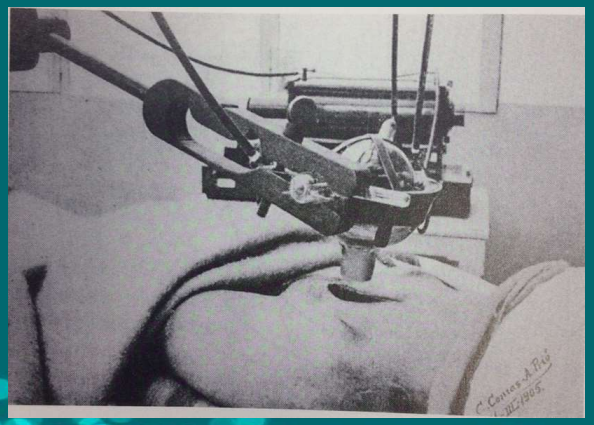
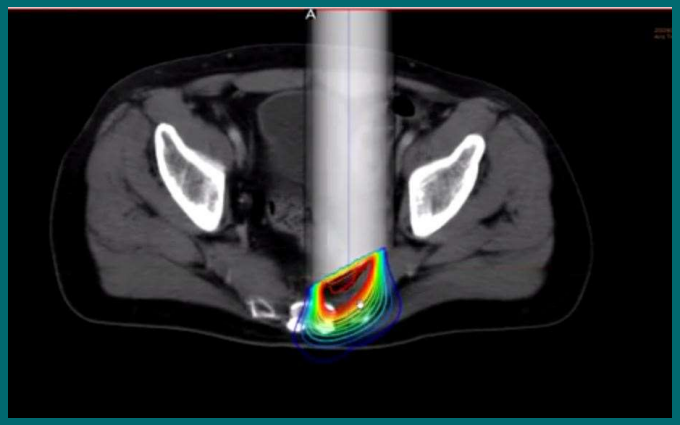
MAYO CLINIC

IORT for Rectal Cancer: Mayo Clinic Experience





Michael G. Haddock, M.D.

ISIORT Brussels Nov 7, 2024

Disclosures

- None

IORT History

Comas C., Prio A. Irradiation roentgen intra-abdominale ,après intervention chirurgicale dans un cas de cancer de l'uterus, Congres International d'Electrologie .Imprenta Francesca Badia,Barcelona,pp 5-14, 1907

IORT History
Stanford, 1937

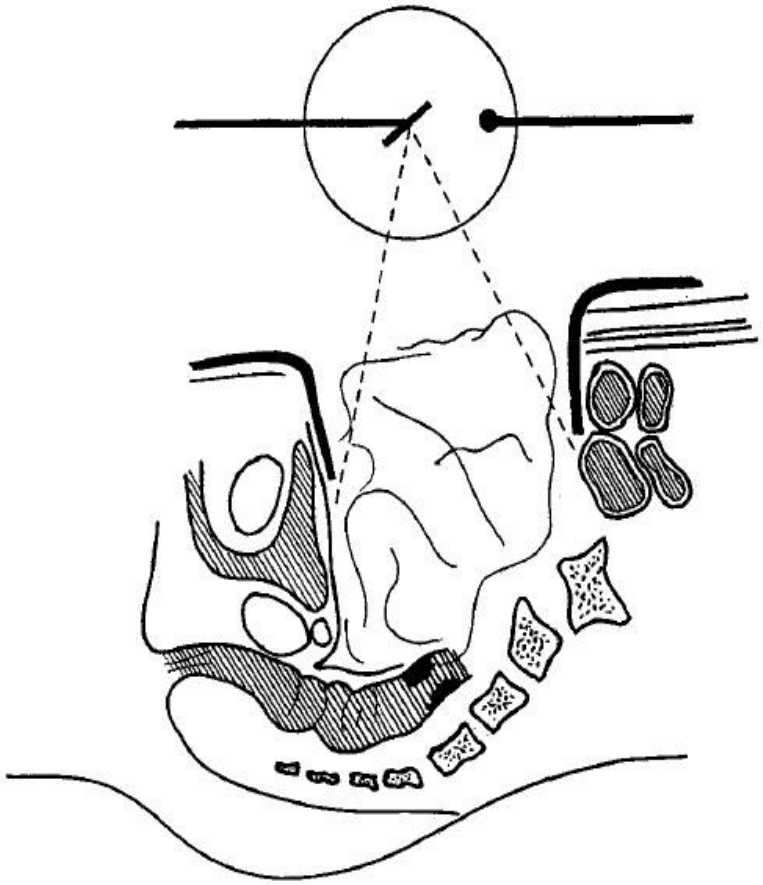


FIG. 1.—Irradiation of cancer of sigmoid (abdominal approach).

Tumor control probability

Radiobiologic Axioms

- Surviving fraction of tumor cells is a function of radiation dose
- Functional radiation effects in normal tissues is related to dose
- The dose needed to obtain tumor control depends on the number of clonogens and may not be achievable in all cases with acceptable normal tissue effects

Radiation Dose Problem

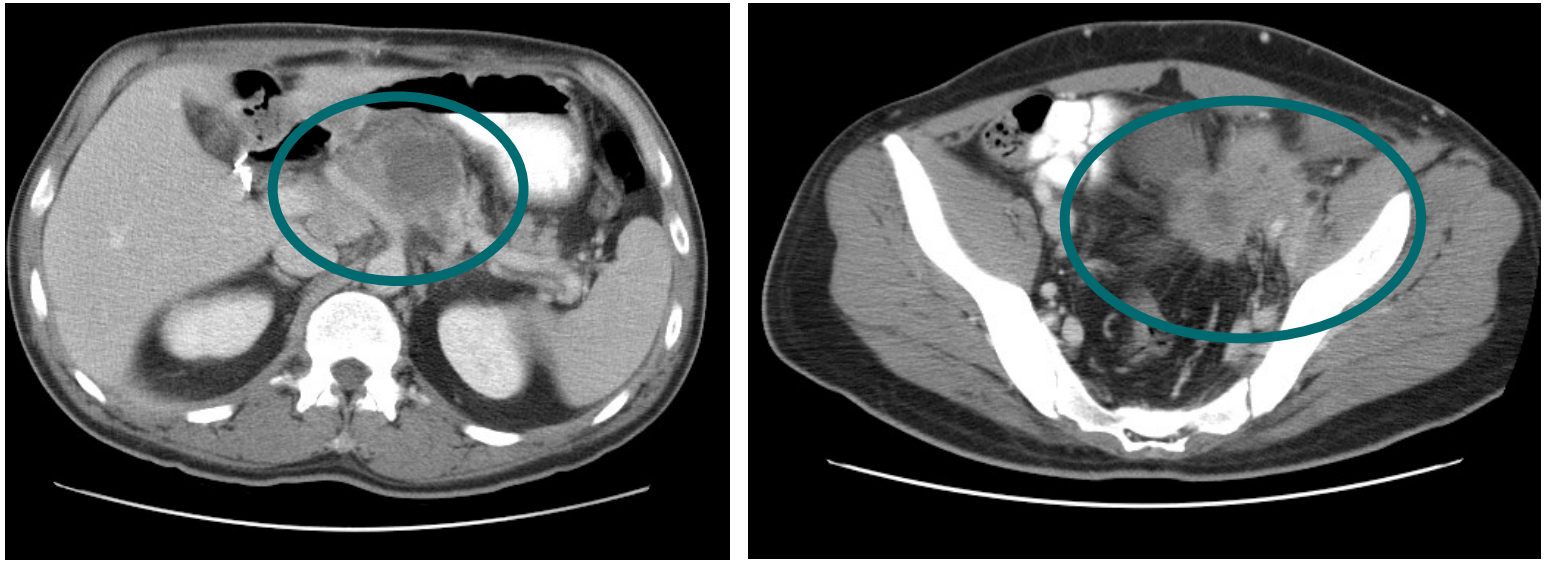
- Dose needed for local control:
  - Complete resection: 50 Gy
  - Microscopic disease: > 60 Gy
  - Gross disease: > 70 Gy
- Small bowel tolerance: 100 cc
  - Ulcer, stricture, perforation, obstruction
  - 45 – 50 Gy: 1-5% risk at 5 years
  - 55 Gy: 25-50% risk at 5 years

IORT
General Rationale

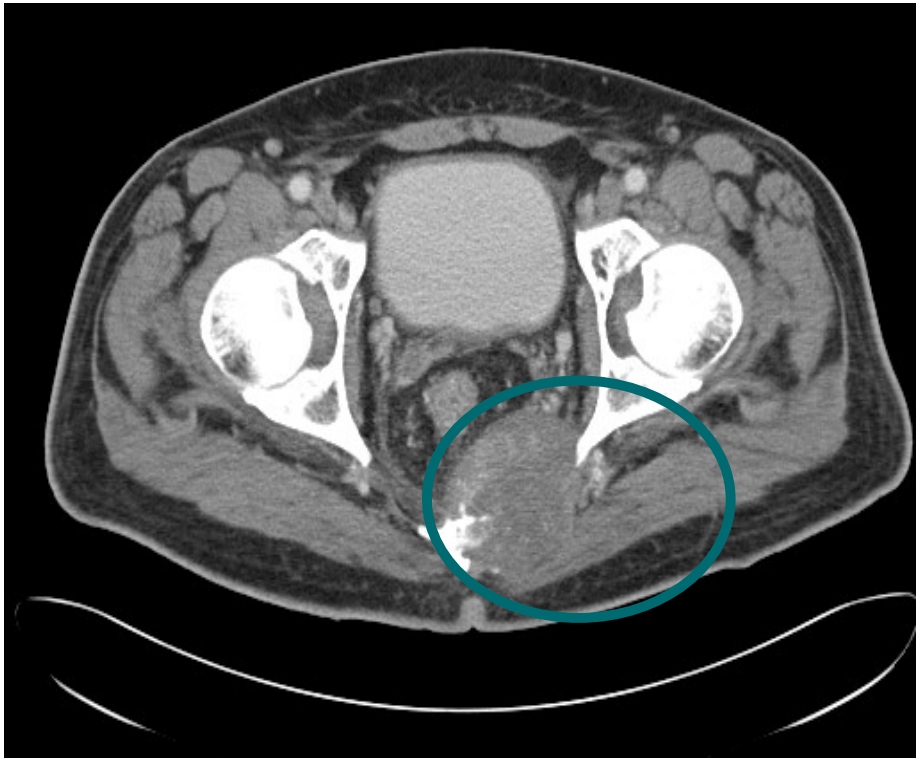
- able to treat small volume of tissue within IORT boost field
- can limit dose to sensitive normal organs such as small bowel
- can increase effective radiation dose

“Unresectable” Cancers

(i.e.fixation to critical structures)



“Unresectable” Colorectal Cancer



Microvascular Radiation Effects

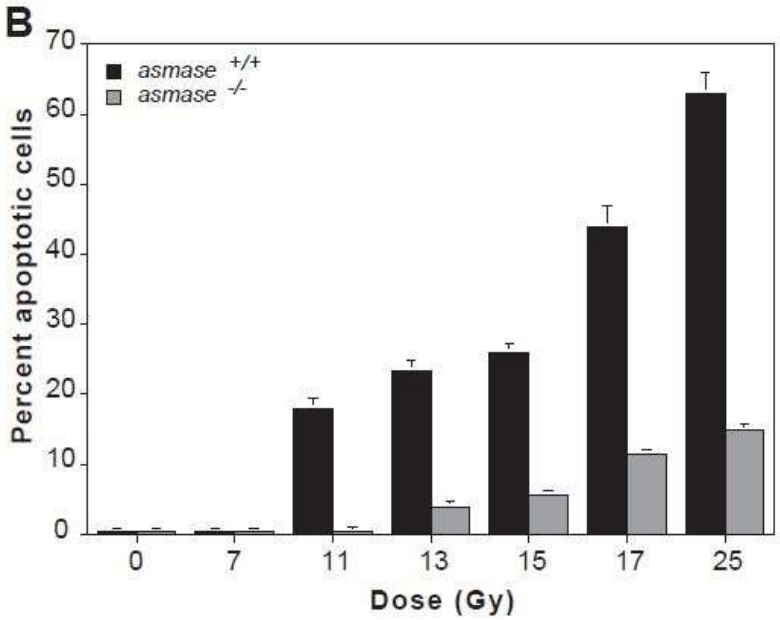
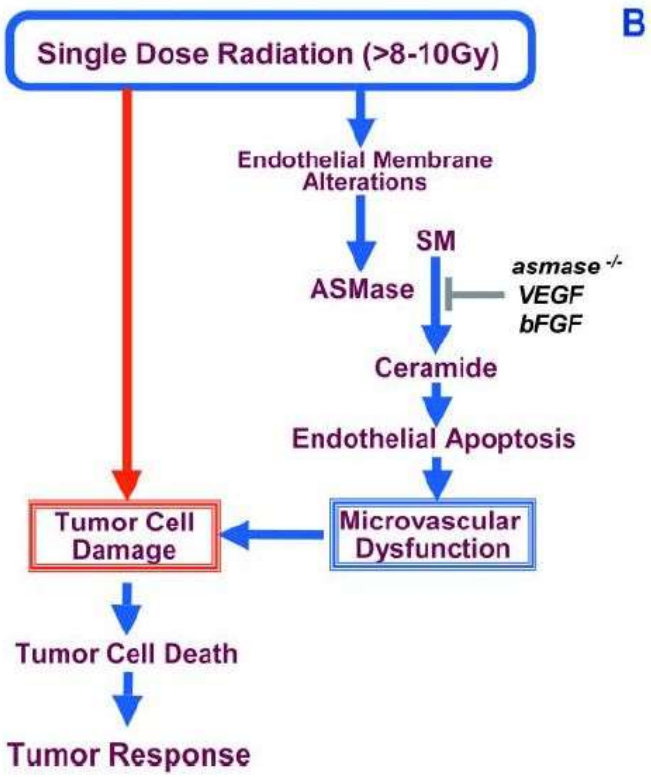


Fig. 4. Radiation effects on microvascular endothelial apoptosis. Radiation induces microvascular endothelial apoptosis in tissue explants from *asmase*$^{+/+}$ but not *asmase*$^{-/-}$ mice harboring MCA/129 fibrosarcomas. (**A**) Tumors

