

Radiation oncology perspectives in uterine cervix cancer

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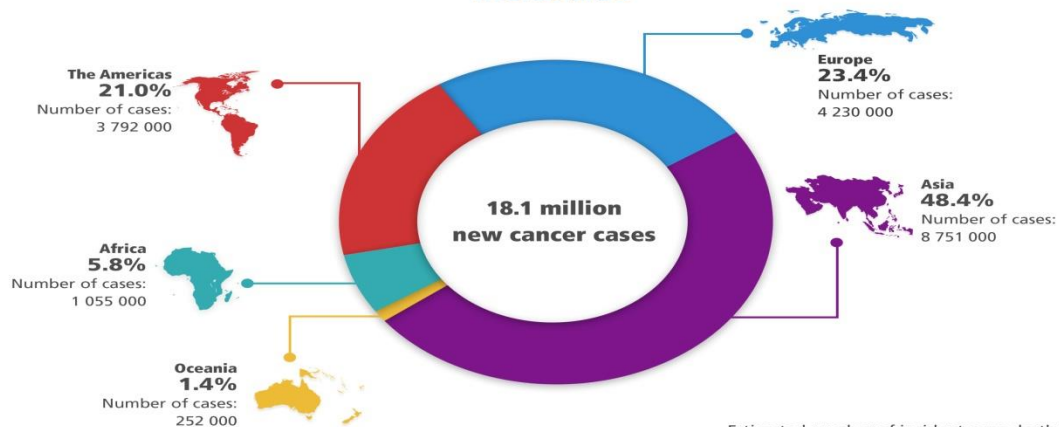
The Oncology Institute “Ion Chiricuță”

Cluj-Napoca

ROMANIA

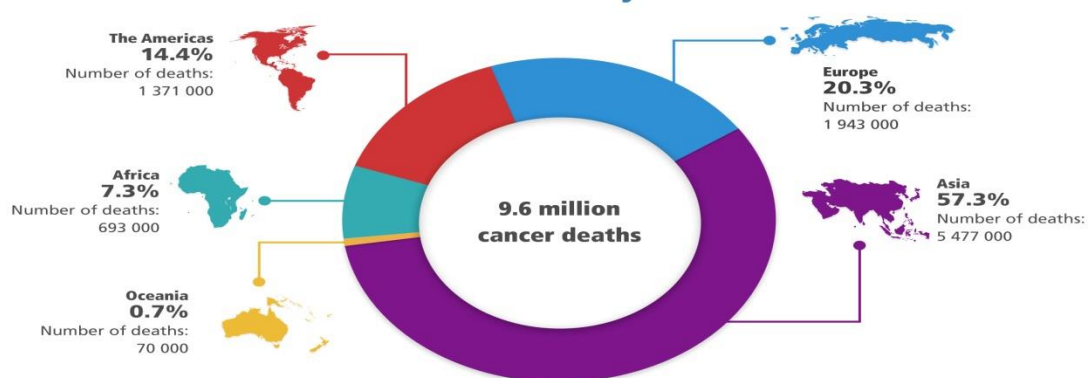
GLOBAL CANCER DATA 2018

Global cancer incidence



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

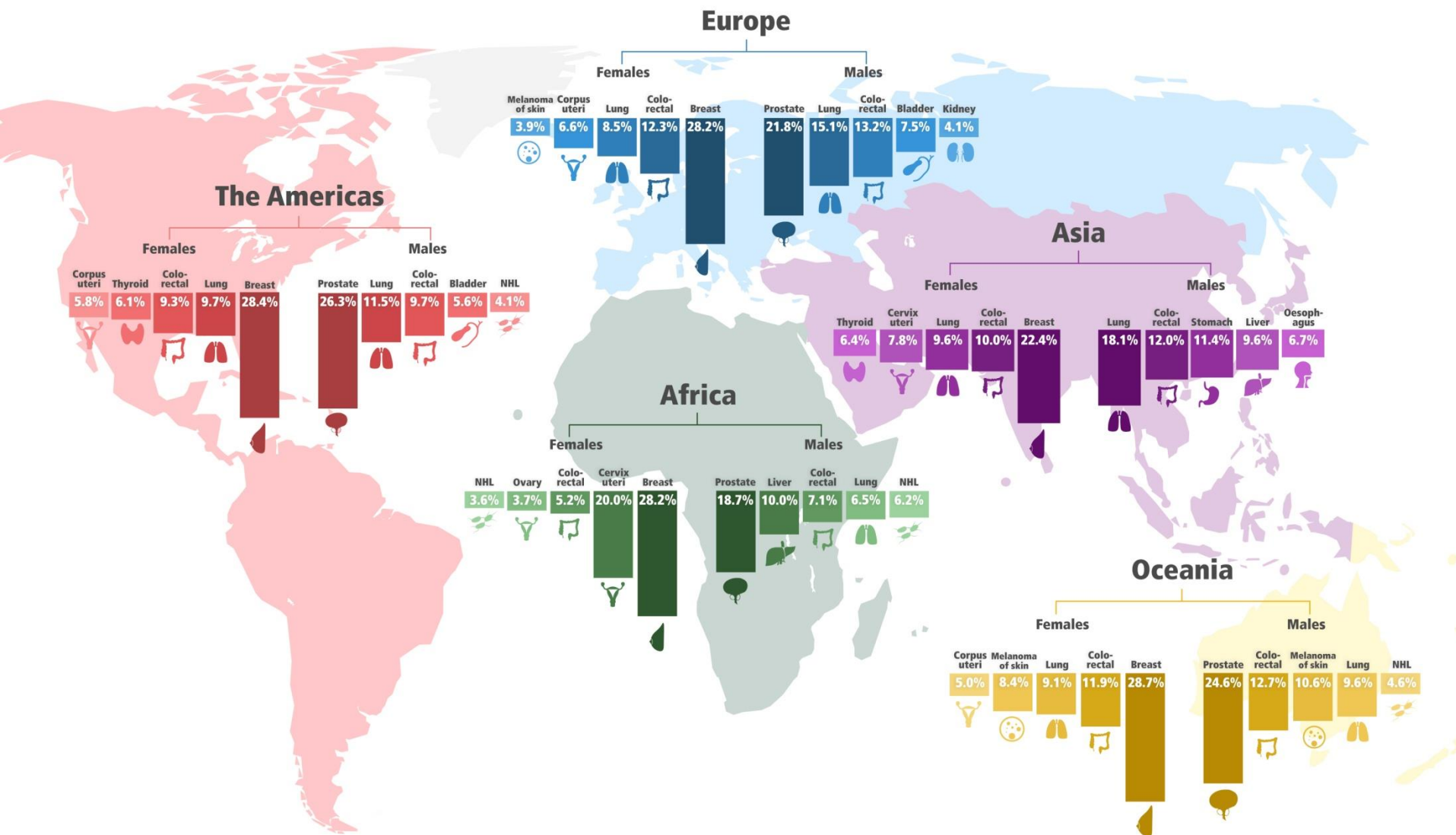
Global cancer mortality



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

GLOBOCAN 2018

Percentages of new cases by cancer type, region, and sex



Data source: GLOBOCAN 2018

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

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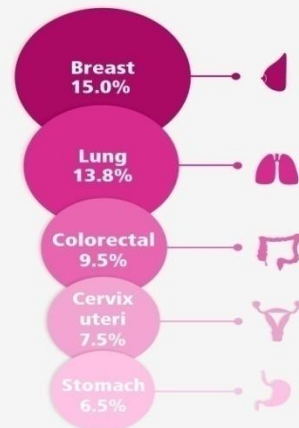
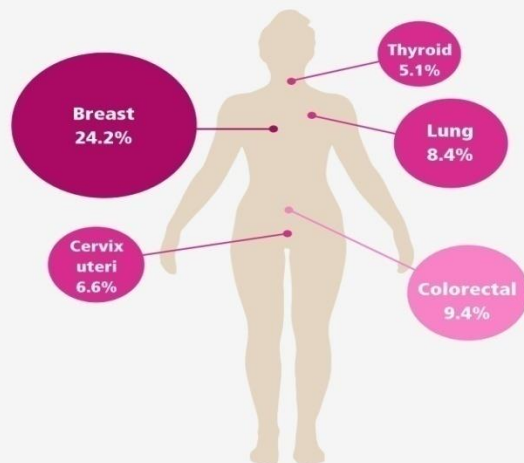
NHL = Non-Hodgkin lymphoma

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

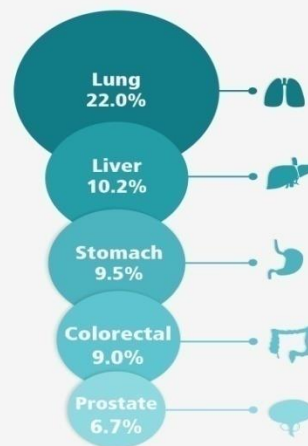
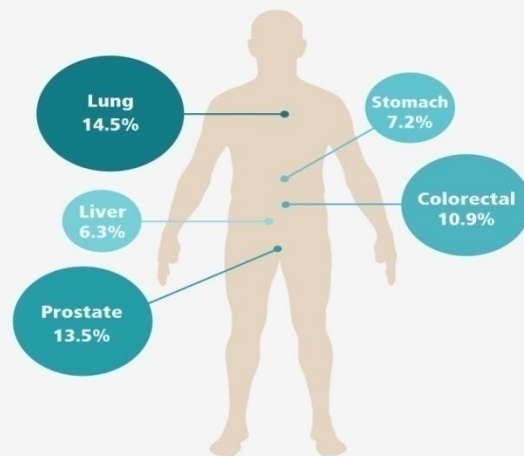
Global cancer incidence

