

## DICHIARAZIONE

Relatore: Andrea Vavassori

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Altro

XXV CONGRESSO NAZIONALE  
**AIRO 2015**

PALACONGRESSI - Rimini, 7-10 novembre



## **SIMPOSIO AIRO-AIOM**

***Trattamento multimodale del carcinoma vescicale***

# ***Ottimizzazione radioterapica: volumi, dosi e tecniche***



**A.Vavassori**

***Divisione Radioterapia - Unità Brachiterapia***

**Istituto Europeo di Oncologia - Milano**



**Rimini 09/11/2015**

# Introduction

Accurately irradiating the bladder while minimizing the dose to surrounding normal tissues is made technically difficult by *day-to-day variations* in bladder *size, shape, and position*



# Introduction

Recent advances in:

- imaging (CT, MR, PET)
- computerized CT planning
- conformal radiotherapy delivery
- on-treatment verification



- allow appropriate patient selection
- improve accuracy of treatment delivery
- reduce irradiation of adjacent normal tissues

# Simulation

Patient supine with a knee support



**Bladder:** emptied immediately before scanning and treatment, to reduce the volume irradiated

**Rectum:** emptied to reduce organ motion

*Partially distended bladder* may be helpful to limit dose to the entire bladder, rectum and bowel

# Target delineation

- bladder maps (cystoscopy)
- operation notes
- histology reports
- imaging



Caution is required in interpreting images obtained soon after TURB or deep muscle biopsies due to the presence of **edema** and **hemorrhage** which may mimic tumor

# Target delineation

## GTV:

- the primary bladder tumor
- any extravesical spread

## CTV:

- the whole bladder
- the proximal urethra
- any microscopic spread
- the pelvic lymph nodes (if indicated)

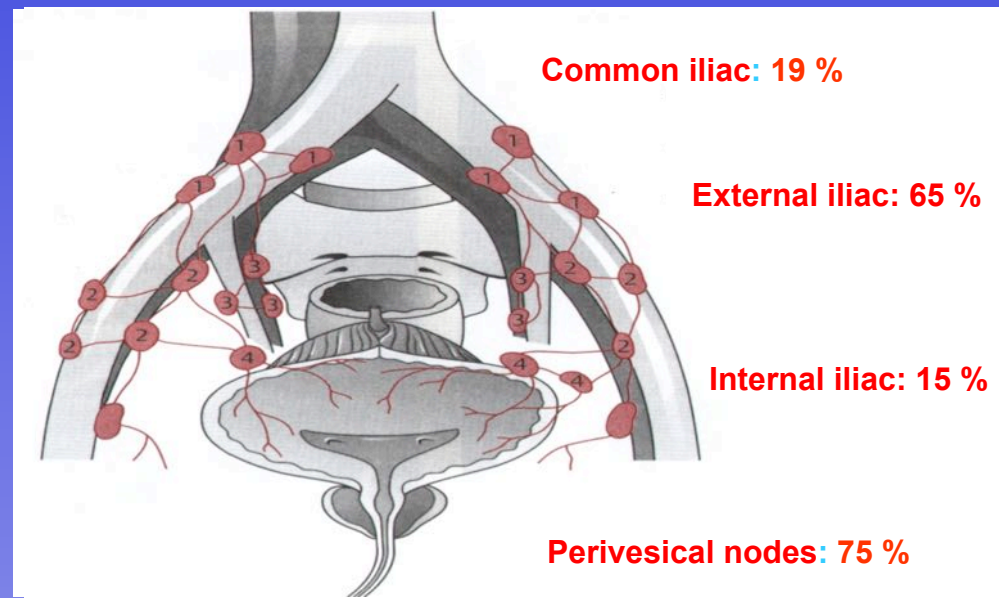


# Lymphatic drainage & therapeutic planning

Omission of regional node irradiation is justified in cN0

The majority of potential involved regional lymph nodes are included even in relatively small fields

CT+RT





# Partial bladder treatment

- lower dose to the whole bladder
- boost (full dose) to the bladder tumor alone

May be considered:

- unifocal tumors
- in elderly patients
- for palliative irradiation



# Partial bladder treatment

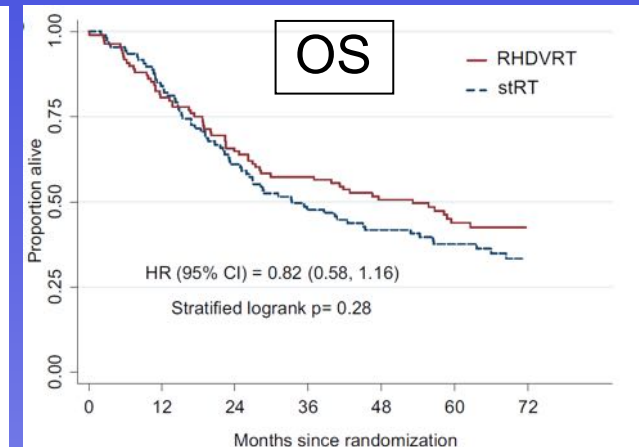
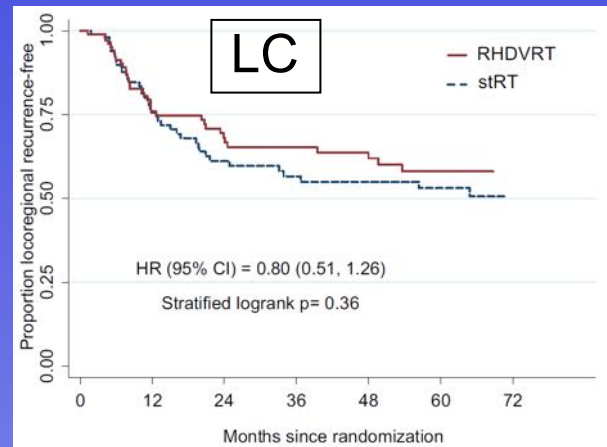
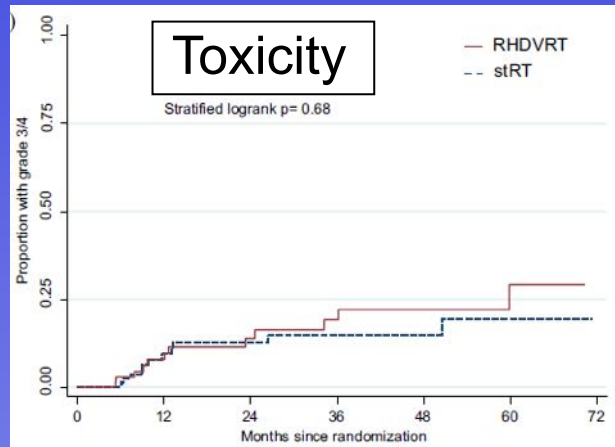
Randomized Noninferiority Trial of Reduced High-Dose Volume Versus Standard Volume Radiation Therapy for Muscle-Invasive Bladder Cancer: Results of the BC2001 Trial (CRUK/01/004)

IJROBP 2013

## BC2001

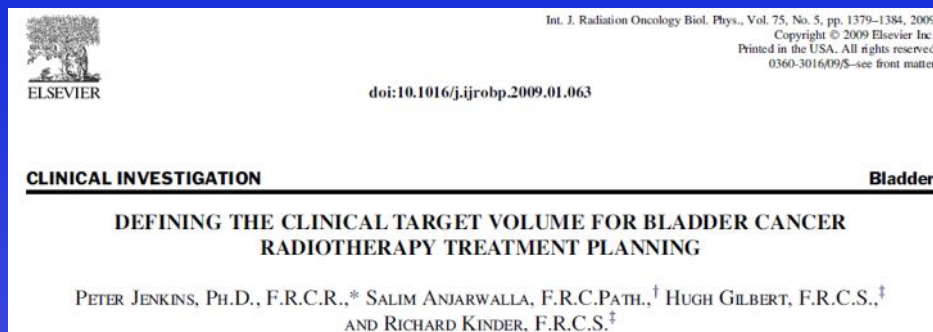
Robert A. Huddart, PhD,<sup>\*,†</sup> Emma Hall, PhD,<sup>\*</sup> Syed A. Hussain, MD,<sup>‡</sup>

- full bladder irradiation = PTV1 100% (55 Gy/20, 64 Gy/32)
- partial bladder irradiation = PTV1 80% + PTV2 20%



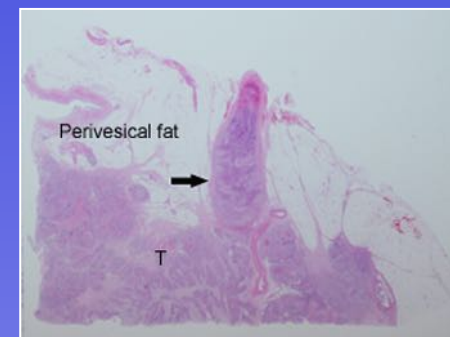
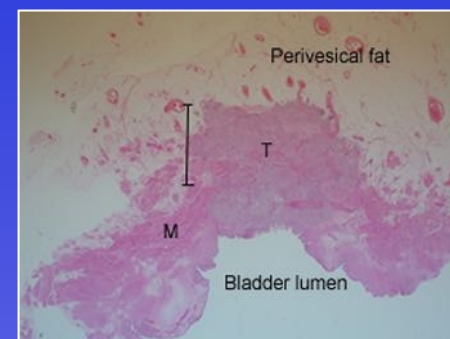
Not all regions of the bladder require the same dose

# Extra-Vesical tumor Extension (EVE)



EVE is more extensive in patients with:

- LVI
- squamoid differentiation
- tumors > 3.5 cm



***Larger CTV expansions may be required !***

# CTV → PTV

Accepted standard practice has been to add **isotropic margins of 1.5 to 3 cm** uniformly around the bladder or bladder tumor

These margins are intended to allow for:

- organ motion
- errors in target delineation
- daily treatment set-up

Meijer, IJROBP 2003

Muren, RO 2003

Pos, IJROBP 2006

Lotz, IJROBP 2006

Muren, RO 2007

# Organ motion / deformation

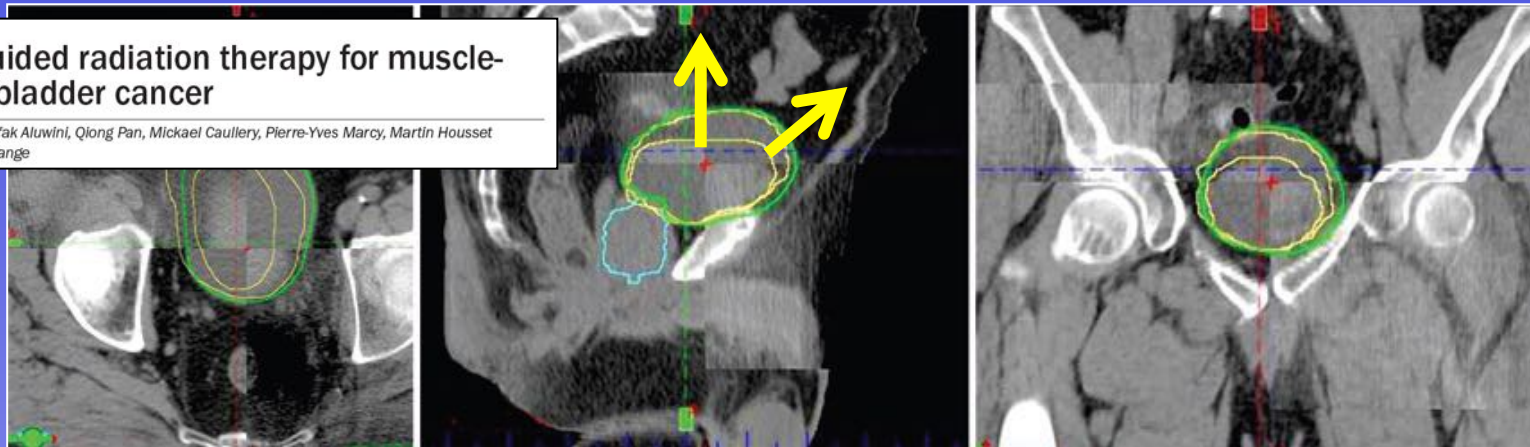
An increase of 50 cc can lead to local bladder wall displacements of up to 1 cm

Lotz, Med Phys 2005

The dominant movement is primarily in the superior direction, and secondarily in the anterior direction

## Image-guided radiation therapy for muscle-invasive bladder cancer

Juliette Thariat, Shafak Aluwini, Qiong Pan, Mickael Caullery, Pierre-Yves Marcy, Martin Housset and Jean-Leon Lagrange



Fused cone-beam CT image performed before and after RT

# Set-up errors

Clinical Oncology 24 (2012) 673–681

Contents lists available at SciVerse ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

Bladder Cancer Radiotherapy Margins: A Comparison of Daily Alignment using Skin, Bone or Soft Tissue

F. Foroudi \*, D. Pham †, M. Bressel \*, J. Wong †, A. Rolfo †, P. Roxby ‡, T. Kron ‡

Skin

	CTV + 0.5	CTV + 1	CTV + 1.5	CTV + 2	CTV + 2.5
Superior	41% [22–61%]	59% [39–78%]	81% [62–94%]	96% [81–100%]	96% [81–100%]
Inferior	37% [19–58%]	74% [54–89%]	96% [81–100%]	100% [87–100%]	100% [87–100%]
Left	48% [29–68%]	81% [62–94%]	100% [87–100%]	100% [87–100%]	100% [87–100%]
Right	70% [50–86%]	93% [76–99%]	100% [87–100%]	100% [87–100%]	100% [87–100%]
Anterior	37% [19–58%]	63% [42–81%]	78% [58–91%]	93% [76–99%]	96% [81–100%]
Posterior	33% [17–54%]	70% [50–86%]	93% [76–99%]	100% [87–100%]	100% [87–100%]
Total	0% [0–13%]	19% [6–38%]	56% [35–75%]	93% [76–99%]	96% [81–100%]

Bone

	CTV + 0.5	CTV + 1	CTV + 1.5	CTV + 2	CTV + 2.5
Superior	37% [19–58%]	70% [50–86%]	93% [76–99%]	96% [81–100%]	96% [81–100%]
Inferior	30% [14–50%]	85% [66–96%]	93% [76–99%]	100% [87–100%]	100% [87–100%]
Left	78% [58–91%]	100% [87–100%]	100% [87–100%]	100% [87–100%]	100% [87–100%]
Right	81% [62–94%]	100% [87–100%]	100% [87–100%]	100% [87–100%]	100% [87–100%]
Anterior	37% [19–58%]	63% [42–81%]	81% [62–94%]	93% [76–99%]	96% [81–100%]
Posterior	52% [32–71%]	81% [62–94%]	93% [76–99%]	96% [81–100%]	100% [87–100%]
Total	0% [0–13%]	41% [22–61%]	63% [42–81%]	89% [71–98%]	96% [81–100%]

Soft tissue

	CTV + 0.5	CTV + 1	CTV + 1.5	CTV + 2	CTV + 2.5
Superior	63% [42–81%]	96% [81–100%]	96% [81–100%]	100% [87–100%]	100% [87–100%]
Inferior	63% [42–81%]	96% [81–100%]	96% [81–100%]	100% [87–100%]	100% [87–100%]
Left	89% [71–98%]	100% [87–100%]	100% [87–100%]	100% [87–100%]	100% [87–100%]
Right	89% [71–98%]	100% [87–100%]	100% [87–100%]	100% [87–100%]	100% [87–100%]
Anterior	70% [50–86%]	89% [71–98%]	96% [81–100%]	100% [87–100%]	100% [87–100%]
Posterior	70% [50–86%]	89% [71–98%]	96% [81–100%]	100% [87–100%]	100% [87–100%]
Total	52% [32–71%]	89% [71–98%]	96% [81–100%]	100% [87–100%]	100% [87–100%]

A margin of 1.0 - 1.5 cm can be used when there is daily soft tissue matching, whereas a margin of 2 cm should be used with skin- or bone-based landmarks