Garcia-Barros, Science 2003:300;1155-1159

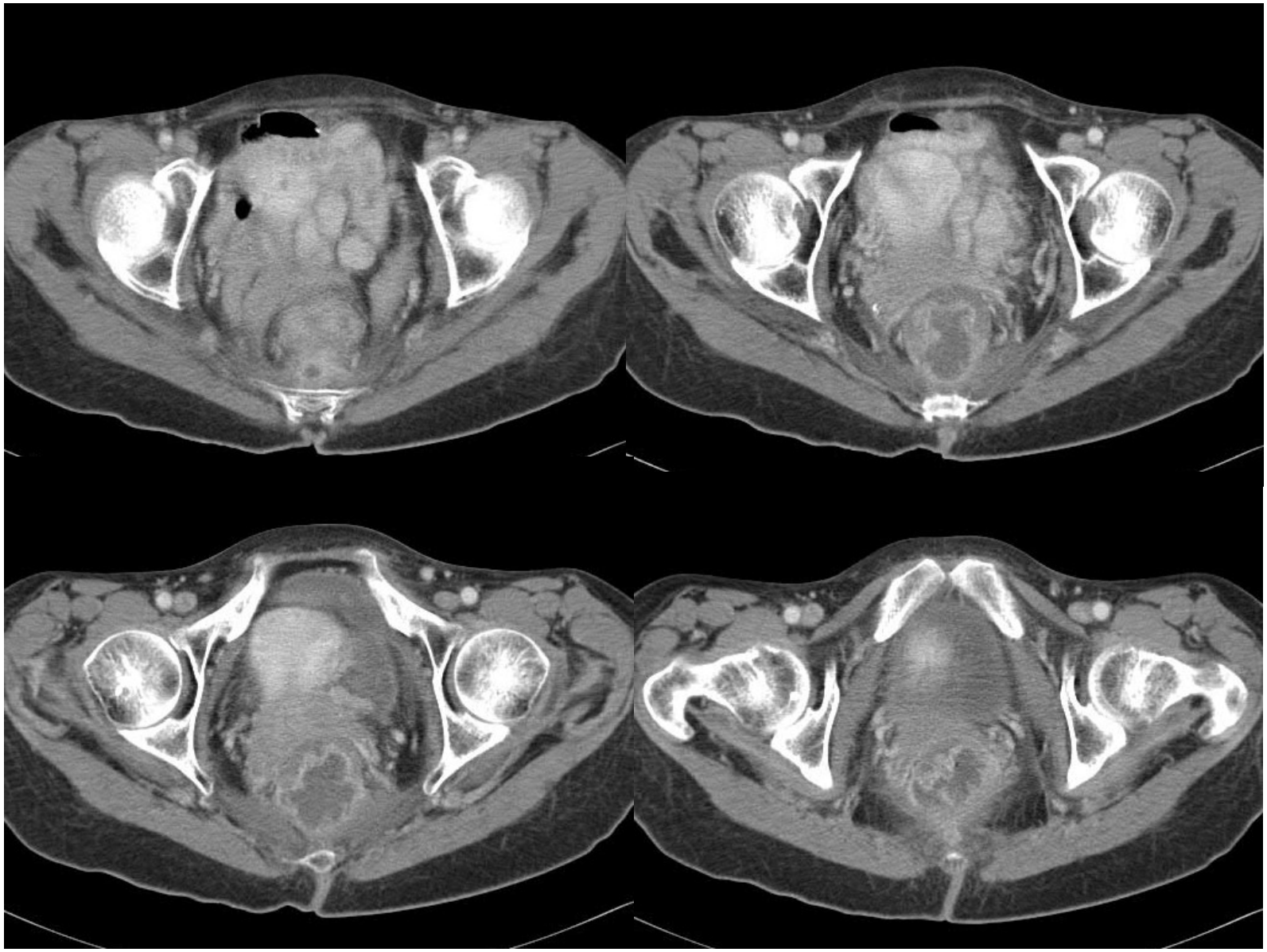
Vascular component of XRT response

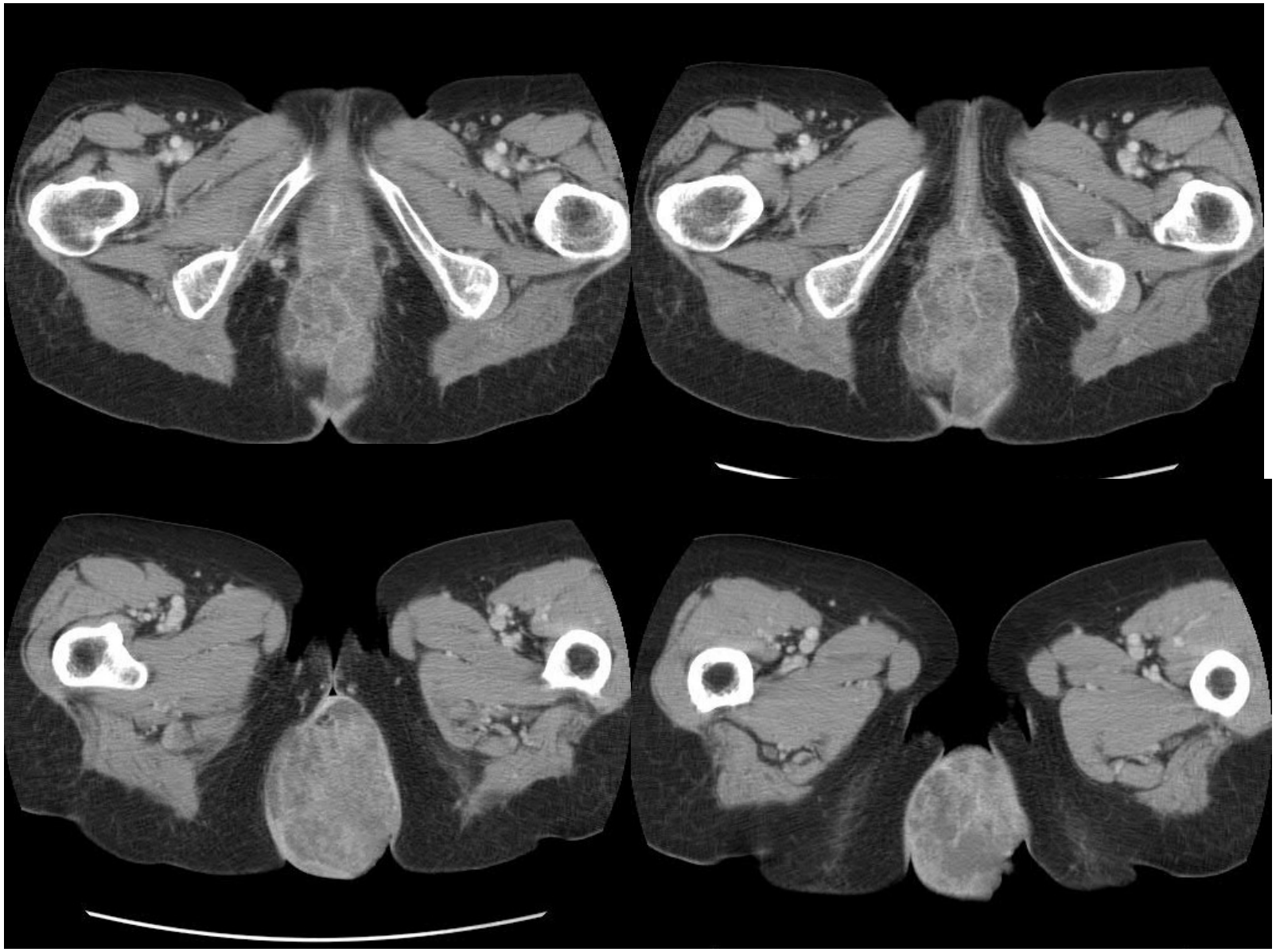


Fuks, Cancer Cell 2005;8:89-91

Recurrent Rectal Cancer
Flap Recurrence

- 54 yof fixed rectal cancer
  - 5580 cGy: unresectable
  - To Mayo: resection + IORT 15 Gy
  - Rectus abdominus flap
- 14 months later: recurrence in flap