Global cancer mortality

Females



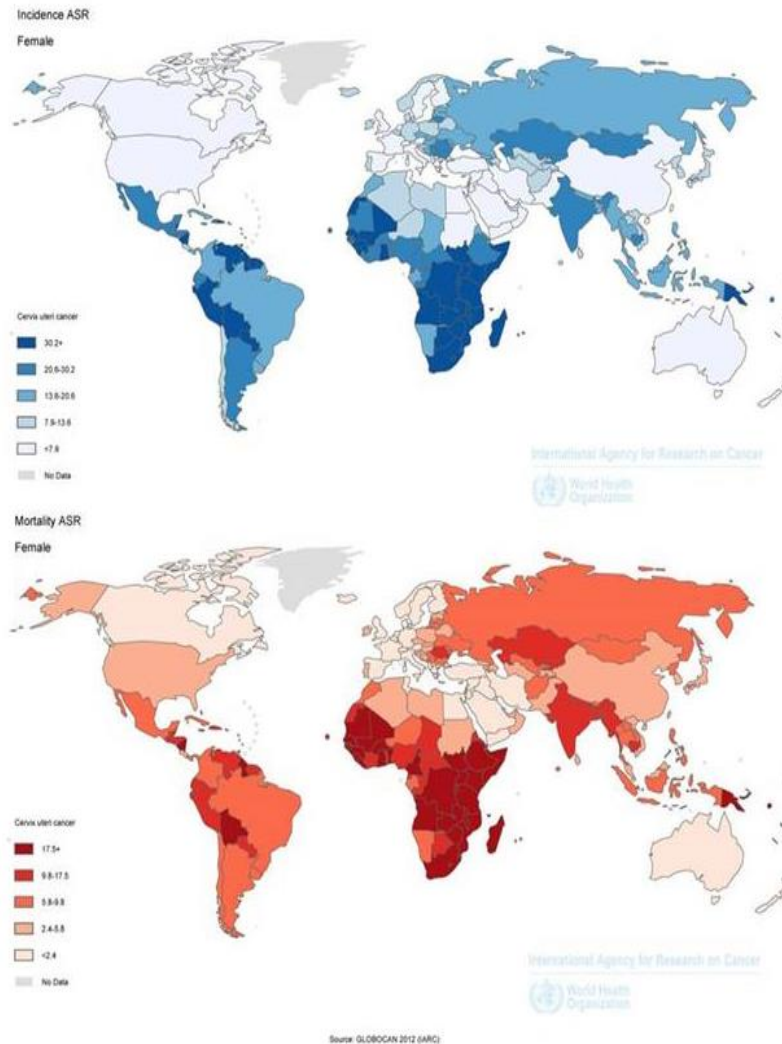
Males



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

Data source: GLOBOCAN 2018
Available at Global Cancer Observatory (<http://gco.iarc.fr/>)
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Economic development and uterine cervix cancer incidence & mortality



(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.	Incidence 13.4 – 39.4 Mortality 4.6 – 17.3			315
Hungary	4.47 mil.				461
Montenegro	0.26 mil.				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

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

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>NACT followed by extrafascial hysterectomy (modification as deemed necessary)</p> <p>Type of recommendation: consensus-based Evidence: insufficient Recommendation: weak</p>	<p>ChemoRT or RT⁶ followed by extrafascial or modified hysterectomy \pm PLND⁷ \pm PANB</p> <p>NACT followed by extrafascial or modified hysterectomy \pm PLND⁷ \pm PANB⁶</p> <p>Type of recommendation: consensus-based Evidence: low/intermediate Recommendation: weak/moderate</p>	<p>Pelvic RT plus concurrent low-dose platinum-based chemotherapy plus brachytherapy</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>Pelvic RT plus concurrent low-dose platinum-based chemotherapy plus brachytherapy</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>Extrafascial hysterectomy when chemotherapy is not consistently available</p> <p>Type of recommendation: consensus-based Evidence: insufficient Recommendation: weak</p>	<p>Extrafascial or modified hysterectomy plus pelvic LND \pm para-aortic LN sampling⁴ plus adjuvant therapy</p> <p>Type of recommendation: consensus-based Evidence: insufficient Recommendation: weak</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>ChemoRT or RT⁶ followed by extrafascial or radical hysterectomy (see Note) ± PLND⁷ ± PANB</p> <p>NACT (followed by radical hysterectomy plus PLND⁷ ± PANB may be an option] and/or palliative care</p> <p>Type of recommendation: consensus-based Evidence: low/intermediate Recommendation: weak/moderate</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</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: RT boost, salvage surgery, or chemotherapy)</p> <p>Type of recommendation: evidence and consensus-based Evidence: high Recommendation: strong</p>
	<p>NACT followed by extrafascial hysterectomy</p> <p>Type of recommendation: consensus-based Evidence: insufficient Recommendation: weak</p>	<p>RT ± concurrent low-dose platinum-based chemotherapy (may offer systemic adjuvant chemotherapy)</p> <p>Type of recommendation: evidence-based Evidence: intermediate Recommendation: moderate</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>	<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, extrafascial hysterectomy is preferred if there is residual disease or initial tumor > 6 cm</p> <p>Type of recommendation: consensus-based Evidence: intermediate Recommendation: weak</p>		

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******

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

- **Paraarotic 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

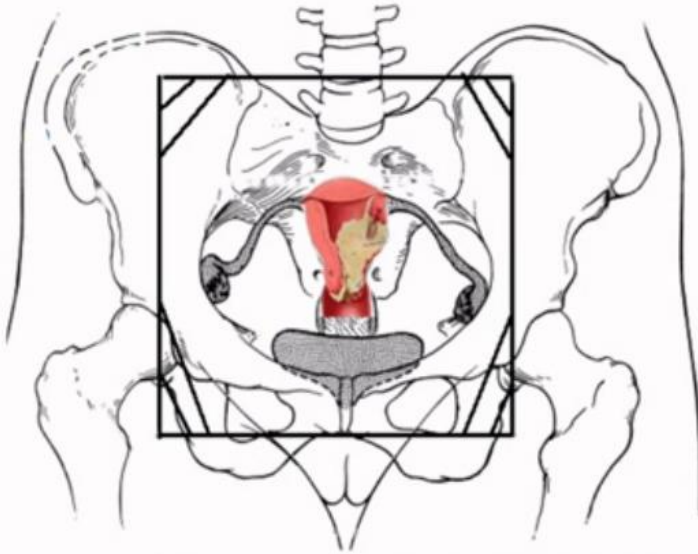
- **EBRT: Pelvic intensity modulated radiotherapy (IMRT)**
45-50 Gy in 5 weeks (+ conc. cis Platin)
- **Image guided Radiotherapy (IGRT) recommended**
- **Targets: tumor and pelvic LNs related**
± paraaortic LNs in case of increased risk
- **Boost involved LNs: preferably simultaneous**
55-60 Gy in 5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

Radiotherapy

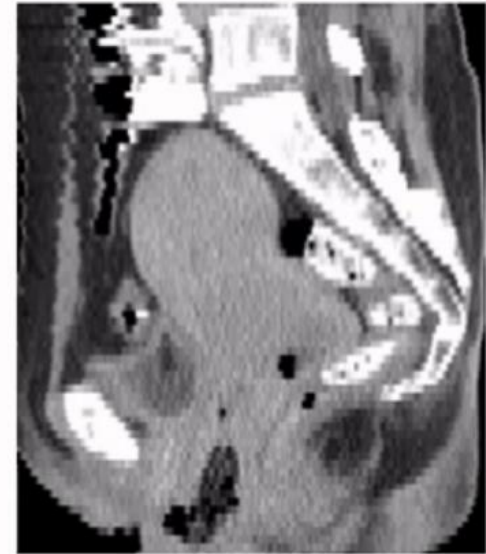
principles: definitive brachytherapy

- **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_{HR})**
residual gross tumor and adjacent cervix/parametria
- **Overall target (CTV_{HR}) dose EBRT+BT: $\geq 85-90$ Gy**
- **Dose constraints for organs at risk**
- **Intracavitary and combined intracavitary/interstitial**
- **Overall treatment time: 1-2 weeks**

