AAPM 2016 JUL 31–AUG 4 COMMUNICATING OUR VALUE IMPROVING OUR FUTURE. 58TH ANNUAL MEETING & EXHIBITION | WASHINGTON, DC

SAM Joint Imaging: Advances and Innovations in Image Guided Brachytherapy

Modern Intracavitary Brachytherapy

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Disclosures

Ad-hoc consultant for Varian Corp., Brachytherapy Division

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International Journal of Radiation Oncology biology • physics
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Clinical Investigation: Gynecologic Cancer

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

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

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

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Purpose: To determine the trends in brachytherapy use in cervical cancer in the United States and to identify factors and survival benefits associated with brachytherapy treatment.
Methods and Materials: Using the Surveillance, Epidemiology, and End Results (SEER) database, we identified 7359 patients with stages IB2-IVA cervical cancer treated with external beam radiation therapy (EBRT) between 1988 and 2009. Propensity score matching was used to adjust for differences between patients who received brachytherapy and those who did not from 2000 onward (after the National Cancer Institute alert recommending concurrent chemotherapy).

Brachytherapy in Gyn Cancer in USA

4-year Cause Specific Survival
64.3% vs 51.5%, P<.001

And Overall Survival
58.2% vs 46.2%, P<.001

* Han et al., 2013

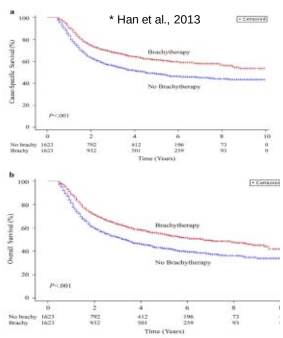

Fig. 2. Survival by brachytherapy use for matched cohort between 2000 and 2009. (a) Cause-specific survival; (b) overall survival, and (c) non-cancer-related survival.

Fig. 1. Brachytherapy use rate between 1988 and 2009 in 18 (a) and the original 9 (b) SEER registries.

This study revealed a concerning decline in brachythe utilization over the past decade in the United States and signifi geographic disparities in brachytherapy use. On multivari analysis of the propensity score-matched cohort, brachythe use was independently associated with better CSS and OS.

We postulate that the sharp decline in brachytherapy utilization in 2003 was the result of increased uptake, despite a dearth of published data, of highly conformal radiation therapy techniques including intensity modulated RT (IMRT) and more recently stereotactic body radiation therapy (SBRT). In a 2002 survey of U.S. radiation oncologists, 15% of the respondents reported using IMRT in gynecology patients; by 2004, 35% used IMRT (14, 15).

EDITORIAL

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

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

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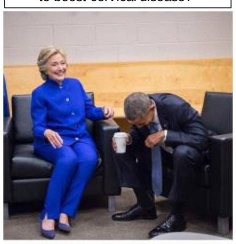
Tanderup et al, IJROBP, March 1, 2014, Volume 88, Issue 3, Pages 537–539

So they are trying IMRT and SBRT to boost cervical disease?



Brachytherapy has been an essential component in the successful treatment of cervical cancer for more than 100 years.

Repeating painful mistakes from the past

1970s – 25MV, shrinking of EBRT fields to deliver 60-70 Gy in stage IIIB → brachy almost eliminated

With poorer survival rates and higher complications, it was abandoned, but it took years.

Tanderup et al, IJROBP, March 1, 2014, Volume 88, Issue 3, Pages 537–539

EMBRACE study

24 Active Centers

https://www.embracestudy.dk/

Prospective trial

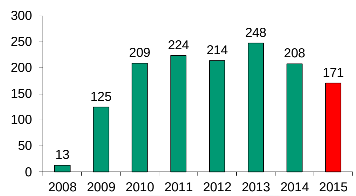
Role of MRI guided brachytherapy (IGBT) in locally advanced cervical cancer

correlate image based DVH parameters for the clinical target volume and for organs at risk with outcome.

Courtesy of C. Kirisits

Overall Accrual

On 31st December 2015 overall number of registered patients was 1412!!!



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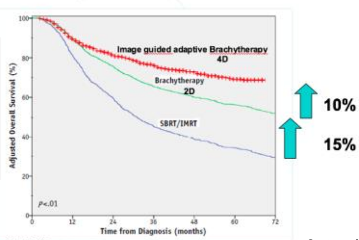
Courtesy of C. Kirisits

10

Overall Survival locally advanced cervical cancer SBRT/IMRT boost vs. 2D BT vs. 4D IGABT



Gill B et al. Int J Radiat Oncol Biol Phys 2014;13:542-7;
Sturdza et al. Improved local control and survival in LACC through image guided adaptive brachytherapy, submitted

Courtesy of C. Kirisits

IG(A)BT – key to excellent overall survival rates

- 3(4)D MRI guidance:
  - Possibility to conform the dose given with BT with regard to volume (3D),
  - And time (adaptive component, 4D): Image at each fraction and plan to take into account OARs and tumor regression

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Role of imaging in modern IB

- Application insertion
- Planning
- Treatment Verification
- Applicator design
- Facilitate real-time dosimetry
- Dose summation
- For response

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Objectives

- Establish common terminology
  - HDR Intracavitary Brachytherapy
  - Current guidelines – GEC-ESTRO/ABS (pre ICRU 89)
- MRI imaging in IGBT
  - Insertion, planning, verification
  - Hybrid techniques: MRI/ CT/CBCT
  - Imaging for applicators design
  - Role in new ICRU 89

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LDR vs. HDR

- Several large studies were designed to compare LDR with HDR for cervical cancer
- Hareyama, 2002 (randomized trial), Japan, ACS
- Wang, 2010, (review), China, The Cochrane Collaboration
- Gaur, 2012 (randomized trial), India, Ind J Clin Practice, v. 23, no. 4, 203-211
- Viani, 2009 (meta-analysis of clinical trials), J Exp & Clin Res

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Journal of Experimental & Clinical Cancer Research

BioMed Central

Research

Open Access

Brachytherapy for cervix cancer: low-dose rate or high-dose rate brachytherapy – a meta-analysis of clinical trials

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* Corresponding author

Abstract

Background: The literature supporting high-dose rate brachytherapy (HDR) in the treatment of cervical carcinoma derives primarily from retrospective series. However, controversy still persists regarding the efficacy and safety of HDR brachytherapy compared to low-dose rate (LDR) brachytherapy, in particular, due to inadequate tumor coverage for stage III patients. Whether LDR or HDR brachytherapy produces better results for these patients in terms of survival rate, local control rate and the treatment complications remain controversial.

Methods: A meta-analysis of RCT was performed comparing LDR to HDR brachytherapy for cervix cancer treated for radiotherapy alone. The MEDLINE, EMBASE, CANCERLIT and Cochrane Library databases, as well as abstracts published in the annual proceedings were systematically searched. We assessed methodological quality for each outcome by grading the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. We used "recommend" for strong recommendations, and "suggest" for weak recommendations.

Results: Pooled results from five randomized trials (2,065 patients) of HDR brachytherapy in cervix cancer showed no significant increase of mortality ($p = 0.52$), local recurrence ($p = 0.68$), or late complications (rectal; $p = 0.7$, bladder; $p = 0.95$ or small intestine; $p = 0.06$) rates as compared to LDR brachytherapy. In the subgroup analysis no difference was observed for overall mortality and local recurrence in patients with clinical stages I, II and III. The quality of evidence was low for mortality and local recurrence in patients with clinical stage I, and moderate for other clinical stages.

Conclusion: Our meta-analysis shows that there are no differences between HDR and LDR for overall survival, local recurrence and late complications for clinical stages I, II and III. By means of the GRADE system, we recommend the use of HDR for all clinical stages of cervix cancer.

