

8th International

# ISIORT Conference

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Cologne/Germany

Cologne Marriott Hotel

## IORT for genitourinary malignancies

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**Conflicts of interest: none**

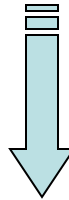
# GENITOURINARY MALIGNANCIES

- **Bladder**
- **Kidney**
- **Prostate**

# BLADDER CANCER

## Radical cystectomy is still the standard therapy for invasive bladder cancer

1. Best long-term survival and DFS rates: DFS: 60-70% @ 5 yrs and 50-65% @ 10 yrs
2. It has relatively low morbidity and mortality
3. It allows pathologic staging of primary bladder tumor and of regional lymph nodes
4. But it has as a consequence a relatively low quality of life



Bladder-sparing protocols have demonstrated similar long-term local control and survival rates in selected series with invasion into but not beyond the bladder muscle (Shipley, Cancer, 1987; Mak, BJU, 2008):

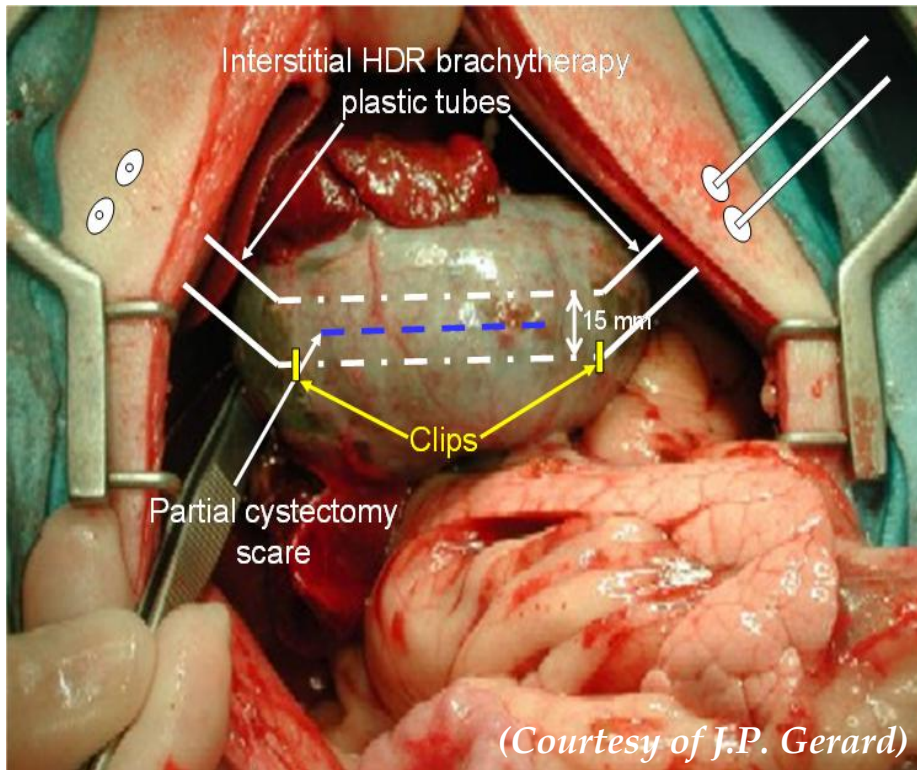
- |  |         |
|--|---------|
| - complete response rates:               | 60-80%, |
| - 5-year survival rates:                 | 50-60%, |
| - survival rates with an intact bladder: | 40-45%  |

# Intra-operative Irradiation for Localized Bladder Cancer

Author	#	Clinical stage	Treatment	5 year Local Control	5 year Survival
Matsumoto 1981	28	T2	IOERT, EBRT	82%	62%
van der Werf-Messing 1983	328	T2	EBRT, Ra-226	77%	56%
Mazeron 1985	24	T2	Resection, Ir-192, EBRT	92%	58%
Batterman 1986	85	T2	EBRT, Ra-226	74%	55%
Nieuwenhuijzen 2005	108	T1-T2	EBRT, Ir-192	73%	62%
Blank 2007	122	T1-T2-T3	EBRT, Ir-192	76%	73%
van Onna 2009	111	T1-T2	EBRT, Ir-192	-	70%
van der Steen-Banasik 2009	76	T1-T2	EBRT, Cs-137, Ir-192	70%	57%

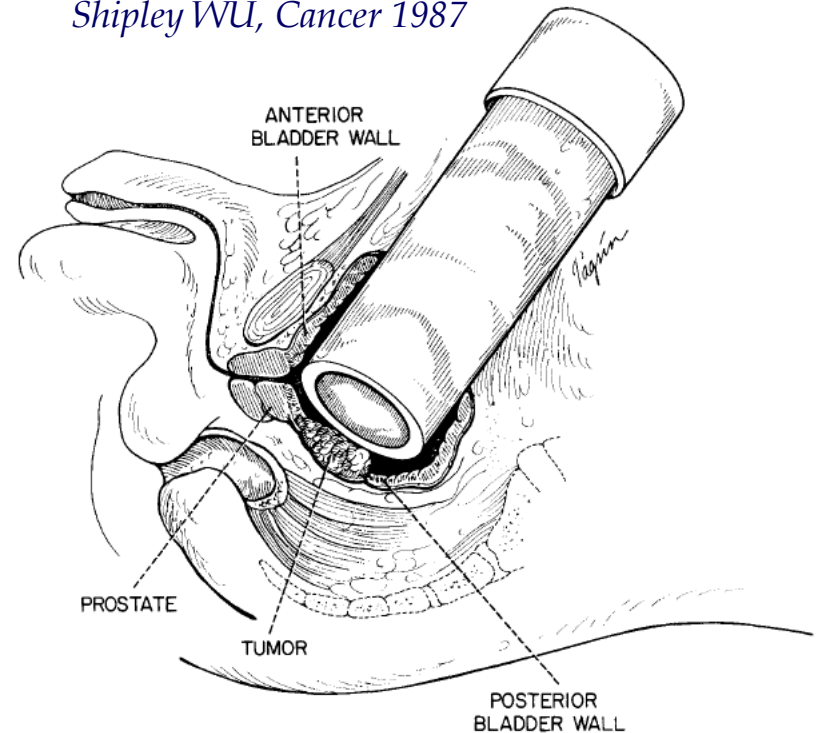


# Intra/Peri-Operative Brachytherapy and IOERT in Bladder Cancer



The BRT technique was introduced and developed in the Netherlands by Brigit Van der Werf-Messing and has been employed mainly in France (*Hoffstetter 1998, Mazon 1988, Pernot 1996, Rozan 1992*) and in Belgium (*Soete 1997, Van Poppel 2000*).

*Shipley WU, Cancer 1987*



Electron beams of 15 to 18 MeV, that penetrate 4 to 5.5 cm are necessary to treat the extra-vesical extensions of advanced tumors. The cylinder is angled latero-inferiorly so that the anus, rectum, and prostate or lower vagina are not in the path of the exit beam.