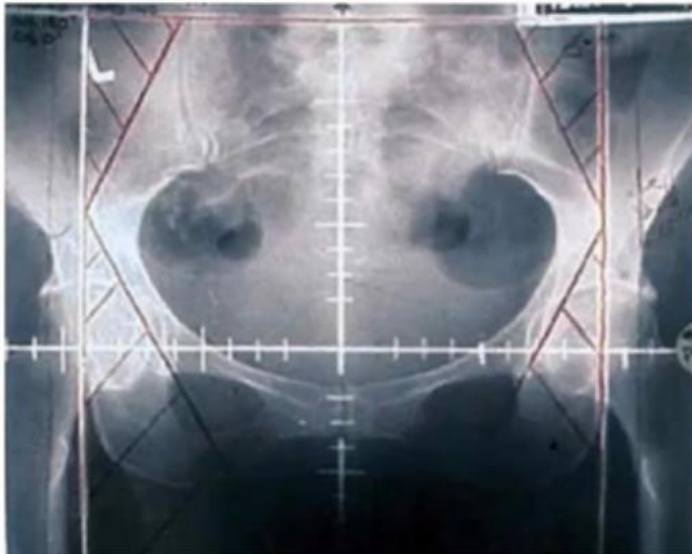
From 2D to 3D: role CT & MRI



CT

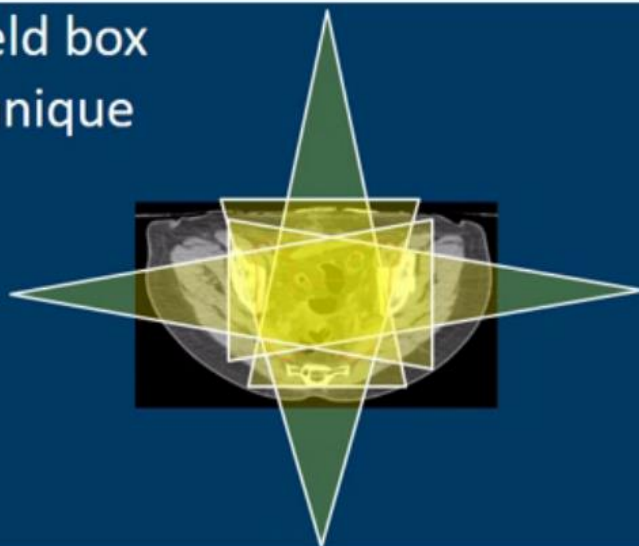


MRI

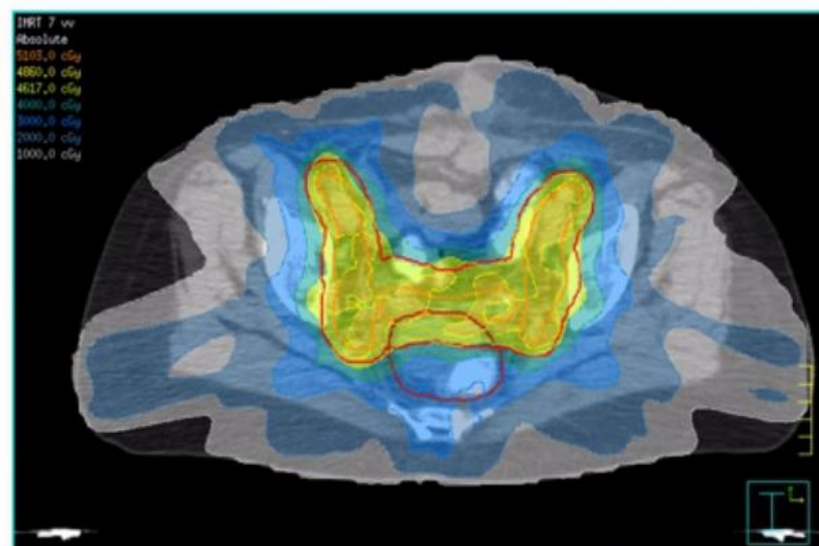
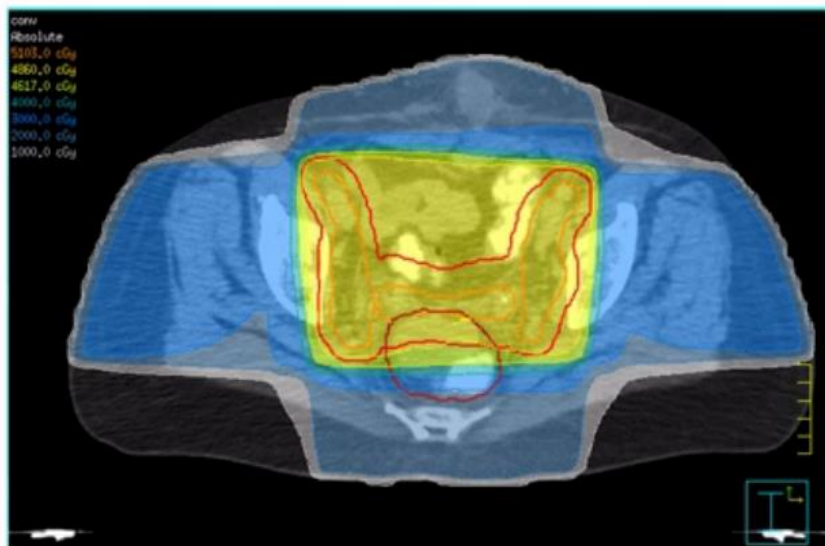
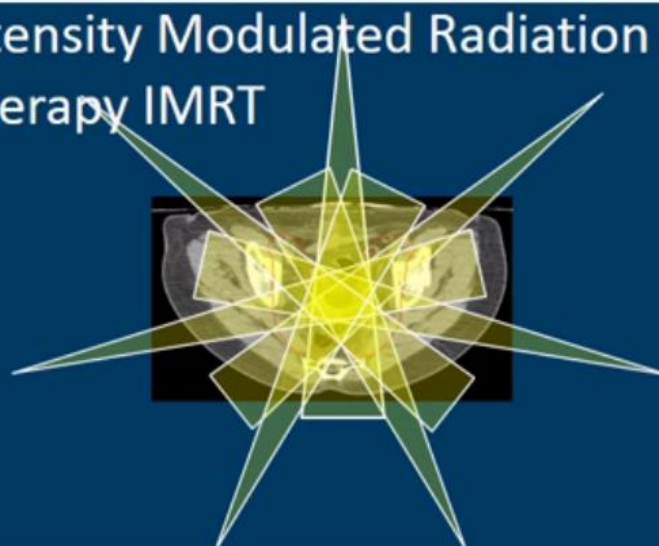


Advances in treatment planning

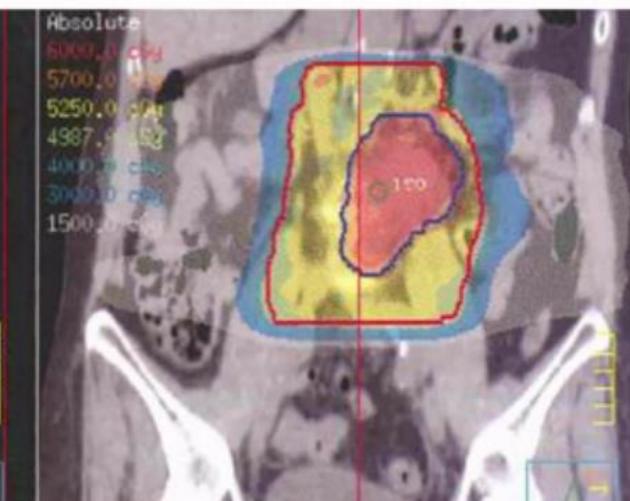
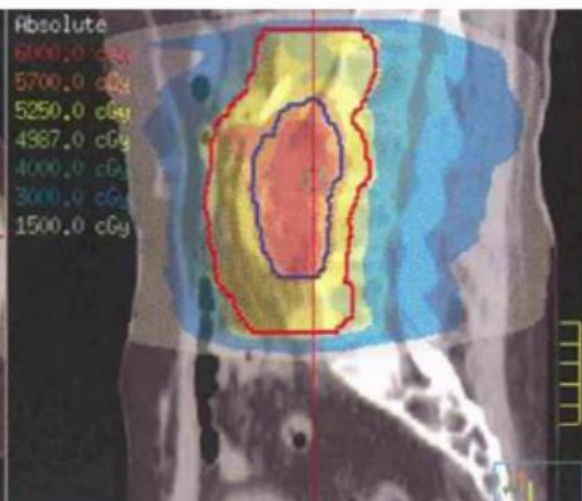
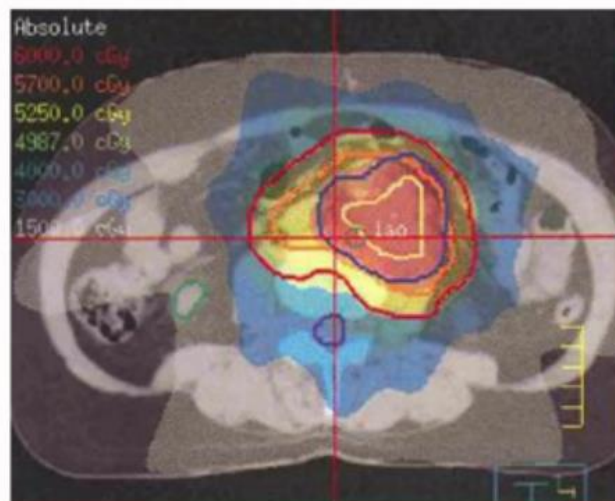
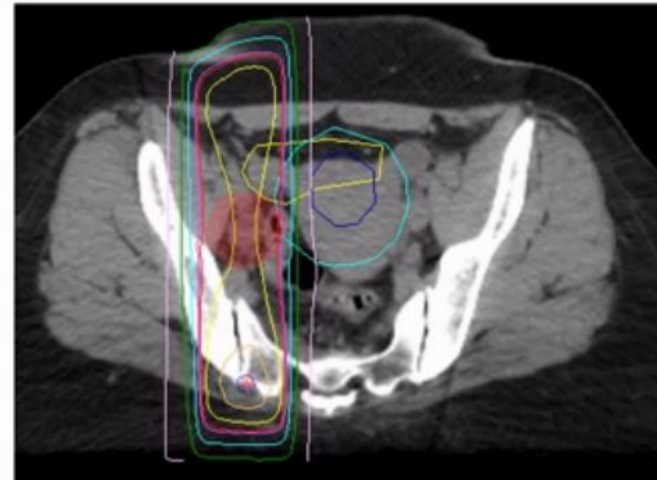
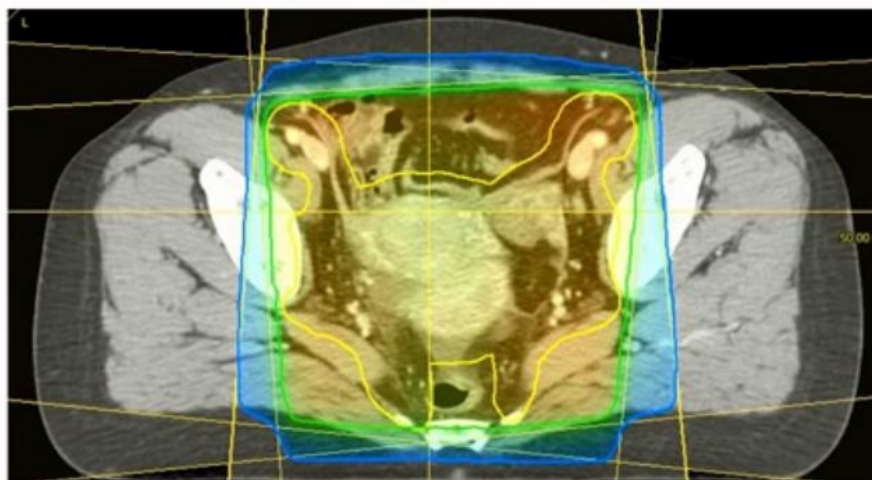
4-field box technique