> 2000 patients

No differences between HDR and LDR in OS, local recurrence and late complications

HDR

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  - Role in new ICRU 89

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Current ABS Guidelines: 2012


BRACHYTHERAPY

ELSEVIER

American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part I: General principles

Akila N. Viswanathan[1,*], Bruce Thomadsen[2],
American Brachytherapy Society Cervical Cancer Recommendations Committee


BRACHYTHERAPY

ELSEVIER

American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part II: High-dose-rate brachytherapy

Akila N. Viswanathan[1,*], Sushil Beriwal[2], Jennifer F. De Los Santos[3], D. Jeffrey Demanes[4], David Gaffney[5], Jorgen Hansen[5], Ellen Jones[6], Christian Kirisits[7], Bruce Thomadsen[8], Beth Erickson[9]

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Part I & II: Summary

- (Volumetric) Imaging:
  - Localization : radiographic images, CT, MRI
  - CT- and MR-based localization allows for correlation of anatomic data with source positioning.
  - MR best modality for normal tissue and tumors of the uterus and uterine cervix
  - Details for MR sequences adequate for contouring and planning
  - Use of US for applicator placement and cervix delineation

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Part I& II: Summary

- Contouring:
  - Follow GEC-ESTRO recommendations (C. Haie-Meder-2005, R. Potter 2006)
  - HR-CTV, IR-CTV, OARs (rectum, bladder, sigmoid)
- Prescription:
  - Target, target dose, dose per fraction, fractionation plan, isotope, dose to OARs, applicator used
- Treatment planning
  - TP and dosimetry SHOULD be performed every time applicators are inserted, even if fixed applicator geometry is used.
  - HR-CTV coverage D90 should equal 100%
  - When using radiographs, prescribe to point A

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TP and dosimetry SHOULD be performed every time applicators are inserted, even if fixed applicator geometry are used.

Inter-/intrafraction variation in cervix cancer BT

1 plan evaluated for images at different time points.
Anatomical changes between irradiations may lead to large random dosimetric uncertainties

© Lang et al. 2013, Radiother Oncol 107

#	patients	treatment	fractions	time range	Image type	images	variation
1	21	HDR	4	18-20 hrs	MRI	84	Intra-app.
2	21	HDR	3	5 hrs	MRI	72	Intra-app.
3	9	PDR	2 x 29 / 32	22 hrs	MRI	36	Intra-app.
4	14	HDR	5	1-22 days	CT	69	Inter-app.
5	27	HDR	4	7-10 days	MRI	54	Inter-app.
6	31	PDR	2 x 20	1 week	MRI	62	Inter-app.
	123 patients			5 h – 3 weeks		377	3 + 3

Nesvacil et al. 2013, Radiother Oncol 107

Courtesy C. Kirisits, Vienna

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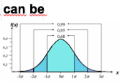
Multicenter Center study of inter-/intrafraction variations for target and OARs in cervix BT

	ΔD_{2cm^3} between 2 acquisitions [%] (fixed plan, variable anatomy)									ΔD_{90} [%] (fixed plan, variable anatomy)		
	bladder			rectum			sigmoid/bowel			HR CTV		
	Mean	median	SD	mean	median	SD	mean	median	SD	mean	median	SD
total	2.7	1.5	20.3%	4.5	4.1	22.0%	1.6	-0.9	26.8%	-1.1	-1.7	13.1%
Intraaplication	1.3	1.5	17.7	3.8	2.3	20.5	-2.3	-3.7	23.5	-2.5	-4.3	10.8
interapplication	3.9	0.0	22.3	5.8	5.2	23.2	6.8	3.7	30.2	0.4	-0.8	15.1

Random uncertainties (1SD) of physical dose per BT fraction can be

- ~ 10% for HR CTV D90
  (contouring uncertainty (Petric, Hellebust R&O 2013))
- ~ 20% for bladder, rectum D_{2cm^3}
- ~ 30% for sigmoid D_{2cm^3}



No correlation with time between images was detected!

Courtesy C. Kirisits, Vienna

Part I& II: Summary

- Dose calculation and guidelines:
  - Recommended conversion of HDR fractionations into biologically equivalent doses in 2-Gy fractions (EQD2)
  - Spreadsheet @ www. americanbrachytherapy.org/guidelines.html.
  - Ability to script (API scripting) in BrachyVision (Varian) to convert raw doses into EQD2 (A. Faught et al, Bracytherapy, vol. 15, S1, S137-138) → point doses
  - SW that calculates 3D distribution of biological doses (Velocity, MIM)

Table 2
Dose limits to the target and to the organs at risk

Dose specified to	Radiographs	3D imaging
Point A	5 × 5–6 Gy	Variable
D_{90}		≥80–≤90 Gy EQD2
ICRU point bladder	5 × ≤3.7 Gy	
ICRU point rectum	5 × ≤3.7 Gy	
D_{2cc} bladder		≤90 Gy EQD2
D_{2cc} rectum		≤75 Gy EQD2
D_{2cc} sigmoid		≤75 Gy EQD2

EQD2 = normalized therapy dose; 3D = three dimensional.

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Part I & II: Summary

- Recommended reporting

The ABS recomm
ters for intracavitary

1. The type of ap
2. The prescriptio
   per fraction an
   a limited targe
   point A;
3. The dose to po
4. Total reference
   (usually ^{192}Ir).
   7.24×10^{-6} Gy
5. Loading patter
6. D_{90}, D_{100}, and
   ning is used; i
   included for interstitial brachytherapy;
7. The doses to the ICRU rectal and bladder points and/ or, if volume-based dosimetry is performed, the $D_{0.1\,cc}$ and $D_{2\,cc}$, to the OAR and the $D_{5\,cc}$ if the organ wall is contoured for OAR per GEC-ESTRO guidelines;

Dose to point A, regardless of imaging modality

Standard parameters to be reported:
D2cc for OARS
D90 and D100 (D98), V100 for HR-CTV

ions in the following planes:
ing the tandem,
l coronal through point A and the
vaginal sources, and
the vaginal sources with isodose

lateral vaginal mucosa and 0.5 cm
inal surface (97). For LDR applica-
al points for tandem and ovoid
fall along the plane of the center of
nd should be limited to less than
int A dose. Vaginal dose should also
be reported for cylinder applications 1.25 cm inferior to the external cervical os along the vaginal surface and at 0.5 cm depth (Fig. 5).

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MRI

- MRI: Gold Standard
  - GEC-ESTRO/ABS Guidelines: Defined role of MRI in IGBT
  - MRI better suited for assessing the target (the cervix and any residual disease)

- [1] Potter R, Haie-Meder C, Limbergen EV, et al. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapyd3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. Radiother Oncol 2006;78:67e77.
- [2] Haie-Meder C, P€otter R, Van Limbergen E, et al. Recommendations from gynaecological (GYN) GEC-ESTRO working group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MR

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US-based clinics practice of IGBT for Cervical Ca.

