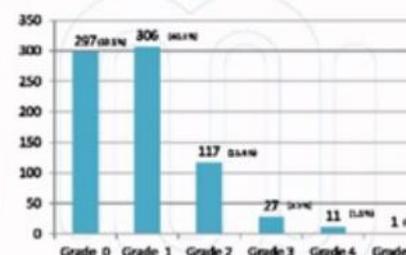
43 events

(15 incomplete remissions + 28 local recurrences)



**3yr Local control:**  
I: 95%, II: 90%, III: 89%, IV: 74%

Crude incidence of any GI morbidity



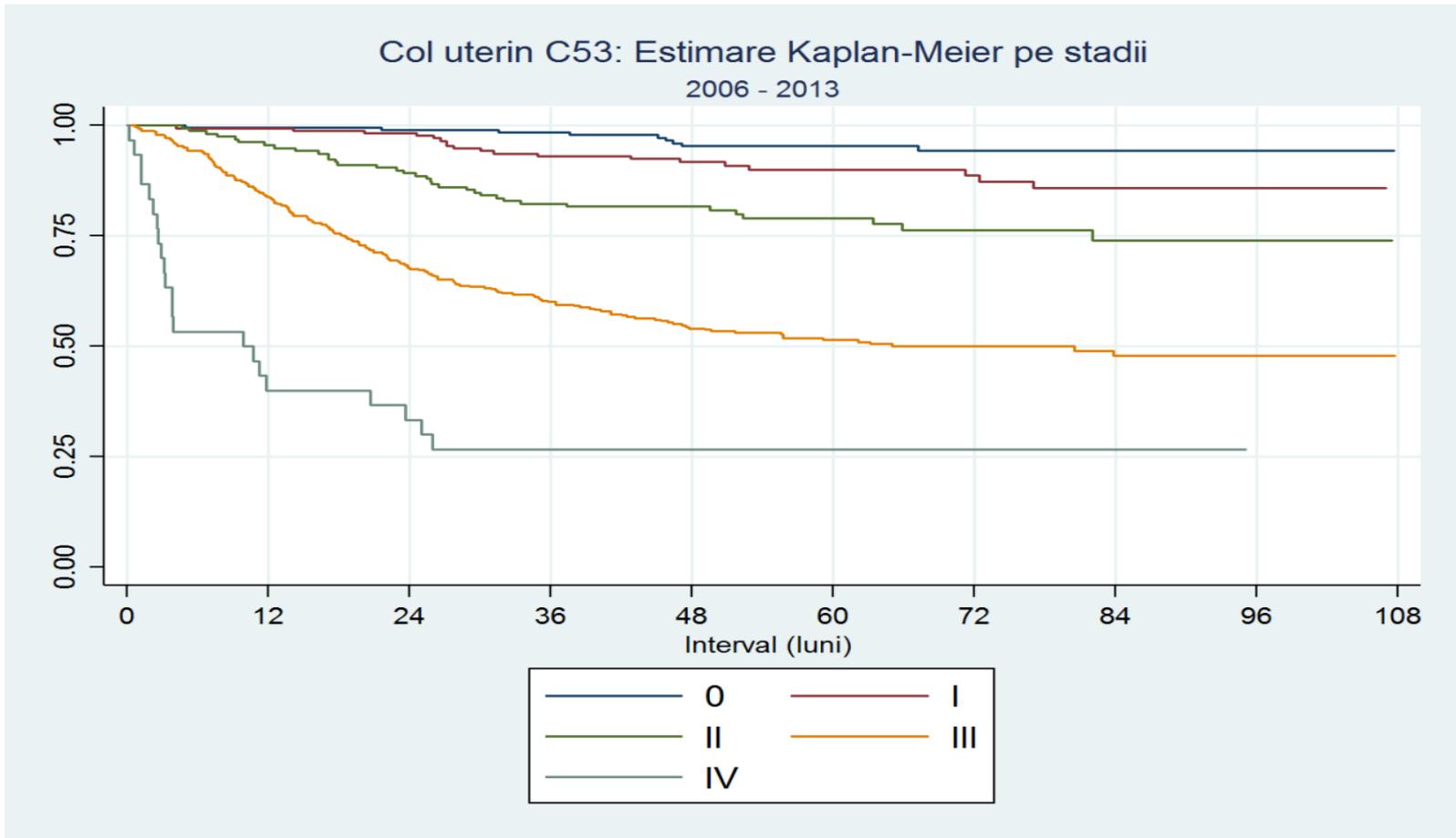
**new volume and dose adaptation paradigm:  
tumor response adapted RT through repetitive imaging:  
adaptation of target in space (3D) and time (4D)**

- *assessment of macroscopic tumour response (GTV)  
and of pathologic residual tissue  
plus assessment of change of overall topography*
- *adaptation of CTV-T according to GTV response  
in 3D (space) and 4D (time) after a first treatment step  
(sufficient to control microscopic disease (e.g 45 Gy))*
- *high radiation doses (up to >90-100 Gy) in limited volumes:  
HR CTV 10-60 ccm, residual GTV 5-20 ccm*

# THE ONCOLOGY INSTITUTE “ION CHIRICUȚĂ” CLUJ-NAPOCA

YEAR	EBRT	BT	STD. I	STD. II	STD. III	STD. IV
2016	463	358	24%	34%	37%	5%
2017	455	466	27%	31%	39%	3%
TOTAL	918	824				

# SV5 UTERINE CERVIX/ TOICN/ 2006 - 2013



# THANK YOU !



2nd International Congress on Oncological Sciences, 20-23 September 2018, ANTALYA