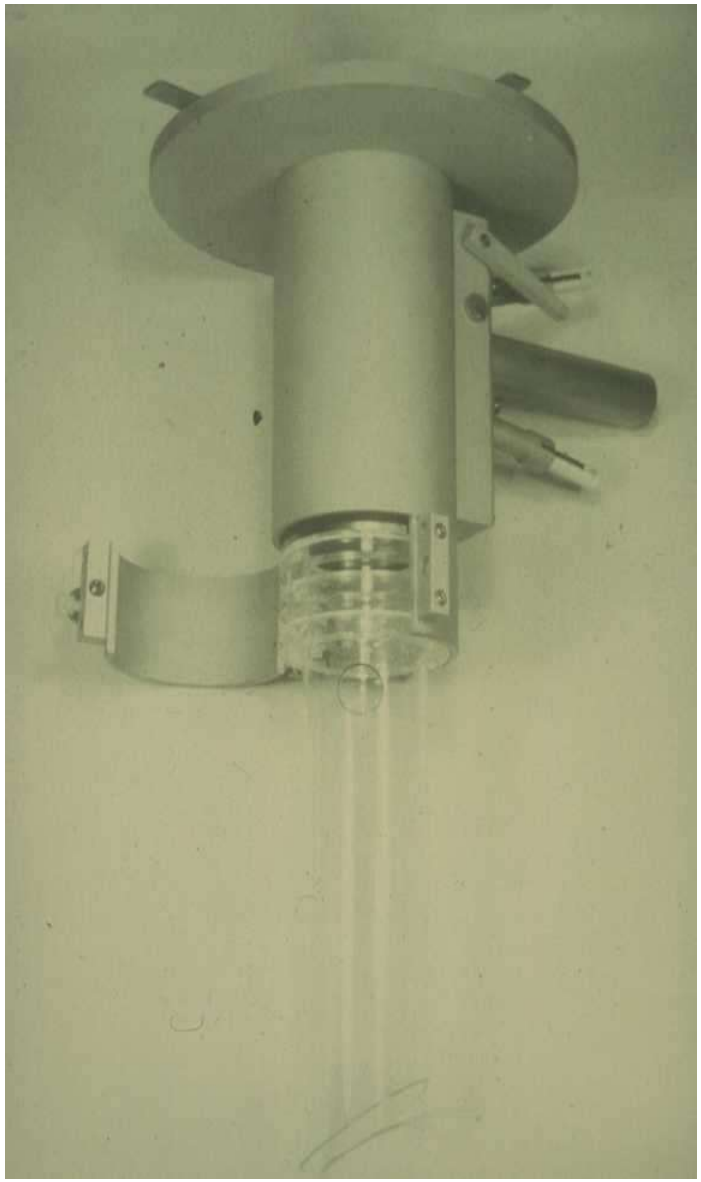




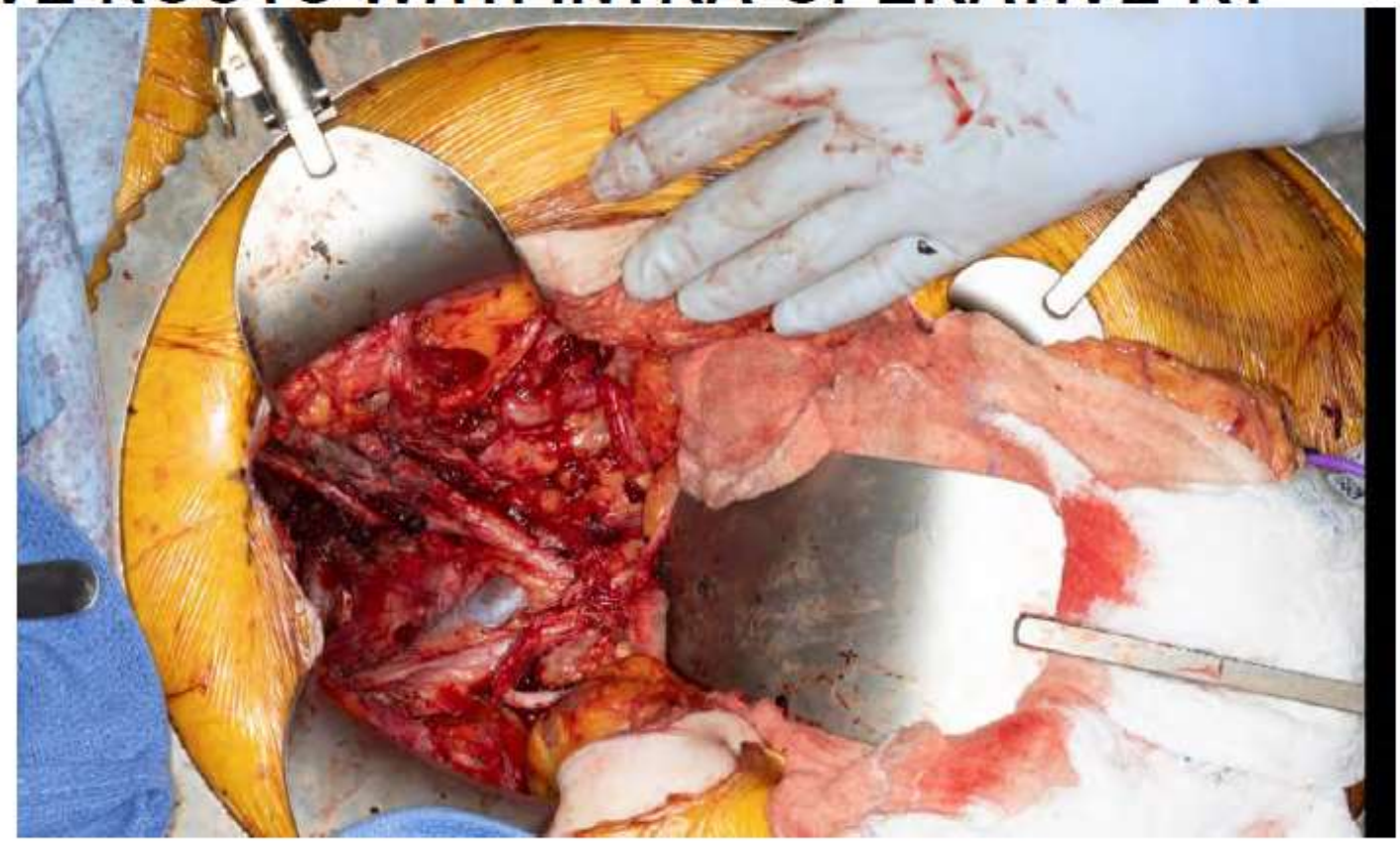
Mayo Clinic IORT Program

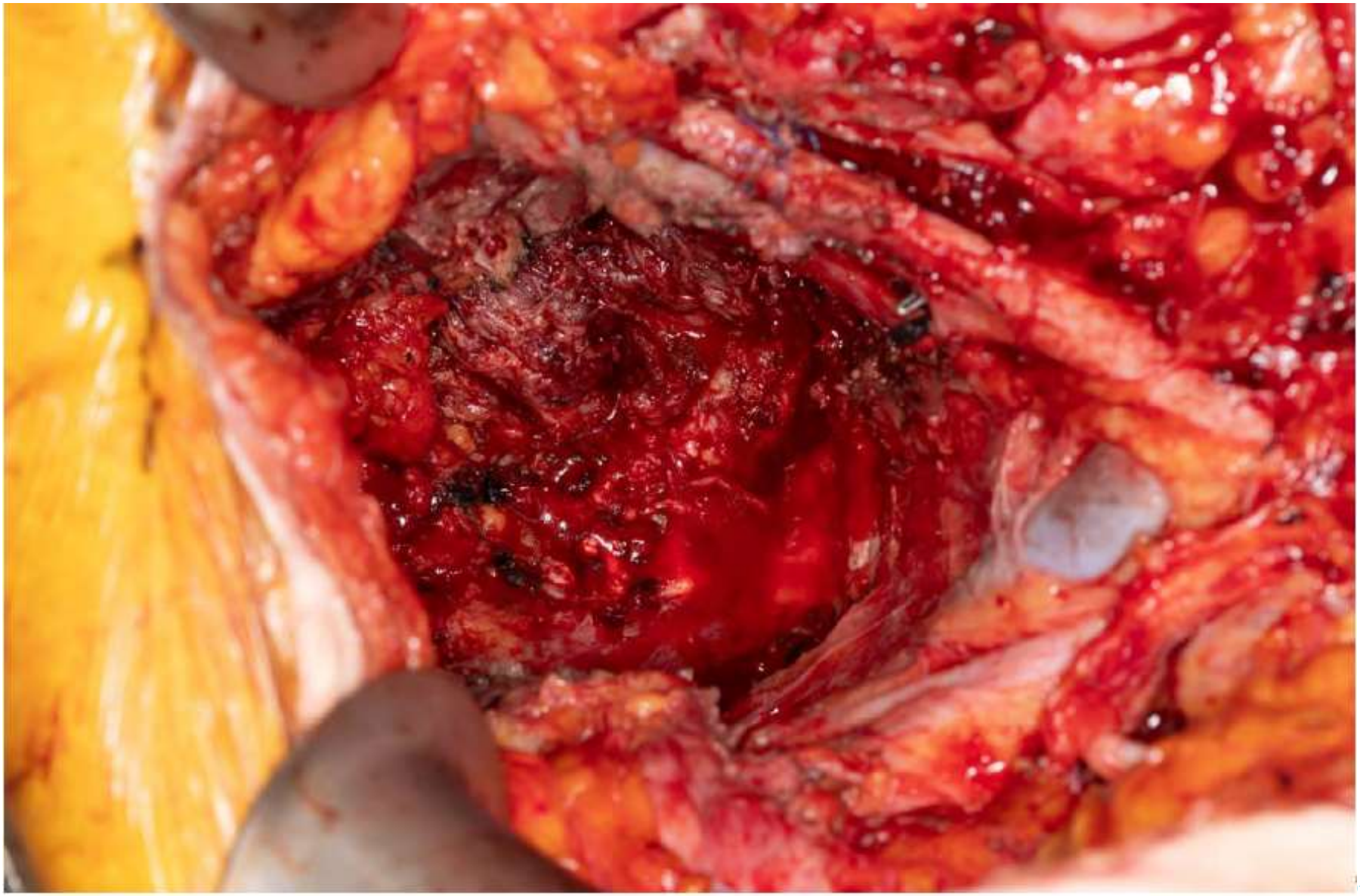
- Rochester
  - 1981: IORT in rad onc department
  - 1988: dedicated OR suite with refurbished linac
  - 2022: 2nd IORT (mobile electron unit)
- Phoenix: mobile electron unit in OR
- Jacksonville: mobile electron unit OR

IOERT - Mayo
Treatment Applicators

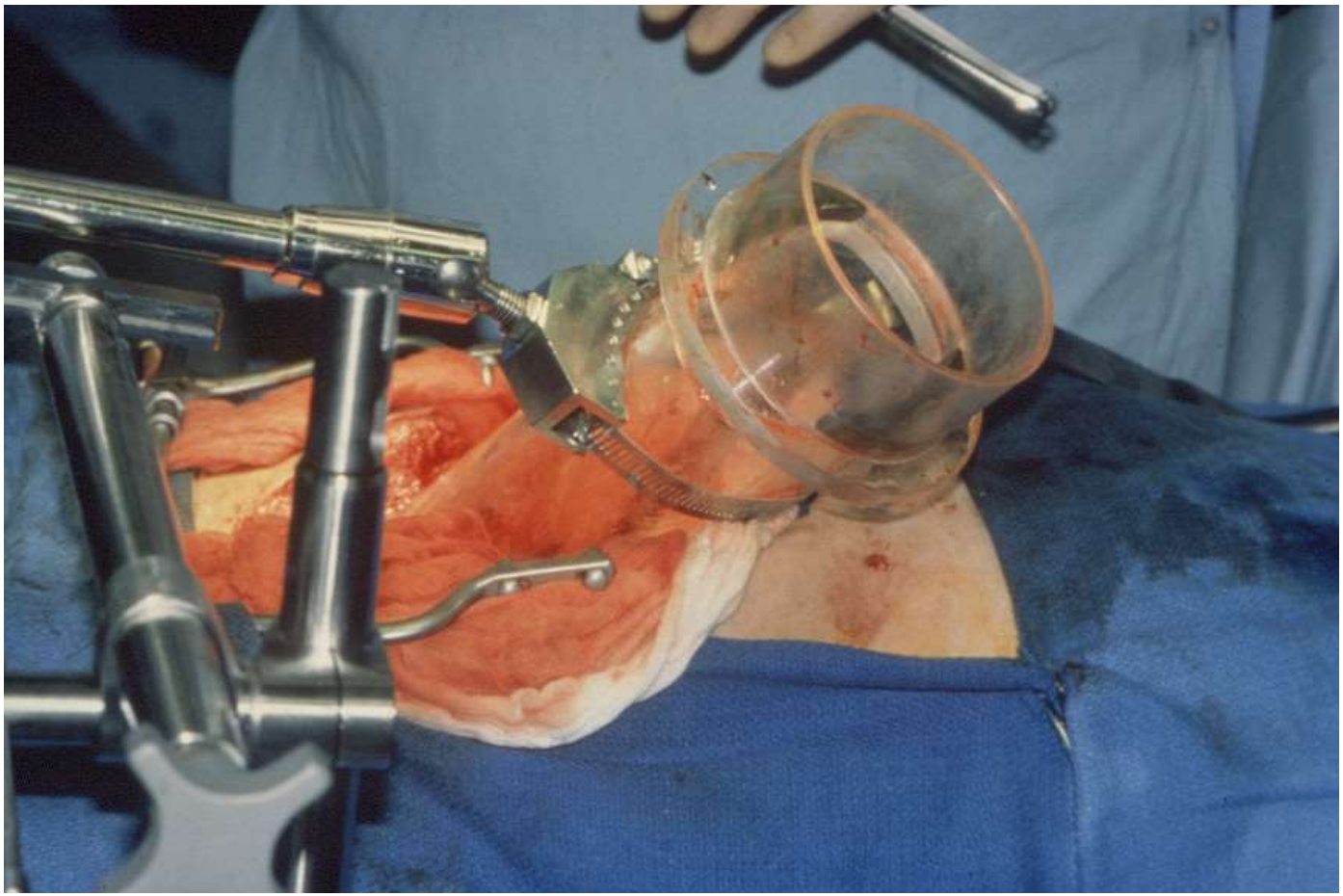


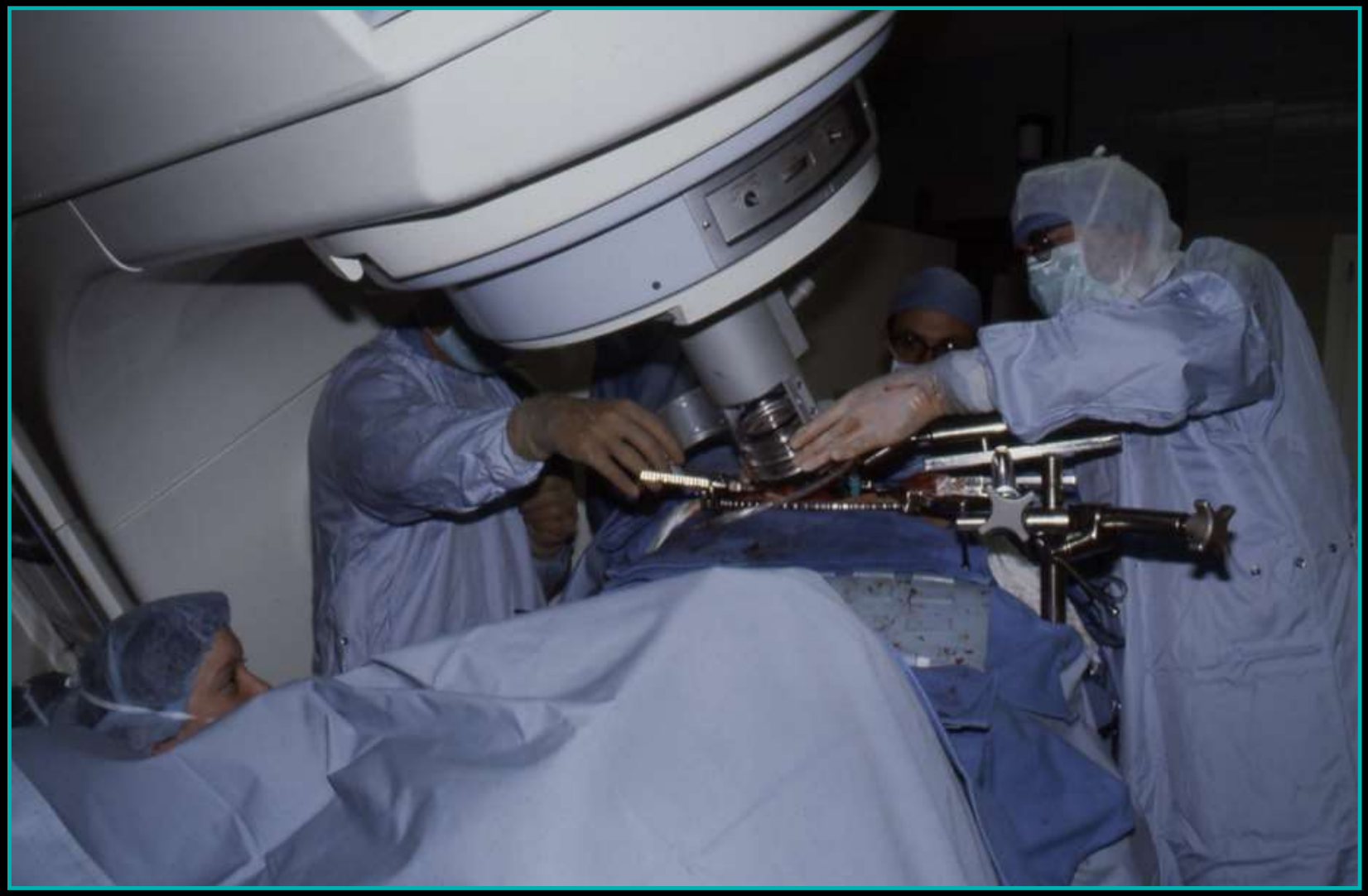
TOTAL EXENTERATION WITH RADICAL SIDE WALL RESECTION INCLUDING PORTION OF S2, S3-4 NERVE ROOTS WITH INTRA-OPERATIVE RT





IOERT - Mayo
Applicator Fixation





CP1044847-33

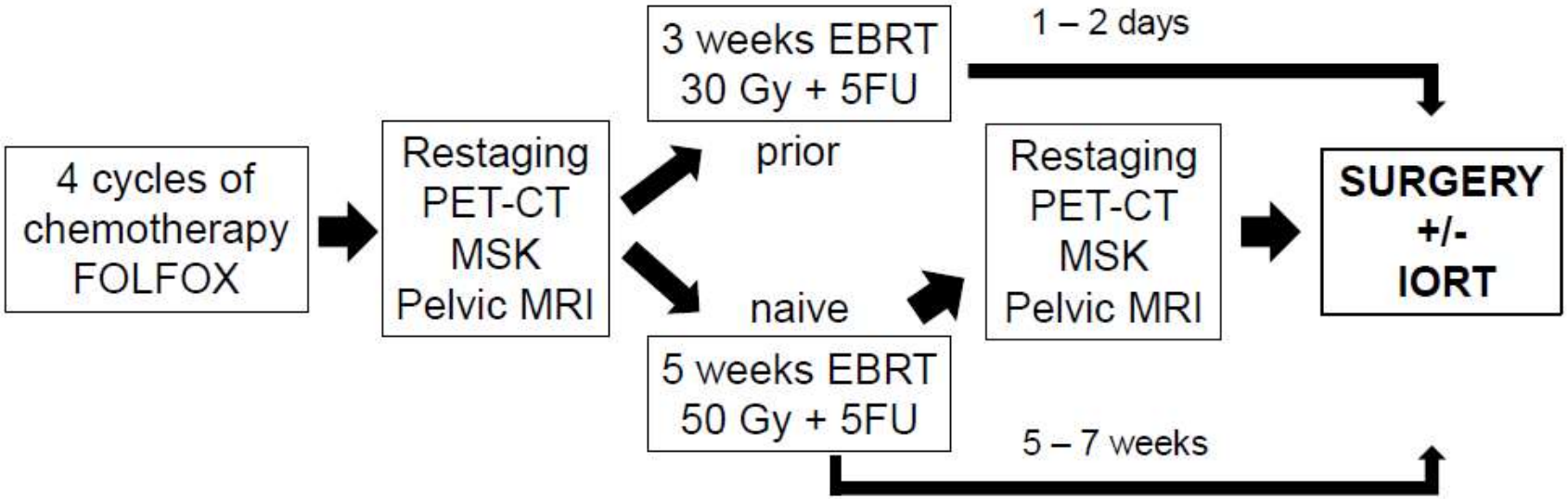
IOERT Cases – Mayo Rochester
April 1981 – May 2024

Site	Primary	Recurrent	Total
GI	513	1109	1622
Soft tissue/bone	593	382	975
GYN	47	283	330
GU	15	66	81
Head and Neck	14	33	47
Miscellaneous	14	20	34
Total	1196	1893	3089