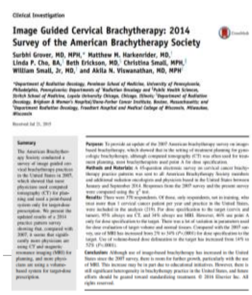
Clinical Investigation

Image Guided Cervical Brachytherapy: 2014 Survey of the American Brachytherapy Society

Surbhi Grover, MD, MPH,[*] Matthew M. Harkenrider, MD,[†] Linda P. Cho, BA,[‡] Beth Erickson, MD,[§] Christina Small, MPH,[‖] William Small, Jr, MD,[†] and Akila N. Viswanathan, MD, MPH[‡]

Table 1 Characteristics and general treatment practices of respondents to the 2014 image guided brachytherapy survey (n = 219)

Characteristic	n	%
Experience level		
Practicing for ≤5 y	46	21
Practicing for 5-10 y	39	18
Practicing or 10-20 y	65	30
Practicing ≥20 y	64	29
Data missing	5	2
Institution type		
Academic hospital-based center	97	44
Academic free-standing clinic	4	2
Private hospital-based center	84	38
Private free-standing clinic	33	15
Data missing	1	0
No. of cervical cancer patients treated per year		
1-5	71	32
6-10	53	24
11-20	53	24
>20	41	19
Data missing	1	0

Table 4 Frequency of MRI use after first and subsequent fractions (fx)

Imaging use for first and subsequent fractions	n (%)
First fx MRI, always; subsequent MRI, never	169 (77)
First fx CT, always; subsequent CT, always	168 (77)
First fx MRI, never; subsequent MRI, never	144 (66)
First fx MRI, always; subsequent CT, always	21 (10)
First fx MRI, always; subsequent MRI, always	14 (6)

Abbreviations as in Table 2.
Values are number (percentage).

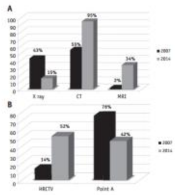

Fig. 1. (A) Comparison of utilization of computed tomography (CT), plain films (X rays), or magnetic resonance imaging (MRI) for target dose specification in 2007 and 2014 surveys. (B) Comparison of percentage of respondents (high dose rate/pulsed dose rate only) using point A versus high-risk clinical target volume (HRCTV) for target prescription in 2007 and 2014 surveys.

MRI for evaluation and management of cervical cancer

Fields and Weiss Radiation Oncology (2016) 11:15
DOI 10.1186/s13014-016-0591-0

Radiation Oncology

REVIEW — Open Access

A practical review of magnetic resonance imaging for the evaluation and management of cervical cancer

Emma C. Fields* and Elisabeth Weiss

Abstract

Cervical cancer is a leading cause of mortality in women worldwide. Staging and management of cervical cancer has for many years been based on clinical exam and basic imaging such as intravenous pyelogram and x-ray. Unfortunately, despite advances in radiotherapy and the inclusion of chemotherapy in the standard plan for locally advanced disease, local control has been unsatisfactory. This situation has changed only recently with the increasing implementation of magnetic resonance image (MRI)-guided brachytherapy. The purpose of this article is therefore to provide an overview of the benefits of MRI in the evaluation and management of cervical cancer for both external beam radiotherapy and brachytherapy and to provide a practical approach if access to MRI is limited.

Keywords: Cervical cancer, Magnetic resonance imaging, Radiotherapy

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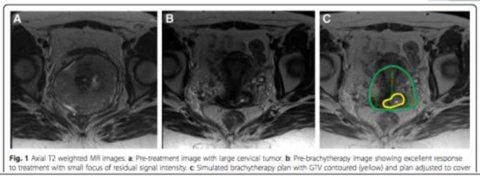

Fig. 1 Axial T2 weighted MR images. **a**: Pre-treatment image with large cervical tumor. **b**: Pre-brachytherapy image showing excellent response to treatment with small focus of residual signal intensity. **c**: Simulated brachytherapy plan with GTV contoured (yellow) and plan adjusted to cover

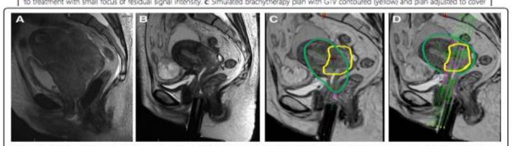

Fig. 2 Sagittal T2 weighted MR images. **a**: Pre-treatment image with large cervical tumor. **b**: Pre-brachytherapy image with good response, but still large residual disease. **c**: Simulated brachytherapy plan with GTV contoured (yellow) and inadequate coverage with tandem and ovoids. **d**: Simulated plan with tandem and interstitial needles with excellent target coverage with 100 % isodose line (green)

Proposed Workflows = f (available imaging)

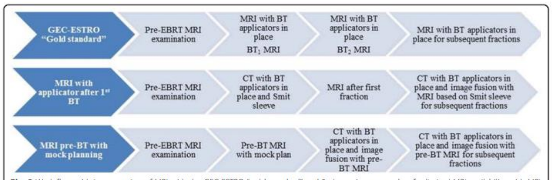

Fig. 3 Work flow with incorporation of MRI with the GEC-ESTRO "gold standard" and 2 alternative approaches for limited MRI availability with MRI after 1[ST] BT and MRI pre-BT with mock planning

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Fields and Weiss *Radiation Oncology* (2016) 11:15

2 Types

- MR in brachy suite:
  - MR guided insertions
  - MR-based (adaptive) planning (MR used at each FX)
  - MR-based treatment verification
- MR ouside brachy suite:
  - MR-based (adaptive) planning (MR used at each FX)

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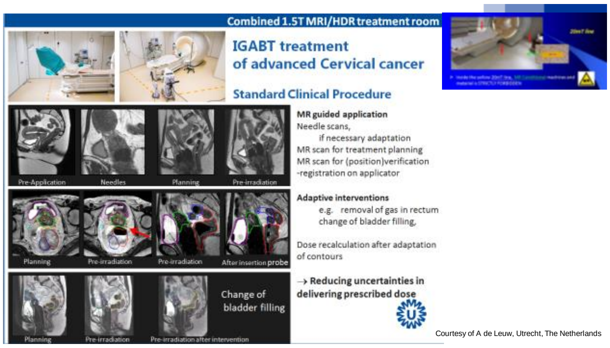


Courtesy of A de Leuw, Utrecht, The Netherlands

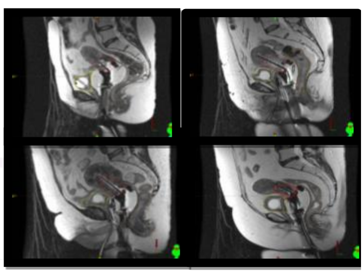
Challenges for MR in Brachy Suite

Courtesy of A de Leuw, Utrecht, The Netherlands

Stability: Vaginal Balloon Packing

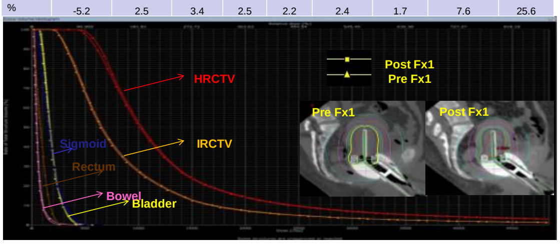
Compatible with T&R and T&O

Balloon can expand and conform to patient anatomy and applicator → **Applicator Stability**



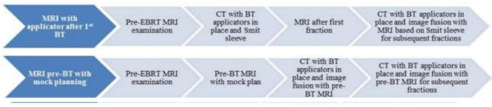
Pre vs. Post Plan, FX1

	HRCTV D90	HRCTV D100	IRCTV D100	A_Lt	A_Rt	Bladder D2cc	Rectum D2cc	Sigmoid D2cc	Bowel D2cc
Pre	640	365	320	593	547	370	230	410	250
Post	607	374	331	608	559	379	234	441	314
%	-5.2	2.5	3.4	2.5	2.2	2.4	1.7	7.6	25.6



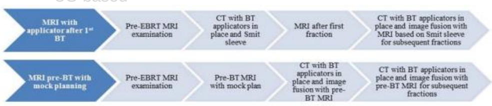
What to do when:

- Limited Access to MRI: Hybrid Methods
  - MRI + CT
  - MRI + CBCT
- NO access to MRI
  - CT alone
  - CBCT alone
  - US-based



What to do when:

- Limited Access to MRI: Hybrid Methods
  - MRI + CT
  - MRI + CBCT
- NO access to MRI
  - CT alone
  - CBCT alone
  - US-based



Limited Access: Hybrid Methods

- Use of MRI at least at 1st FX and identify HRCTV/IRCTV
- Continue subsequent fractions with
  - CT
  - CBCT
- Why MRI 1st FX?
- Is the Hybrid Flow an acceptable alternative to MRI for each FX?