**RESULTS OF BLADDER-CONSERVING TREATMENT, CONSISTING OF  
BRACHYTHERAPY COMBINED WITH LIMITED SURGERY AND EXTERNAL BEAM  
RADIOTHERAPY, FOR PATIENTS WITH SOLITARY T1-T3 BLADDER TUMORS LESS  
THAN 5 CM IN DIAMETER**

LEO E. C. M. BLANK, M.D.,\* KEES KOEDOODER, PH.D.,\* ROB VAN OS, B.SC.,\* MARLOU VAN DE KAR,\*  
J. HAITZE VAN DER VEEN, M.D.,<sup>†</sup> AND CARO C. E. KONING, M.D., PH.D.\*

122 pts; pathologic stage distribution: 30 pT1, 81 pT2, and 11 pT3

Tx: EBRT – SURGERY – BRT (99 LDR, 23 PDR)

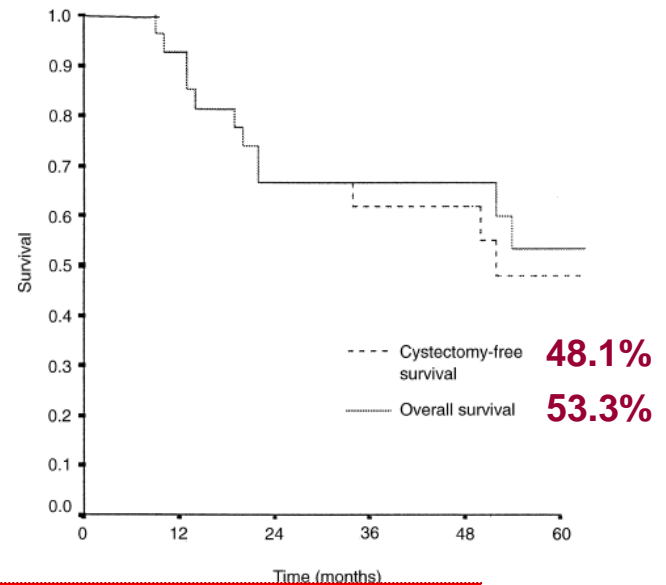
- 5-yr local: 76%
- 5 and 10-yr relapse-free survival: 69% and 66%
- 5 and 10-yr OS: 73% and 49%
- Low toxicity
- No difference between the LDR and PDR groups.

## Intra-operative electron radiotherapy as a conservative treatment for infiltrating bladder cancer

Y.A. Rostom<sup>a</sup>, O. Chapet<sup>a</sup>, S.M. Russo<sup>a</sup>, P. Dubernard<sup>b</sup>, J.M. Maréchal<sup>c</sup>,  
I. Sentenac<sup>a</sup>, F.N. Gilly<sup>d</sup>, J.P. Gérard<sup>a,\*</sup>

TUR → EBRT (48 Gy, 2/die) + CDDP → IOERT, 9 MeV, 15 Gy

- 27 pts: 22 cT2, 5 cT3
- Radical TUR 12 pts (44%)
- Response rate at 4 wks cystoscopy = **100%**  
(75% complete clinical response)
- 10/27 (37%) distant metastasis,
- 5/27 (19%) local recurrence
- **3/27 mucosal necrosis and ureteral stenosis**



*“ we recommend an IOERT dose of 12 Gy ”*



# Intraoperative and external preoperative radiotherapy in invasive bladder cancer: effect of neoadjuvant chemo-RT in tumor downstaging

University of Navarra, Pamplona, Spain

**EBRT 46 Gy**  
(bladder and  
pelvic nodal areas)  
+  
**Chemotherapy**

**4-6 weeks after**

**Radical cystectomy**

**+**

**IOERT 15 Gy**  
(range 10 to 20 Gy)  
with electron energies  
of 9 to 12 MeV

40 patients

7 = T2  
17 = T3  
11 = T4  
5 = N+

**Post-treatment pathology showed 27 pT0 (67%) and 15 pN+ (37%).**

Median follow-up: 35 months (range 2 - 96 months)

7-year actuarial survival rate = 46% (T2=85%; T3=48%; T4=10%)

*(courtesy of F. Calvo and J. Aristu, unpublished data)*

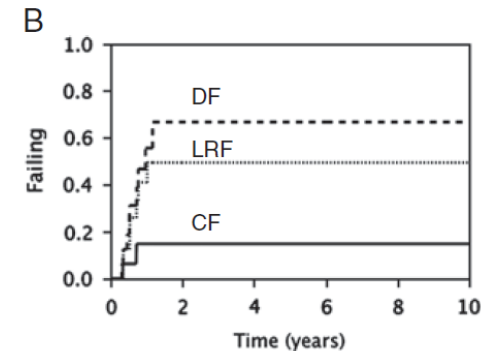
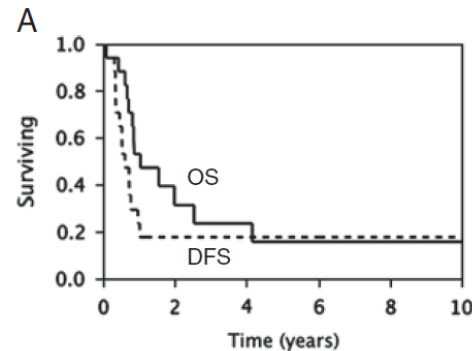
# Multimodality Therapy Including Surgical Resection and Intraoperative Electron Radiotherapy for Recurrent or Advanced Primary Carcinoma of the Urinary Bladder or Ureter

*Christopher L. Hallemeier, MD,\* Robert J. Karnes, MD,† Thomas M. Pisansky, MD,\* Brian J. Davis, MD, PhD,\* Leonard L. Gunderson, MD,‡,† Bradley C. Leibovich, MD,† Michael G. Haddock, MD,\* and Richard Choo, MD\**

**Urinary bladder: 13 (76%)**  
**Ureter: 2 (24%)**

**TABLE 2.** Treatment Characteristics

	N (%)
Surgery	
No residual disease (R0)	7 (41)
Microscopic residual disease (R1)	1 (6)
Gross residual disease (R2)	9 (53)
IOERT	
Dose (Gy)	
Median	12.5
Range	10-20
Energy (MeV)	
Median	9
Range	6-18
No. fields	
One	15 (88)
Two	1 (6)
Three	1 (6)
Perioperative EBRT	
Timing	
No EBRT	1 (6)
Preoperative EBRT	14 (82)
Postoperative EBRT	2 (12)
Total dose (Gy)	
Median	50.4
Range	0-60
Concurrent chemotherapy	
Yes	5 (29)
No	12 (71)



**TABLE 3.** Outcomes for Locoregionally Recurrent Bladder or Ureter Carcinoma

Series	DM at Recurrence (%)	Treatment	Median OS*(mo)
Dhar et al <sup>4</sup>			
n = 48	0	Chemotherapy	5.5
n = 7	0	EBRT	3.6
n = 75	0	None	4.6
Hautman and Simon <sup>3</sup>			
n = 22	40	Chemotherapy +/- EBRT	12
n = 22		None	3
Westney et al <sup>6</sup>			
n = 18	17	Chemotherapy +/- EBRT +/- surgery	8
Greven et al <sup>7</sup>			
n = 13	NS	NS	4
Current series			
n = 15	0	EBRT, surgery, IOERT +/- chemotherapy	14.4

# BLADDER CANCER: CONCLUSIONS

- Intraoperative boost by BRT or IOERT combined with EBRT is an effective treatment in T2-T3 disease allowing for bladder preservation as a sole treatment or in combination with TUR and chemotherapy.
- Sterilization rate of invasive bladder cancer after IOERT, confirmed by pathology after cystectomy, is high (~ 65%) and seems to be increased by the addition of neoadjuvant chemo.
- Intraoperative IOERT in combination with EBRT could improve the results in locally advanced and recurrent disease.

# RENAL CANCER

Standard therapy for renal cell carcinoma is radical nephrectomy

Author (Reference)	# of pts	5-Year Survival (%)			
		I	II	III	IV
McNichols et al. (1981)	506	67	51	34	14
Selli et al. (1983)	115	93	63	80	13
Golimbu et al. (1986)	326	88	67	40	2
Dinney et al. (1992)	314	73	68	51	20
Guinan et al. (1997)	337	100	96	59	16
Javidan et al. (1999)	381	95	88	59	10
Kinouchi et al. (1999)	350	96	95	70	24
Tsui et al. (2000)	643	91	74	67	32
Brown et al. (2006)	184	90	80	55	30
Margulis et al. (2009)	1,363	91	75	54	12

# Is there a potential benefit of IOERT in renal cancer ?

- positive margins
- local recurrences
- large tumor volume (?)