IOERT Cases – Mayo Rochester
April 1981 – May 2024

Site	Primary	Recurrent	Total
Esophogogastric	43	17	60
Small bowel	33	13	46
Hepatobiliary	26	7	33
Pancreas	137	14	151
Colon	56	271	327
Rectum	225	752	977
Anus	17	41	58
Total	537	1115	1652

SEQUENCING OF MODALITIES FOR RECTAL CANCER
(CURRENT APPROACH)



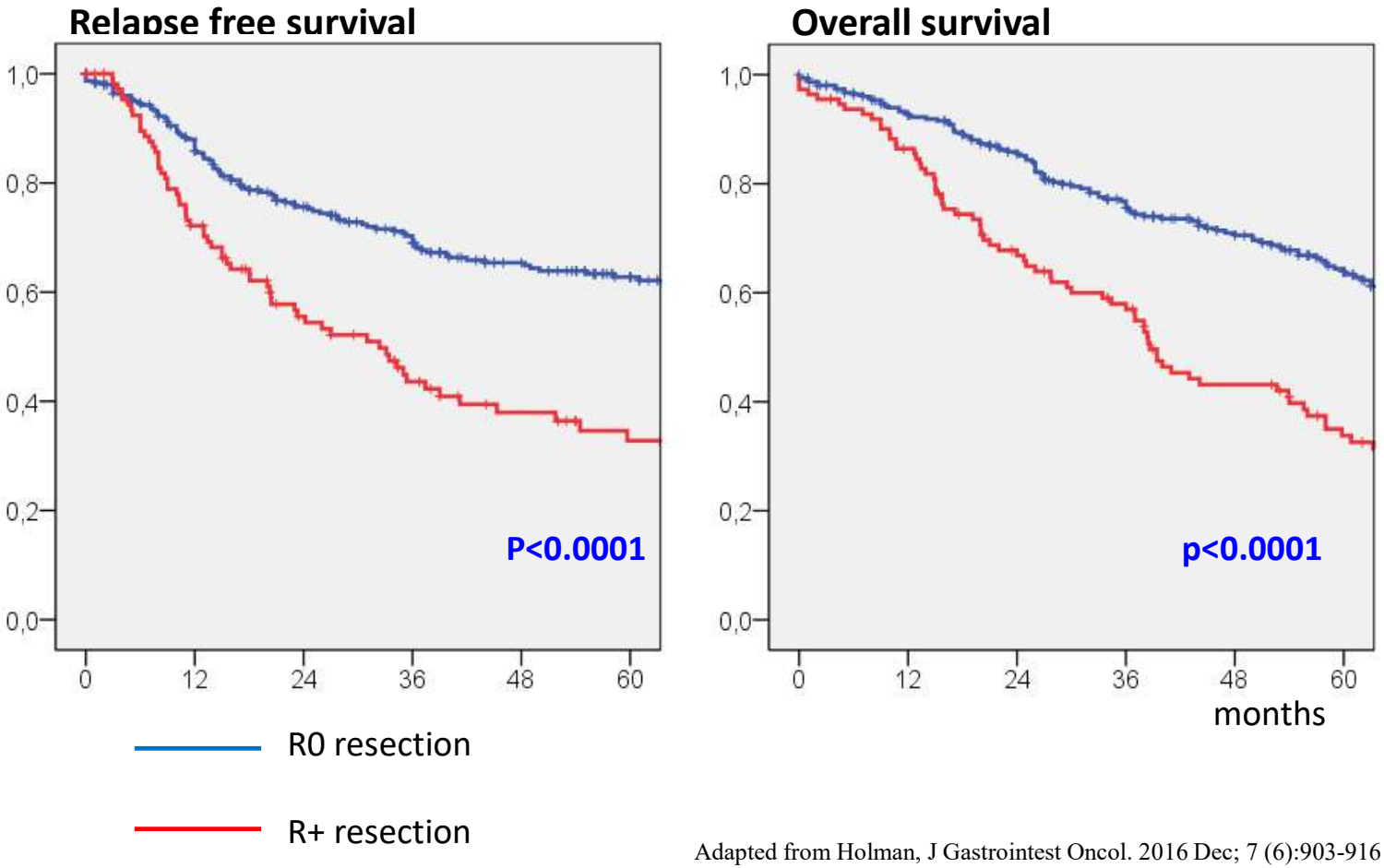
Locally Advanced Rectal Cancer
Selected Series

Study	# Pts	Years	EBRT , Gy	Margins	IORT , Gy	5-yr LC	5-yr DM	5-yr OS
Willett, MGH	20	1978-1989	50.4	R0	10-20	88%	-	53%*
Valentini, Rome	29	1991-2006	45-55	R0	10-15	100%	-	-
Alberda, Rotterdam	31	1996-2012	45-50**	R1	10^	84%	-	-
Zhang, Shanghai	71	1994-2007	45-50.4	R0-1	10-20	90%	54%	75%
Sadahiro, Japan	99	1991-2001	20	ns	15-25	98%	20%	79%
Mathis, Mayo Clinic	106	1981-2007	50.4	R0-2	7.5-25	86%^^	49%^^	49%
Roeder, Heidelberg	243	1991-2004	41.4	R0-2	10-15	92%	-	-
Sole, Madrid	335	1995-2010	45-50.4	R0-1	10-15	92%	25%***	75%
Kusters, European pooled[32]	605	to 2005	45-50.4	R0-2	10-12.5	88%	29%	67%

*DFS, **some pts 25/5, ***crude, ^IOHDR, ^^40 colon primary

T4 Rectal CA – IOERT Pooled Analysis, MCR-CHE

Survival Outcomes vs Radicality of Resection-417 pts

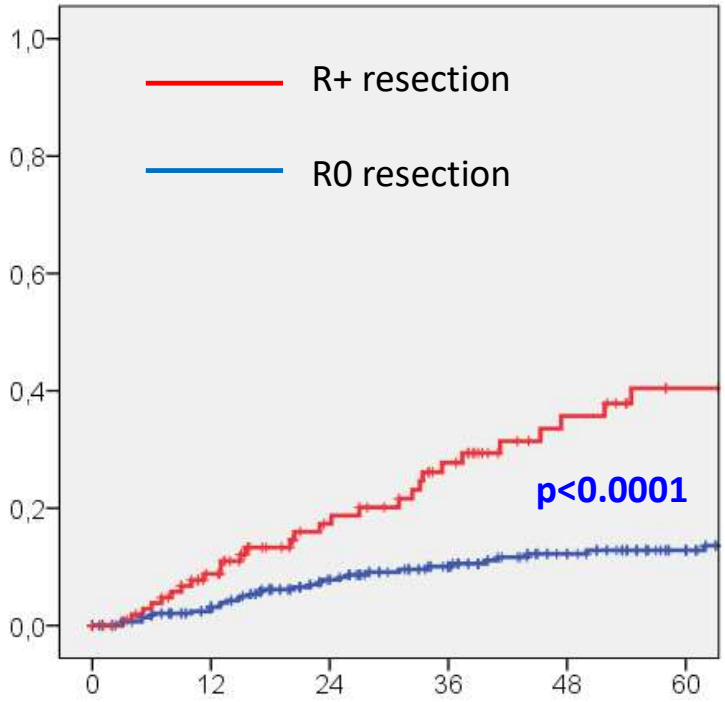


Adapted from Holman, J Gastrointest Oncol. 2016 Dec; 7 (6):903-916

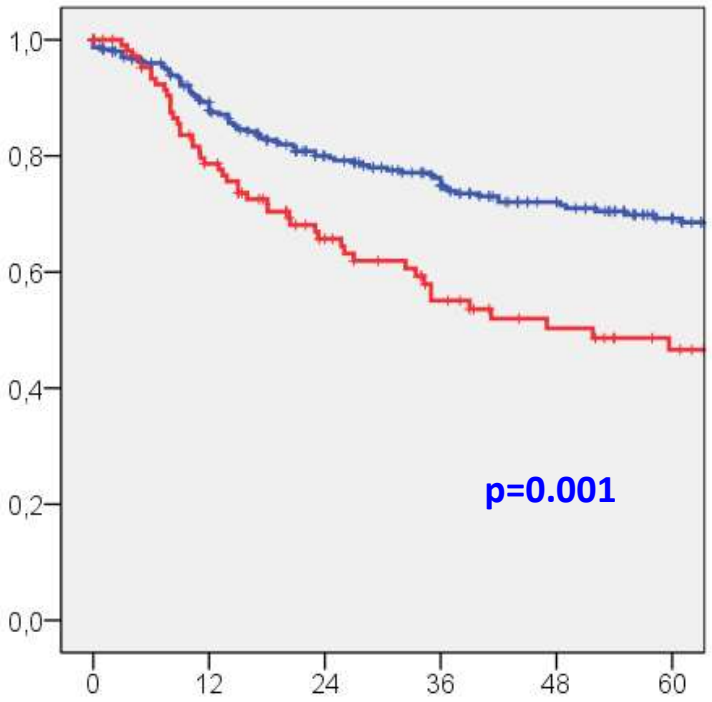
T4 Rectal CA – IOERT Pooled Analysis, MCR-CHE

Relapse Outcomes vs Radicality of Resection – 417 pts

Local recurrence rate



Metastasis free survival rate

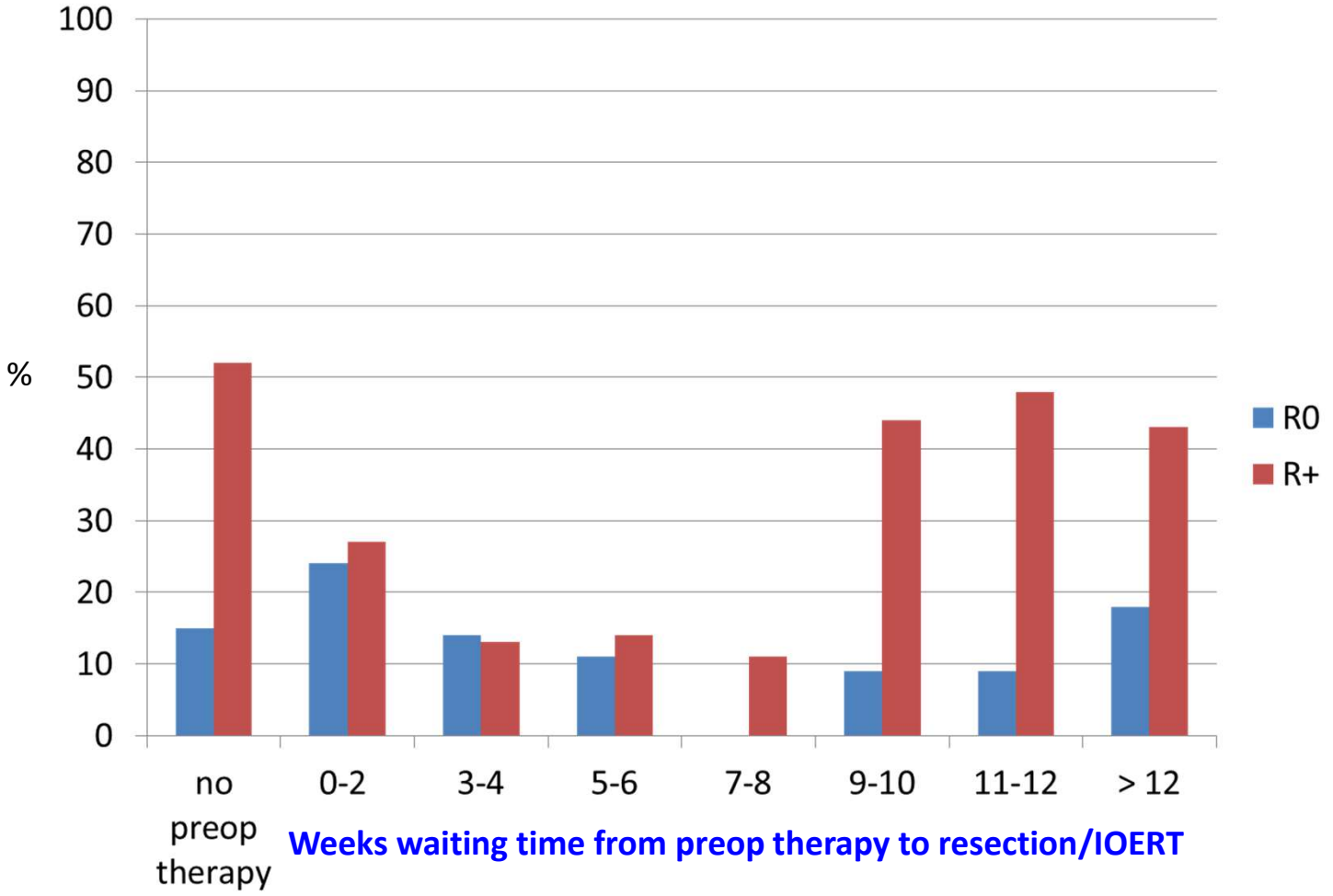


months

Adapted from Holman, J Gastrointest Oncol. 2016 Dec; 7 (6):903-916

T4 Rectal CA, IOERT Pooled Analysis, MCR-CHE

3-year Local Relapse vs Waiting Times, R0/R+ Resection



Adapted from Holman, J Gastrointest Oncol. 2016 Dec; 7 (6):903-916

Recurrent Rectal Cancer

- 29 yof with T3N2 rectal cancer at 12 cm
- LAR, 9 of 26 nodes +, margins –
- 6 months of 5-FU + leucovorin
- 1 year later: anastomotic and presacral relapse