Intensity Modulated Radiation Therapy IMRT

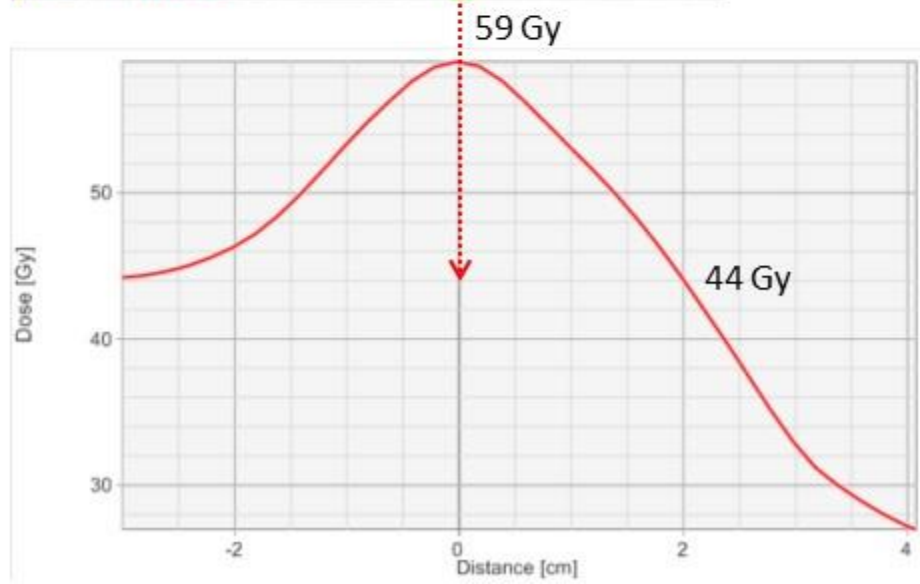
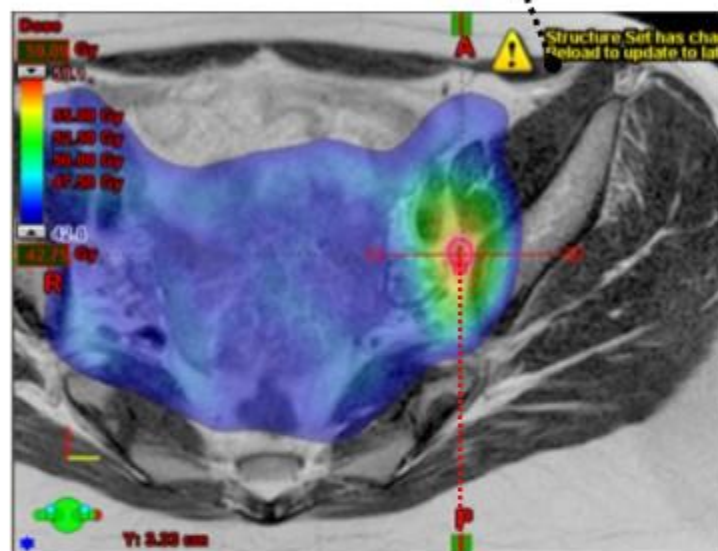


Sequential or simultaneous integrated boost

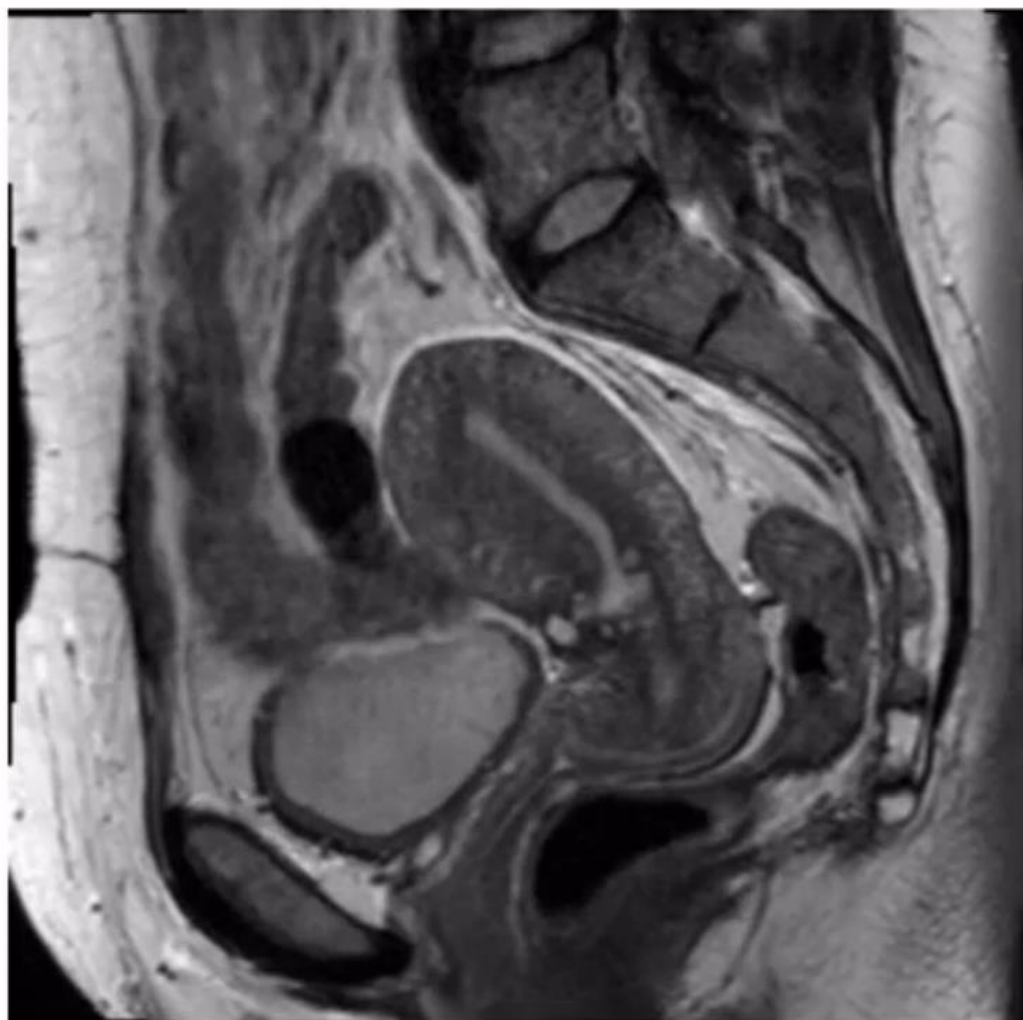


Simultaneous Integrated Boost (CoP) for lymph node boost: Clinical example

- 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_{EQD2} EBRT
 - 4 Gy_{EQD2} BT
-
- 60Gy_{EQD2} total