# Treatment margins

Different magnitude of errors for different regions of the bladder

Anisotropic margins should be used

Table 1 CTV to PTV Margin Widths Suggested by Meijer et al<sup>30</sup>

	Without Correction Protocol (cm)	With Correction Protocol (cm)
Cranial	2.0	2.0
Caudal	1.2	1.0
Left	1.0	0.7
Right	1.0	0.7
Anterior	1.0	0.7
Posterior	1.4	1.3

Meijer 2003

# Assessment of bladder movement





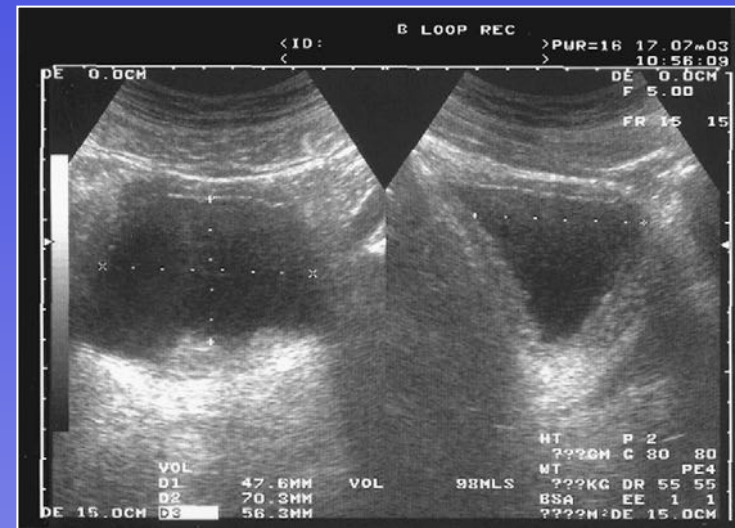
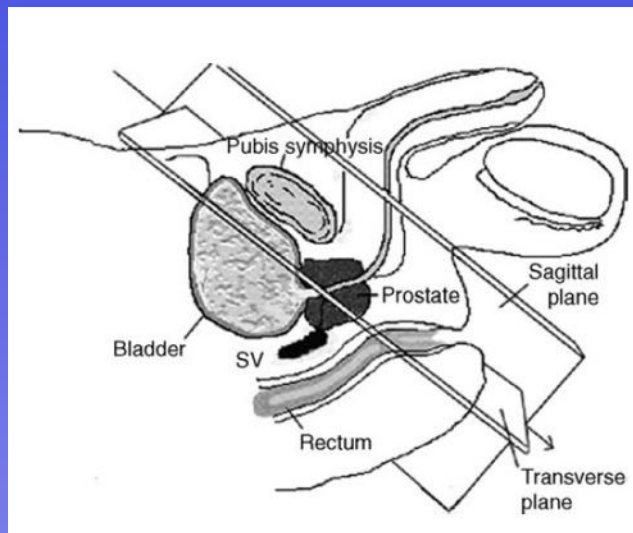
# IGRT: US

## Ultrasound Imaging to Assess Inter- and Intra-fraction Motion during Bladder Radiotherapy and its Potential as a Verification Tool

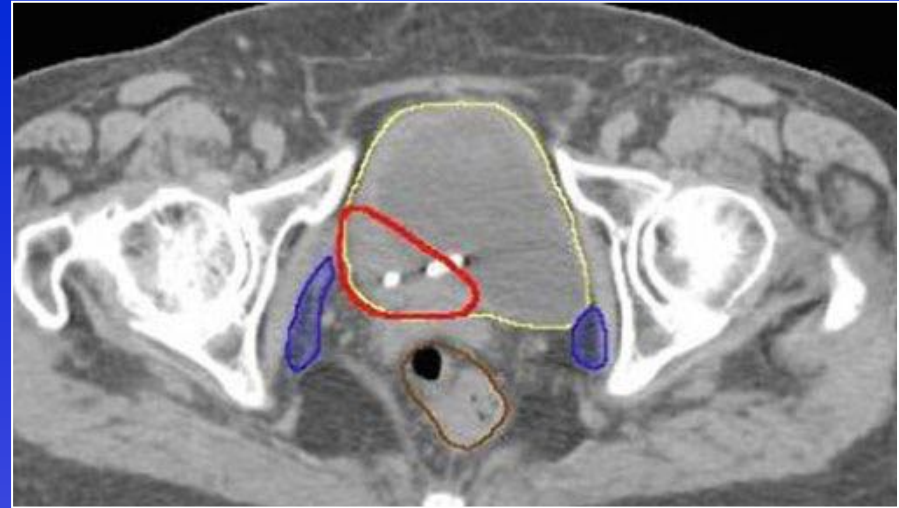
C. A. McBain\*, M. M. Green\*, J. Stratford†, J. Davies†, C. McCarthy†, B. Taylor‡, D. McHugh§, R. Swindell¶, V. Khoo\*, P. Price\*

