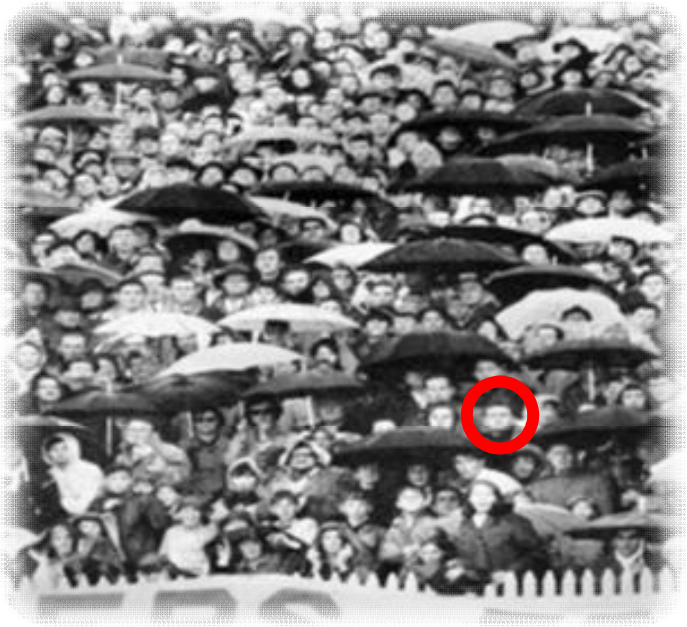
Intraoperative Electron Radiotherapy

&

Surgical Margin Status



Cancer Outcome after Local Intensification

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Hospital General Universitario Gregorio Marañon
Universidad Complutense, Madrid, Spain

Arguments for skeptics…

Is radiotherapy…

Is precise radiotherapy…

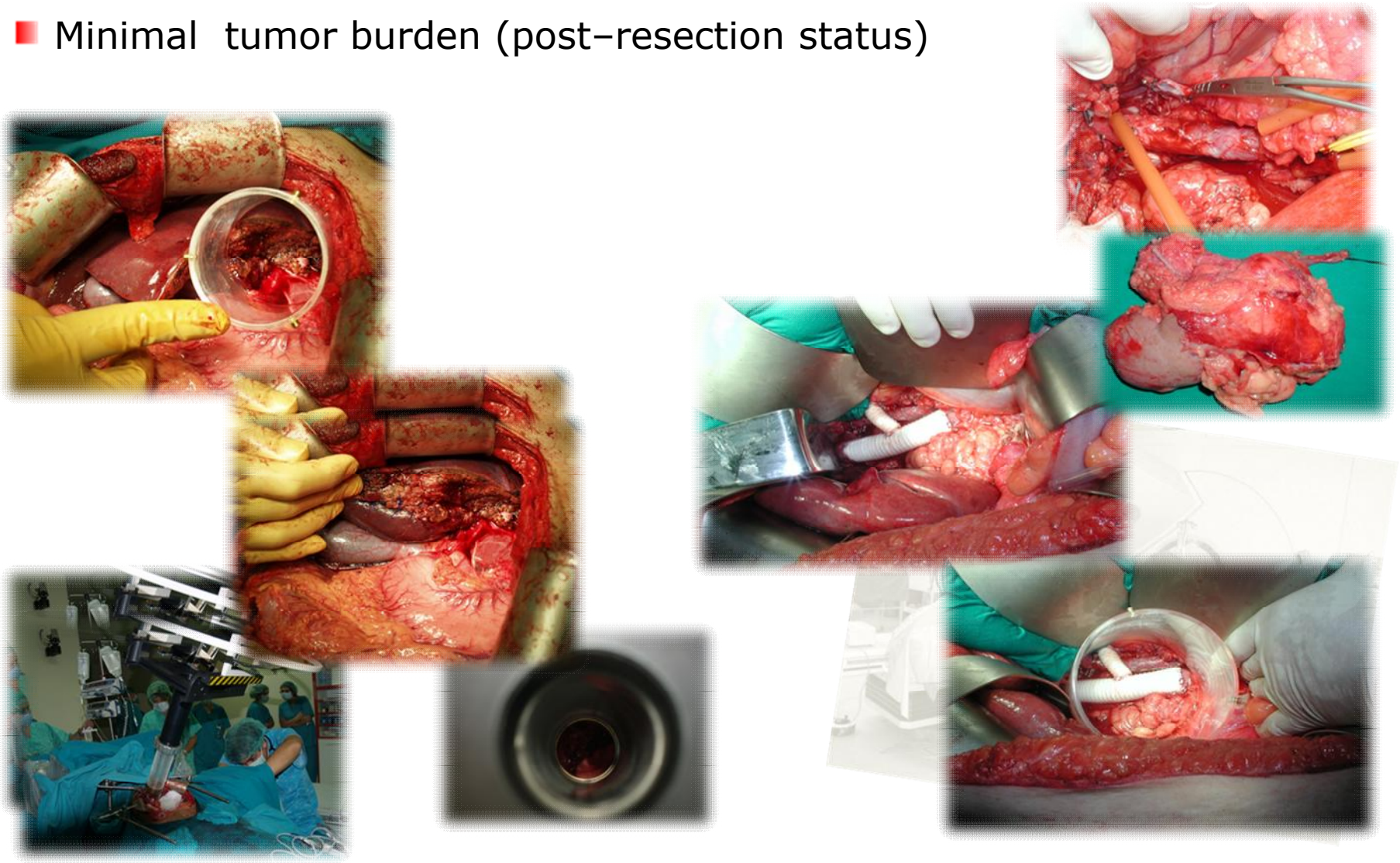
Is a precise component of RT for dose-escalation…

Adds a radiobiological safety margin to surgical resection…

Does not interferes with systemic therapy

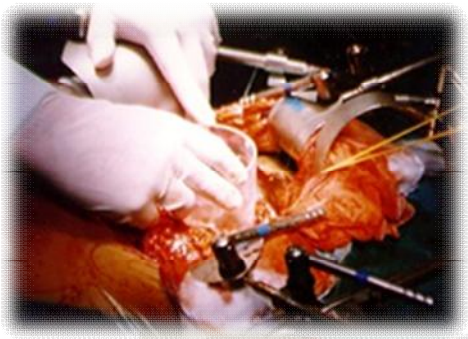
FUNDAMENTALS: DEFINITION

- RT during cancer
- Protection of normal tissues (temporary displacement)
- Minimal tumor burden (post–resection status)