Potential Setting

## Historical randomized trials on pre-operative or post-operative RT

- Fugitt 1973
- Van der Werf-Messing 1973
- Juusela 1977
- Kjaer 1987

No advantage either for local control or overall survival

Study limits:

- inadequate patient selection
- low-radiation doses
- poor radiation technique

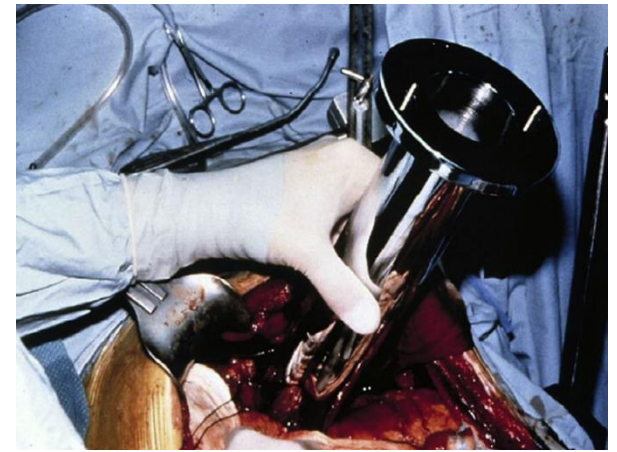
# IORT for Renal Cancer Literature Studies

	Primary/ recurrent	Median F/U (y)	IORT dose (Gy)	EBRT dose (Gy)	3-y OS (%)	Local control (%)
<b>Santos, Pamplona, 1989</b>	8 / 3	0.7	15 (mean)	NS	NS	91
<b>Eble, Heidelberg, 1997</b>	3 / 9	3.3	16.2 (mean)	40 (mean)	47	100
<b>Master, San Francisco, 2005</b>	0 / 10	5.9	15 (mean)	None	33	80
<b>Hallemeier, Mayo, 2012</b>	3 / 19	9.9	13.5 (mean)	48 (mean)	50	77
<b>Calvo, Madrid Pamplona, 2013</b>	15 / 10	22.2	14 (median)	44 (median)	38	84
<b>Habl, Heidelberg, 2013</b>	0 / 17	1.5	15 (median)	40 (median)	63	88
<b>Paly, multicentric, 2014</b>	27 / 71	3.5	15 (median)	preop 45 (median) postop 40 (median)	primary @ 5 y: 37 recurrent @ 5 y: 55	NS



## Outcomes in a Multi-institutional Cohort of Patients Treated With Intraoperative Radiation Therapy for Advanced or Recurrent Renal Cell Carcinoma

Jonathan J. Paly, BS,\* Christopher L. Hallemeier, MD,† Peter J. Biggs, PhD,\* Andrzej Niemierko, PhD,\* Falk Roeder, MD,‡ Rafael Martínez-Monge, MD,§ Jared Whitson, MD, MAS,|| Felipe A. Calvo, MD,¶ Gerd Fastner, MD,# Felix Sedlmayer, MD,# William W. Wong, MD,\*\* Rodney J. Ellis, MD,†† Michael G. Haddock, MD,† Richard Choo, MD,† William U. Shipley, MD,\* Anthony L. Zietman, MD,\* and Jason A. Efstathiou, MD, DPhil\*



Advanced: 27 (26%)  
 pT1-T2 2  
 pT3-T4 22  
 Recurrent: 71 (74%)  
 Sarcomatoid: 11 (12%)  
 N+ 16 (18%)  
 Surg. margins+ 57 (59%)

IORT dose: 15 (9-20) Gy  
 Energy: 9 (4-15) MeV EBRT  
 preop. 45 Gy (27%)  
 postop. 40 Gy (35%)  
 Median F/U: 3.5 years  
 5-y OS: 37% (adv); 55% (rec)  
 5-y DFS: 39% (adv); 52% (rec)

**Table 3** Multivariate analysis of factors significant for overall survival

Cohort	Variable	Hazard ratio (95% CI)	P value
Recurrent and primary	Higher IORT dose	1.3 (1.2-1.5)	<i>P</i> <.001
Recurrent and primary	Positive nodal status	2.9 (1.2-6.9)	<i>P</i> =.016
Recurrent and primary	Presence of sarcomatoid features	6.9 (2.5-18.9)	<i>P</i> <.001
Recurrent	Higher IORT dose	1.3 (1.1-1.4)	<i>P</i> <.001
Recurrent	Positive nodal status	4.0 (1.1-13.8)	<i>P</i> =.03
Recurrent	Presence of sarcomatoid features	4.6 (1.1-18.7)	<i>P</i> =.03
Recurrent	Recurrent positive surgical margin status*	2.6 (1.3-5.3)	<i>P</i> =.009

## **Outcomes in a Multi-institutional Cohort of Patients Treated With Intraoperative Radiation Therapy for Advanced or Recurrent Renal Cell Carcinoma**

Jonathan J. Paly, BS,\* Christopher L. Hallemeier, MD,† Peter J. Biggs, PhD,\* Andrzej Niemierko, PhD,\* Falk Roeder, MD,‡ Rafael Martínez-Monge, MD,§ Jared Whitson, MD, MAS,|| Felipe A. Calvo, MD,¶ Gerd Fastner, MD,# Felix Sedlmayer, MD,# William W. Wong, MD,\*\* Rodney J. Ellis, MD,†† Michael G. Haddock, MD,† Richard Choo, MD,† William U. Shipley, MD,\* Anthony L. Zietman, MD,\* and Jason A. Efstathiou, MD, DPhil\*

**Although a similar proportion of IORT (69%) and surgery-only (65%) patients compared to the Margulis study, a few results appear favorable:**

- the 5-year DFS (52% vs 30%)**
- the median DFS (66 months vs 11 months)**
- the 5-year DSS (60% vs 50%)**

**Although 59% of the recurrent patients had positive surgical margins, only 24% of all relapses were local (76% of first relapses were distant), suggesting a potential benefit in local control after IORT**

# RENAL CANCER: CONCLUSIONS

- For locally advanced renal cancers, the series from Mayo Clinic, Pamplona, University of Heidelberg and UCSF suggest an aggressive approach containing IOERT in selected cases.
- The addition of IOERT to surgery and EBRT is associated with a high rate of local and central control with acceptable toxicity. The best candidates are untreated patients with large tumor volume and risk of positive margins after radical nephrectomy and patients with local recurrences.
- Since distant relapse is common, especially in patients with recurrent disease, future treatment strategies should evaluate a systemic component of treatment (new targeted therapies).