*Clinical Oncology* (2009) 21: 385–393

- before treatment
- identify patients who are unable to void bladder



# Fiducial markers

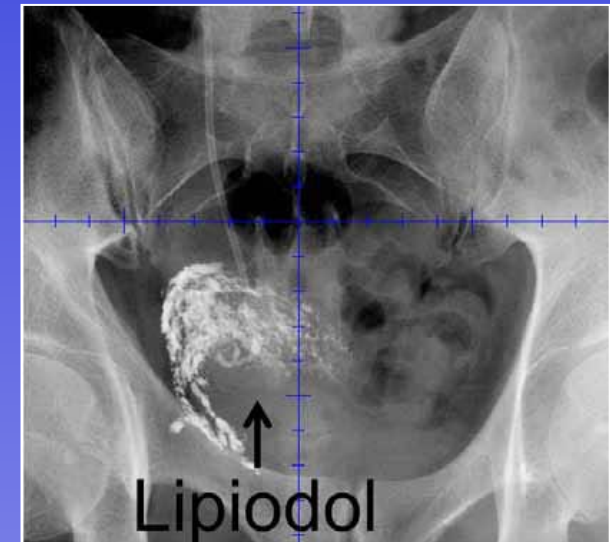
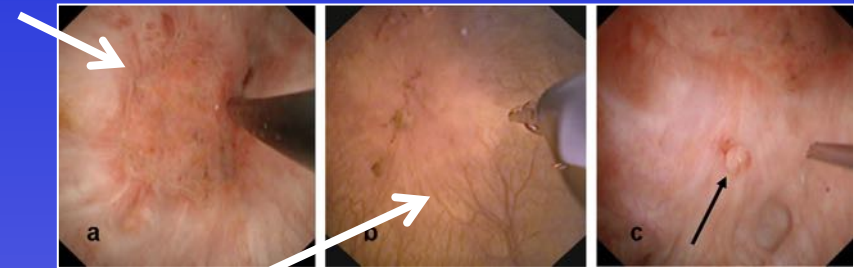


- Rigid cystoscope
- It can be difficult to reach the lower hemisphere
- Loss of fiducial markers: 50% @ 11.5 days

Hulshof, Br J Radiol 2007  
Mangar, Radiother Oncol 2007

# LIPIODOL

- Immediately following maximal TURB
- Flexible cystoscope
- 2-3 mm from the resection margin
- 0.5 ml per injection / 20-30 injections
- High retention rate  
(loss of 24% in Lipiodol volumes @ 6 weeks)



# LIPIODOL

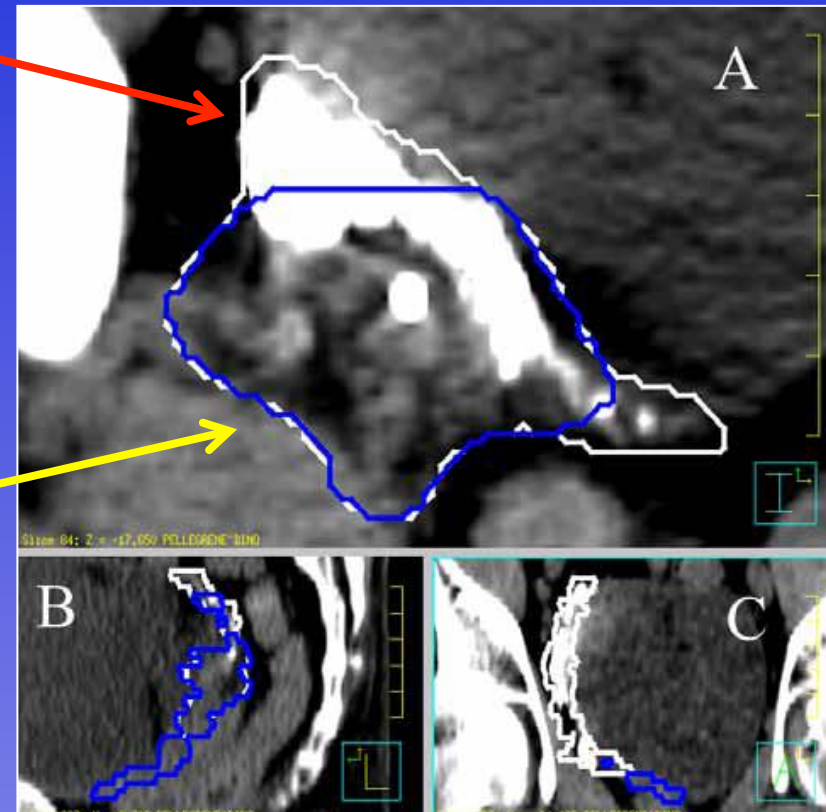
## Lipiodol as a Fiducial Marker for Image-Guided Radiation Therapy for Bladder Cancer

Int Braz J Urol. 2014; 40: 190-7

Jessica M. Freilich, Philippe E. Spiess, Matthew C. Biagioli, Daniel C. Fernandez, Ellen J. Shi, Dylan C. Hunt, Shilpa Gupta, Richard B. Wilder

Tumor bed with Lipiodol

Tumor bed based upon cystoscopy & CT



# In-room soft tissue imaging & adaptive RT

The use of high quality images acquired during or just prior to treatment delivery for modification of plans

- **offline ART**: a single adaptive treatment plan is generated using various repeated CT or CBCT over the first fractions (to account for the inaccuracies observed)
- **online ART**: the daily treatment plan is chosen from a library of pre-planned treatment plans based on CBCT