Fundamentals: description

- Vision guided RT
- Fingers (tactile) guided RT
- Surgical guided RT



Original article

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Clinical and technical characteristics of intraoperative radiotherapy

Analysis of the ISIORT-Europe database

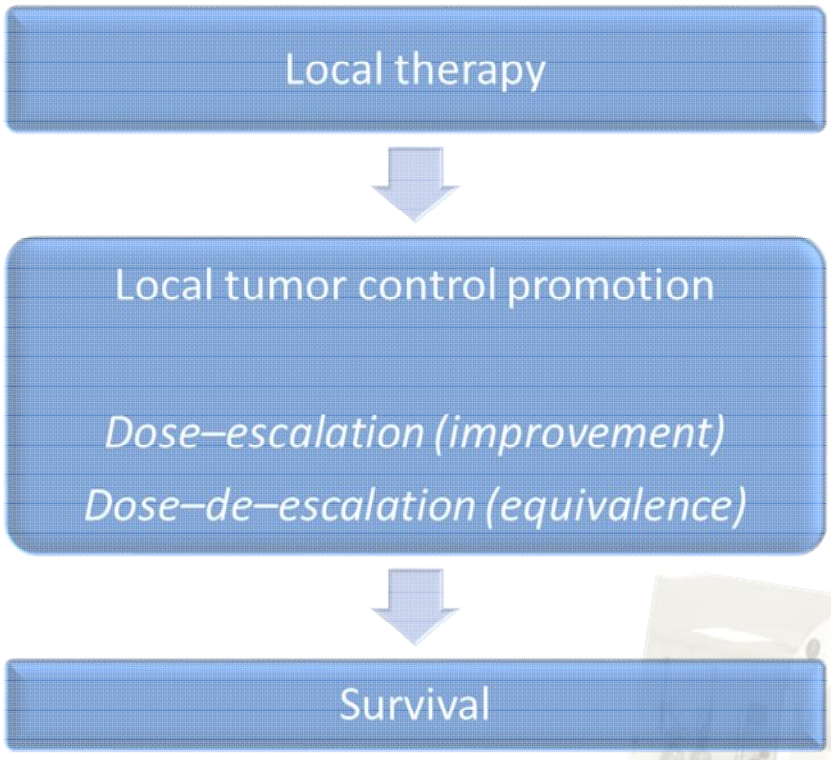
Tab. 2 Tumour sites treated with intraoperative radiation therapy

Tumour site	No. of cases	Percent
Breast	2395	63.8
Rectum	598	15.9
Soft tissue sarcoma	221	5.9
Prostate	108	2.9
Pancreas	80	2.1
Oesophagus	51	1.4
Uterine cervix	46	1.2
Stomach	44	1.2
Brain	34	1.0
Head and neck	23	0.6
Ovary	16	0.5
Kidney	8	0.2
Biliary tract	7	0.2
Colon	6	0.2
Lung	6	0.2
Sacrum	6	0.2
Bladder	5	0.1
Adrenal glands	5	0.1
Uterine body	4	0.1
Vertebral body	2	0.1
Other or undefined sites	89	2.0

Tab. 1 Radiation oncology centres that participated in data collection

University Hospital Gregorio Marañon, Madrid, Spain	1995–2011	986	26.3
University Hospital, Salzburg, Austria	2006–2010	820	21.8
[illegible]	[illegible]	[illegible]	[illegible]
University Hospital, Verona, Italy	2006–2009	350	9.3
National Cancer Research Institute (IST), Genova, Italy	2009–2010	212	5.6
University Medical Center, Mannheim, Germany	2008–2010	179	4.8
Greater Poland Cancer Center, Poznan, Poland	2008–2010	155	4.1
University Hospital, Novara, Italy	2005–2011	149	4.0
Hospital S. Croce and Carle, Cuneo, Italy	2009–2010	85	2.3
Hospital San Giovanni Battista, Foligno, Italy	2009–2010	69	1.8
University Hospital Sant'Andrea, Roma, Italy	2009–2010	55	1.5
Hospital Santa Chiara, Trento, Italy	2010	51	1.4
Hospital San Francisco de Asís, Instituto Madrileño de Oncología, Madrid, Spain	1992–2002	50	1.3
San Filippo Neri Hospital, Roma, Italy	2009	37	1.0
Medical University of Lublin, Lublin, Poland	2009	34	1.0
Institute of the Mediterranean, Catania, Italy	2008–2011	33	1.0
Hospital, Treviso, Italy	2009–2010	32	1.0
Ramban Health Care Campus, Haifa, Israel	2006–2010	31	1.0
Hospital Santa Maria Nuova, Reggio Emilia, Italy	2006–2010	23	0.6
Regional Centre for the Fight against Cancer (CRLC) Val D'Aurelle, Montpellier, France	2008–2011	21	0.6
Hospital Multimedica, Castellanza, Italy	2008–2010	19	0.5