# Prostate Cancer

**High risk, locally advanced**

Conventional approaches (S/EBRT/HT):

37-62% Relapse-Free Survival @ 5 yrs

40% Local Failure after radical prostatectomy

## Locally Advanced Prostate Cancer: EBRT

### LOW-INTERMEDIATE RISK:

DFS @ 5 yrs 80-92%, DSF @ 10 yrs 76-92%

### HIGH RISK or LOCALLY ADVANCED:

**-EBRT+/-HT** (studies with F/U of 10 yrs)

- ∞ **RTOG 9202** (T2c-4 N0-1 M0) (Horwitz, JCO 2008)  
DFS 22.5%; **bDFS 48.1 % @ 10 aa**
- ∞ **EORTC 22863** (T1-2 M0 pd, T3-4 N0-1 M0)  
(Bolla, Lancet Oncol 2010) **DFS 47.7% @ 10aa**
- ∞ **TROG 9601** (T2b-4 N0 M0) (Denham, Lancet 2011)  
DFS 36%; **bDFS 47.2% @ 10 aa**

# Locally Advanced Prostate Cancer

## - RADICAL PROSTATECTOMY + EBRT



International Journal of  
Radiation Oncology  
biology • physics

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Guidelines

### Adjuvant and Salvage Radiation Therapy After Prostatectomy: American Society for Radiation Oncology/American Urological Association Guidelines

Richard K. Valicenti, MD, MBA,\* Ian Thompson Jr., MD,† Peter Albertsen, MD, MS, Brian J. Davis, MD, PhD,§ S. Larry Goldenberg, MD,|| J. Stuart Wolf, MD,¶ Oliver Sartor, MD,# Eric Klein, MD,\*\* Carol Hahn, MD,†† Jeff Michalski, MD, MBA, Mack Roach III, MD,§§ and Martha M. Faraday, PhD|||

Int J Radiation Oncol Biol Phys, Vol. 86, No. 5, pp. 822–828, 2013

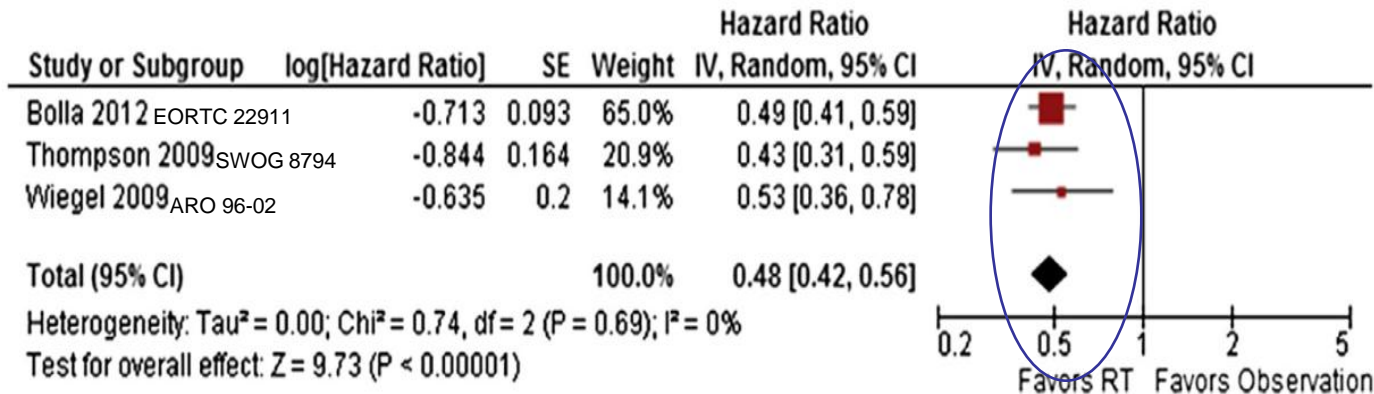
Adjuvant radiotherapy following radical prostatectomy for pathologic T3 or margin-positive prostate cancer: A systematic review and meta-analysis

Scott C. Morgan<sup>a,b</sup>, Tricia S. Waldron<sup>c,\*</sup>, Libni Eapen<sup>a,b</sup>, Linda A. Mayhew<sup>c</sup>, Eric Winquist<sup>d,e</sup>, Himu Lukka<sup>c,f,g</sup>, on behalf of the Genitourinary Cancer Disease Site Group of the Cancer Care Ontario Program in Evidence-based Care<sup>1</sup>

Radiotherapy and Oncology 88 (2008) 1–9

Randomized Trials with adjuvant EBRT in case of risk factors:  
T3a/b and R+

## Advantage in terms of bRFS





# RADIOBIOLOGY



## CLINICAL INVESTIGATION

Genitourinary Cancer

### DOSE-FRACTIONATION SENSITIVITY OF PROSTATE CANCER DEDUCED FROM RADIOTHERAPY OUTCOMES OF 5,969 PATIENTS IN SEVEN INTERNATIONAL INSTITUTIONAL DATASETS: $\alpha/\beta = 1.4$ (0.9–2.2) GY

RAYMOND MIRALBELL, M.D.,\*<sup>†</sup> STEPHEN A. ROBERTS, PH.D.,<sup>‡</sup> EDUARDO ZUBIZARRETA, M.D.,<sup>§</sup>  
AND JOLYON H. HENDRY, PH.D.<sup>||</sup>

ANTICANCER RESEARCH 33: 1009-1012 (2013)

### Is the $\alpha/\beta$ Ratio for Prostate Tumours Really Low and Does It Vary with the Level of Risk at Diagnosis?

JACK F. FOWLER<sup>1</sup>, IULIANA TOMA-DASU<sup>2</sup> and ALEXANDRU DASU<sup>3</sup>

$\alpha/\beta$ : 1.55

Low  $\alpha/\beta \rightarrow$  sensitivity to high dose/fraction:  
rationale for single dose and hypofractionation



Potential advantage on local control

# IORT for Prostate Cancer Literature Studies

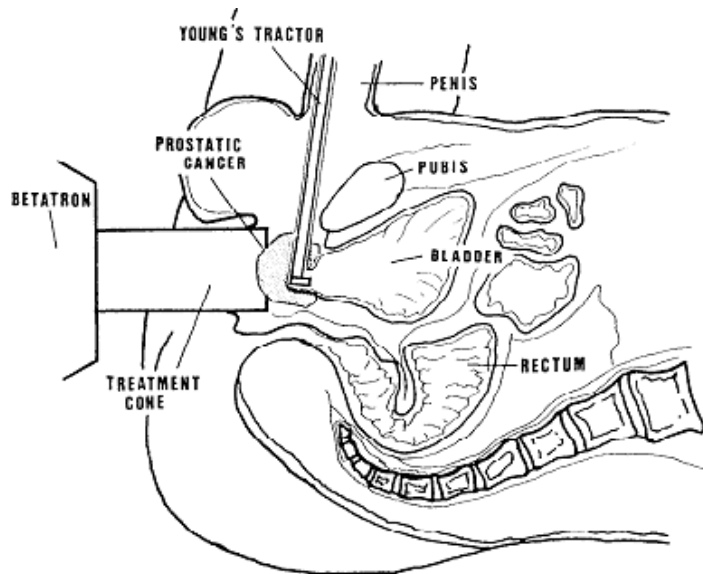
*Int. J. Radiation Oncology Biol. Phys.*, Vol 11, pp. 147-151  
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## INTRAOPERATIVE RADIOTHERAPY IN THE DEFINITIVE TREATMENT OF LOCALIZED CARCINOMA OF THE PROSTATE

MASAJI TAKAHASHI, M.D.,\* KENICHIRO OKADA, M.D.,† YUHTA SHIBAMOTO, M.D.,\*  
MITSUYUKI ABE, M.D.\* AND OSAMU YOSHIDA, M.D.‡

1985

Kyoto University School of Medicine, Sakyoku, Kyoto 606, Japan



Lithotomy position  
Perineal access  
No RP  
IORT as a boost,  
followed by EBRT

### ● *Original Contribution*

## INTRAOPERATIVE RADIOTHERAPY: THE JAPANESE EXPERIENCE

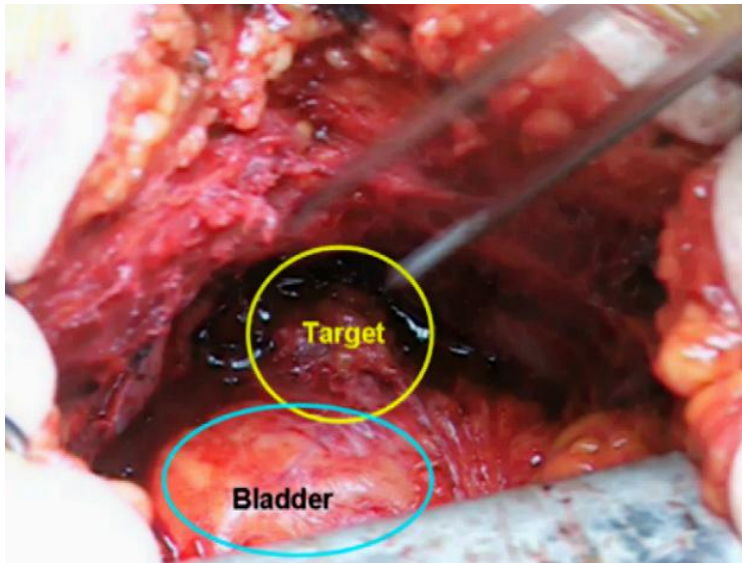
MITSUYUKI ABE, M.D. AND MASAJI TAKAHASHI, M.D.