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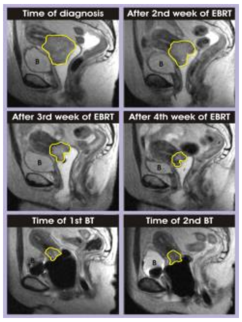
Tumour regression



Dimopoulos et al. Radiother & Oncol Suppl 2004

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Duke: Role of MRI for each fraction

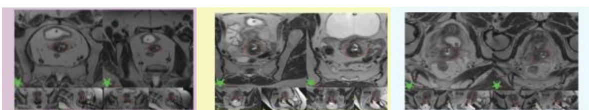

Figure 1. MRI based HRCTV contours for patient 4 showing good accord across fractions with minimal volume diffence. Plans varied to optimize sparing of normal tissue on each fraction.

Figure 2. MRI based HRCTV contours for patient 1 showing subtle volume differces due to tandem rotation within the pelvis. Plans varied to optimize sparing of normal tissue on each fraction

Figure 3. MRI based HRCTV contours for patient 6 showing large deviation of the HRCTV due to tandem divergence into the myometrium during placement. Plans varied to cover HRCTV and spare normal tissues.

- The HRCTV volumes displayed variability between fractions (median 47% @planning, 33%), and resulted in variability in the plans developed to meet GEC-ESTRO dose goals.
- Use MRI for each FX

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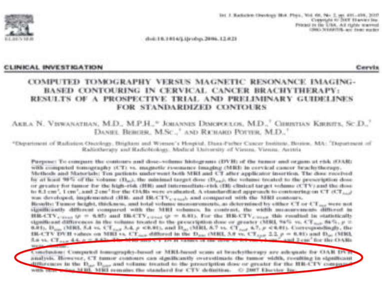
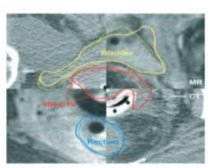
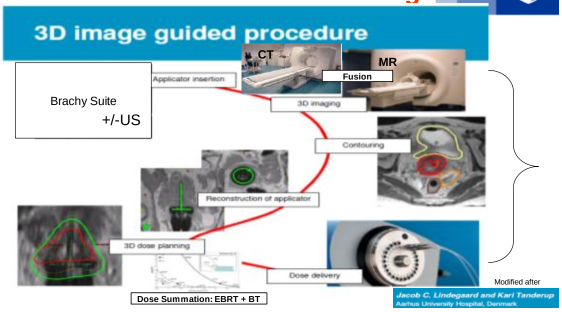
J. Chino et al. Brachytherapy, 2012, S107.

Why at least 1 MRI? For HR CTV delineation





Advanced MRI-based HDR Planning



ELSEVIER

BRACHYTHERAPY

Brachytherapy 15 (2016) 40–48

Gynecologic Oncology

Hybrid (CT/MRI based) vs. MRI only based image-guided brachytherapy in cervical cancer: Dosimetry comparisons and clinical outcome

Ee Siang Choong[1,*], Peter Bownes[2], Hima Bindu Musunuru[1], Sree Rodda[1], Carolyn Richardson[2], Bashar Al-Qaisieh[2], Sarah Swift[3], Jane Orton[1], Rachel Cooper[1]

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[3]Department of Radiology, St James's Institute of Oncology, St James's University Hospital, Leeds, UK

ABSTRACT **PURPOSE:** Limited access to MRI has restricted implementation of MRI-based image-guided brachytherapy (IGBT) in line with GEC-ESTRO guidelines in many centers. This work reports our experience using an alternative CT/MRI based (hybrid) approach for IGBT, dosimetry comparisons, and its impact on long-term clinical outcome and major toxicity.

METHODS AND MATERIALS: Seventy-six patients diagnosed with locally advanced cervical cancer between May 2008 and May 2012 treated with IGBT were analyzed. The hybrid approach is the default IGBT approach during this study period. Forty-nine had hybrid approach and 27 patients had "3-fraction conformal MRI" approach (17 within EMBRACE study). Treatment consisted of 48 Gy in 24 fractions of conformally planned external beam radiotherapy with weekly cisplatin followed by three weekly fractions of brachytherapy to high-risk clinical target volume (HR-CTV). All patients have a prebrachytherapy MRI 4 days before treatment and with the applicators in place on Fraction 1. MRI only or CT is used for subsequent fractions. Using image registration techniques and the assumption that the HR-CTV is fixed with respect to the applicator, the HR-CTV from MRI at Fraction 1 is transferred onto subsequent fraction CT image sets for the hybrid approach.

Table 3
Dosimetric data (mean ± 1 SD) and late toxicity incidences according to image-guided brachytherapy technique compared with Vienna (3)

	3F-MRI	Hybrid	p-Values	Vienna (3)
Patients	27	49		156
Median follow-up (months) [range]	33 [23–50]	47 [25–71]		42
HR-CTV (cm^3)	23 ± 14	21 ± 14		Not stated
D_{90} (EQD2) ($Gy_{\alpha/\beta10}$)	96 ± 6	97 ± 11	0.730	93 ± 13
V_{100} (%)	99 ± 2	98 ± 3		—
Bladder D_{2cc} (EQD2) ($Gy_{\alpha/\beta3}$)	76 ± 9	83 ± 9	0.002	86 ± 17
Rectum D_{2cc} (EQD2) ($Gy_{\alpha/\beta3}$)	64 ± 7	64 ± 6	0.858	65 ± 9
Sigmoid D_{2cc} (EQD2) ($Gy_{\alpha/\beta3}$)	61 ± 6	66 ± 8	0.006	64 ± 9
Small bowel D_{2cc} (EQD2) ($Gy_{\alpha/\beta3}$)	57 ± 6	59 ± 8	0.214	—
Late toxicity	CTCAE version 4.0 Grade 3+			Vienna (3) Lent-Soma Grade 3+
Rectum, n (%)	0 (0)	1 (2.0)		5 (3.2)
Small bowel, n (%)	1 (3.7)	4 (8.2)		0 (0)
Bladder, n (%)	0 (0)	3 (6.1)		3 (1.9)

HR-CTV = high-risk clinical target volume; 3F-MRI = 3-fraction conformal MRI; SD = standard deviation; EQD2 = 2-Gy equivalent dose; Lent-Soma = late effects normal tissue task force-subjective, objective, management, analytic.

RESULTS: Median follow-up was 41 months (range, 23–71 months). Excellent 3-year local control, overall progression-free survival, and overall survival of 92.6%, 78.8%, and 77.7% were seen with the hybrid approach and 92.2%, 66.3%, and 69.6% with a 3-fraction conformal MRI approach, respectively. Dosimetry achieved and late toxicity rates were comparable in the two groups.
CONCLUSIONS: Hybrid IGBT in locally advanced cervical cancer offers an alternative approach when access to MRI restricts implementation of IGBT.

Advantages of a CBCT in Brachy Suite

- Intra-operative imaging
- Large mechanical clearance (scan in stirrups, make adjustments)
- Can be easily combined with other imaging modalities
- Minimize applicator/needles motion
- Ability to image and verify before treatment
- Can scan, plan and treat under anesthesia

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How to set meaningful clinical flows?