Academic contribution: multidisciplinary oncology



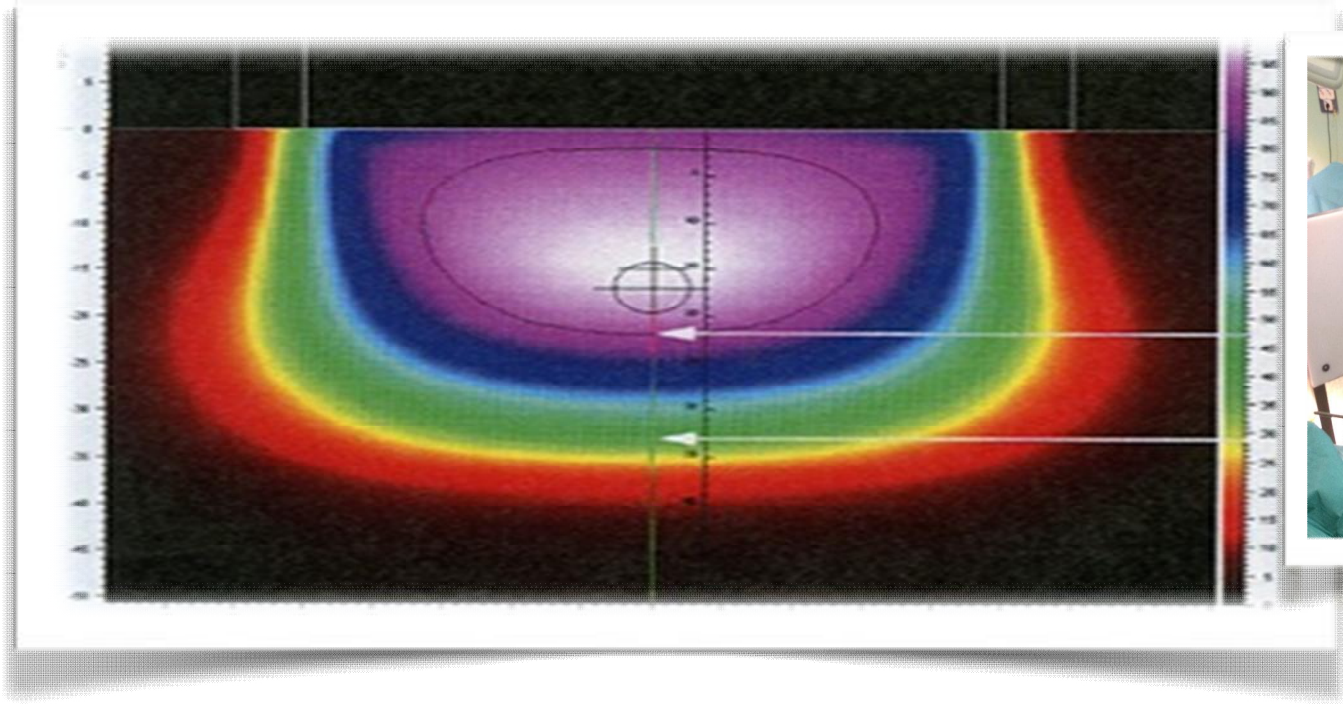
- Topography of intensification
- Dose-dense radiotherapy (shorter treatment time)
- Normal tissue tolerance balance

Treatment Strategy: Dose–escalation vs Dose-de-escalation

IOERT boost + EBRT (+/- Hypofractionated)

vs **10 – 20 Gy + 50 Gy *vs* 15 – 25 Gy**

IOERT alone (exclusive RT component)



IOERT *boost* + RT external

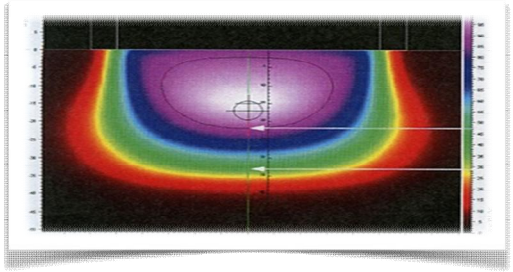
Personalized risk-adapted intensification:
R0-closed, R1, R2

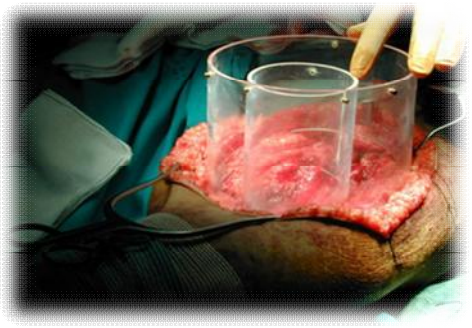
Boost Treatment Strategy: Dose–escalation & Cancer sites

GI: pancreas, colo-rectal, gastric

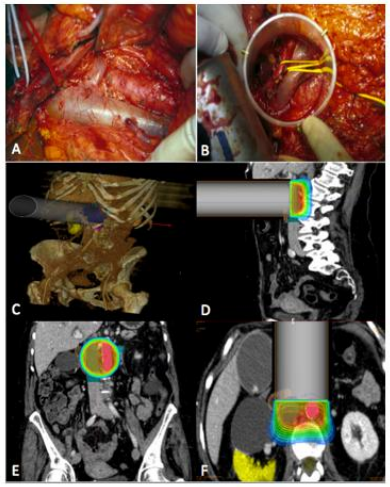
Sarcomas: retroperitoneal, extremity, bone

Breast: unselected and post-neoadjuvant CT

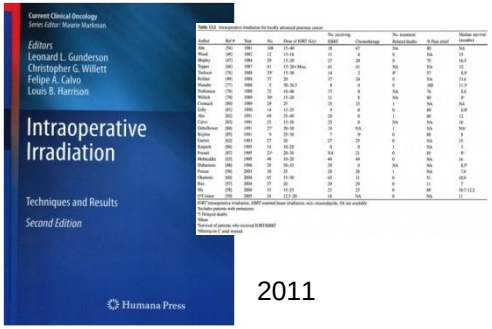




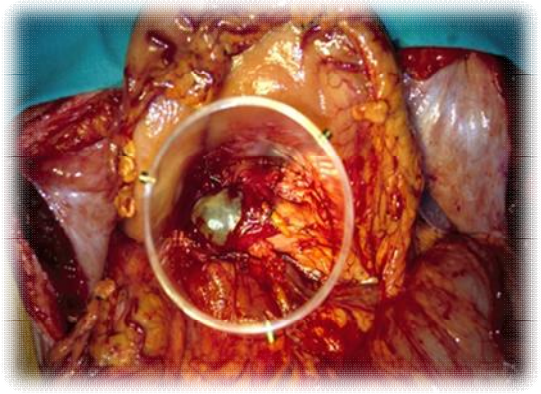
Supplemental figure. Intrasurgical target volume view (A, B), 3D (C) and 2D (D, E, F) CT scan-based IOERT planning technology.



IORT Results: Locally advanced unresectable pancreatic cancer



2011



1981-2005, 23 Institutions, 862 patients
8-16 months median survival time (12 months)
50-100% pain relieve effect (80%)

ORIGINAL ARTICLES

Long-term Results of Intraoperative Electron Beam Irradiation (IOERT) for Patients With Unresectable Pancreatic Cancer

Christopher G. Willett, MD, Carlos Fernandez Del Castillo, MD,† Helen A. Shih, MD,* Savelt Goldberg, PhD,* Peter Biggs, PhD,* Jeffrey W. Clark, MD,‡ Gregory Lauwers, MD,§ David P. Ryan, MD,‡ Andrew X. Zhu, MD, PhD,‡ and Andrew L. Warshaw, MD†*

2005

1978-2001, 150 patients, MGH-Boston
13 months MST, 8 long-term survival
<6 cm ⌀ applicator 17% 3-y OS

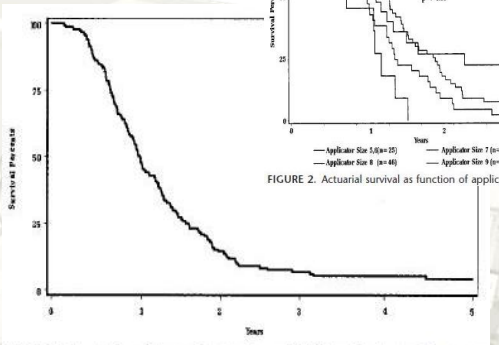


FIGURE 1. Actuarial survival rates of 150 patients with unresectable pancreatic cancer receiving intraoperative electron beam radiation therapy.