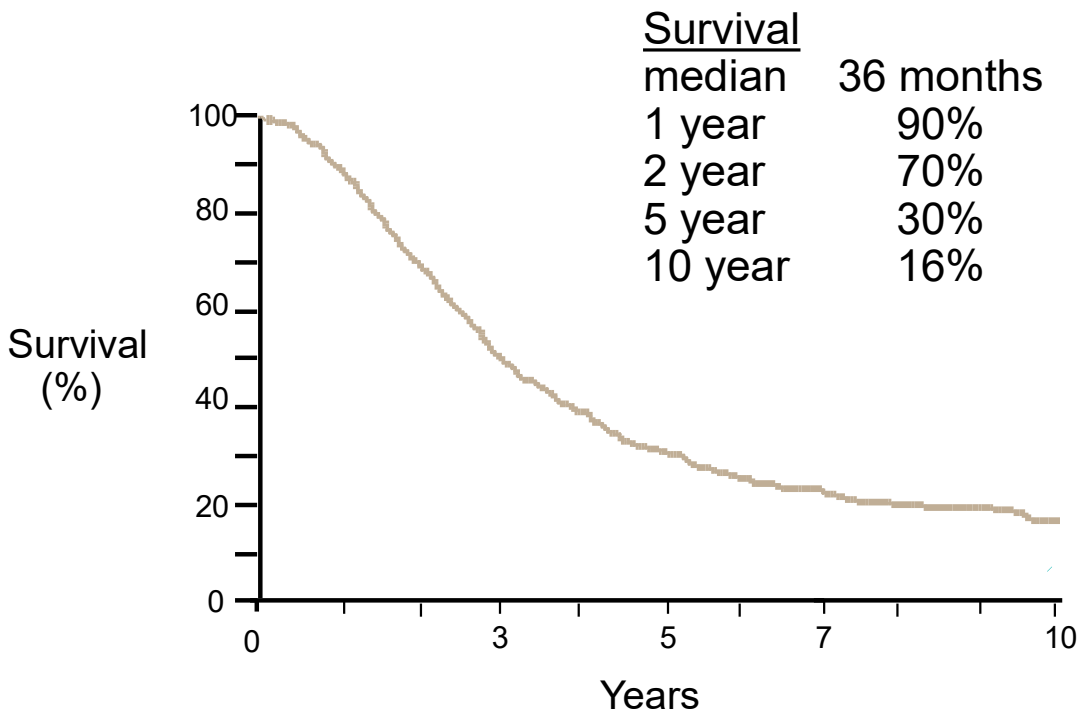
IORT Case
Recurrent Rectal Cancer

- EBRT 5040 cGy in 28 fxs with 5-FU
- Proctectomy with coloanal anastomosis
- R1 resection
- IOERT 1500 cGy, 6.5 cm cone, 9 MeV

IORT Case
Recurrent Rectal Cancer

- J-pouch fistula requiring resection and permanent colostomy at year 5
- Stress urinary incontinence
- NED at 10 years

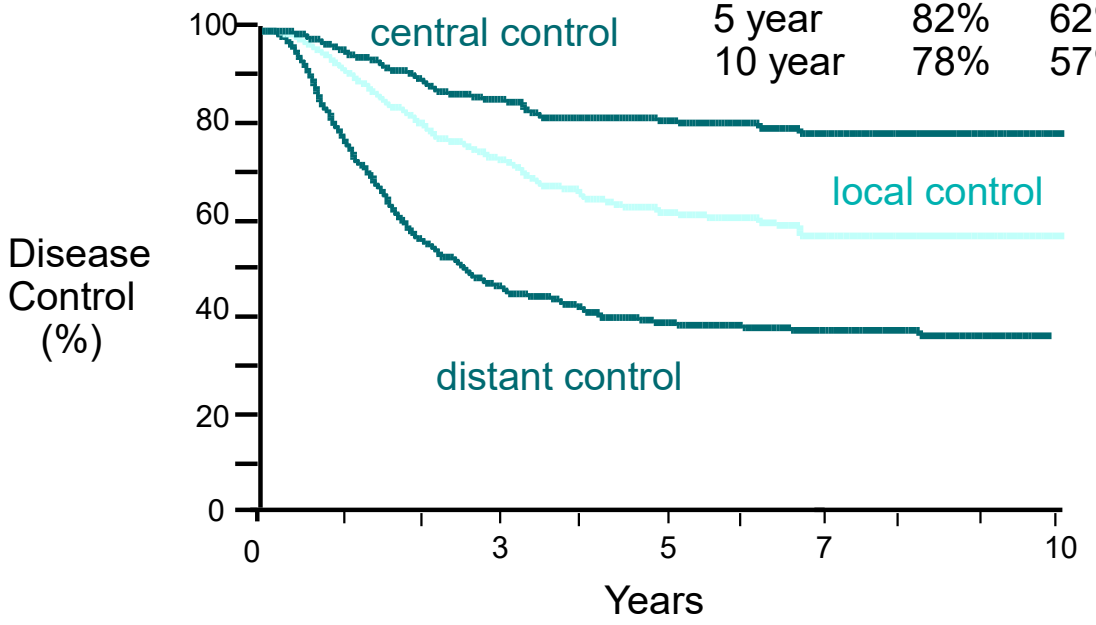
Overall Survival
Recurrent Colorectal IOERT



Adapted from Haddock, Int J Radiat Oncol Biol Phys 2011;79:143-150

Disease Control - Recurrent Colorectal Ca

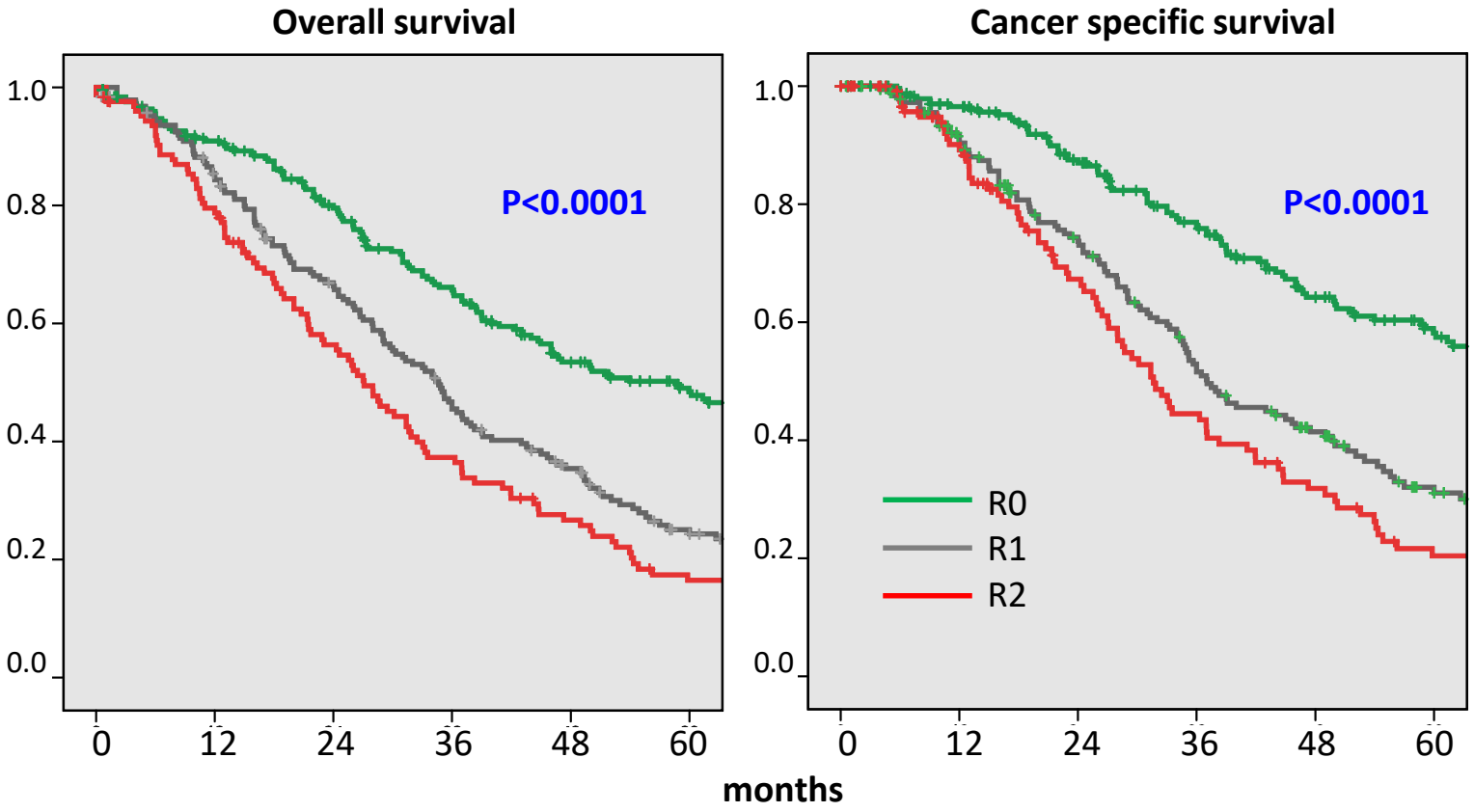
Endpoint	CC	LC	DC
crude	87%	74%	51%
1 year	96%	92%	78%
2 year	90%	80%	56%
5 year	82%	62%	38%
10 year	78%	57%	36%



Adapted from Haddock, Int J Radiat Oncol Biol Phys 2011;79:143-150

LRRC – IOERT Pooled Analysis, MCR-CHE, 565 pts

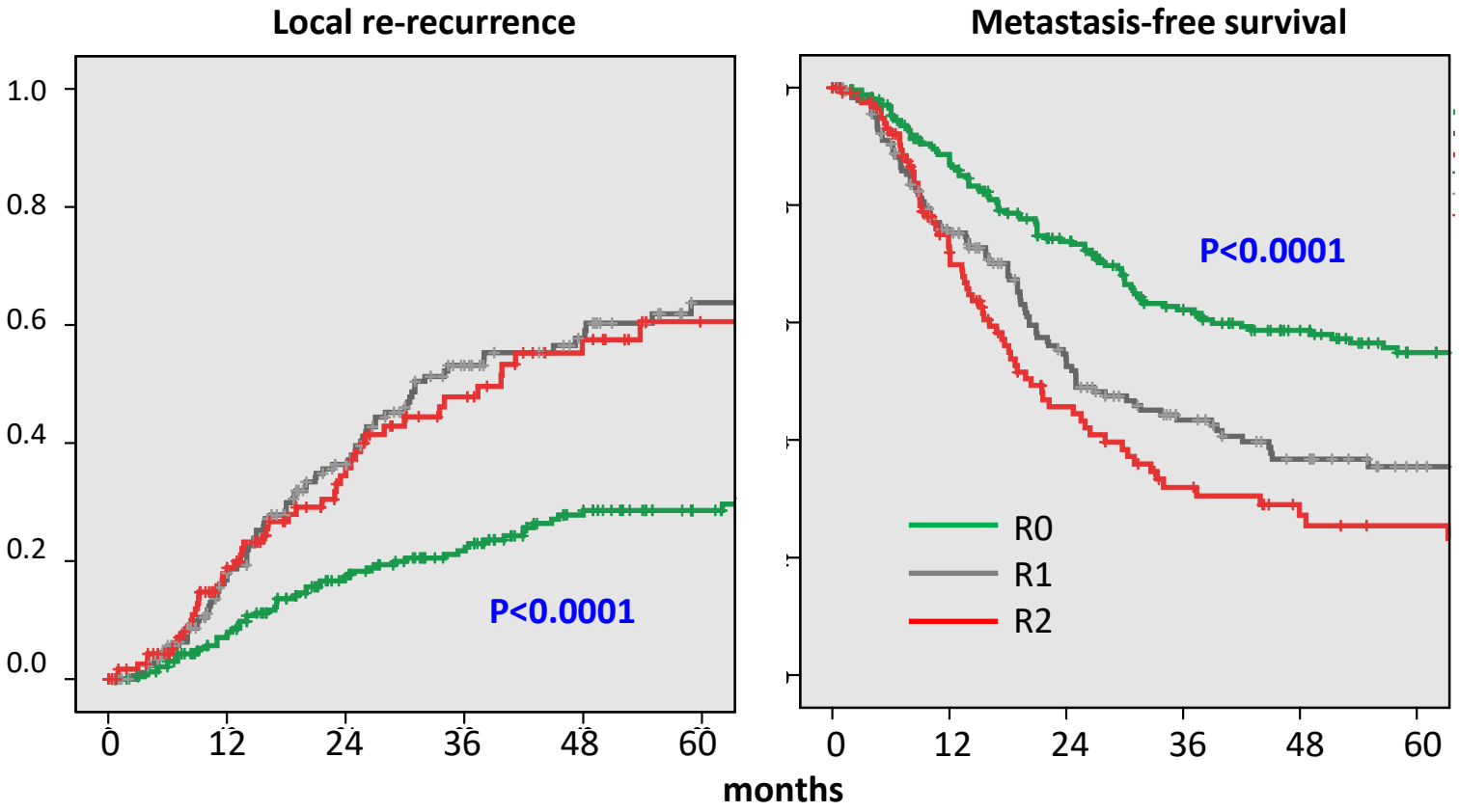
Survival Outcomes vs Radicality of Resection



Adapted from Holman, Eur J Surg Oncol. 2017 Jan; 43 (1):107-117

LRRC – IOERT Pooled Analysis, MCR-CHE, 565 pts

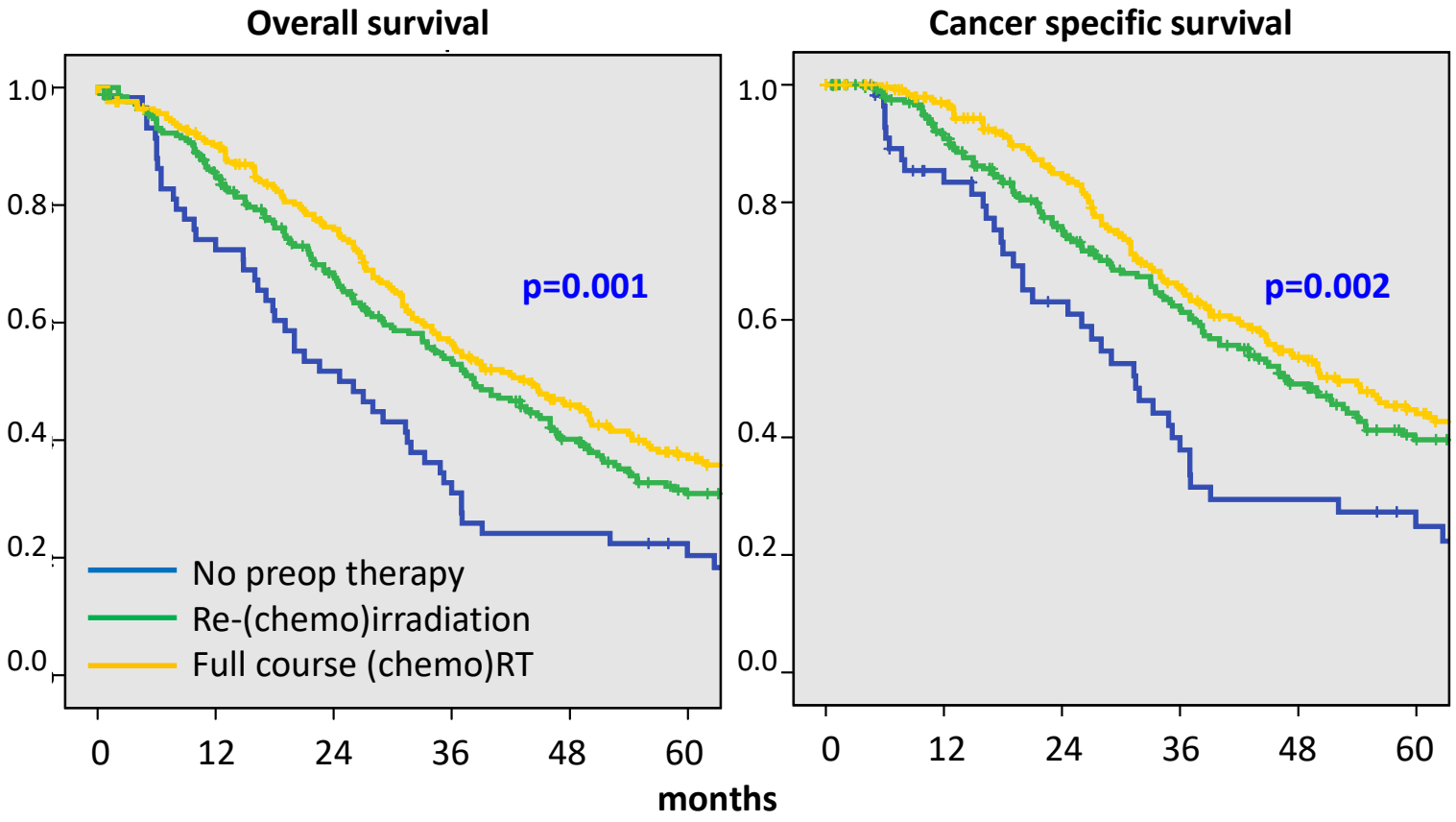
Relapse Outcomes vs Radicality of Resection