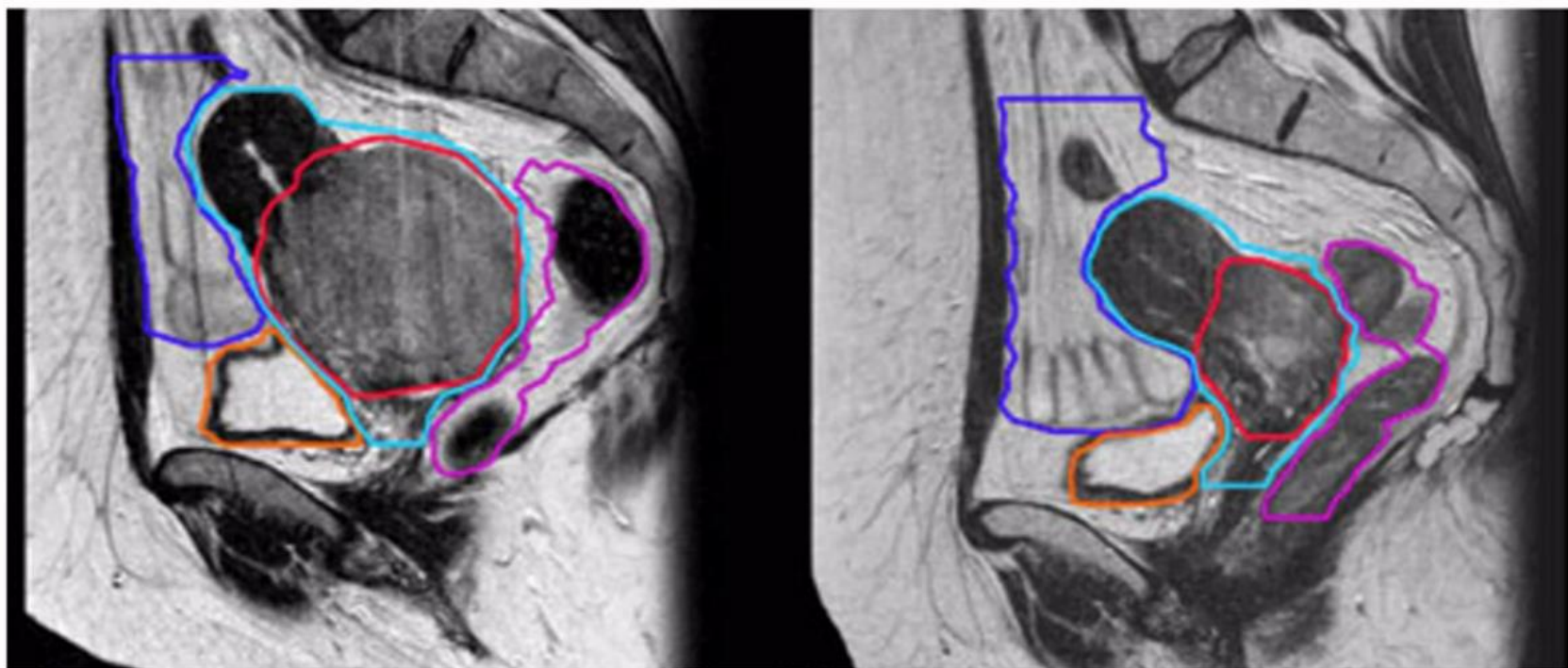


Pelvic organ movement: 4 dimensional MRI



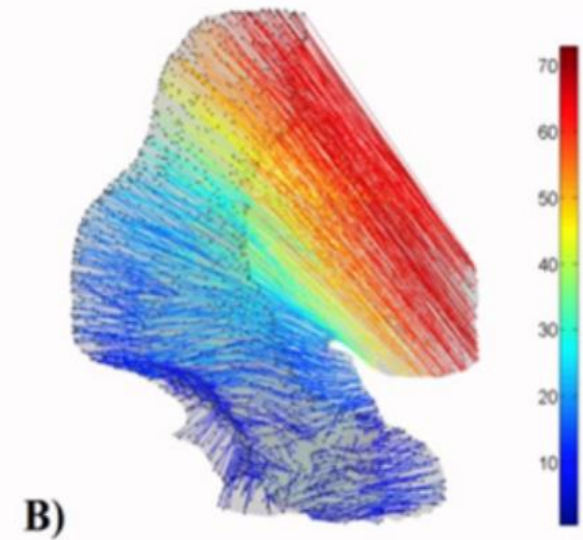
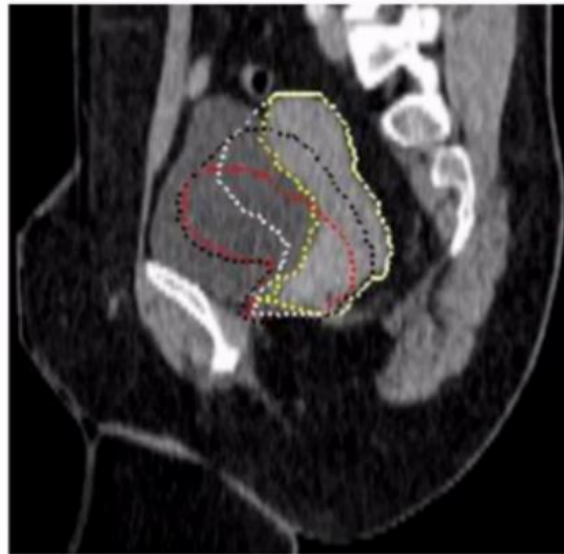
- Innovation in diagnostic imaging: CT & MRI
- Increased understanding of 3- and 4-dimensional individual anatomy
- MRI: functional information

Tumour regression during treatment

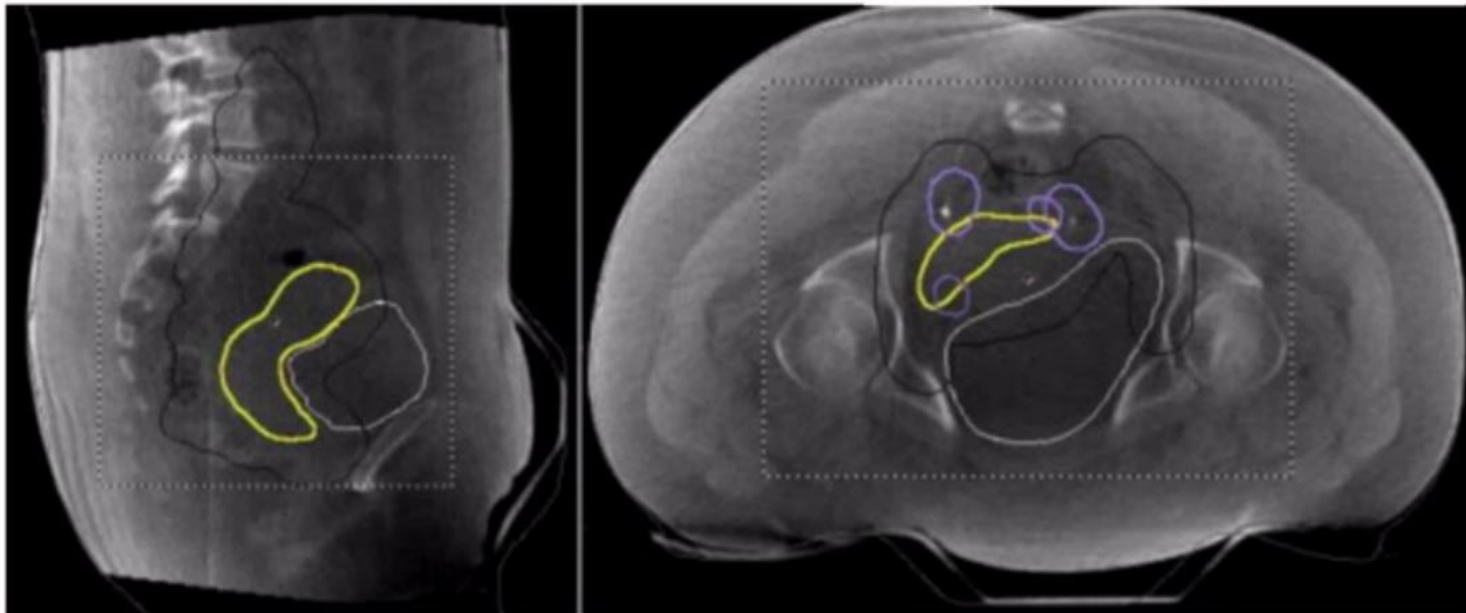


From 3D to 4D: adaptive radiotherapy

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

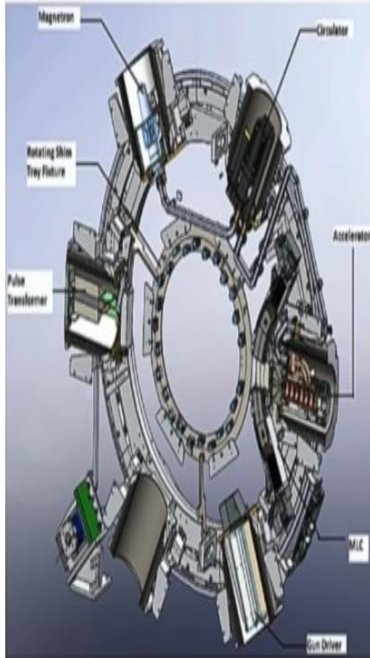


- Cone beam CT to choose 'plan of the day'



MRI integrated LINAC

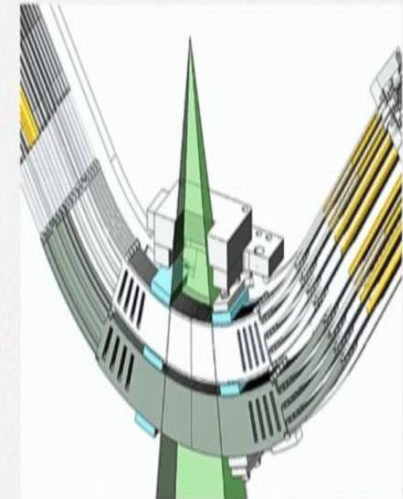
MR-Linac Design



- 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

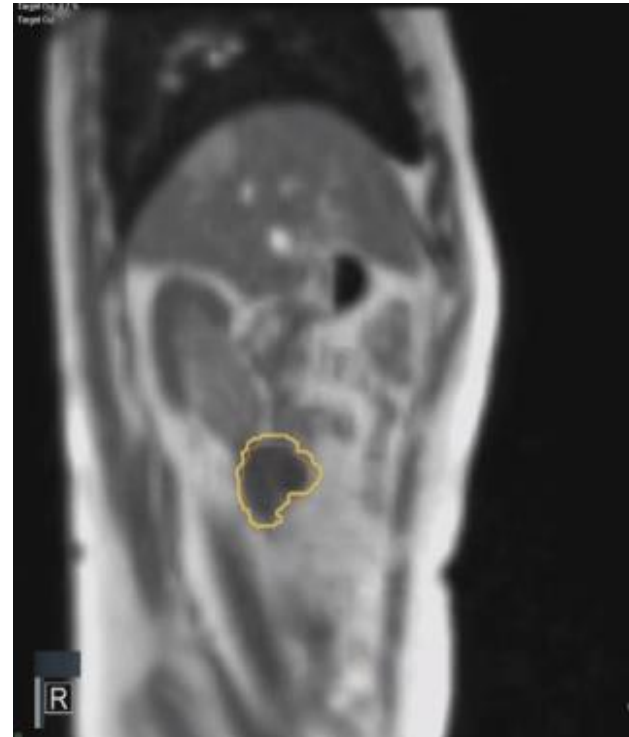
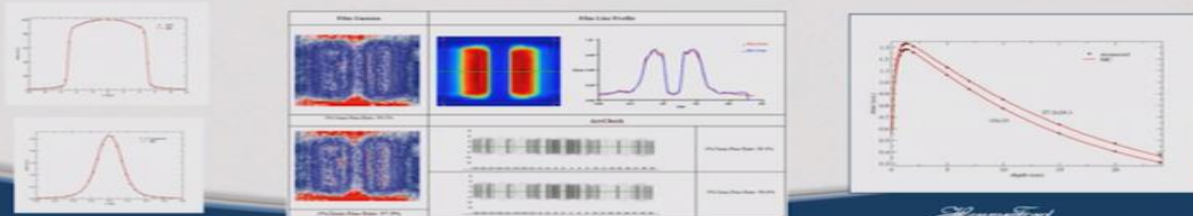
- Double Focused Leaves
 - ~8 mm leaf width
 - SAD – 90cm
 - Leaves traverse entire distance across field
 - Lower stack is offset by 4mm
 - No Tongue and Groove
- Nominal dose rate ~645 MU/min
- Step & Shoot IMRT
- Field Size:
 - Minimum: 0.2 cm by ~0.4 cm
 - Maximum: 27.4cm x 24.1 cm