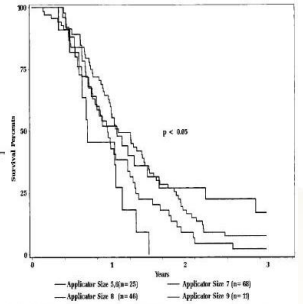


FIGURE 2. Actuarial survival as function of applicator size.

Updated Long-Term Outcomes and Prognostic Factors for Patients With Unresectable Locally Advanced Pancreatic Cancer Treated With Intraoperative Radiotherapy at the Massachusetts General Hospital, 1978 to 2010

Sophie Cai, BA[1]; Theodore S. Hong, MD[2]; Saveli I. Goldberg, PhD[2]; Carlos Fernandez-del Castillo, MD[3]; Sarah P. Thayer, MD, PhD[3]; Cristina R. Ferrone, MD[3]; David P. Ryan, MD[4]; Lawrence S. Blaszkowsky, MD[4]; Eunice L. Kwak, MD, PhD[4]; Christopher G. Willett, MD[5]; Keith D. Lillemoe, MD[3]; Andrew L. Warshaw, MD[3]; and Jennifer Y. Wo, MD[2]

Cancer 2015

194 pts

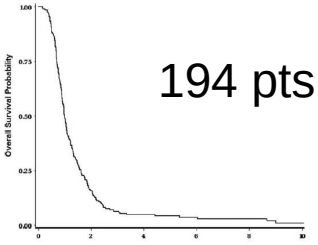


Figure 1. Overall survival is shown among patients with unresectable locally advanced pancreatic cancer who were treated with intraoperative radiotherapy (N = 194).

Charlson +/- CT

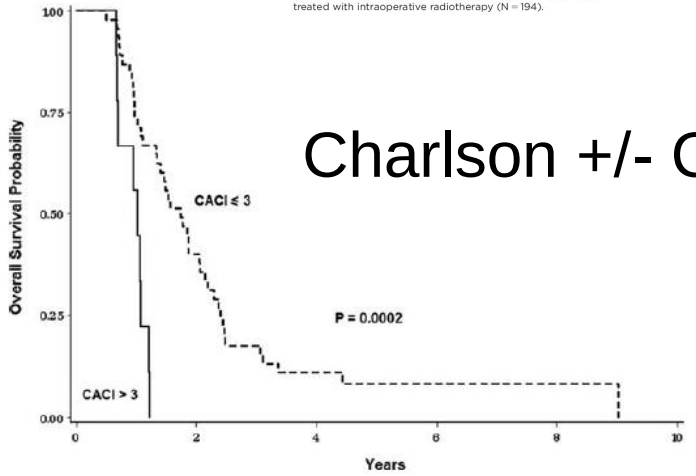
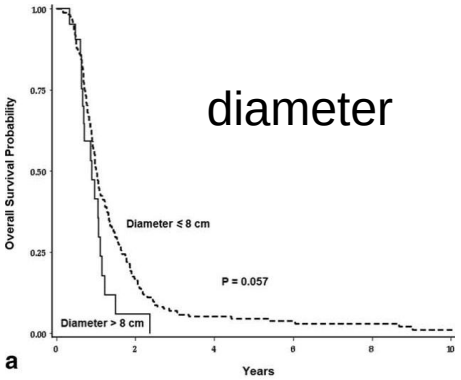
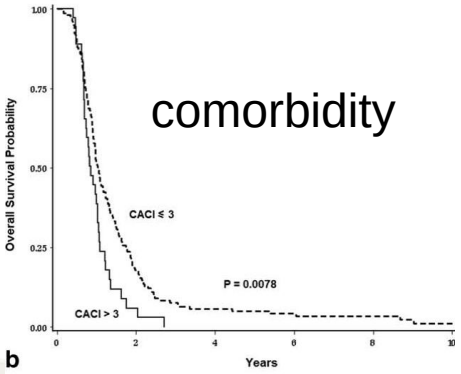


Figure 3. Overall survival of patients treated with chemotherapy is shown stratified by Charlson age-comorbidity index (CACI) (N = 57).

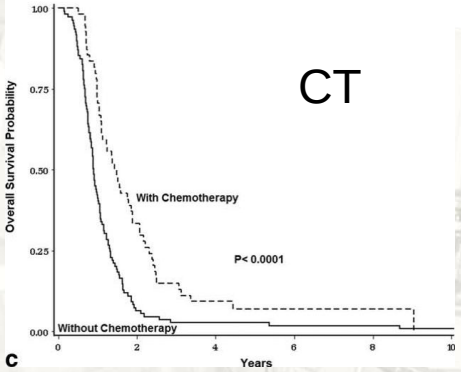
diameter



comorbidity

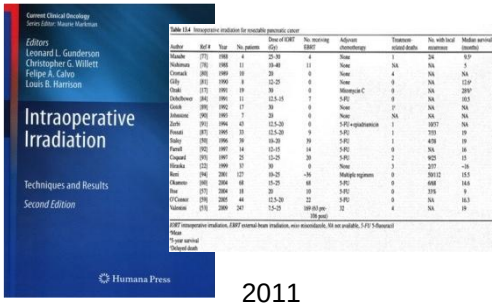


CT

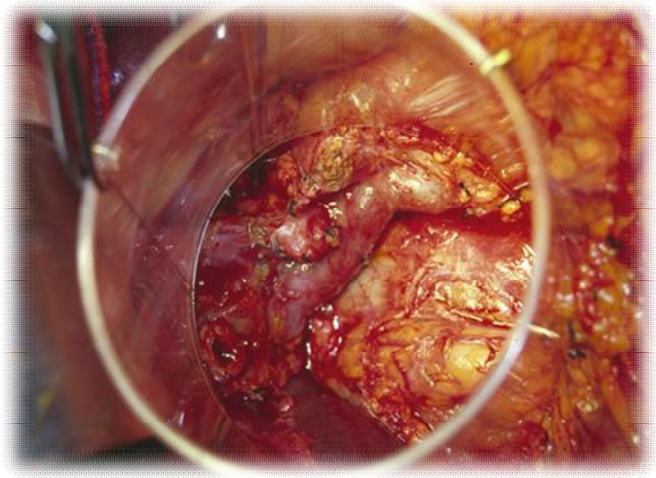


Cancer December 1, 2013

IORT Results: pancreatic cancer post-resected *ISIORT pooled analysis*



2011



data	period	# pts	# centers	outcome
Gunderson et al	1985-2009	778	23	9-19 mo MST (14)
ISIORT-Europe	1985-2006	270	5	**preCRT MST 30 vs 20 mo**