Adapted from Holman, Eur J Surg Oncol. 2017 Jan; 43 (1):107-117

LRRC – IOERT Pooled Analysis, MCR-CHE, 565 pts

Survival Outcomes vs Preoperative Treatment



Adapted from Holman, Eur J Surg Oncol. 2017 Jan; 43 (1):107-117

IORT Results – Recurrent Colorectal Ca
R0 resection

Series	#Pts	EBRT (Gy)	IORT (Gy)	5-yr S (%)	LR (%)
Vermaas 2005	17	50	10	45 (3yr)	65
Alektiar 2000	53	45-50	10-18	36	57
Abuchaibe 2000	8	40-50	15	29	50
Dresen 2008	84	30-50	10	59 (3yr)	25
Lindel 2001	25	50	10-15	40	44
Eble 1998	14	41.4	12-20	71(4yr)	21
Wiig 2002	18	46-50	15	60	30
Valentini 1999	11	45-47	10-15	41	20
Haddock 2010	236	30-50	12.5	46	28

IORT Results – Recurrent Colorectal Ca R1 resection

Study	# Pts	EBRT dose, Gy	IORT dose, Gy	IORT technique	5-year LC	5-yr DM	5-yr OS
Alektiar, MSKCC	21	50.4*	10-18	IOHDR	26%	-	11%
Wiig, Norway	29	46-50	15-20	IOERT	50%	-	20%
Eble, Heidelberg**	9	41.4	10-20	IOERT	67%	33%	33%^
Dresen, Eindhoven***	34	50.4^^	12.5	IOERT	29%	69%	27%
Haddock, Mayo Clinic	224	50.4^^^	15	IOERT	56%	62%	27%

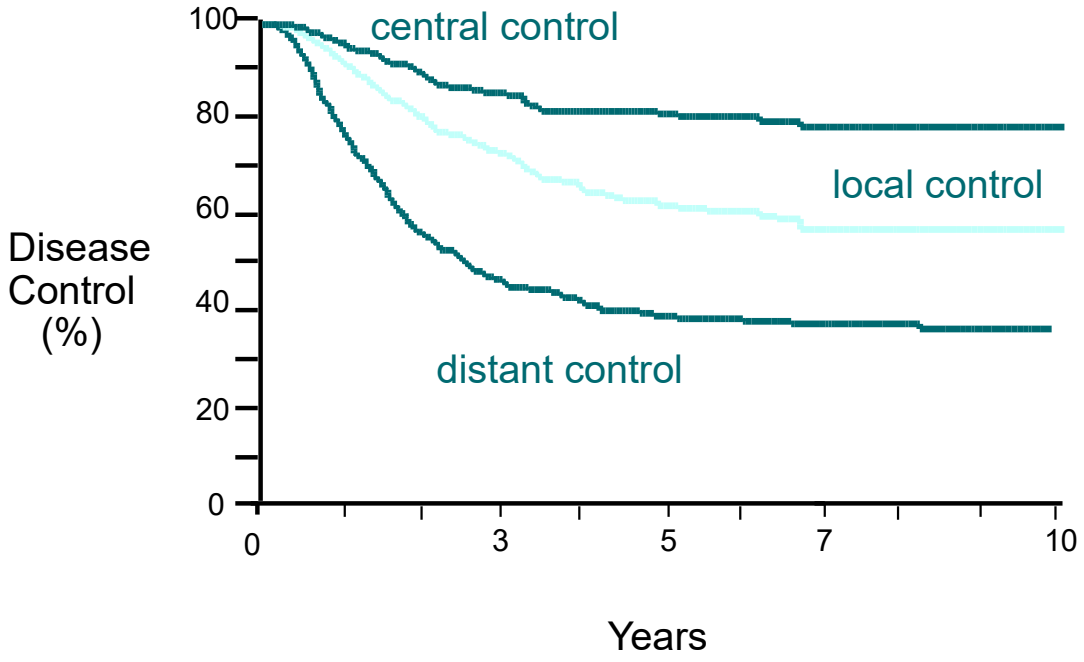
*50.4 in patients with no prior EBRT; no EBRT in patients with prior radiation
**4-year results
^4-year relapse free survival^^30.6 Gy in previously irradiated patients
^^^5-39.6 Gy in previously irradiated patients
***3-year results

IORT Results- Recurrent Colorectal Ca R2 resection

Study	# Pts	EBRT dose, Gy	IORT dose, Gy	5-year LC	5-yr DM	5-yr OS
Lindel, MGH	15	50.4*	15-20	12%	-	13%
Eble, Heidelberg**	8	41.4	10-20	60%	75%	25%^
Dresen, Eindhoven	29	50.4^^	15-17.5	29%	71%	24%
Haddock, Mayo Clinic	156	50.4^^^	20	49%	73%	16%

*20-50 Gy in previously irradiated patients
**4-year results
^4-year relapse free survival
^^30.6 Gy in previously irradiated patients
^^^5-39.6 Gy in previously irradiated patients

Disease Control - Recurrent Colorectal Ca

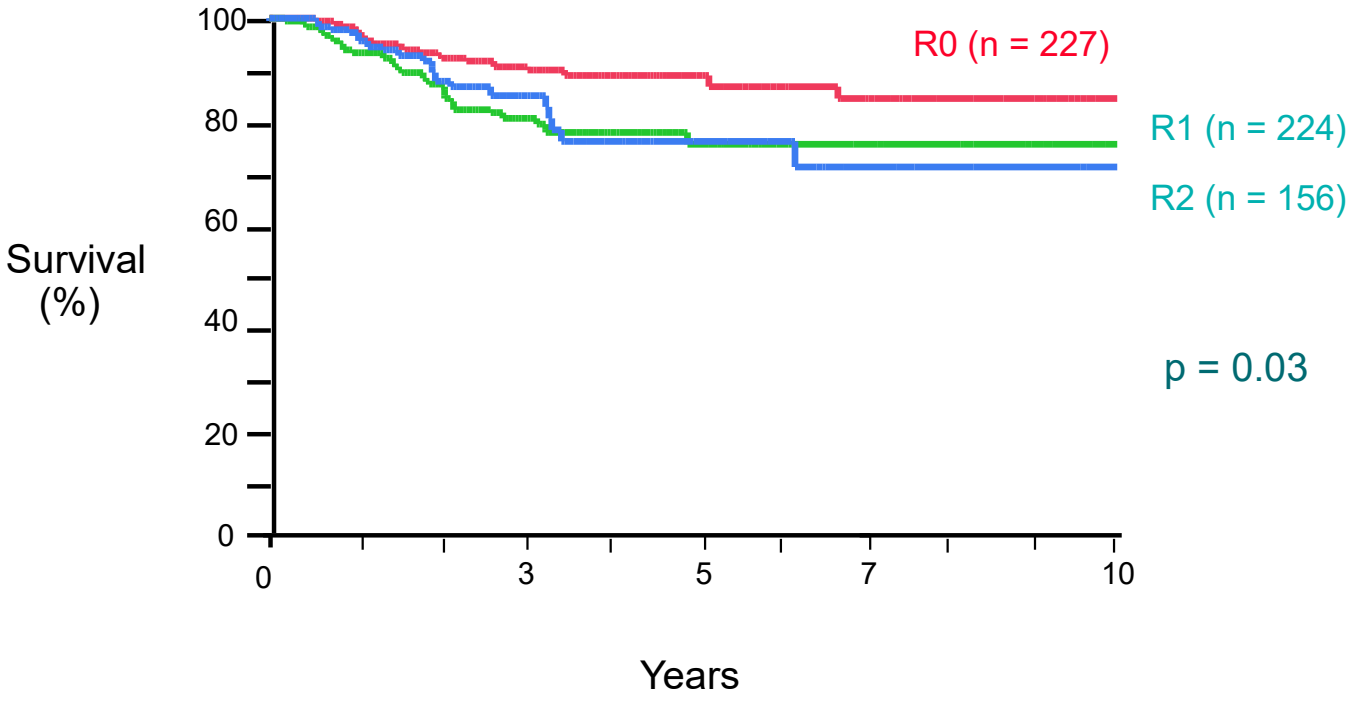


Endpoint	CC	LC	DC
crude	87%	74%	51%
1 year	96%	92%	78%
2 year	90%	80%	56%
5 year	82%	62%	38%
10 year	78%	57%	36%

Central Disease Control

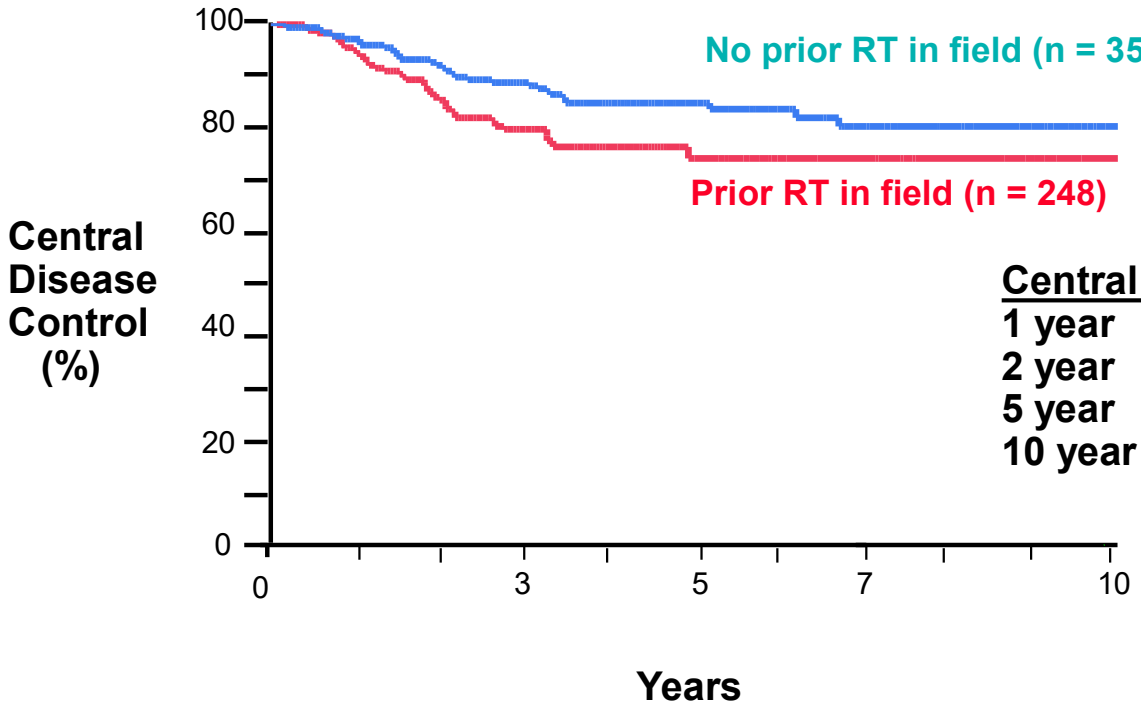
R0 vs. R1 vs R2

Central Control	R0	R1	R2
1 year	98%	93%	97%
2 year	93%	87%	88%
5 year	89%	76%	76%
10 year	84%	76%	71%



Central Disease Control

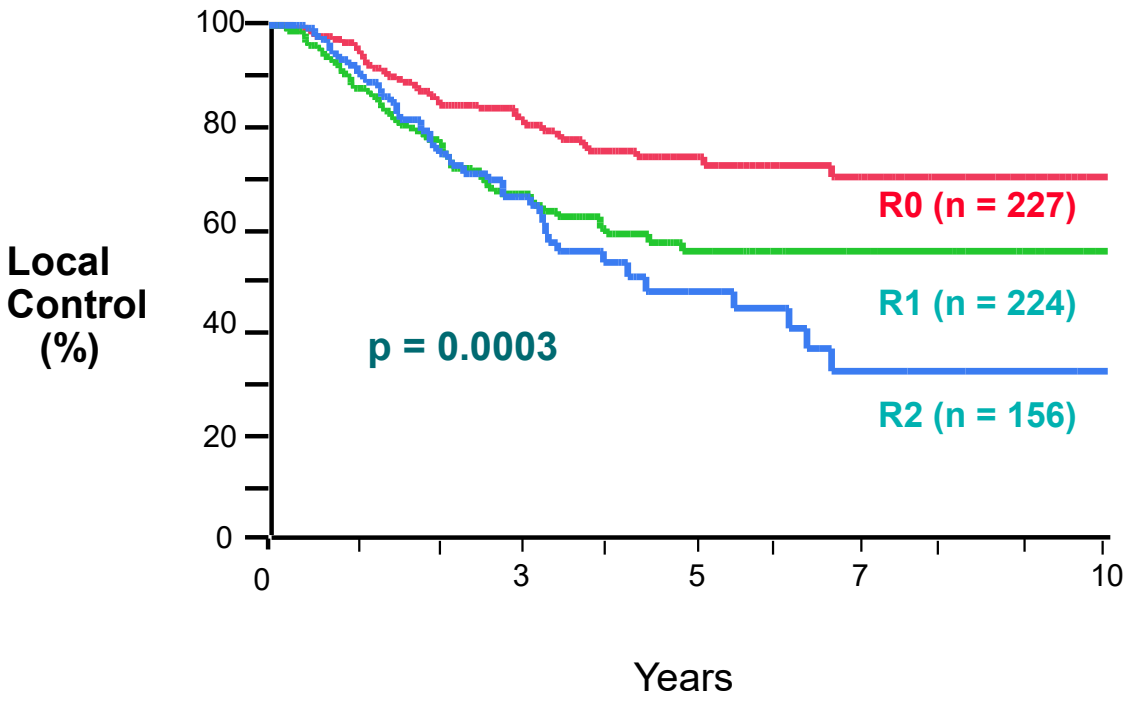
Recurrent Colorectal Ca - Prior RT in field