*Int. J. Radiation Oncology Biol. Phys.*, Vol. 7, pp. 863-868  
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1991

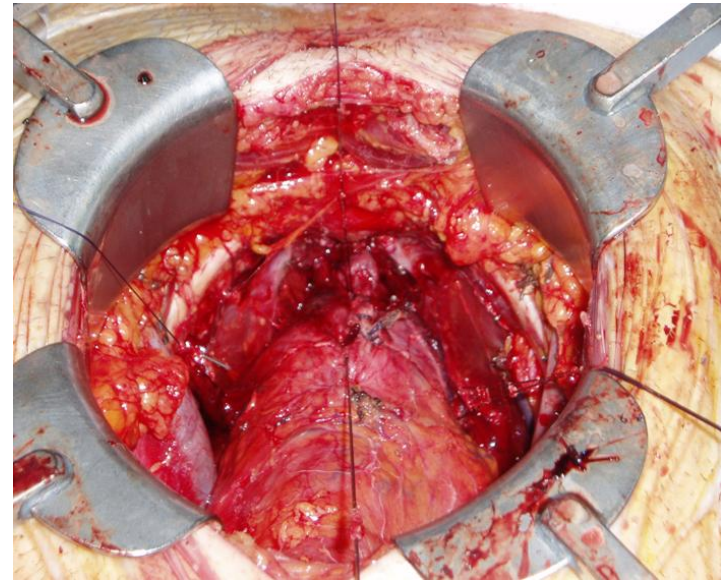
# IORT for Prostate Cancer Literature Studies

High risk, locally advanced



*(Saracino, 2008)*

- Italian series :



*(courtesy of R. Orecchia)*

- Inst. Regina Elena, Rome (after prostate removal)
- EIO, Milan; UO of Novara (before prostate removal)

# Treatment factors of the series of locally advanced prostate cancer treated by IOERT

Author	#	Patients' selection	Surgical approach	IOERT Energy / Dose	EBRT
Takahashi 1985	14	Stage B2-D2	Perineal No RP	10-14 MeV / 28-35 Gy (single dose) 20-25 Gy combined with EBRT	50 Gy to pelvic lymph nodes
Abe 1991	21	Stage B2-D2	Perineal No RP	8-14 MeV / 28-35 Gy (single dose) or 20-25 Gy combined with EBRT	50 Gy to pelvic lymph nodes
Higashi 1998	35	Stage B-C	Perineal/retropubic No RP	25-30 Gy	30 Gy, 2 Gy/fx
Kato 1998	54	Stage B2-D1	Perineal/retropubic No RP	25-30 Gy	30 Gy, 2 Gy/fx
Orecchia 2007	11	Interm.-high risk	Retropubic IOERT-RP	8-10 MeV / 12 Gy	45 Gy, 1.8 Gy/fx
Saracino 2008	34	Interm. risk	Retropubic RP-IOERT	7-9 MeV / 16-22 Gy (dose escalation)	no
Rocco 2009	33	Interm.-high risk	Retropubic IOERT-RP	8-10 MeV / 12 Gy	45 Gy, 1.8 Gy/fx
Krengli 2010	38	Interm.-high risk	Retropubic IOERT-RP	9-12 MeV / 10-12 Gy	46-50 Gy, 2 Gy/fx

# Results of the series of locally advanced prostate cancer treated by IOERT

Author	Local control and F/U	Survival	Toxicity
Takahashi 1985	82% (4-140 mos)	-	Delayed wound healing of perineal incision No severe IORT related
Abe 1991	81% @ 5 yrs	72% OS @ 5 years	100% early hematuria 10% early pollakiuria 1 chronic cystitis, 1 late urethral stricture
Higashi 1998	-	92% (stage B), 87% (stage C) OS @ 5 years	No critical cystitis, proctitis, anal bleeding
Kato 1998	83% @ 5 yrs	89% DSS, 74% BRFS @ 5 yrs	20% early rectal G3-G4 (without rectal spacer) 7% early rectal G3 (with rectal spacer)
Orecchia 2007	-	-	Peri-operative: 1 lymphocele, 3 anastomotic leakage
Saracino 2008	91% (19-59 mos)	77% BRFS @ 3 years	No urinary or rectal toxicity $\geq$ G1
Rocco 2009	-	97% BRFS @ 2 yrs, 100% OS (3-24 months)	GU: 17% G $\geq$ 2 (early), 7% G $\geq$ 2 (late) GI: 10% G $\geq$ 2 (early), 0% G $\geq$ 2 (late)
Krengli 2010	98% (6-46 mos)	82% BRFS, 100% OS (6-46 months)	Peri-operative: lymphocele 16%, hematoma 6%; After EBRT: 11% G2 early rectal G2 11%, early urinary G2 4%; bladder neck stricture 7%

# IORT for Prostate Cancer Literature Studies

## Patient selection in the 3 Italian Series

	<b>IRE - Rome</b>	<b>IEO - Milan</b>	<b>UO - Novara</b>
General criteria	One of the followings: Gleason $\geq 7$ , c- stage $> T2c$ , PSA of 11–20 ng/mL	Organ confined disease $< 25\%$	Organ confined disease $< 25\%$
PSA (median)	10 ng/ml	14.2 ng/ml	39.5 ng/ml
Gleason $\geq 7$	56%	88%	85%
C-stage $> T2$	41%	73%	71%



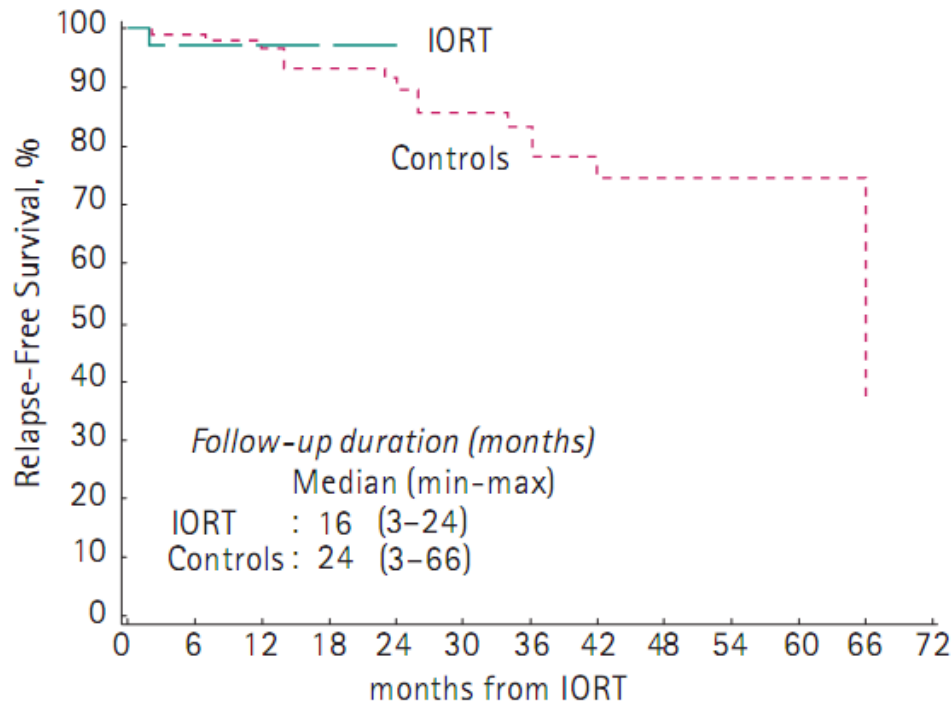
# Intraoperative radiotherapy during radical prostatectomy for intermediate-risk to locally advanced prostate cancer: treatment technique and evaluation of perioperative and functional outcome vs standard radical prostatectomy, in a matched-pair analysis