- Understand CBCT limitations
- Initially compare CBCT contours for OARs with other imaging modalities (CT, MRI)
- Compare dose metrics (D_{2cm^3}) for OARs between planning image and pre-TX image
  - CBCT volumes vs. CBCT volumes
  - MRI volumes vs. CBCT volumes
- > 75 fractions analyzed

Craciunescu et al, Brachytherapy 2016, S135

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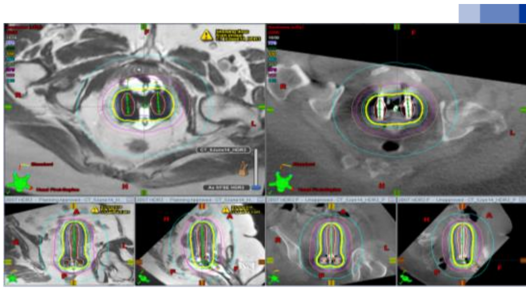

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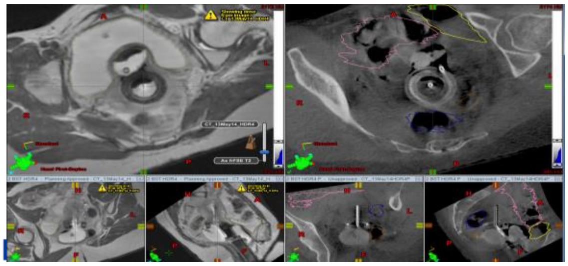
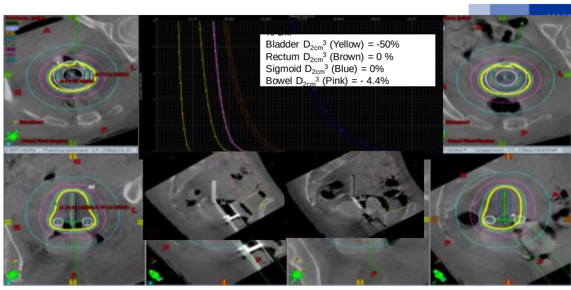
Good

Craciunescu et al, Brachytherapy 2016, S135

2) Different cont MRI and pre-TX CBCT





Actual changes in contours

What have we learned?

- Anatomical variations in OAR between planning and Pre-TX (3-4 hrs. later) can be large so imaging before TX is recommended
- Pre treatment kV-CBCTs can be used as a check of the applicator positioning
- Potential large variations between MRI and CBCT planning contours
  - Attention for when CBCT is used alone
- In some cases, the kV-CBCT can identify a true change in anatomy that might confer more realistic dose metrics for dose summation purposes.

Objectives

- Establish common terminology
  - HDR Intracavitary Brachytherapy
  - Current guidelines – GEC-ESTRO/ABS (pre ICRU 89)
- MRI imaging in IGBT
  - Insertion, planning, verification
  - Hybrid techniques: MRI/ CT/CBCT/US
  - Imaging for applicators design
  - Role in new ICRU 89

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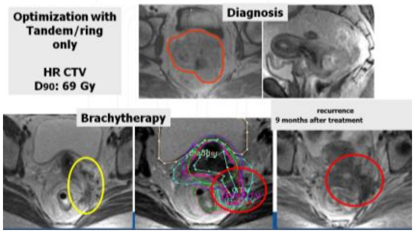
What has access to MRI given us?

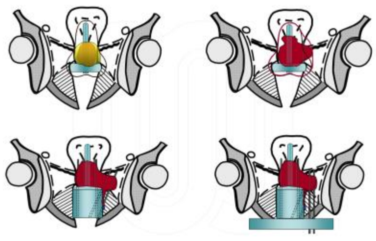
IIIB, 8 cm width, insufficient response (11/99)
no adaptation of application technique
intracavitary approach only



- Ability to clearly identify the target
- Realization that existent applicators are not optimal to cover the extent of the disease (intracavitary approach only)

Courtesy C. Kirisits, Vienna

What has access to MRI given us?



- GTVs->CTV
- Ambitious planning aims and dose–volume constraints
- New IC/IS techniques

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Courtesy C. Kirisits, ICRU 89

Vienna-style // Elekta and Varian

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Utrecht-style // Elekta

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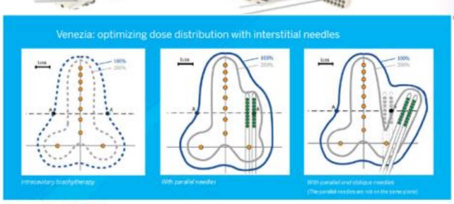
Venezia // Elekta

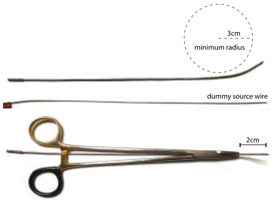


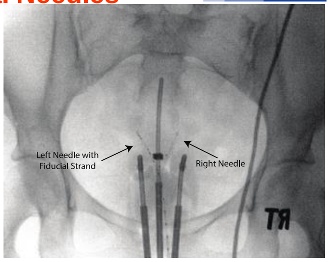
- IC/IS approach
- Hybrid between ring and ovoids

Adapted from Kirisits C et al

https://wavelength.elekta.com/2016/04/new-brachytherapy-applicator-expands-reach-of-gyn-cancer-treatment/

Free-hand Interstitial Needles





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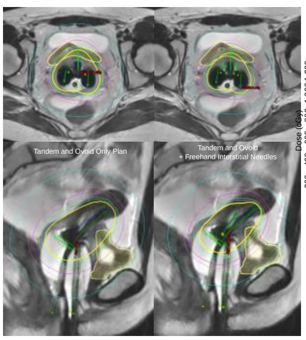
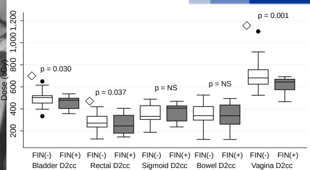
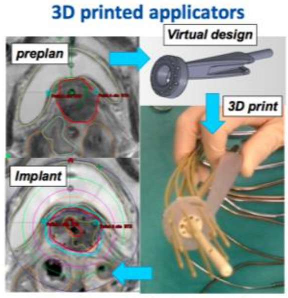
Olsen, Craciunescu et al., under review, 2016



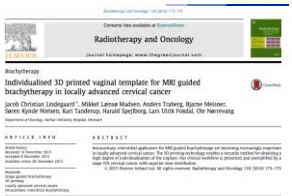


- Intracavitary and custom bent free-hand interstitial needles is associated with reduced dose to the rectum, bladder and vagina.

Olsen, Craciunescu et al., under review, 2016



Courtesy – J. Lindegaard, Aarhus & Lindegaad et al. Radiother Oncol 2016 in press


Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Brachytherapy

Individualised 3D printed vaginal template for MRI guided brachytherapy in locally advanced cervical cancer

Jacob Christian Lindegaard *, Mikkel Lænsø Madsen, Anders Traberg, Bjarne Meisner, Søren Kynde Nielsen, Kari Tanderup, Harald Spejlborg, Lars Ulrik Fokdal, Ole Nørrevang

ARTICLE INFO

ABSTRACT

EMBRACE II interventions

- Dose prescription (EBRT+BT):
  - Dose escalation in large tumours (HR-CTV vol > 40 cm3)
  - Dose de-escalation in small tumours (HR-CTV vol < 20 cm3)
  - OAR dose de-escalation as appropriate
  - Vaginal dose de-escalation in small and limited size tumors
- EBRT:
  - Application of IMRT + IGRT with reduced PTV margins (5 mm)
  - Application of risk adapted EBRT target volume
  - Focussed lymph node boosting

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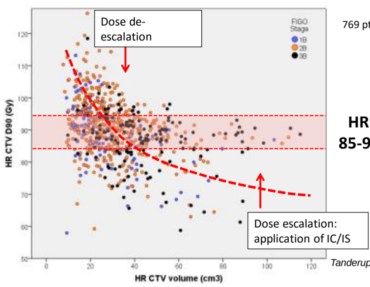
Courtesy C. Kirisits