2009

Preoperative chemoradiation and IOERT for unresectable or borderline resectable pancreas cancer

Jonathan B. Ashman[1], Adyr A. Moss[2], William G. Rule[1], Matthew G. Callister[1], K. Sudhakar Reddy[2], David C. Mulligan[2], Joseph M. Collins[3], Giovanni De Petris[4], Leonard L. Gunderson[1], Mitesh Borad[5]

[1]Department of Radiation Oncology, [2]Division of Transplant/Pancreas and Hepatobiliary Surgery, [3]Department of Radiology, [4]Department of Laboratory Medicine and Pathology, [5]Division of Medical Oncology and Hematology, Mayo Clinic Cancer Center - Arizona (MCCC-A), Scottsdale/Phoenix, AZ, USA

Corresponding to: Jonathan B. Ashman, MD, PhD. Department of Radiation Oncology, Mayo Clinic in Arizona, 5777 E. Mayo Blvd., Phoenix, AZ 85054, USA. Email: ashman.jonathan@mayo.edu.

Mayo Clinic
2002-2010

48 pts: 11 borderline (BR)

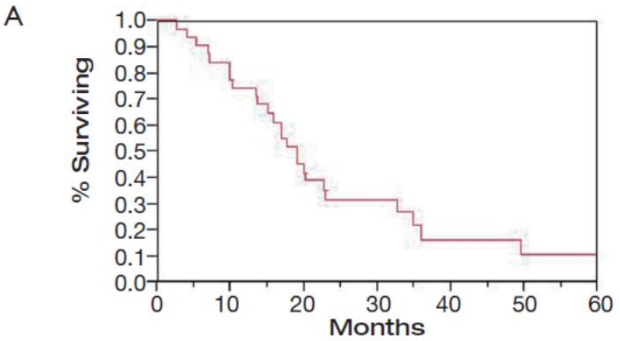
Preop CRT
31 resected

5 LF
22DF

R0/R1 vs R2/NR p=0.002

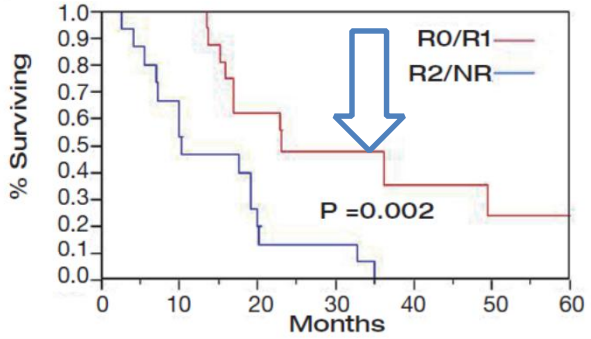
BR vs UR p=0.06

A



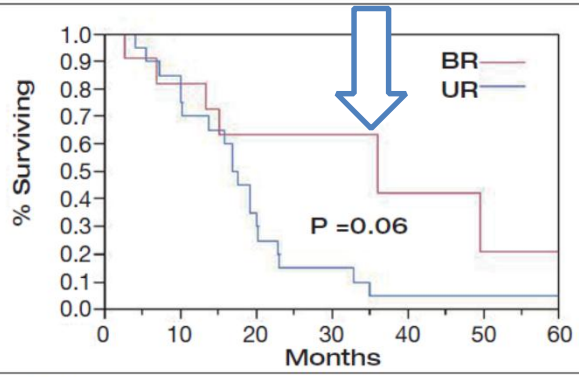
No. at risk							
	31	26	14	9	4	3	3

B



No. at risk							
R0/R1	16	16	11	7	4	3	3
R2/NR	15	10	4	3			

C



No. at risk							
BR	11	10	8	6	3	2	2
UR	20	17	7	4	1	1	1

Intraoperative Radiotherapy in the Era of Intensive Neoadjuvant Chemotherapy and Chemoradiotherapy for Pancreatic Adenocarcinoma

Florence K. Keane, MD, Jennifer Y. Wo, MD,† Cristina R. Ferrone, MD,‡ Jeffrey W. Clark, MD,§ Lawrence S. Blaszkowsky, MD,§ Jill N. Allen, MD,§ Eunice L. Kwak, MD, PhD,§ David P. Ryan, MD,§ Keith D. Lillemoe, MD,‡ Carlos Fernandez-del Castillo, MD,‡ and Theodore S. Hong, MD†*

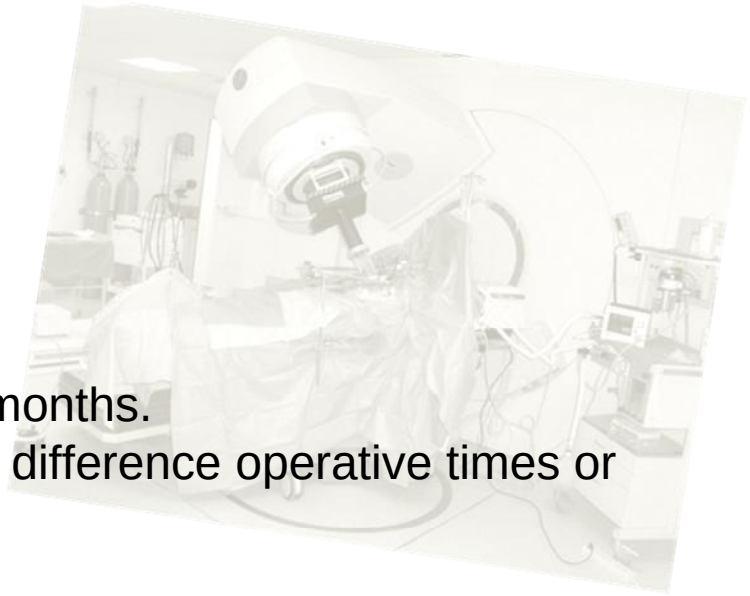
Am J Clin Oncol 2016

RESULTS:
68 patients post-FOLFIRI , 41 (60.3%) resected,18 (26.5%) unresectable, 9 (13.2%) metastatic.