Bernardo Rocco\*, Barbara A. Jerezek-Fossa\*\*, Deliu-Victor Matei\*, Fabrizio Verweij\*, Luigi Santoro<sup>5</sup>, Andrea Vavassori\*, Juan Camillo Ospina\*, Francisco Cedeira\*, Mario Ciocca<sup>1</sup>, Roberto Orecchia\*\* and Ottavio de Cobelli\*\*

\*Division of Urology, \*\*Radiation Oncology, <sup>1</sup>Medical Physics and <sup>5</sup>Epidemiology and Biostatistics Division, European Institute of Oncology, and <sup>1</sup>Faculty of Medicine, University of Milan, Milan, Italy

Accepted for publication 18 March 2009

GRAPH 1. Relapse-Free Survival (RFS) in IORT patients and controls



Toxicity grade	IORT (a)	Controls (b)*
N patients	33	84
<b>Acute toxicity</b>		
Genitourinary		
0-1	26	79
≥2	7 <sup>a</sup>	5 <sup>b</sup> <i>P=0.014</i>
Unknown	0	0
Gastrointestinal		
0-1	30	80
≥2	3	4
Unknown	0	0
<b>Late toxicity</b>		
Genitourinary		
0-1	21	74
≥2	3 <sup>c,d</sup>	1 <sup>e</sup> <i>P=0.016</i>
Unknown	9	9
Gastrointestinal		
0-1	24	74
≥2	0	1
Unknown	9	9

# PROSTATE CANCER: CONCLUSIONS

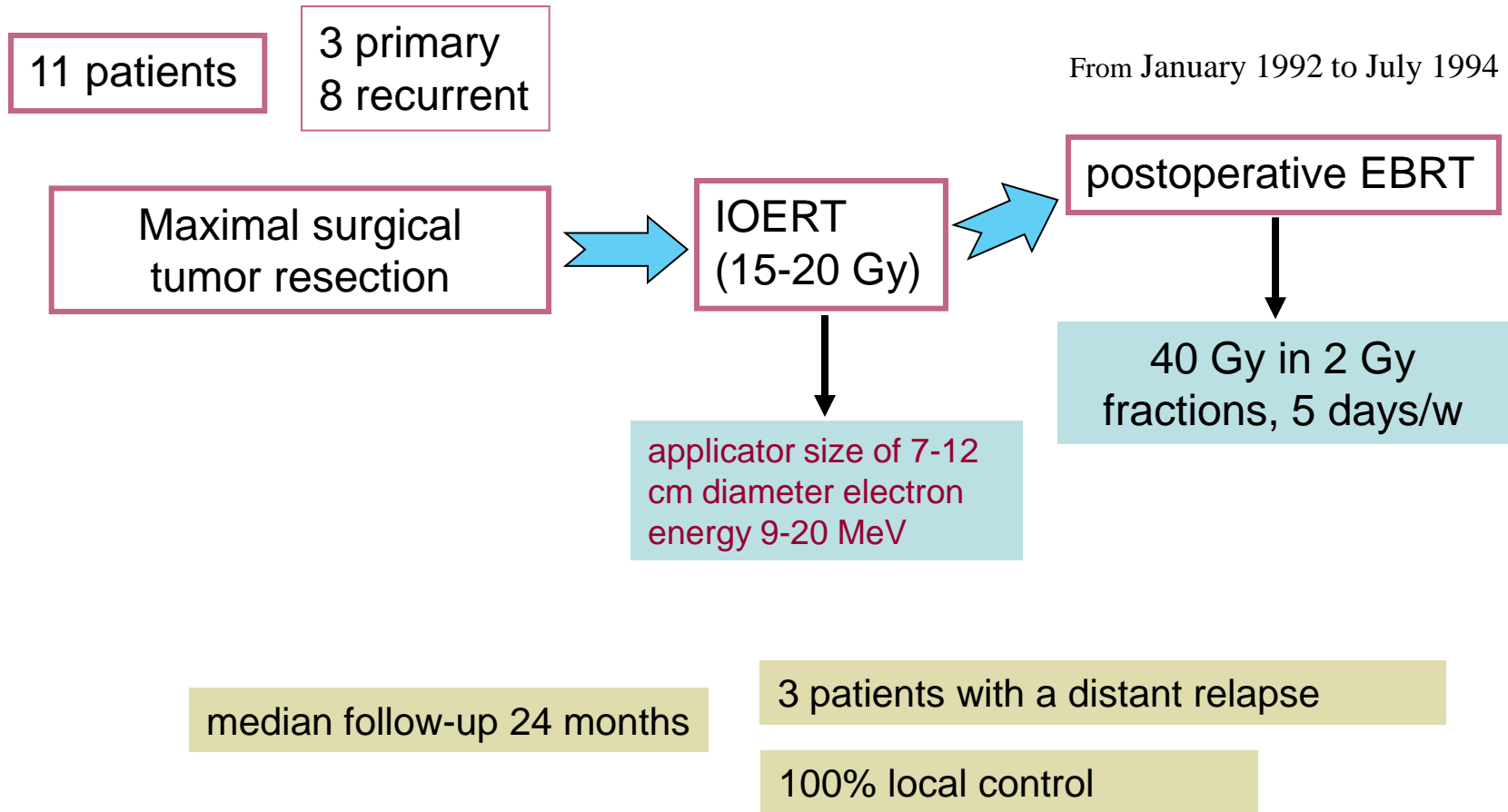
- Radiobiological data about the low  $\alpha/\beta$  value of prostate cancer cells support the delivery of large dose per fraction and therefore the use of IOERT.
- Preliminary clinical studies have shown the feasibility of the procedure.
- **Open issues** possibly requiring further studies:
  - which patients could benefit from IOERT?
  - is single dose IOERT safe and adequate for tumor control or should IOERT be combined with EBRT; if so how long should be the interval between IOERT/EBRT?
  - could hypofractionated EBRT be combined with IOERT boost to shorten the overall treatment time?