EMBRACE II dose prescription



769 pts EMBRACE

HR CTV D90
85-95Gy EQD2

Tanderup, unpublished

Courtesy C. Kirisits

Objectives

- Establish common terminology
  - HDR Intracavitary Brachytherapy
  - Current guidelines – GEC-ESTRO/ABS (pre ICRU 89)
- MRI imaging in IGBT
  - Insertion, planning, verification
  - Hybrid techniques: MRI/ CT/CBCT/US
  - Imaging for applicators design
  - Role in new ICRU 89

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ICRU 89: https://www.aapm.org/pubs/ICRU/detail.asp?docid=79

Started in 2009 under the guidance of Potter and Kirisits

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Reporting

Concepts and terminology for
prescribing
recording and reporting

In a level concept:

- **Level 1 - *Minimum standard for reporting***
- **Level 2 - *Advanced standard for reporting***
- **Level 3 - *Research oriented reporting***

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Courtesy C. Kirisits

Need for common terminology according to ICRU reports on proton treatment and IMRT

- **Planning aim dose**
  → Set of dose and dose/volume constraints for a treatment
- **Prescribed dose**
  → Finally accepted treatment plan (which is assumed to be delivered to an individual patient)
- **Delivered dose**
  → Actually delivered dose to the individual patient

Chapter 8

Need for common terminology according to ICRU reports on proton treatment and IMRT

Example:

~~Previously: 4x7 Gy ~ 84 Gy EQD2 prescribed, D90 was mean 93 Gy~~

Planning aim was to deliver 4 x 7 Gy ~ 84 Gy, D_{2cm^3} for rectum, sigmoid < 70 Gy EQD2, bladder < 90 Gy EQD2

Prescribed dose was mean 93 Gy ± 13 Gy (1SD) EQD2 to D_{90} HR CTV

Delivered dose ? *Depending on variations and uncertainties – on average no systematic deviation from prescribed dose*

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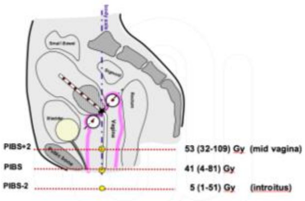
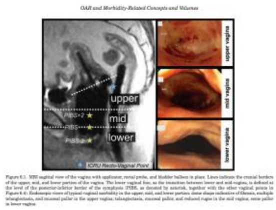
Courtesy C. Kirisits

Vaginal reference points





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Conclusions: Role of Imaging in Modern Brachytherapy

- Unprecedented target visualization (MRI)
  - New guidelines for gynecological brachytherapy (ICRU 89)
    - Traget delineation
    - Dose-volume metrics
  - New applicator design
- Design of new studies (Embrace II)
- Treatment response and prognosis via functional imaging

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Thank you!

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EMBRACE II - dose prescription protocol

	D90 CTV_{HR} $EQD2_{10}$	D98 CTV_{HR} $EQD2_{10}$	D98 GTV $EQD2_{10}$	D98 CTV_{IR} $EQD2_{10}$	Point A $EQD2_{10}$
Planning Aims	> 90 Gy < 95 Gy	> 75 Gy	>95 Gy	> 60 Gy	> 65 Gy
Limits for Prescribed Dose	> 85 Gy	-	>90 Gy	-	-

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Courtesy C. Kirisits

EMBRACE II - dose prescription protocol

	Bladder D_{2cm^3} $EQD2_3$	Rectum D_{2cm^3} $EQD2_3$	Recto-vaginal point $EQD2_3$	Sigmoid/ Bowel D_{2cm^3} $EQD2_3$
Planning Aims	< 80 Gy	< 65 Gy	< 65 Gy	< 70 Gy*
Limits for Prescribed Dose	< 90 Gy	< 75 Gy	< 75 Gy	< 75 Gy*

* for the sigmoid/bowel structures these dose constraints are valid in case of non-mobile bowel loops resulting in the situation that the most exposed volume is located at a similar part of the organ

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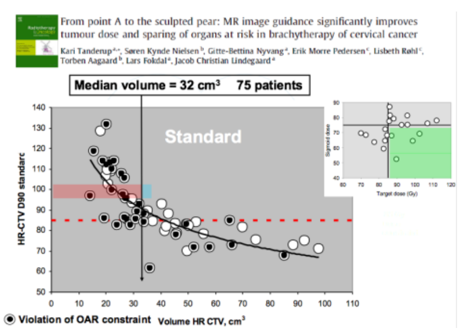
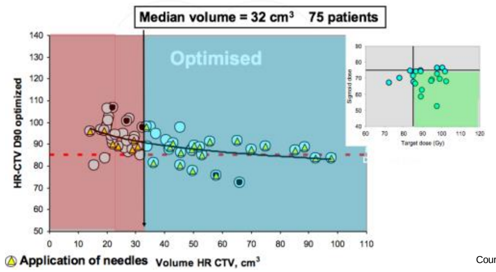


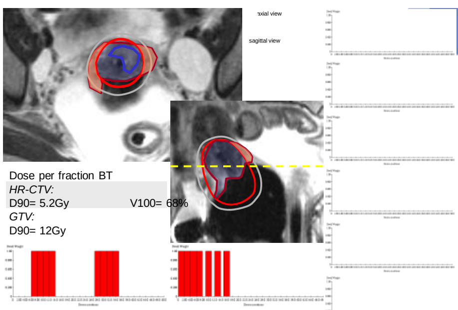
Courtesy C. Kirisits

From point A to the sculpted pear: MR image guidance significantly improves tumour dose and sparing of organs at risk in brachytherapy of cervical cancer

Kari Tanderup[a,*], Søren Kynde Nielsen[b], Gitte-Bettina Nyvang[a], Erik Morre Pedersen[c], Lisbeth Røhl[c], Torben Aagaard[b], Lars Fokdal[a], Jacob Christian Lindegaard[a]