Central Control	Prior RT	No Prior RT
1 year	95%	97%
2 year	85%	92%
5 year	77%	85%
10 year	74%	81%

Local Control

Recurrent Colorectal Ca – R0 vs R1 vs R2

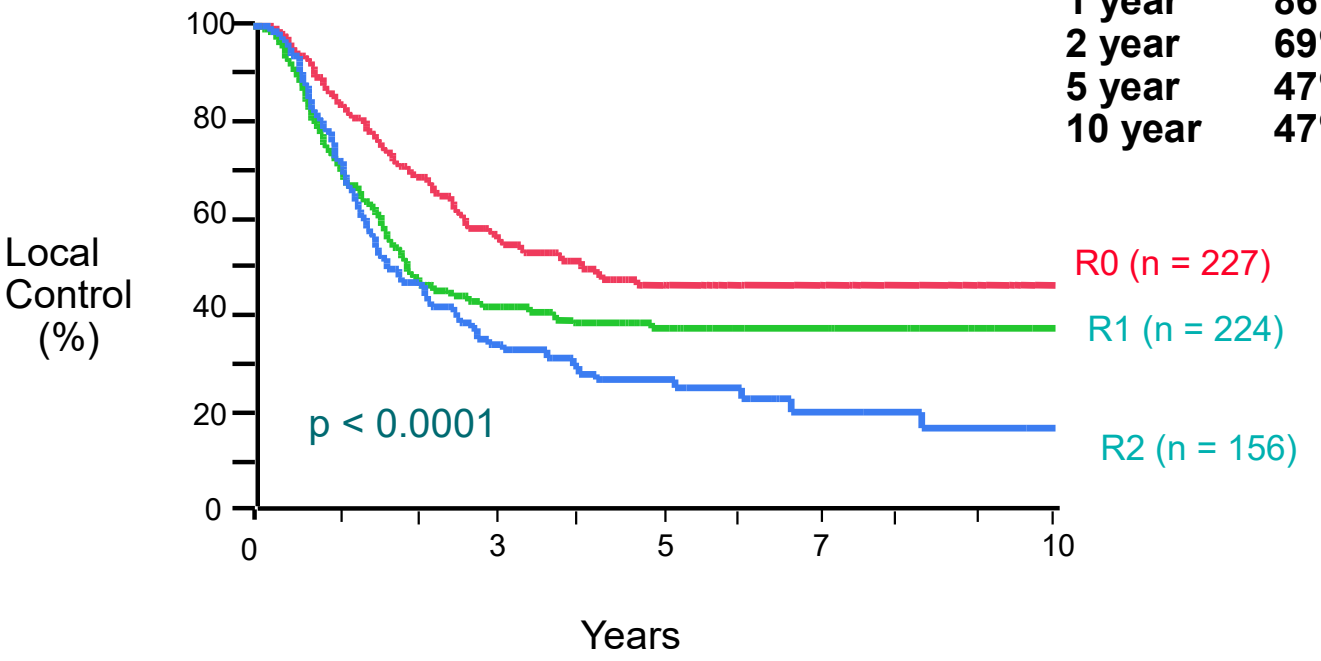


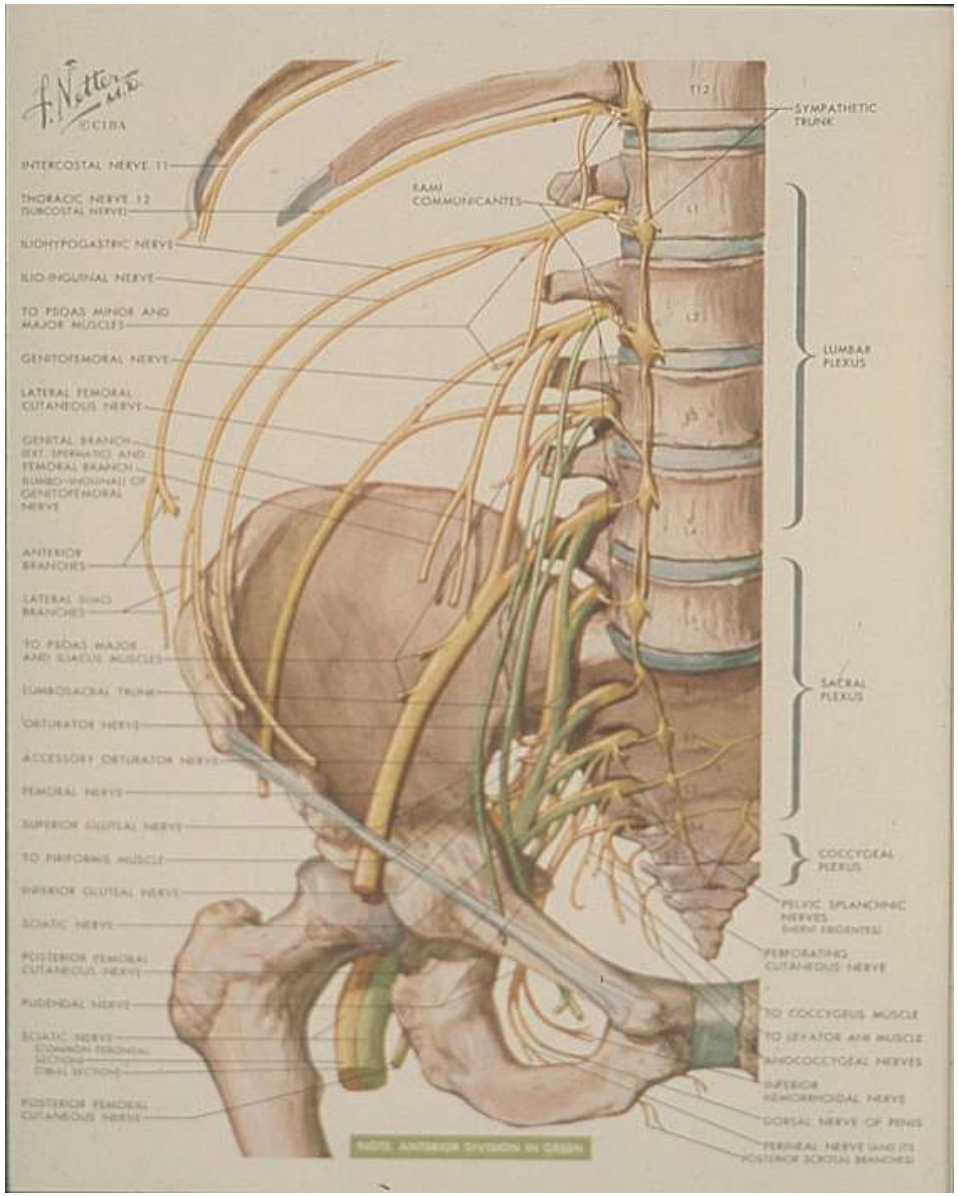
Endpoint	R0	R1	R2
1 year	97%	88%	92%
2 year	85%	78%	76%
5 year	74%	56%	49%
10 year	71%	56%	33%

Distant Control

Recurrent Colorectal Ca – R0 vs R1 vs R2

Endpoint	R0	R1	R2
1 year	86%	72%	76%
2 year	69%	49%	47%
5 year	47%	38%	27%
10 year	47%	38%	17%





IOERT Related Neuropathy

Recurrent Colorectal Cancer

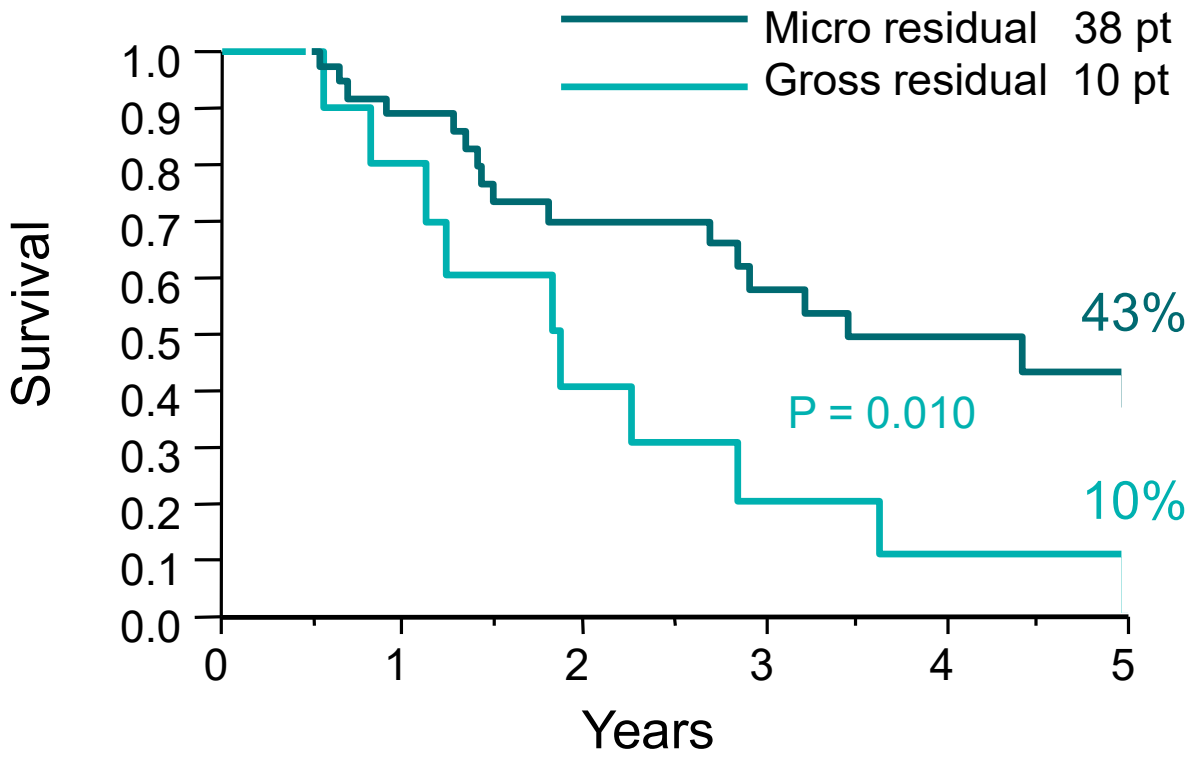
	IOERT Dose	
	≤ 1250 cGy	> 1250 cGy
any neuropathy	9%	21%
Grade 1	3%	7%
Grade 2	4%	10%
Grade 3	1%	4%