*Thanks !*



# The Heidelberg Series, Germany



The 4-year OS was 47% and DFS 34%

*“With IORT the dose limitation in the radiotherapy of renal cell carcinoma could be overcome”.*

*Eble MJ, Strahlenther Onkol 1998*

Table 3. Outcomes after surgery and intraoperative radiotherapy for primary or recurrent renal cell carcinoma

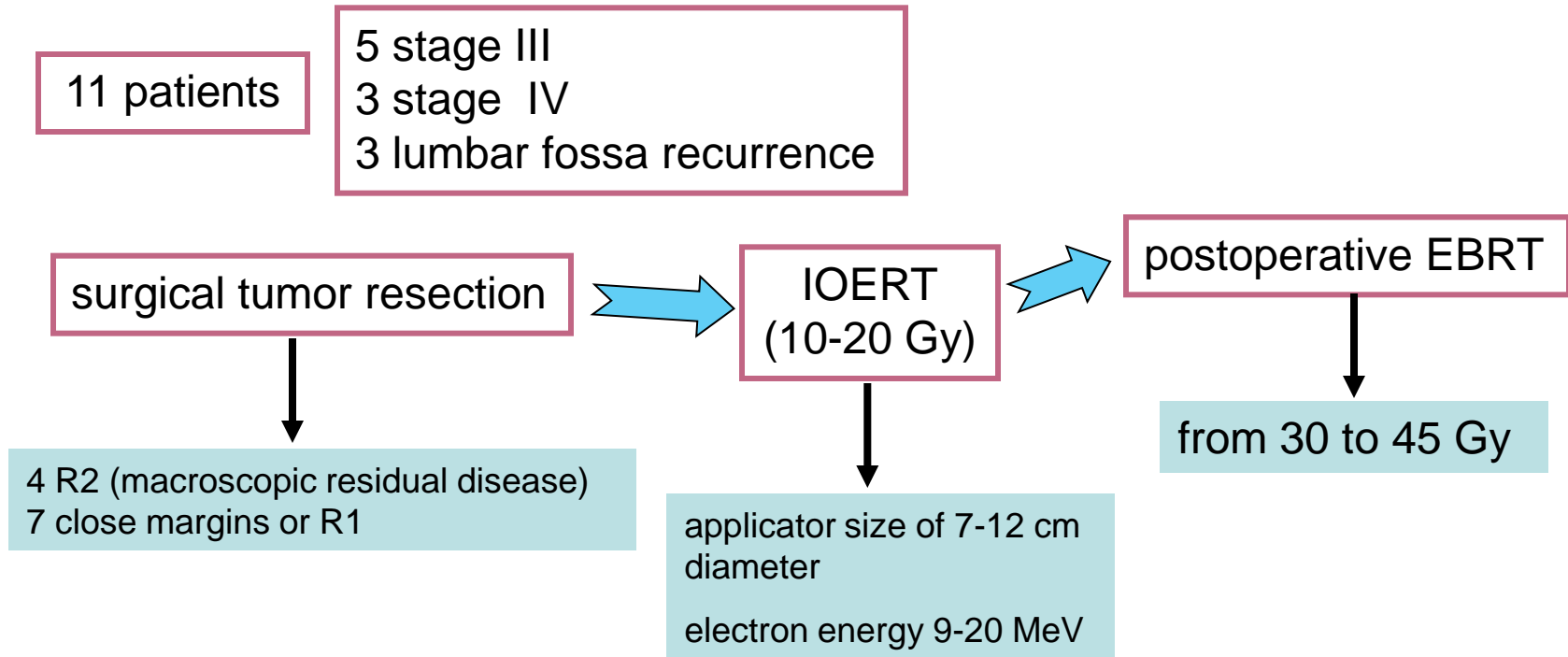
Study authors <sup>Ref</sup>	Primary/ Recurrent	Median follow-up (y)	Mean IORT dose (Gy)	Mean EBRT dose (Gy)	3-Year OS (%)	Local control
Santos <i>et al.</i> (22) ( <i>n</i> = 11)	8/3	0.7	15	NS*	NS	10/11
Master <i>et al.</i> (7) ( <i>n</i> = 10)	0/10	5.9	15	None	~33	8/10
Eble <i>et al.</i> (21) ( <i>n</i> = 12)	3/9	3.3	16.2	40	47	12/12
Current series ( <i>n</i> = 22)	3/19	9.9	13.5	48	50	17/22 <sup>†</sup>

**Table 2 Outcomes after surgery + IOERT +/- EBRT for primary/recurrent renal cell carcinoma**

Series	Primary/recurrent	f/u med (y)	Median IORT dose (Gy)	Median EBRT dose (Gy)	EBRT number	3-y OS (%)	Local control
Pamplona [13]	8/3	0.7	15	30-45	7/15	Not stated	10/11
San Francisco [14]	0/10	5.9	15	none	0/10	36	8/10
Mayo [10]	3/19	9.9	13.5	48	21/22	50	17/22
Madrid-Pamplona (pooled) [11]	15/10	22.2	14	44	15/25	38	21/25
Current study	0/17	1.5	15	40	11/17	63	15/17

# The Pamplona Series

University Clinic of Navarra, Spain



median follow-up: 8 months (2 to 33)

3 patients with distant relapse

3 long-term survivors without evidence of recurrent disease (more than 3 years).

No early or late relevant toxicity

# The UCSF Series

from 1990 to 2003

14 patients surgical tumor resection



IOERT

Mean size of the recurrent tumor was 6.35 cm (range 2 to 17)

Mean time to recurrence was 40 months (range 5 - 180)

no difference in survival due to adjuvant IOERT

Survival was 40% at 2 years and 30% at 5 years from surgery

## **CONCLUSIONS:**

Selected patients with isolated local recurrence in the renal fossa may have favorable and durable outcomes following surgical resection and IOERT for isolated renal fossa recurrence following radical nephrectomy.



# LONG-TERM OUTCOMES AFTER MAXIMAL SURGICAL RESECTION AND INTRAOPERATIVE ELECTRON RADIOTHERAPY FOR LOCOREGIONALLY RECURRENT OR LOCOREGIONALLY ADVANCED PRIMARY RENAL CELL CARCINOMA

CHRISTOPHER L. HALLEMEIER, M.D.,\* RICHARD CHOO, M.D.,\* BRIAN J. DAVIS, M.D., PH.D.,\*  
 THOMAS M. PISANSKY, M.D.,\* LEONARD L. GUNDERSON, M.D.,† BRADLEY C. LEIBOVICH, M.D.,‡  
 AND MICHAEL G. HADDOCK, M.D.\*

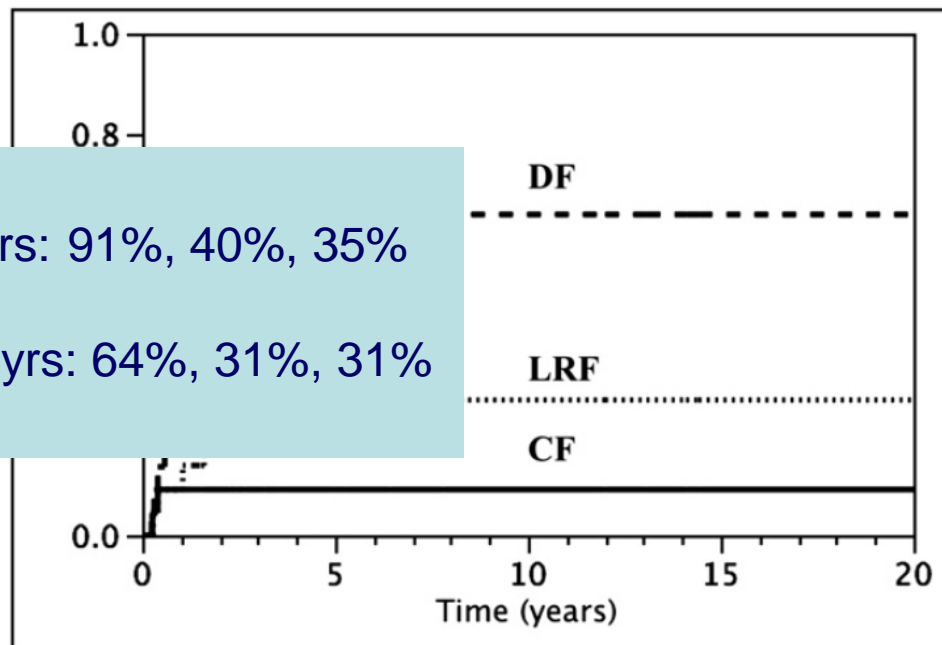
Primary: 3 (14%)  
 Recurrent: 19 (86%)