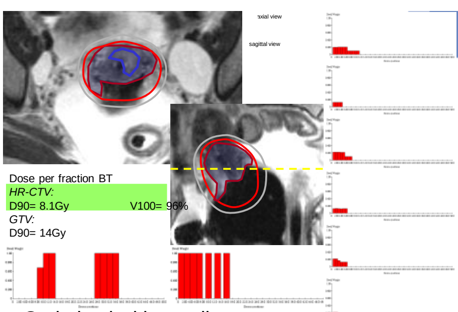


Courtesy C. Kirisits



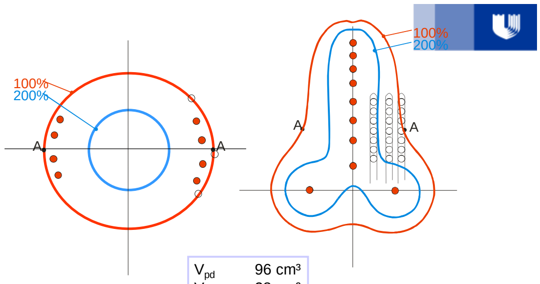
Standard without needles

Courtesy C. Kirisits



Optimized with needles

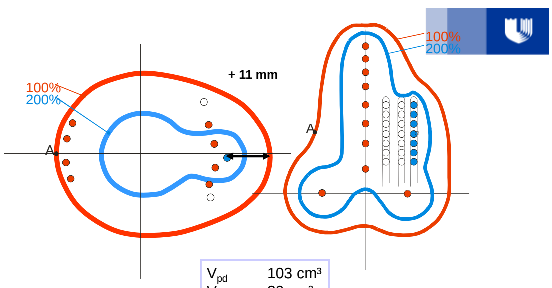
Courtesy C. Kirisits



V_{pd}	96 cm³
V_{2pd}	28 cm³

standard plan: prescribed dose to point A (left and right)
no needles

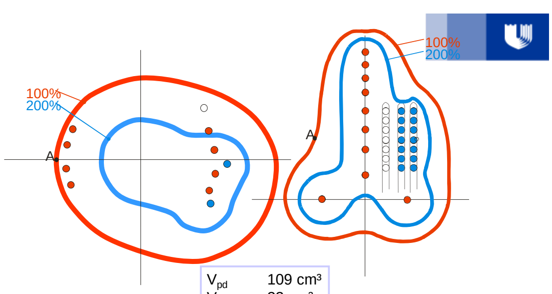
Courtesy C. Kirisits



V_{pd}	103 cm³
V_{2pd}	30 cm³

optimized plan: prescribed dose to point A (right)
1 needle loaded

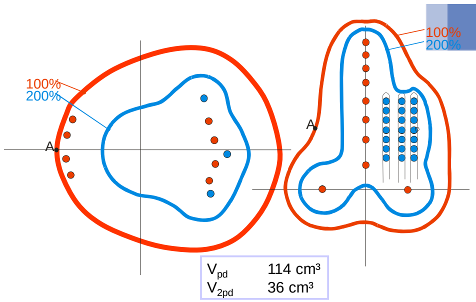
Courtesy C. Kirisits



V_{pd}	109 cm³
V_{2pd}	33 cm³

optimized plan: prescribed dose to point A (right)
2 needles loaded

Courtesy C. Kirisits



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Courtesy C. Kirisits

Objectives

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  - Insertion, planning, verification
  - Hybrid techniques: MRI/ CT/CBCT/US
  - Imaging for applicators design
  - Role in new ICRU 89
  - Functional imaging for response assessment

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FULL TEXT ARTICLE

Diffusion MR Imaging for Monitoring of Treatment Response

Anwar R. Padhani MBBS, FRCP, FRCR and Dow-Mu Koh MD, MRCP, FRCR

Magnetic Resonance Imaging Clinics of North America, 2011-02-01, Volume 19, Issue 1, Pages 181-209, Copyright © 2011 Elsevier Inc.

Functional imaging techniques are increasingly being used to monitor response to therapies, often predicting the success of therapy before conventional measurements are changed. This review focuses on magnetic resonance imaging (MRI) depicted water diffusivity as a tumor response parameter. Response assessments are undertaken by noting changes in signal intensity on high b-value images or by using measurements of apparent diffusion coefficient values. The different diffusion-weighted (DW)-MRI appearances in response to treatment of soft tissue disease and bone metastases are discussed. DW-MRI changes observed in response to cytotoxics, radiotherapy, antiangiogenics, embolization, and thermocoagulation are detailed.

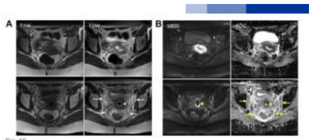

Fig. 10

Response of cervix carcinoma to chemoradiation. A 30-year-old woman undergoing examinations before and after chemoradiation for locally advanced squamous carcinoma of the cervix. (*A*) Anatomic T1- and T2-weighted images before (*top row*) and 6 months after therapy (*bottom row*). The tumor has responded well to therapy with a reduction in tumor size (*arrowhead*). There are new edematous changes in the pelvic fat and pelvic side walls (*arrows*) consistent with microvessel leakage and inflammation occurring after radiotherapy. Radiation-induced fatty marrow atrophy also appears. (*B*) Corresponding b800 and ADC images show a marked increase in ADC values in the cervical stroma and in the pelvic fatty tissues (*arrows*). However, persistent increases on high b-value images associated with decreased ADC values are seen at the edge of the excavated cervix tumor (*arrowhead*), raising the suspicion of residual active disease.

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Eur Radiol (2008) 18: 1058–1064
DOI 10.1007/s00330-007-0843-3

UROGENITAL

Diffusion-weighted MRI in cervical cancer

Patrick Z. McVeigh
Aejaz M. Syed
Michael Milosevic
Anthony Fyles
Masoom A. Haider

Received: 17 August 2007
Revised: 18 November 2007
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Published online: 12 January 2008

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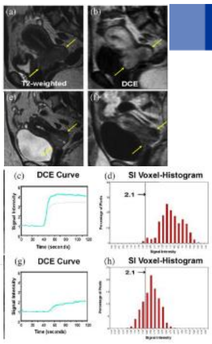
Abstract The purpose was to investigate the potential value of apparent diffusion coefficient (ADC) measurement with MRI in the assessment of cervix cancer. Diffusion-weighted MRI was performed in 47 patients with cervical carcinoma undergoing chemoradiation therapy and 26 normal controls on a 1.5-T system with a b-value of 600 s/mm^2. FIGO stage, tumor volume, nodal status, interstitial fluid pressure (IFP) and oxygen measurements were recorded. Response was defined as no visible tumor 3–6 months following completion of therapy. The average median ADC (mADC) of cervical carcinomas ($1.09 \pm 0.20 \times 10^{-3}$ mm^2/s) was significantly lower than normal cervix ($2.09 \pm 0.46 \times 10^{-3}$ mm^2/s) ($P<0.001$). There was no correlation between mADC, nodal status, tumor volume, IFP or oxygen measurements. mADC was significantly lower in FIGO stages T1b/T2a (0.986×10^{-3} mm^2/s) compared to T2b (1.21×10^{-3} mm^2/s) and T3/T4 (1.10×10^{-3} mm^2/s) ($P<0.001$). In patients with squamous carcinomas the 90th percentile of ADC values was lower in responders than non-responders ($P<0.05$). Median ADC in cervix carcinoma is significantly lower compared to normal cervix. ADC may have predictive value in squamous tumors, but further long-term study will determine the ultimate clinical utility.

Keywords Apparent diffusion coefficient · Magnetic resonance · Cervical cancer · Cervix · Uterus



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BOLD Imaging

Blood oxygenation level-dependent MR imaging as a predictor of therapeutic response to concurrent chemoradiotherapy in cervical cancer: a preliminary experience

Chan Kyo Kim · Sung Yoon Park · Byung Kwan Park · Won Park · Seung Jae Huh

Received: 24 December 2013 /Revised: 13 March 2014 /Accepted: 28 March 2014 /Published online: 25 April 2014

Abstract
Objectives To investigate the value of blood oxygenation level-dependent (BOLD) magnetic resonance imaging (MRI) as a predictor of therapeutic response in cervical cancer patients undergoing concurrent chemoradiotherapy (CCRT).
Methods Thirty consecutive patients with biopsy-proven cervical cancer were examined by BOLD MRI before (preTx) and after CCRT (postTx). The R2* value (s^{-1}) was calculated in the tumour and normal myometrium for preTx and postTx studies. Final tumour responses, as determined by changes of tumour size or volume on MRI, were correlated with tumour R2* values at preTx.
Results The mean R2* values of tumours at preTx (21.1) were significantly lower than those at postTx (39.4 s^{-1}) ($p<0.001$), while those of normal myometrium were similar between preTx and postTx ($p=0.363$). At preTx, tumour R2* values showed significantly negative correlation with final tumour size response ($p=0.022$, Spearman's coefficient=-0.415). However, tumour R2* values at preTx were not associated with final tumour volume response ($p=0.069$).
Conclusions BOLD MRI at 3 T, as an imaging biomarker, may have the potential to evaluate therapeutic response in cervical cancers. The association between BOLD MRI findings and CCRT responses warrants further validation.
Key points
• *Hypoxia in cervical cancer is an independent risk factor*
• *BOLD MRI reflect oxygenation status of tissue adjacent to perfused microvessels*
• *Pretreatment tumour R2* reveal negative correlation with final tumour size response*
• *Accurate oxygenation assessment in cervical cancer may help clinical decision making*