# Adaptive RT

CLINICAL INVESTIGATION

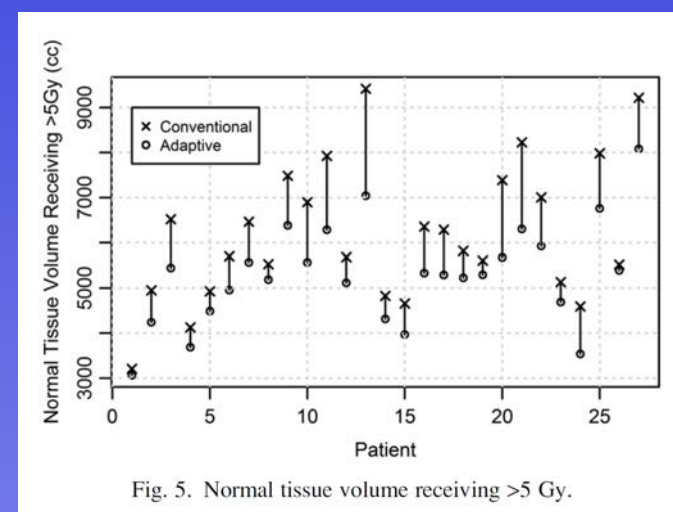
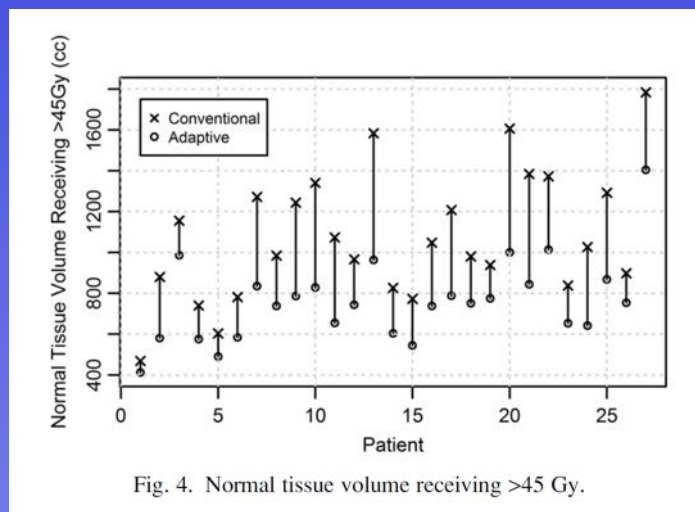
Bladder

## ONLINE ADAPTIVE RADIOTHERAPY FOR MUSCLE-INVASIVE BLADDER CANCER: RESULTS OF A PILOT STUDY

FARSHAD FOROUDI, M.B., B.S., M.P.A., F.R.A.N.Z.C.R.,\* JACKY WONG, M.Sc., R.T.T.,†

IJROBP 2011

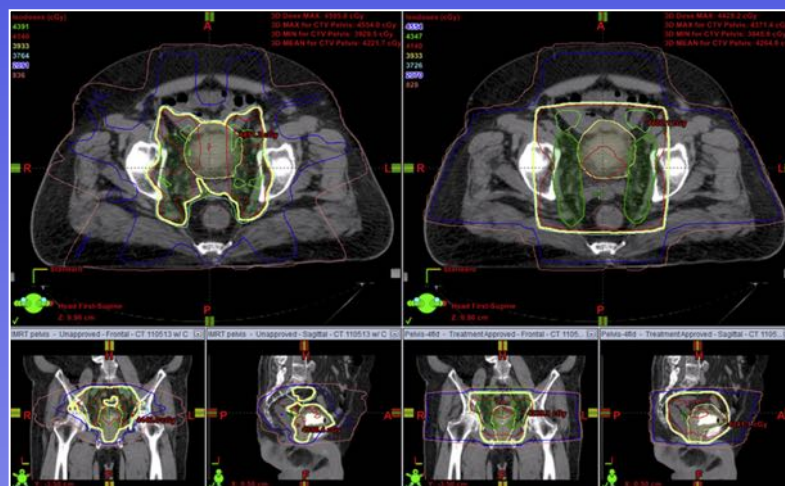
The use of an adaptive technique significantly reduces the volume of normal tissue irradiated



Mean volume receiving >45 Gy was 29% less in ART

# IMRT: PRO

- allow partial bladder irradiation
- allow the delivery of a synchronous boost
- permit dose escalation to the tumor
- can reduce the dose to normal tissues



# IMRT: CONTRA

- requires excellent immobilisation
- requires increased time (risk of bladder filling and changes in bladder shape and size)





# IMRT & integral dose



- IMRT increases the MU demand compared to 3D-CRT
- The dose from CBCT was of 3 cGy in the imaged volume
- The reduction in margin and choice of best plan of the day resulted in a lower total dose in most patients despite daily volumetric imaging

The effect on secondary cancer induction is small

	#	Simulationimaging	Total dose	Whole bladder dose	Partial bladder dose	Fraction size (Gy)	Fraction #	EQD2 (Gy)
Duncan and Quilty (1986) <sup>a</sup>	889	2D	55–57.5	55–57.5	–	2.75–2.88	20	60.2–63.8
Moonen et al. (1997) <sup>a</sup>	15	3D	66	66	–	2	Last 8 BID	66
	25	–	66	66	–	2	Last 13 BID	–
Rodel et al. (2002) <sup>a</sup>	186 <sup>a</sup>	2D	45–69.4	45–69.4	–	1.8–2	25–33	45–69.4
Scholten et al. (1997) <sup>a</sup>	123	2D	36	36	–	6	6 (2×/week)	54
Mameghan et al. (1992) <sup>a</sup>	330	2D	65	45–65	–	1.8–2.5	25–30	43.9–69
Perdona et al. (2008) <sup>a,b</sup>								4
Mangar et al. (2006) <sup>a</sup>								64
(C D)	75	–	60–64	48–52	12	2	24–26	52/60–64
Cowan et al. (2004) <sup>a,d</sup>	25	3D	52.5	52	–	2.63	20	56.3
(P B)	22	–	57.5	–	57.5	2.88	20	56.3–63.8
(P B)	16	–	55	–	55	3.44	16	57.1–64.9
Yavuz et al. (2003) (CD)	87	3D	45/67.5	45	22.5	1.8/1.5 CB	35	43.9–65
Pos et al. (2003)	47	3D	55	55	–	2/2.75 CB	20	40/55
(C D)		–	40	40	15	–	–	–
Efstathiou et al. (2009) (C D)	157	2D	64–65	52–55	12–15	1.8/1.5–1.8	36–42	60.9–62.2