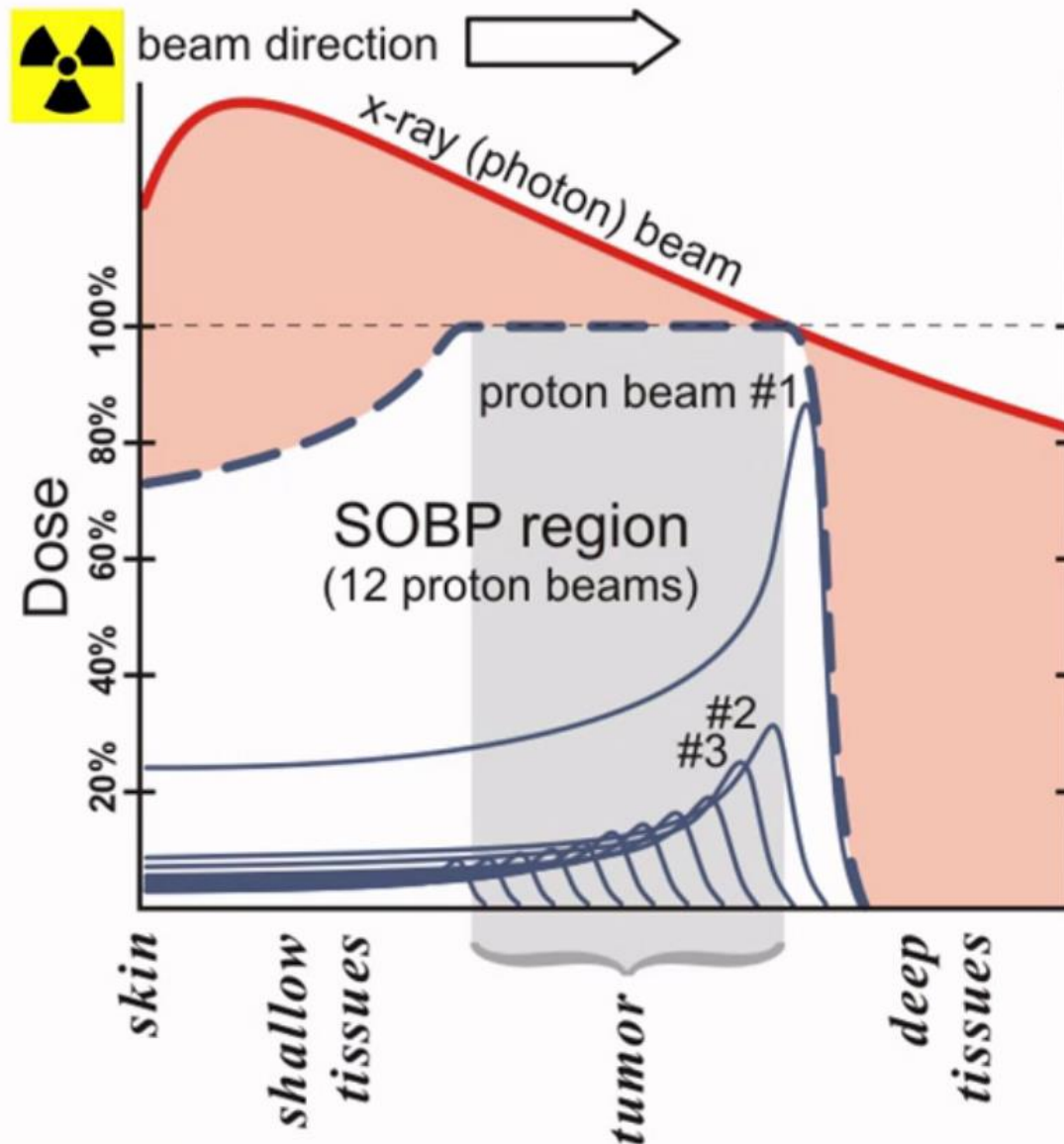
ADVANTAGES MRI - LINAC

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!)



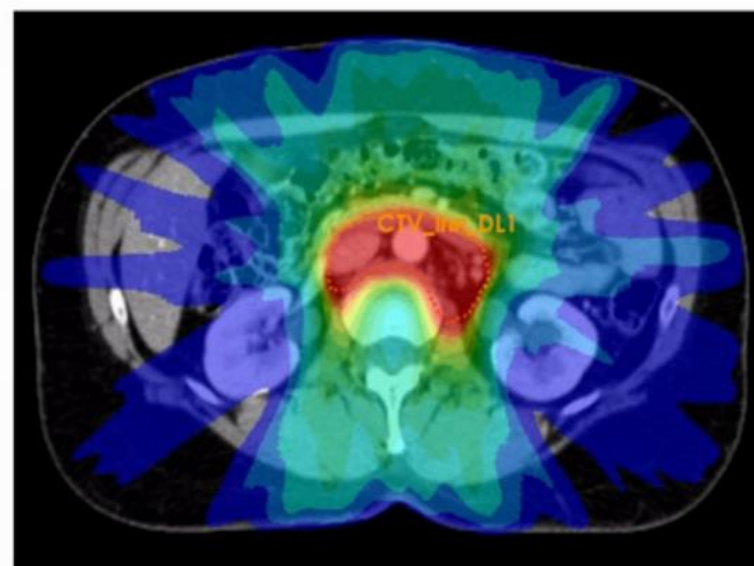
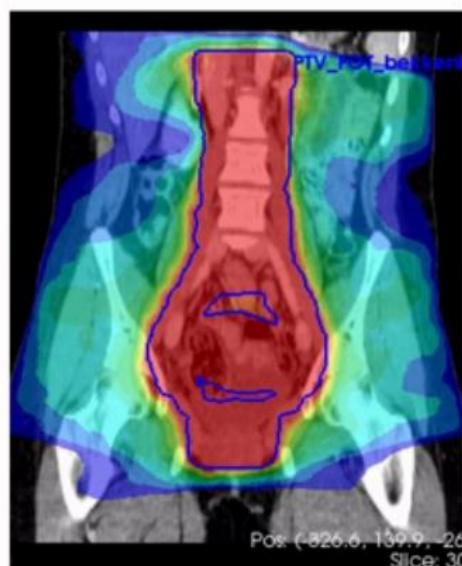
Proton therapy



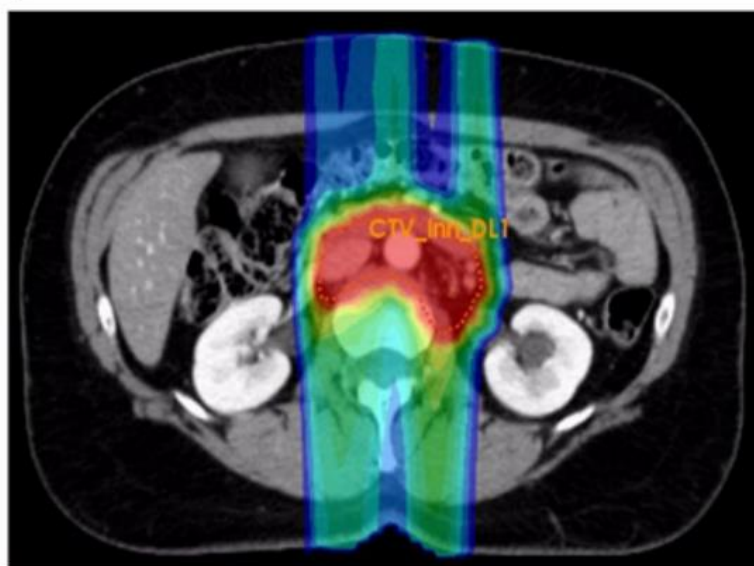
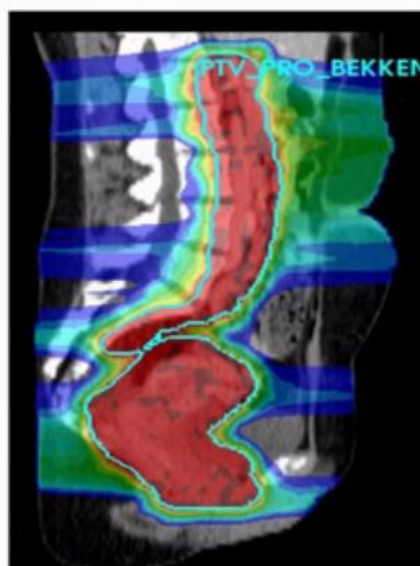
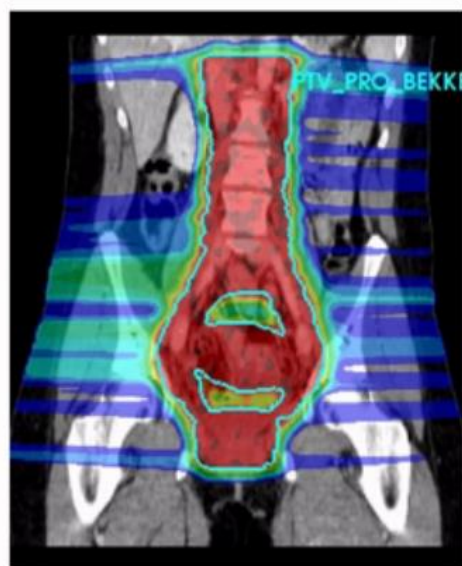
- Protons: particle therapy
- Spread Out Bragg Peak
- Protons more sensitive for differences in tissue density (bone, air, muscle)