Keywords Cervical cancer · MRI · Concurrent chemoradiotherapy · Blood oxygenation level-dependent MRI · Biomarker

Abbreviations

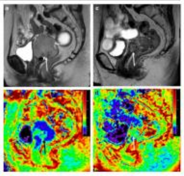
BOLD	Blood oxygenation-level dependent
CCRT	Concurrent chemoradiotherapy
DCE	Dynamic contrast enhanced
PreTx	Before treatment
PostTx	Post treatment
mFFE	Multiple fast field echo
SCC	Squamous cell carcinoma
FIGO	Federation of International Gynecology and Obstetrics
LN	Lymph node
EBRT	External beam radiotherapy
ICR	Intracavitary brachytherapy

Table 2 R2* value of tumours and normal myometrium, and the size and volume of tumours at preTx and postTx

	PreTx	PostTx
Tumour R2*	21.1±6.7 (18.7−23.5)	39.4±8.6 (16.2−42.7)
Normal myometrium R2*	24.9±3.7 (23.5−26.3)	24.1±2.8 (23.0−25.2)
Tumour volume (cm^3)	52.1±39.7 (37.3−66.9)	2.0±3.6 (0.7−3.3)
Tumour size (cm)	5.6±1.6 (5.0−6.2)	1.6±1.2 (1.2−2.0)

Data are the mean ± standard deviation (95 % confidence interval)

PreTx before treatment, *PostTx* 1 month after the completion of treatment



MS-MRI: Improve visualization of target, OARs, applicators

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Clinical implementation of multisequence MRI-based adaptive intracavitary brachytherapy for cervix cancer

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C. Treatment planning

T2W images, PDW images, and ADC maps were transferred to a radiation therapy treatment planning system (BrachyVision TPS, Varian Medical Systems, Inc., Palo Alto, CA) for contouring and isodose planning. Because the images were acquired in the same imaging session, the datasets upon import into the TPS were automatically registered based on their shared frame of reference and then manually verified using the applicator and surrounding anatomy. T2W images were utilized for contouring of OARs (i.e., bladder, rectum, and sigmoid). Point A was defined relative to the applicator using the classical definition on the T2W images.[7] The delineation of the GTV, defined as the primary cervical gross tumor volume, was generally carried out on the T2W images, then verified against the registered ADC map and, if necessary, adjusted to improve agreement. The PDW images were used for reconstruction of the intrauterine tandem and the vaginal colpostats using the signal void resulting from the titanium applicator.[22] Forward treatment planning was performed using standard source distribution rules with a dose of 6.5 Gy/fraction normalized to Point A.

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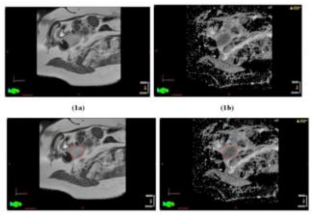
GTV contouring- T2W and ADC map

125 Zoberi et al.: MRI-based adaptive intracavitary brachytherapy 125



(1a) (1b) (1c) (1d)

FIG. 1. A parasagittal slice in the T2W image dataset (a) and the corresponding slice in the ADC map (b) about 1.5 cm lateral to the tandem for Patient 1. The same slices in the T2W image dataset (c) and ADC map (d) displayed with the contour for GTV (in red). Organ-at-risk contours for bladder (yellow) and sigmoid (light green) are displayed on the T2W images (a) and (c).

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Applicator Identification-PDW-MRI

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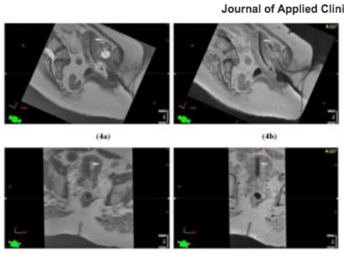

(4a) (4b) (4c) (4d)

FIG. 4. A parasagittal slice displaying the tandem (as indicated by the arrow) relative to the surrounding anatomy in the T2W-MRI (a) and in the corresponding slice in the PDW-MRI (b) for Patient 3. For the same dataset, a paracoronal slice displaying the tandem (as indicated by the arrow) in the T2W-MRI (c) and in the corresponding slice in the PDW-MRI (d).

Plan Adaptation

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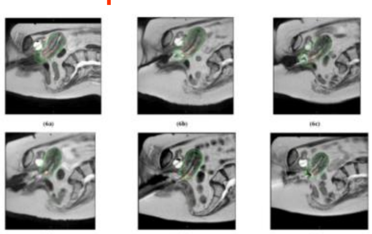
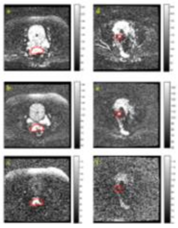


FIG. 6. Parasagittal slices from T2W datasets for fractions 1–6 ((a)-(f)) for Patient 3, displaying the prescription isodose (in green) relative to the shrinking tumor volume (in red) and OARs (bladder in yellow, rectum in brown, and sigmoid in light green). Ovoids were implanted for first 5 fractions, but not activated for fractions 4–5. No ovoids were implanted for the last fraction.

Multisequence MRI technique: 1) improved visualization of the target volume, critical structures, and applicator.
2) implementation of the dose tracking tools and dose adaptation technique by simply de-escalating Point A-based brachytherapy dose distributions will help balance target volume coverage with OAR sparing, without the need for more complex adaptation schemes.

MS-MRI: For TX response assessment using texture features



DWI-MRI acquired before EBRT treatment: (a) b = 0 s/mm² (b) b = 500 s/mm² (c) b = 1000 s/mm²;
DWI-MRI acquired before 5th HDR treatment: (d) b = 0 s/mm² (e) b = 500 s/mm² (f) b = 1000 s/mm²

- 12 patients with GYN cancer received external beam radiotherapy (EBRT) treatment followed by 5 fractions of high-dose-rate (HDR) brachytherapy
  - EBRT treatment (1.8Gy/fx, total dose of 45 Gy)
  - HDR treatment (5.5 Gy/fx, total dose 27.5 Gy)

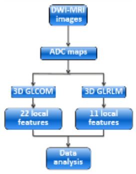
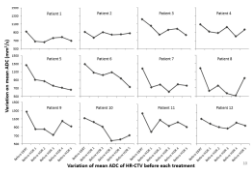


Table 1. ADC mean value relative changes of gynecological cancer patients

before 1st fx of HDR / before EBRT		before 5th fx of HDR / before 1st fx of HDR		before 5th fx of HDR / before EBRT	
Relative change	p value	Relative change	p value	Relative change	p value
0.766±0.132	0.002*	0.991±0.243	0.814	0.735±0.136	0.002*

"*" indicates statistical changes after radiotherapy



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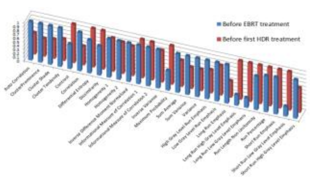
MS-MRI: For TX response assessment using texture features



Significantly changed texture features of ADC maps

- For ADC maps calculated from DWI-MRI
  - After EBRT treatment, 28 out of 33 HR-CTV features significantly changed
  - After HDR treatment (before 5th fx of HDR / before 1st fx of HDR), same 28 out of 33 HR-CTV features significantly changed
  - For the whole treatment process, same 28 out of 33 HR-CTV features significantly changed

- Texture features with significantly numerical changes can be used in monitoring radiotherapy effect in gynecological cancer
- Texture features might be used as biomarkers which are supplementary to ADC for assessment of radiotherapy response in gynecological cancer.

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