22 received IORT for close/positive resection margins on frozen section.

Median OS

35.1 months resection + IOERT
24.5 months resection alone
24.3 months IOERT alone



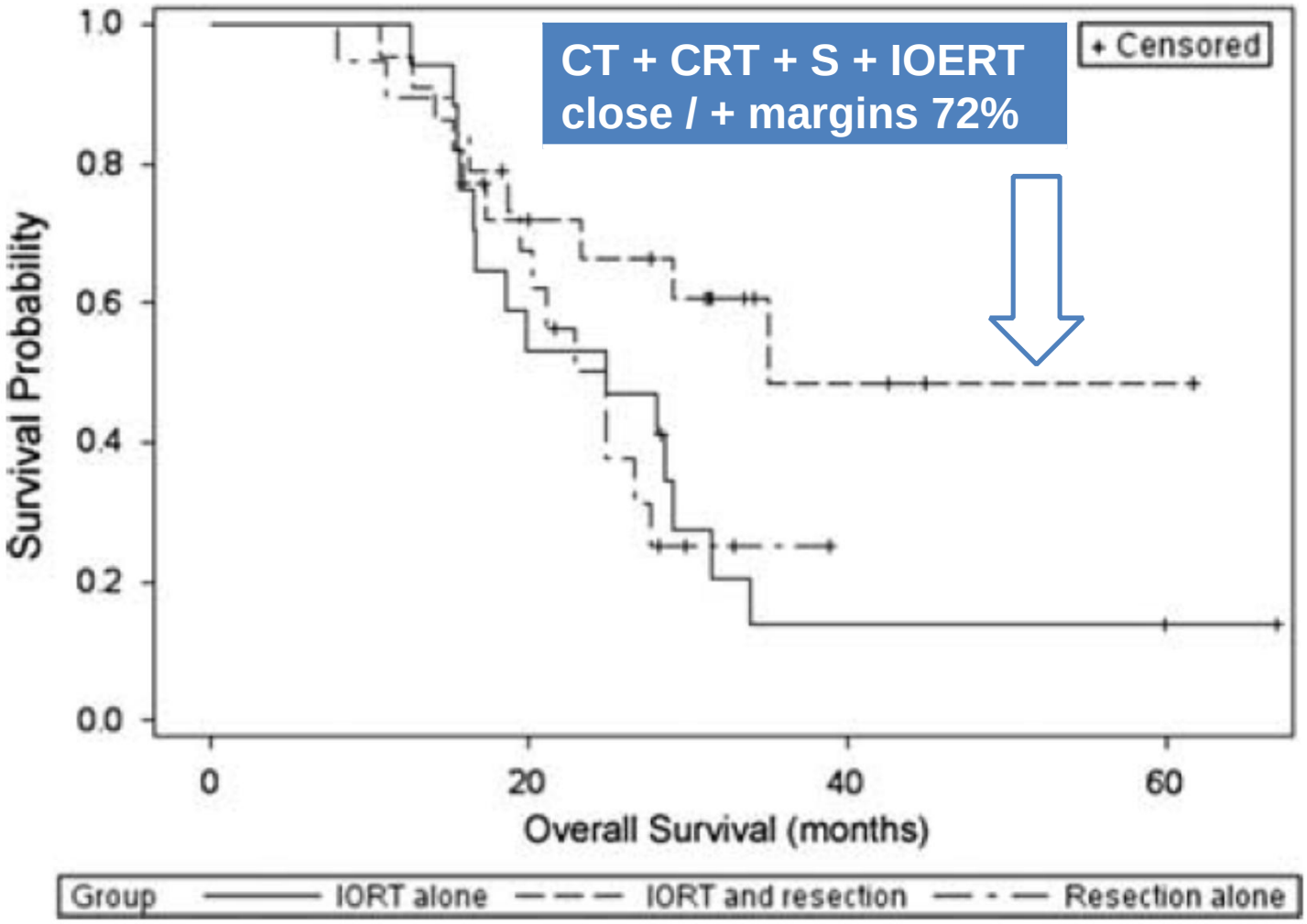
Unresectable disease (18): median OS 24.8 months.
IORT increased hospital stay (4 vs. 3.5 d), no difference operative times or morbidity

TABLE 1. Clinical Characteristics

Characteristic	Entire Cohort (n = 68)
Age at diagnosis (y)	
Median	63
Range	(37-80)
Sex	
Male (n [%])	37 (54.4)
ECOG performance status (n [%])	
0	31 (45.6)
1	36 (52.9)
2	1 (1.5)
Charlson comorbidity score	
Median	3
Range	0-5
BMI (kg/m^2)	
Median	23.7
Range	17.2-34.4
Tumor size on CT (cm)	
Median	3.6
Range	1.8-7.1
Tumor resectability at diagnosis (n [%])	
Locally advanced unresectable	60 (88.2)
Borderline resectable	8 (11.2)

TABLE 2. Summary of Neoadjuvant Treatment

Characteristic	Entire Cohort (n = 68)
Neoadjuvant chemotherapy (n [%])	
FOLFIRINOX	59 (86.8)
Gemcitabine with nab-paclitaxel	4 (5.8)
FOLFOX	5 (7.4)
Cycles of neoadjuvant chemotherapy	
Median	8
Range	4-12
Median RT dose (range) (Gy)	50.4 (24-55)
IMRT dose painting to vasculature to 58.8 Gy (n [%])	40 (58.8)
Concurrent chemotherapy during chemoradiotherapy (n [%])	
CI 5-FU	41 (60.4)
Capecitabine	21 (30.9)
CI 5-FU + other	2 (2.9)
Gemcitabine	2 (2.9)
None	2 (2.9)
Pretreatment CA19-9 (median [range])	221.0 (2-25,020)
Posttreatment CA19-9 (median [range])	27 (1-529)


CT + CRT + S + IOERT
close / + margins 72%
+ Censored
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
Overall Survival (months)
Group
IORT alone
IORT and resection
Resection alone

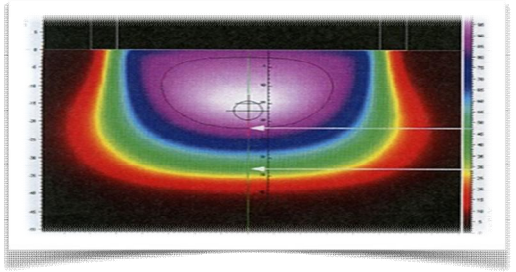
Boost Treatment Strategy: Dose–escalation & Cancer sites