# FRACTIONATION

# Dose & fractionation

## Conventional:

60 - 66 Gy in 30 - 33 fractions

## Hypo-fractionation:

52.5 - 55 Gy in 20 fractions (2.75 Gy)

30 - 36 Gy in 5-6 fractions (6 Gy)

## Accelerated hyper-fractionation:

whole pelvis = 45 Gy (1.8 Gy x 25)

boost = 22.5 Gy (second daily fraction, 1.5 Gy x 15)

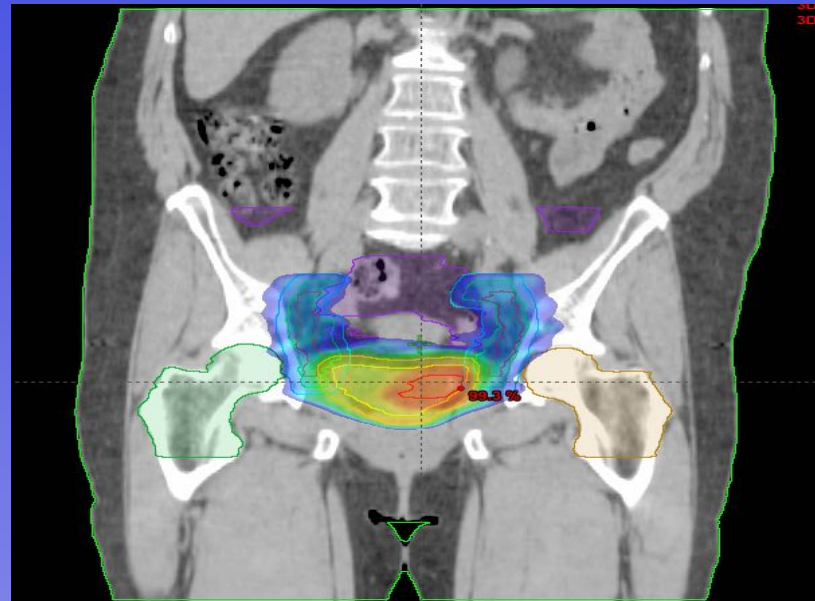
# Rete Oncologica Lombarda

## SIB

Pelvis: 51.2 – 54.4 Gy (1.6 – 1.7 Gy x 32)

Whole bladder: 57.6 – 60.8 Gy (1.8 – 1.9 Gy x 32)

Tumor bed: 64 Gy (2 Gy x 32)



# Brachytherapy

Inclusion criteria are:

- stage pT1–T3, N0, M0
- unifocal carcinoma
- size  $\leq 5$  cm diameter
- not in the trigone or bladder neck (not easily accessible)

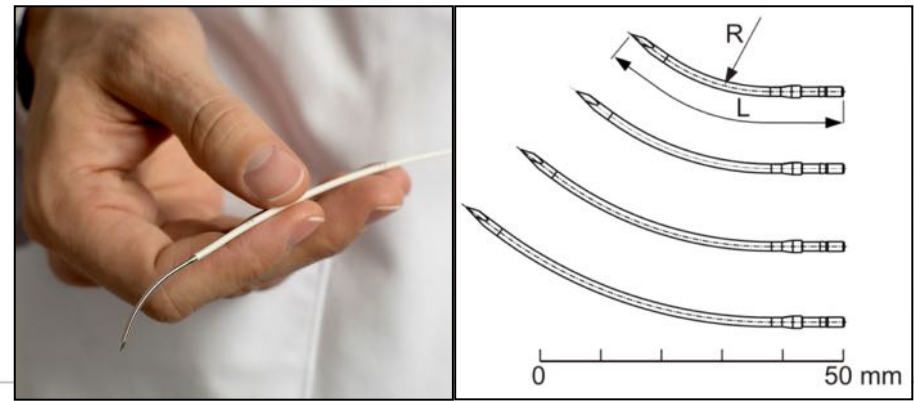
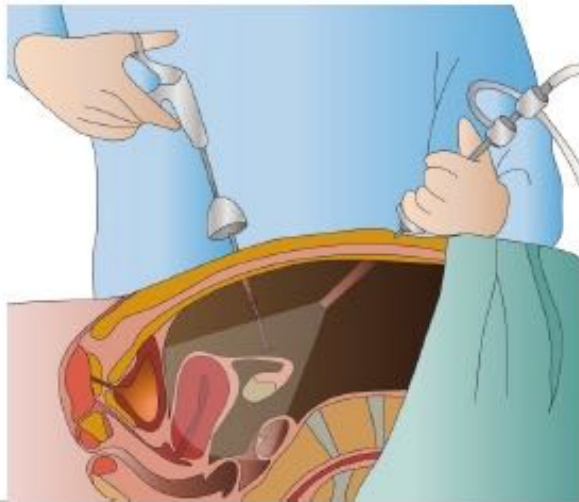
2-4 flexible catheters