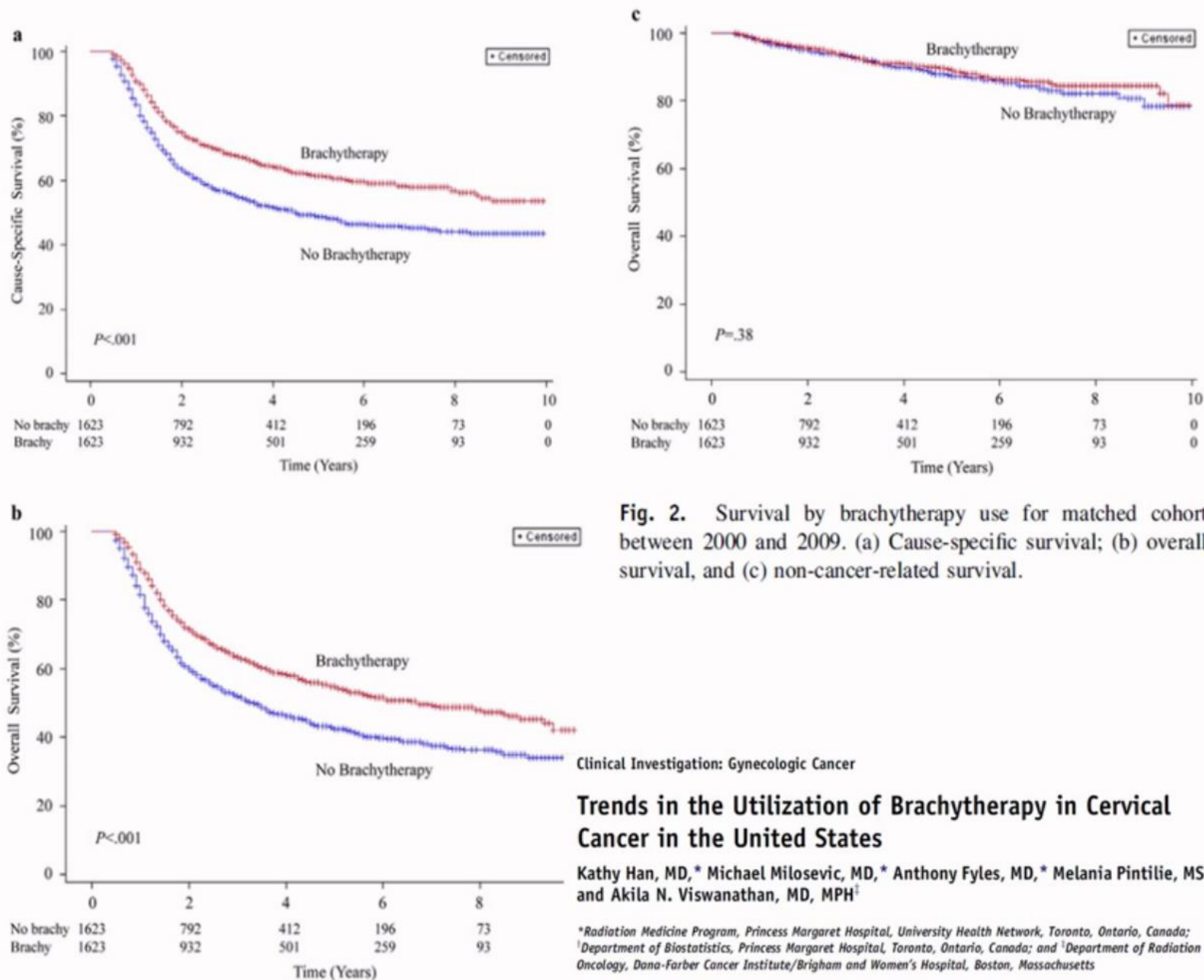
Photons versus protons

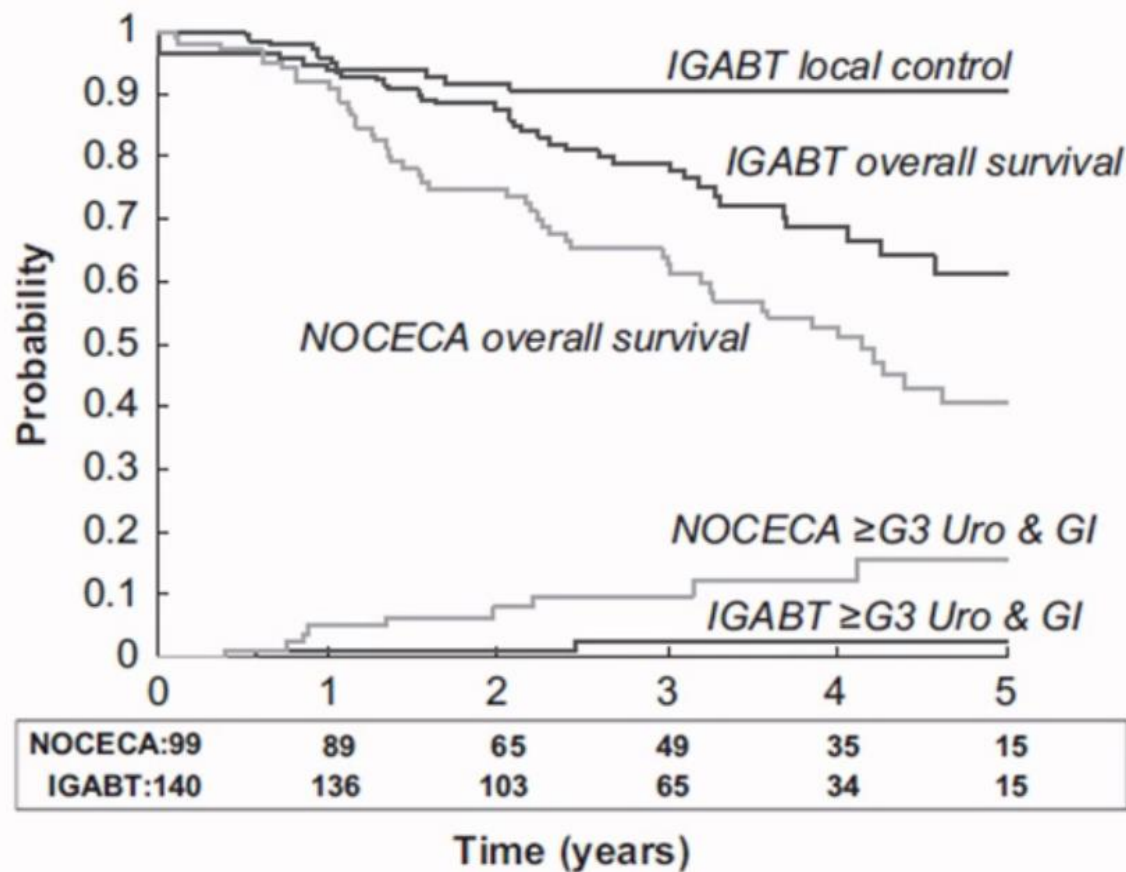
Photons



Protons

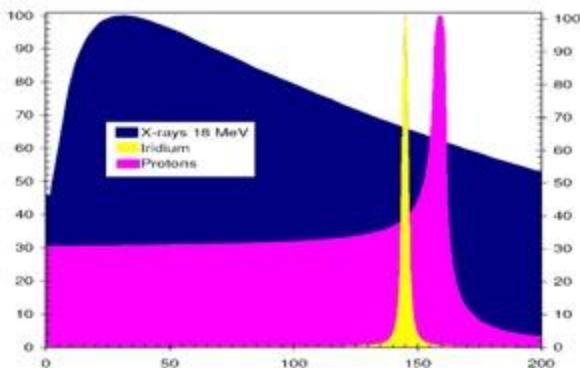






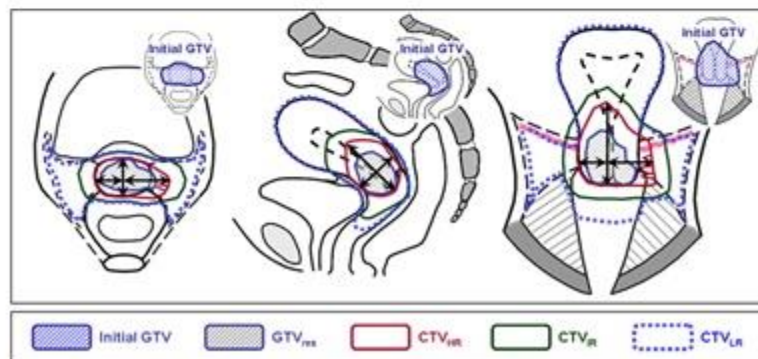
LC 3 y: 90%
 OS 3 y:
 IGABT: 79%
 NOCECA: 63%
 morbidity 3y \geq G3:
 IGABT: 3%
 NOCECA: 10%

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.