GI: pancreas, colo-rectal, **gastric**

Sarcomas: retroperitoneal, extremity, bone

Breast: unselected and post-neoadjuvant CT

Prostate: exclusive and post-prostatectomy



Radiotherapy and Oncology 102 (2012) 51–55

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Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

IORT in gastric cancer

Adjuvant chemoradiotherapy with or without intraoperative radiotherapy for the treatment of resectable locally advanced gastric adenocarcinoma

Qing Zhang [a], Jeremy Tey [b], Lihua Peng [a], Zhe Yang [c], Fei Xiong [a], Ruiyao Jiang [a], Taifu Liu [d], Shen Fu [a,*], Jiade J. Lu [b]

[a] Department of Radiation Oncology, Sixth Hospital of Jiao Tong University, Shanghai, People's Republic of China; [b] Department of Radiation Oncology, National University Hospital, Singapore; [c] Department of Surgery, Sixth Hospital of Jiao Tong University, Shanghai, People's Republic of China; [d] Department of Radiation Oncology, Fudan University, Shanghai, People's Republic of China

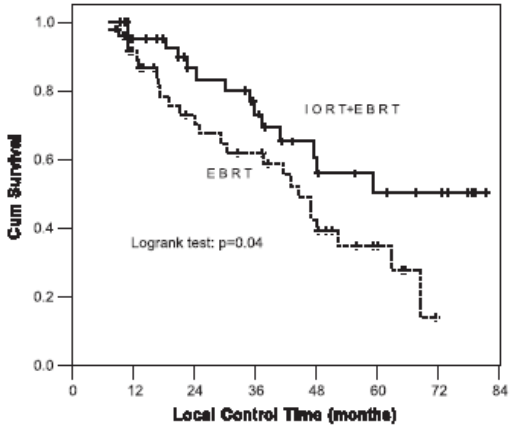


Fig. 1. Local control rate after radiotherapy.

Table 2
Patterns of local regional failure after adjuvant chemoradiotherapy.

Patterns of failure	Group	
	IOERT + EBRT (%)	EBRT (%)
Anastomosis	8 (57%)	9 (36%)
Posterior to pancreatic head	4 (29%)	2 (8%)
Hepatoduodenal ligment	1 (7%)	4 (16%)
Tumor bed	1 (7%)	7 (28%)
Common hepatic artery	0 (0%)	2 (8%)
Celiac axis	0 (0%)	1 (4%)
Total	14 (100%)	25 (100%)

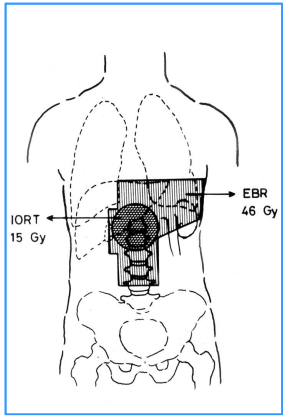


Table 3
Multivariate analysis for

Variable	*P* value			
	Overall survival	Local regional control	Metastatic free survival	Disease free survival
IOERT (Yes vs. No)	0.06	0.02	0.10	0.05
T (T1–2 vs.T3 vs. T4)	<0.001	0.03	<0.001	<0.001
N (N0 vs. N1 vs. N2 vs. N3)	<0.001	0.002	<0.001	<0.001
R (R0 vs. R1)	0.07	0.14	0.01	0.006

Intraoperative radiotherapy in gastric and esophageal cancer: meta-analysis of long-term outcomes and complications

Peng GAO [1], Chengche TSAI [1], Yuchong YANG [1], Yingying XU [2], Changwang ZHANG [1], Cong ZHANG [1], Longyi WANG [1], Hongpeng LIU [1], Zhenning WANG [1]

[1] Department of Surgical Oncology and General Surgery, First Hospital of China Medical University, Shenyang, China; [2] Department of Breast Surgery, First Hospital of China Medical University, Shenyang, China

PubMed, Embase, March 2016

EVIDENCE SYNTHESIS:

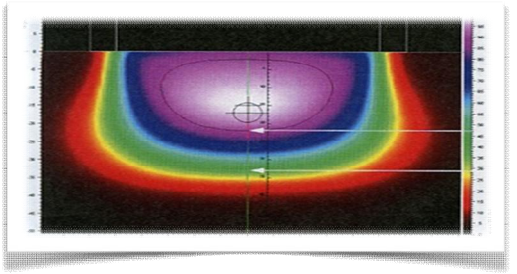
11 studies, 9 gastric cancer and 2 for esophageal cancer.
1581 patients, 570 in the IORT group and 1011 in the control group
no significant difference in overall survival (OS)
Gastric and esophageal cancer had similar results (P=0.08)

IORT favorable effects in stage II and stage III
IORT had advantage in loco-regional control

Complications no significant different IORT vs control group (P=0.50).

Minerva Medica 2017 February;108(1):74-83

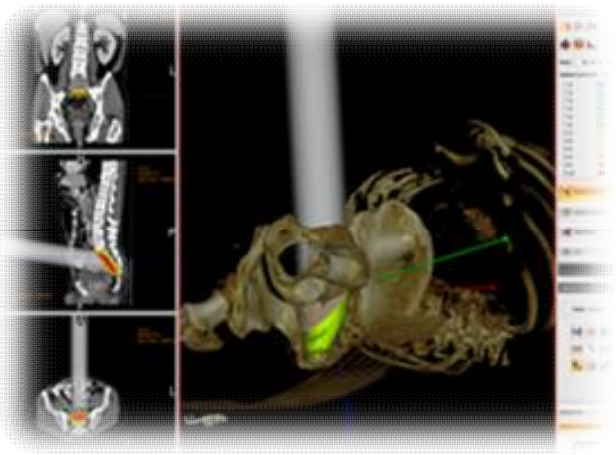
Boost Treatment Strategy: Dose–escalation & Cancer sites



GI: pancreas, **colo-rectal,** esophago-gastric

Sarcomas: retroperitoneal, extremity, bone

Breast: unselected and post-neoadjuvant CT



IORT Results: Locally advanced rectal cancer

original article

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Results of European pooled analysis of IORT-containing multimodality treatment for locally advanced rectal cancer: adjuvant chemotherapy prevents local recurrence rather than distant metastases