Open or laparoscopic surgery

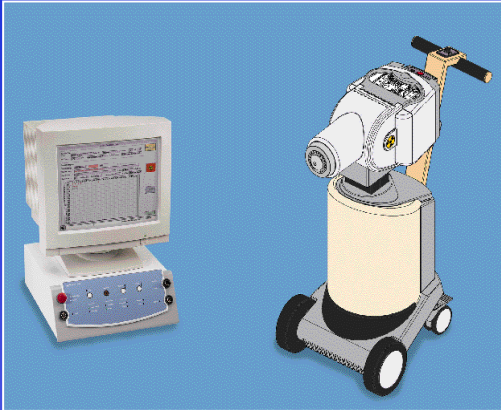


# Brachytherapy

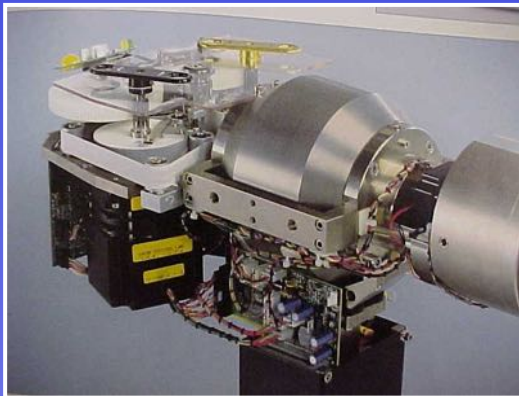
- Minimally invasive laparoscopic brachytherapy procedures
  - Robotic-assisted laparoscopic surgery
  - Conventional laparoscopic surgery



# Brachytherapy



- TURB
- EBRT 30-40 Gy to the pelvis
- Surgical exploration and implantation
- BT: 25 - 40 Gy (HDR or PDR)



# Brachytherapy

Combination therapy of EBRT and BT shows equivalent patient outcome results compared to cystectomy

Radiotherapy and Oncology 93 (2009) 352–357

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: [www.thegreenjournal.com](http://www.thegreenjournal.com)

Bladder cancer radiotherapy

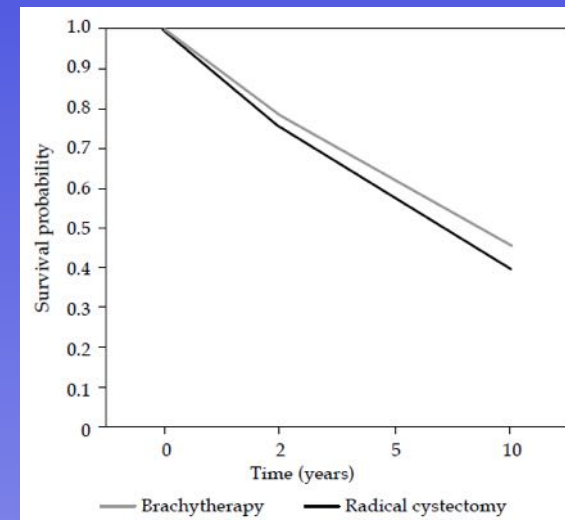
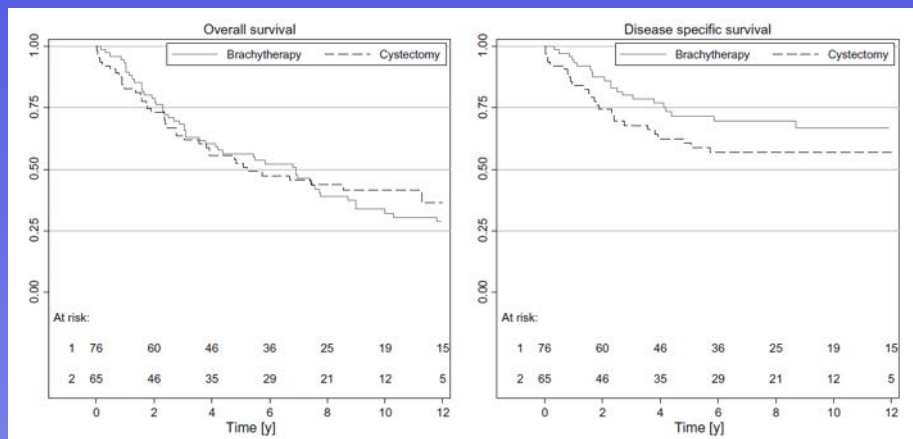
Brachytherapy versus cystectomy in solitary bladder cancer: A case control, multicentre, East-Netherlands study

Elzbieta van der Steen-Banasik<sup>a,\*</sup>, Martine Ploeg<sup>b</sup>, Johannes A. Witjes<sup>b</sup>

Bladder preservation with brachytherapy compared to cystectomy for T1-T3 muscle-invasive bladder cancer: a systematic review

Manouk K. Bos, Rafael Ordoñez Marmolejo, MD, Coen R.N. Rasch, MD, PhD, Bradley R. Pieters, MD, PhD

J Contemp Brachytherapy 2014; 6, 2: 191-199





# Take-home message

Significant bladder volume and asymmetrical shape changes occur during the course of RT

IGRT can be used to adapt the RT (IMRT) plan to individual interfractional and intrafractional changes

Techniques are dependant on local protocols and infrastructure availability

# GRAZIE PER L'ATTENZIONE