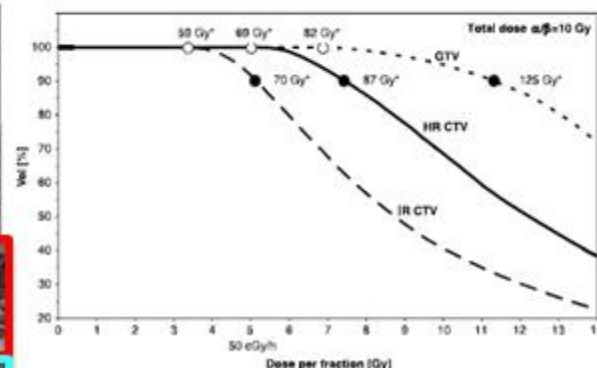
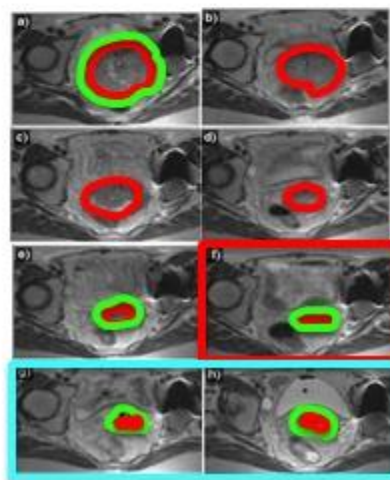


The New Paradigm: individual Doses in adaptive Volumes (Vienna data 1998-2008)

LR CTV-T	$\sim 300 \text{ cm}^3$	$\geq 45 \text{ Gy EQD2}$
IR CTV-T	$\sim 85 \text{ cm}^3$	$\sim 66 \text{ Gy EQD2}$
HR CTV-T	$\sim 39 \text{ cm}^3$	$\sim 89 \text{ Gy EQD2}$
Res. GTV	$\sim 9 \text{ cm}^3$	$\sim 119 \text{ Gy EQD2}$



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

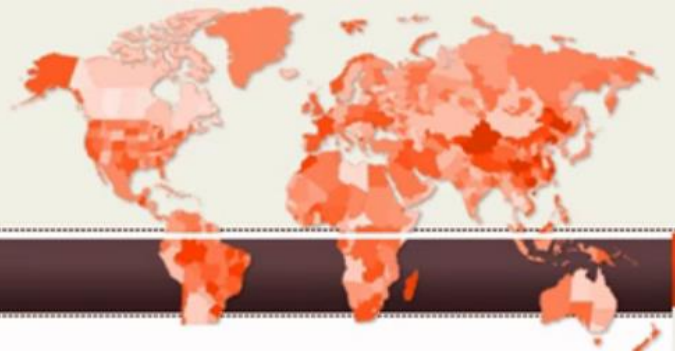


GEC ESTRec II, 2006
Schmid et al. StrOnk 2013



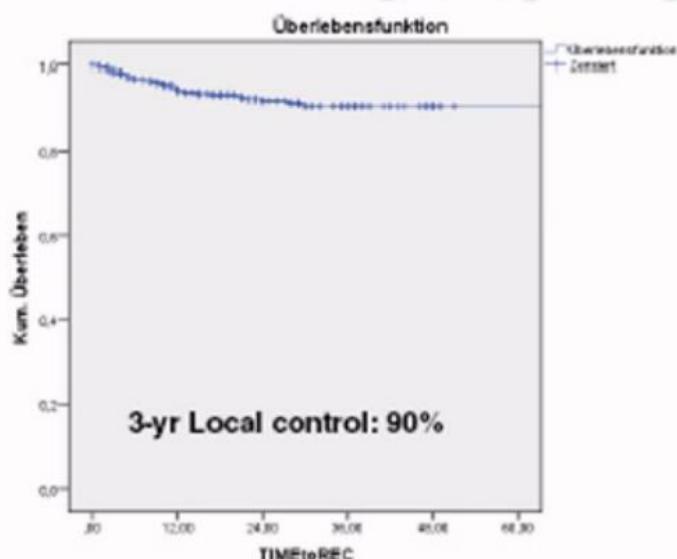
EMBRACE

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



[About Embrace](#) [Contacts](#) [Participation](#) [Data entry](#) [Tools](#) [Members info](#) [Logout](#)

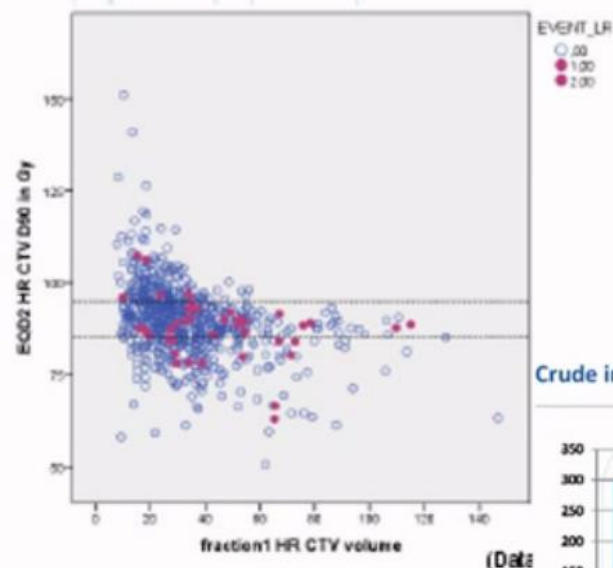
Local Recurrences - overall



N = 714

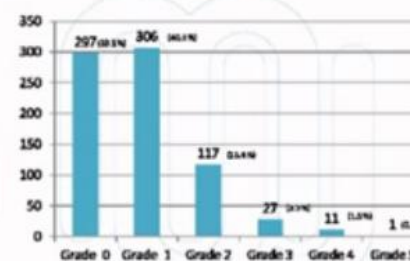
43 events

(15 incomplete remissions + 28 local recurrences)



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

Crude incidence of any GI morbidity



EMBRACE

5th Annual EMBRACE Meeting – Vienna January 2014

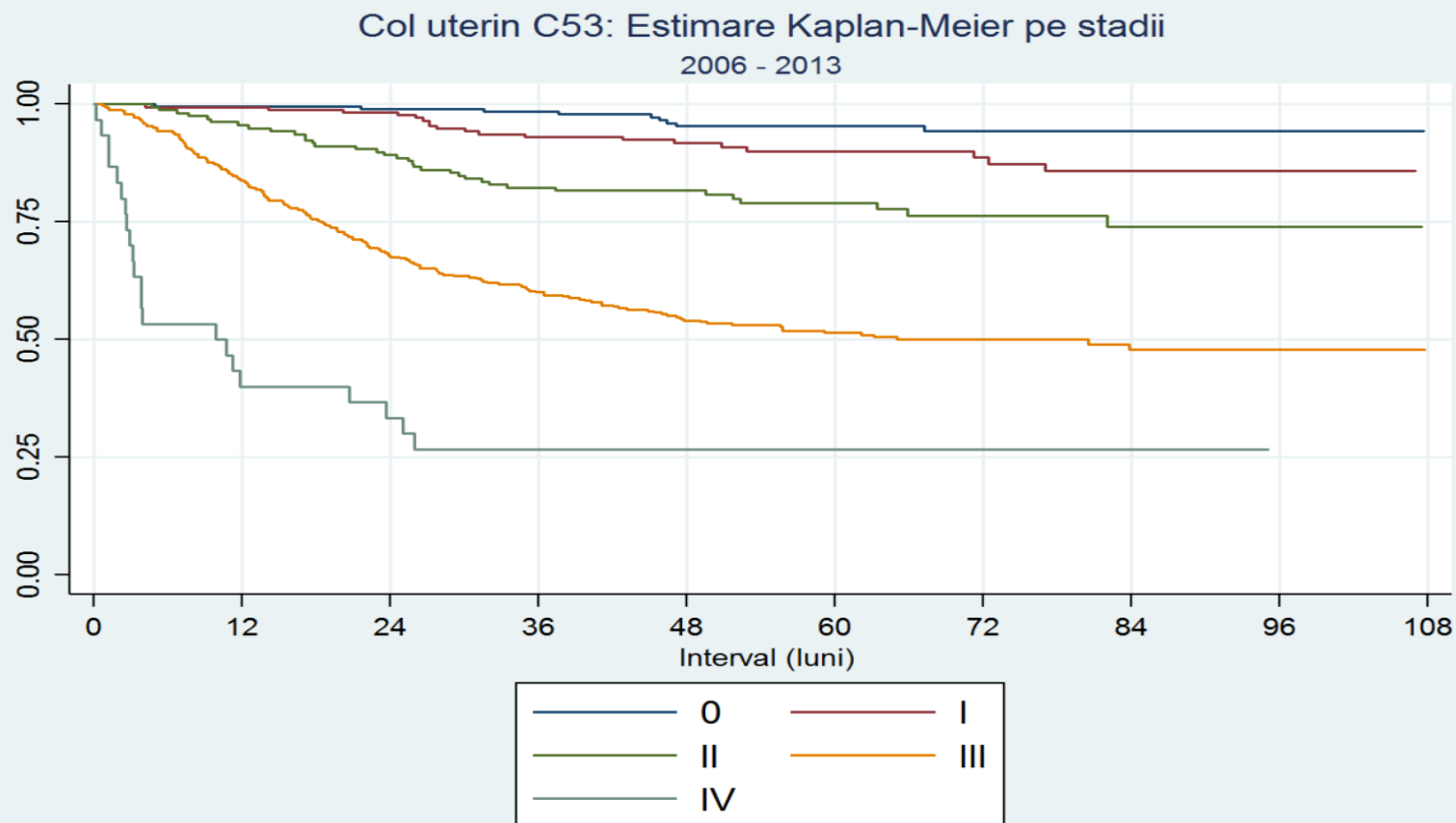
**new volume and dose adaptation paradigm:
tumor response adapted RT through repetitive imaging:
adaptation of target in space (3D) and time (4D)**

- *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*

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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 !



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