P = 0.0003

Haddock, Int J Radiat Oncol Biol Phys 2011;79:143-150

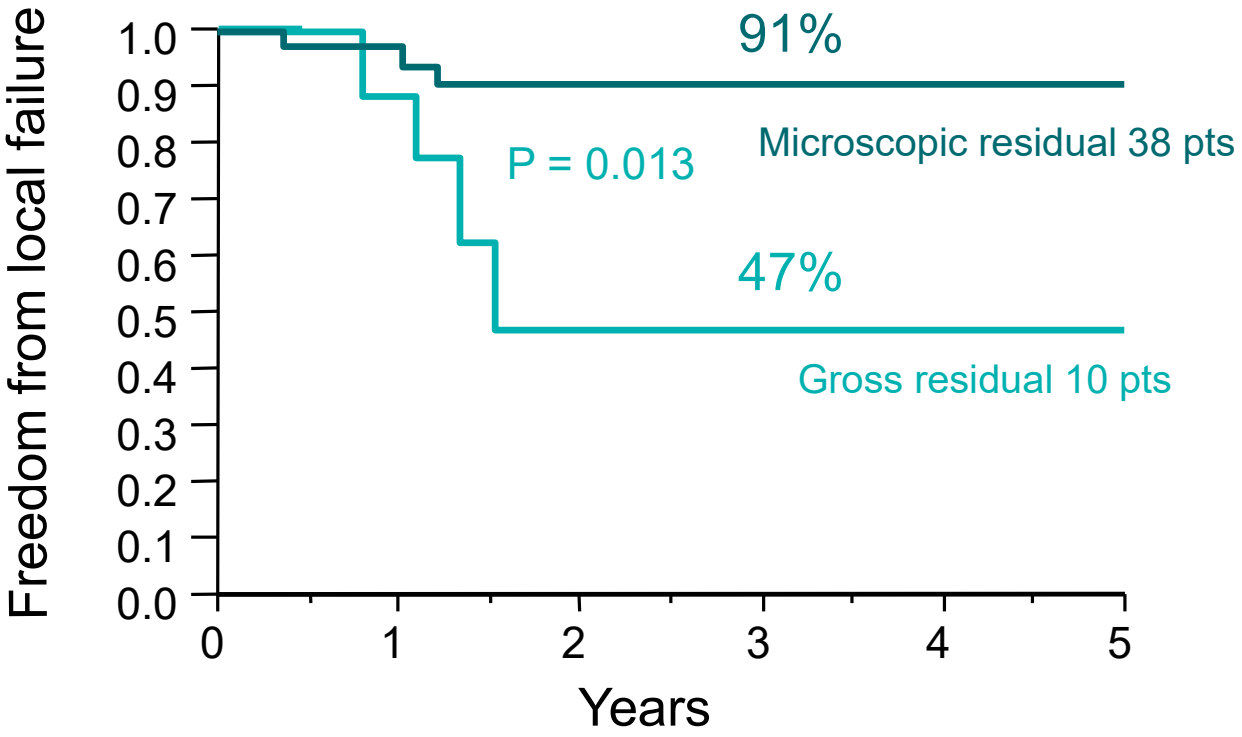
IOERT for Colorectal Nodal Mets

Survival by volume of residual



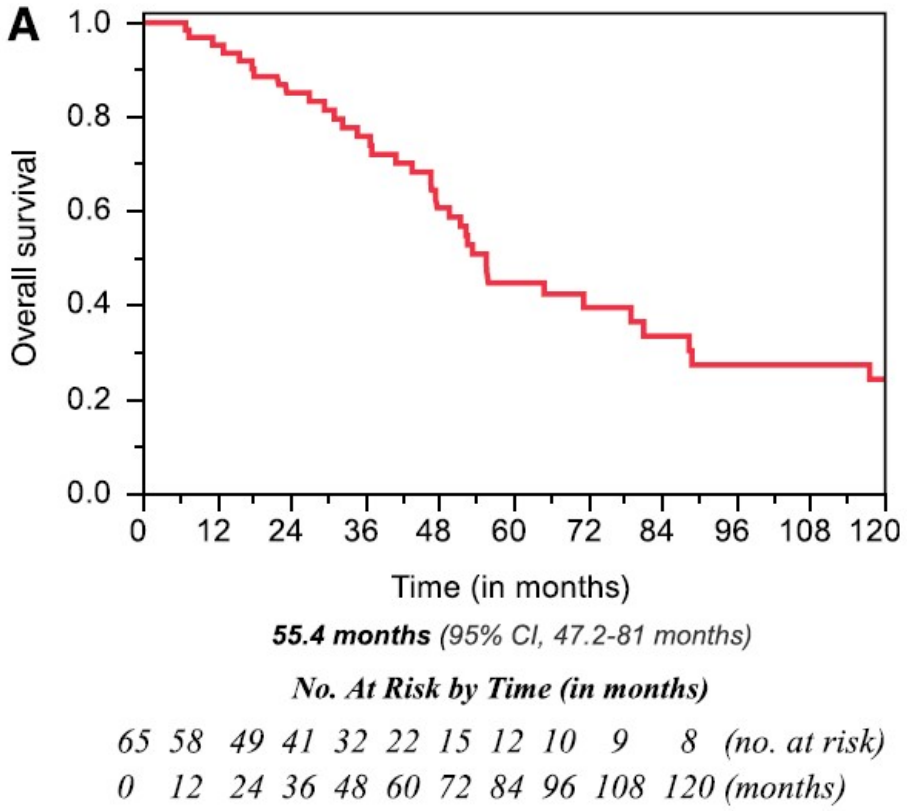
Adapted from Haddock et al, Int J Radiat Oncol Biol Phys 56:966-973, 2003

IOERT for Colorectal Nodal Mets
Local control by residual



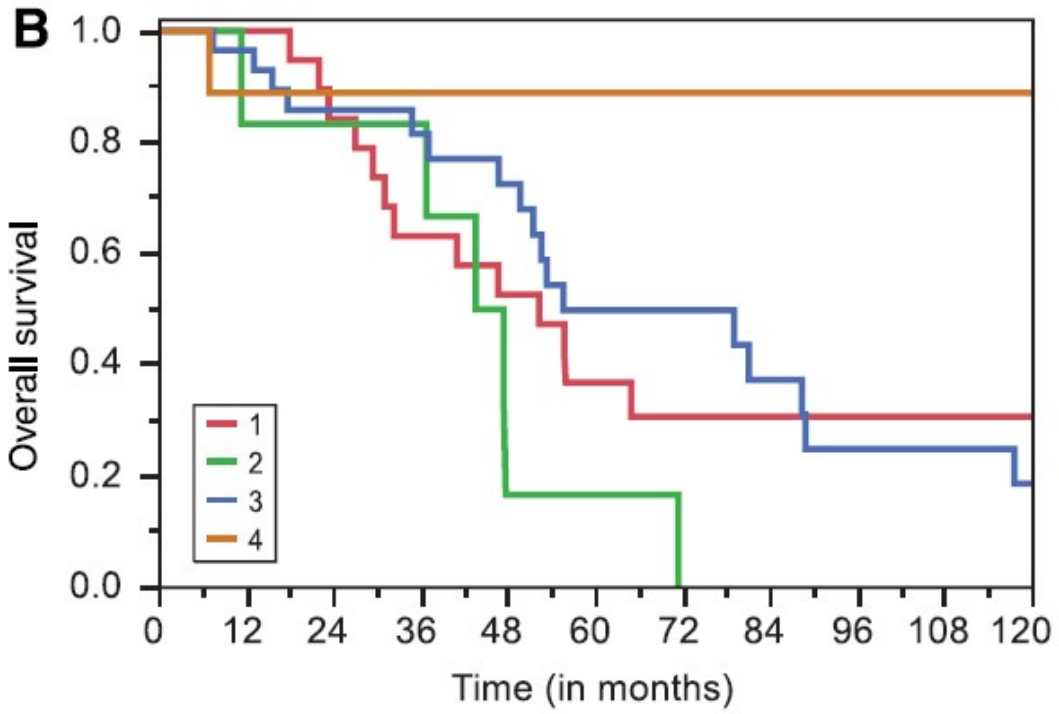
Adapted from Haddock et al, Int J Radiat Oncol Biol Phys 56:966-973, 2003

IOERT for Colorectal Nodal Mets
Mayo Update – 65 patients



Adapted from Johnson, The Oncologist 2018;23:679–685

IOERT for Colorectal Nodal Mets
Mayo Update – 65 patients



1 = R1
2 = R2
3 = R0
4 = pCR

Adapted from Johnson, The Oncologist 2018;23:679–685

IORT for Colorectal Cancer

Conclusions

- IORT associated with improved disease control in patients with locally advanced primary and recurrent colorectal cancer
- IORT likely has tumoricidal and vascular effects
- Gross total resection is key prognostic factor
- IORT dose ≥ 15 Gy associated with more frequent and more severe neuropathy
- Systemic therapy is key component of treatment

Case #1

- 70 yom with T4N0 cecal cancer
- Resection with positive radial margin
- No adjuvant therapy
- Tumor bed relapse one year later

Case #1
Recurrent Colon Cancer

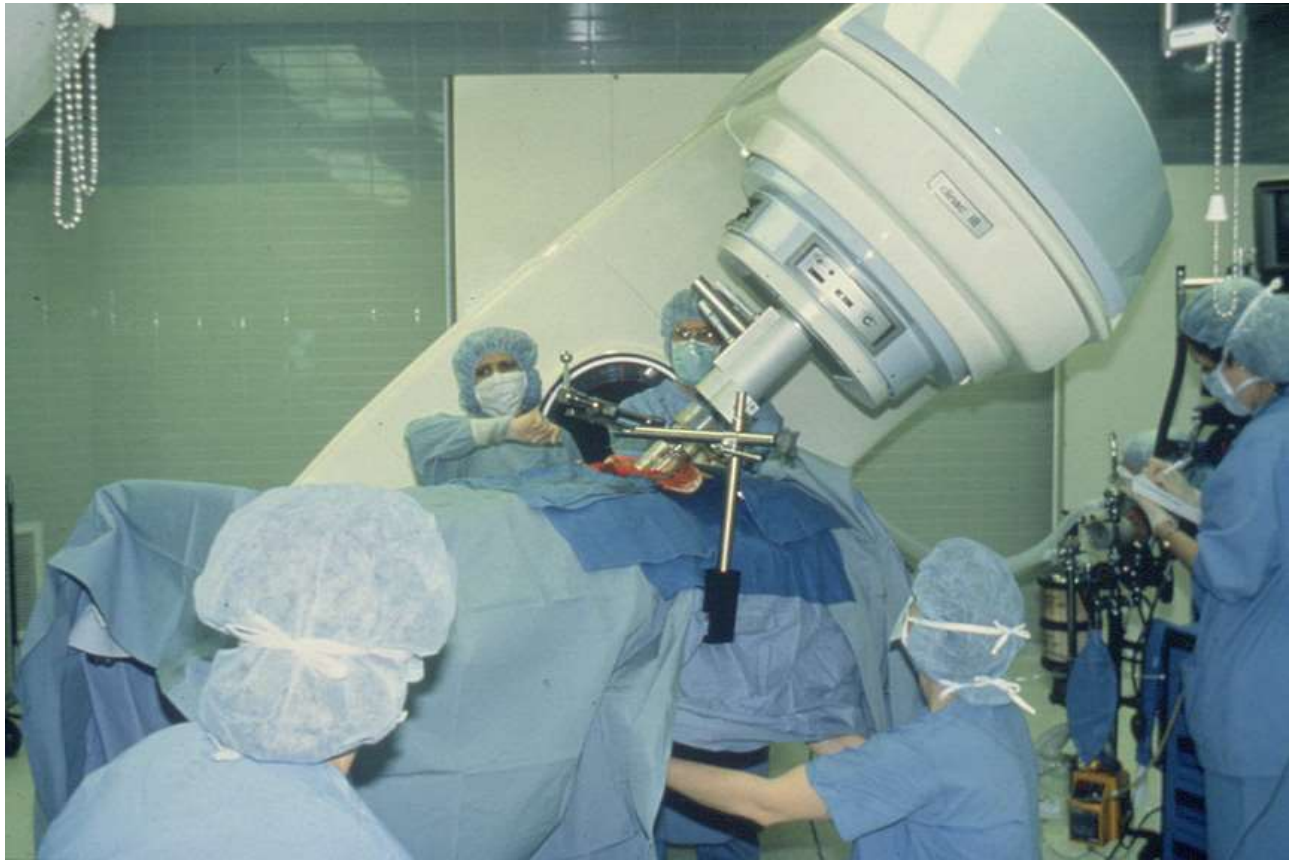
- EBRT: 5040 cGy in 28 fractions
- Concomitant 5-FU
- Resection: 3 nodular masses
  - All gross disease resected
  - IOERT 1250 cGy, 6 x 11 cm ellipse
  - Ureter in the field
- 6 month 5-FU + leucovorin

Case #1
Recurrent Colon Cancer

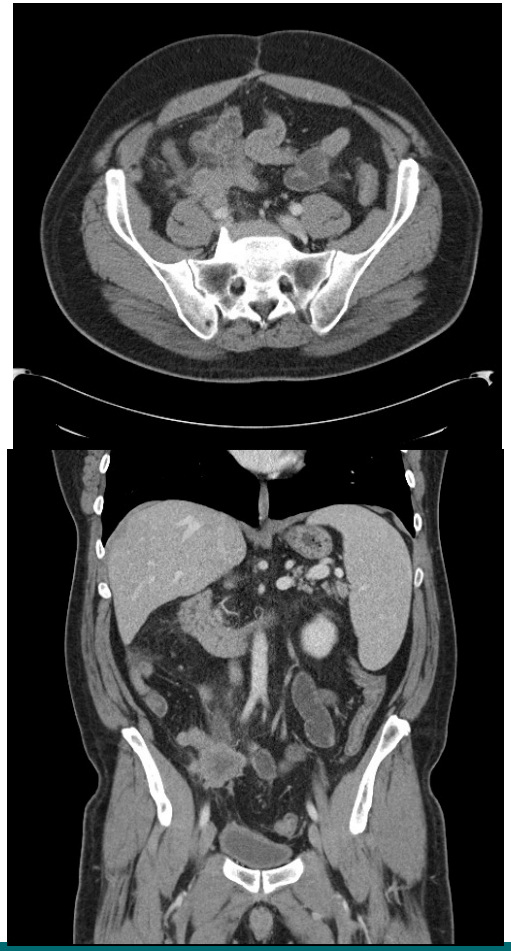
- NED at 8 years
- R ureteral obstruction requiring chronic stent

IOERT - Mayo

Linac – Hard docking system



Advanced Primary Colon Cancer



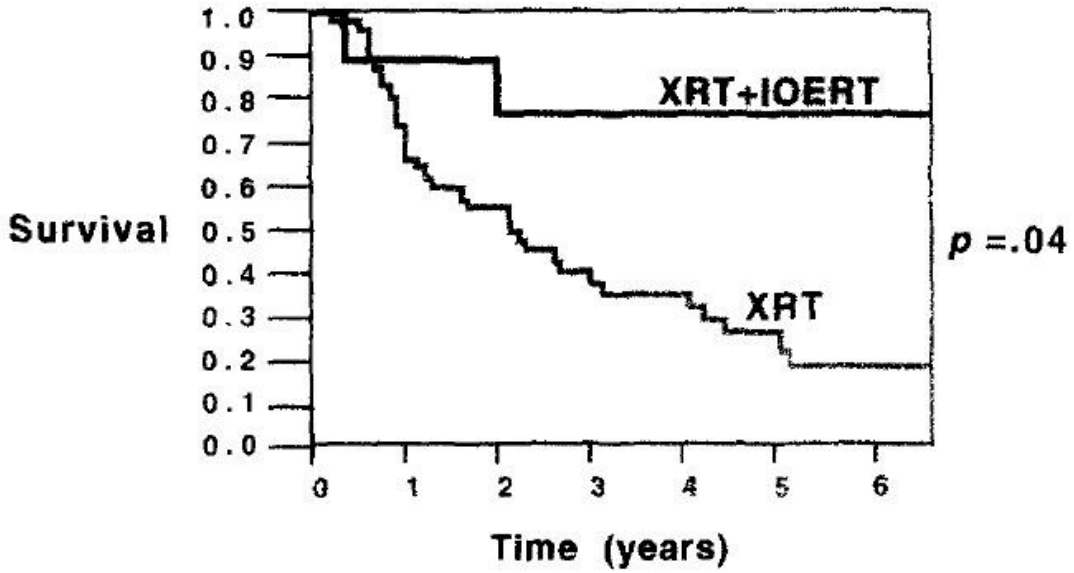
Locally Advanced Colon Cancer
Mayo Clinic Results

Group	# Patients	5-year LR	5-year DM	5-year OS
R0 resection	50	10%	~30%	66%
R1 resection	18	54%	~57%	47%
R2 resection	35	79%	~68%	23%
		$p < 0.0001$	$p = 0.002$	$p = 0.0009$
EBRT > 50 Gy	73	36%	-	50%
EBRT ≤ 50 Gy	30	50%	-	45%
		$p = 0.18$		$p = 0.16$
R1-2 + IOERT	9	11%	~12%	76%
R1-2, no IOERT	44	82%	~76%	26%
		$p = 0.02$	$p = 0.01$	$p = 0.04$

MAYO CLINIC

Schild, Red Journal 37:51-58,1997

Primary Colon Cancer
IOERT for subtotal resection



Schild, Red journal 37:51, 1997