Table 2. Treatment characteristics of study patients

Perioperative EBRT ( <i>n</i> = 21)	
Total dose, cGy	
Median	4,500
Range	4,140–5,500
Timing	
Preoperative only	
Postoperative only	
Preoperative and postoperative	
Surgery	
No residual disease (R0), <i>n</i> (%)	
Microscopic residual disease (R1), <i>n</i> (%)	
IOERT	
Dose, cGy	
Median	9
Range	6–12
Energy, MeV	
Median	9
Range	6–12
No. of fields, <i>n</i> (%)	
One	19 (86)
Two	3 (14)

OS @ 1,5,10 yrs: 91%, 40%, 35%

DFS @ 1,5,10 yrs: 64%, 31%, 31%



# Intraoperative electron radiation therapy (IOERT) in patients with locally recurrent renal cell carcinoma

Gregor Habl<sup>1\*</sup>, Matthias Uhl<sup>1</sup>, Frank Hensley<sup>1</sup>, Sascha Pahernik<sup>2</sup>, Juergen Debus<sup>1</sup> and Falk Röder<sup>1</sup>

**Table 1 Lesion and treatment characteristics**

	n	%		n	%
<b>Age</b>			<b>EBRT</b>		
Median	61		Yes	11	65
Range	32-76		No	6	35
<b>Gender</b>			<b>EBRT dose</b>		
Male	11	65	Median	40	
Female	6	35	Range	36-43,2	
<b>Time to rec.</b>			<b>Adj. CHT</b>		
Median	26		Yes	2	12
Range	2-115		No	15	88
<b>Histology</b>			<b>Resection margin</b>		
Clear cell	14	82	R0	6	35
Papillary	2	12	R1	9	53
Sarcomatoid	1	6	R2	2	12
<b>Tumor size</b>			<b>IOERT dose</b>		
Median	7		Median	15	
Range	3-14		Range	10-20	
<b>Grading</b>			<b>IOERT energy</b>		
G1/2	13	76	Median	8	
G3	4	24	Range	6-12	
<b>Distant met.*</b>			<b>IOERT cone</b>		
Yes	7	41	Median	10	
No	10	59	Range	6-18	

- Median follow-up: 18 months
- Local recurrences: 2 pts
- Actuarial 2-year local control rate: 91%
- Distant failures: 8 (liver and bone)
- Actuarial 2-year PFS: 32%
- Improved PFS rate in pts with a larger time interval between initial surgery and recurrence (> 26 months).
- Actuarial 2-year OS: 73%
- Lower histological grading (G1/2) was the only factor associated with improved OS
- Perioperative complications: 4 pts.

# The National Medical Center Hospital experience (Tokyo)

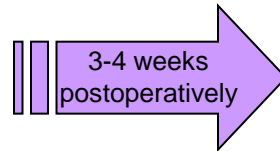
from 1965 to 1978, update 1989

## Bladder preservation protocol:

116 pz treated

- Ta 32 patients
- T1 34 patients
- T2 18 patients

high dose IORT boost  
25-30 Gy



fractionated EBRT, 30-40 Gy in  
15 to 20 fractions

After median F/U of 5 years, the freedom from local recurrence rates were:

94% for stage Ta  
88% for stage T1  
82% for stage T2

These rates are substantially better than the recurrence-free rates following transurethral resection alone (20% @ 5 years) or intravesical chemotherapy (39% @ 5 yrs). The actuarial 5-year survival rates were 100% for stage Ta and T1, and 62% for stage T2.

3% complications in 4 pts: 3 had transient ureterovesical junction obstruction and 1 bilateral hydronephrosis requiring urinary diversion.

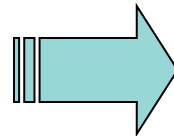
# The Van Der Werf Messing's Experience

1983: 41 pts,

c T3 NxMx

$\emptyset \leq 5$  cm

EBRT by 8 MeV photons 3x3.5 Gy to the pelvis



Radium implant  
65 Gy, 168 hrs



EBRT by 8 MeV photons 30 Gy in 5 fractions of 2 Gy

5-yr OS: 57%; 5-yr DSS: 74%

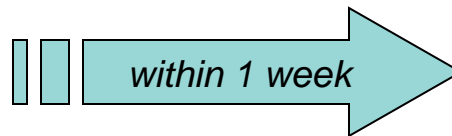
Severe complications: 19.5%

1989: 90 pts,

48 T2 and 42 T3

$\emptyset \leq 5$  cm

EBRT 40 Gy 2/die to the pelvis



Cs-137 at a dose reduced to 50% of the application time, meaning the biological equivalent of 65 Gy in 7 days

5-yr OS: 70%; 5-yr DSS: 80%

Severe complications: 6.7%

# Bladder-conserving surgery and interstitial brachytherapy for lymph node negative transitional cell carcinoma of the urinary bladder: results of a 28-year single institution experience

Renaud de Crevoisier<sup>a,\*</sup>, Aziz Ammor<sup>a</sup>, Bernard Court<sup>b</sup>, Pierre Wibault<sup>a</sup>, Erick Chirat<sup>a</sup>, Karim Fizazi<sup>c</sup>, Christine Theodore<sup>c</sup>, Sue Sun Yom<sup>a,1</sup>, Christine Haie-Meder<sup>a</sup>

## 58 pts

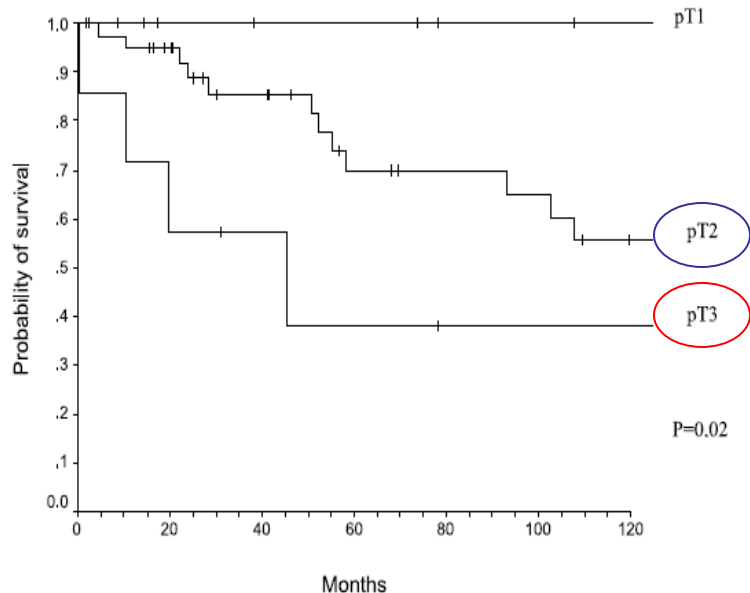
- short-course preop. EBRT
- iliac node dissection
- tumor resection and insertion of plastic tubes
- iridium-192 brachytherapy

Pelvic EBRT delivered 24 hrs prior to surgery to a total dose of 5 Gy in one fraction or 10.5 or 17 Gy in 2 fxs

If pN+, patient was treated with EBRT + Chemo

median total dose BRT: 60 Gy (range, 25–70)

median duration of BRT: 5.8 days (range, 2.7–12.6)



Pathologic stage distribution: 10 pT1, 41 pT2, 7 pT3

disease-free @ 5 yrs = 50%  
cause-specific @ 5 yrs = 70%

disease-free @ 5 yrs = 29 %  
cause-specific @ 5 yrs = 40 %

Late toxicity observed in 13 pts (24%): urinary frequency, bladder calcification, ureteral stenosis, bowel necrosis (resection).