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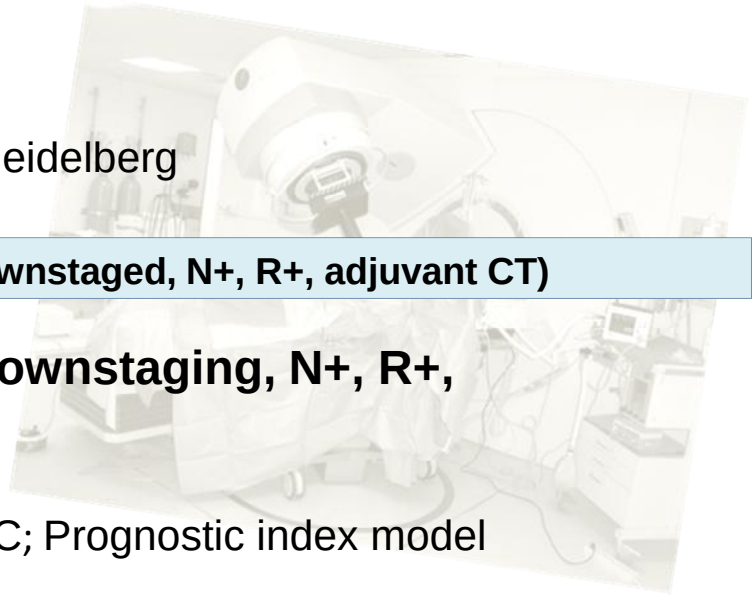
1989 – 2005

605 patients Catharina, Marañón, Gemelli, Heidelberg

12% local recurrence @ 5-y (downstaged, N+, R+, adjuvant CT)

68% OS @ 5-y (male, >70 years, no-downstaging, N+, R+, CT)



“Seed and soil” adjuvant chemotherapy on LC; Prognostic index model

(*Am J Clin Oncol* 2015;38:11–16)

Adjuvant Chemoradiation Plus Intraoperative Radiotherapy Versus Adjuvant Chemoradiation Alone in Patients With Locally Advanced Rectal Cancer

Qing Zhang, MD, Jeremy Tey, MD,† Zhe Yang, MD,‡ Ping Li, MD,* Lihua Peng, MD,* Shen Fu, MD, PhD,* Guofeng Huang, BS* Fei Xiong, BS* and Jiade J. Lu, MD, MBA†*

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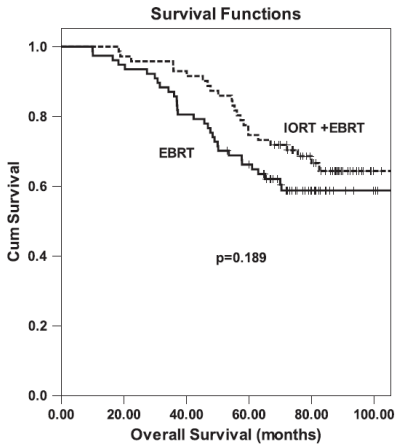

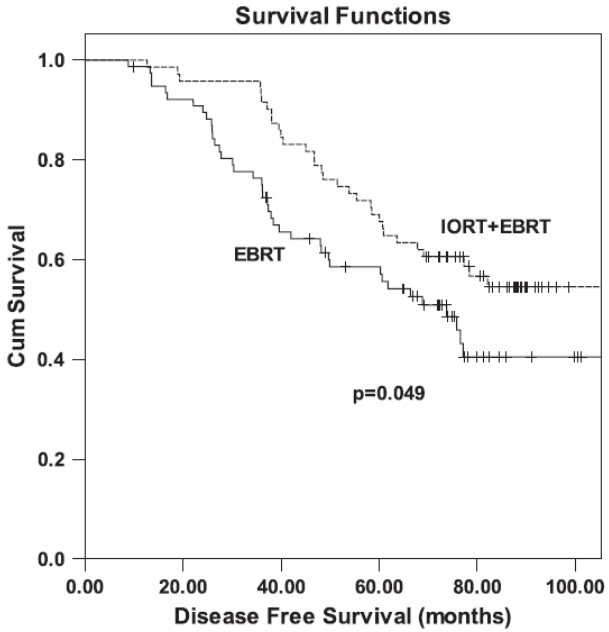

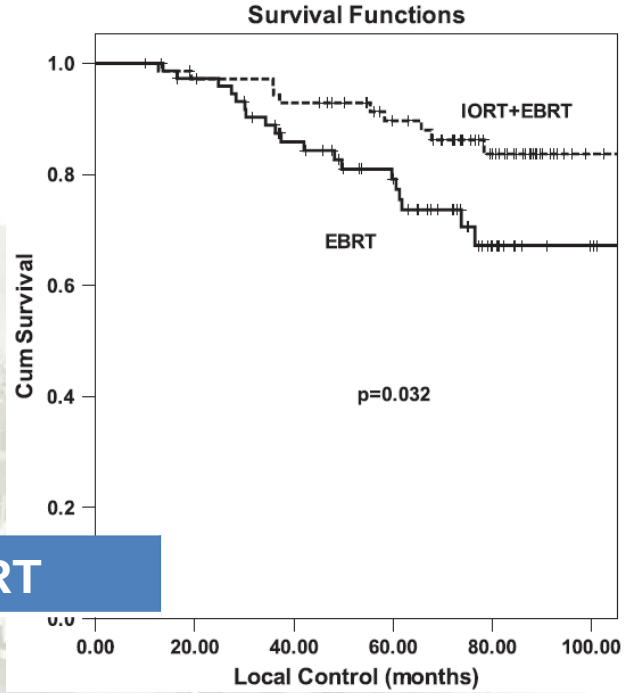

125 pts; 68 IOERT; 39% T4; 77% N+; adjuvant CRT

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(*Am J Clin Oncol* 2015;38:11–16)

TABLE 2. Multivariate Analysis for Overall Survival, Local Control, Metastatic-free, and Disease-free Survival

	P		
Variables	**Overall Survival**	**Local Regional Control**	**Disease-free Survival**
Age	0.559	0.355	0.234
Sex	0.159	0.731	0.551
IORT (yes vs. no)	0.539	0.079	0.161
T (T1-2 vs.T3 vs. T4)	0.016	0.044	0.000
N (N0 vs. N1 vs. N2)	0.000	0.001	0.000
R (R0 vs. R1)	0.947	0.113	0.224

IORT indicates intraoperative radiotherapy.

. Patients Characteristic Between IORT Group and EBRT Group

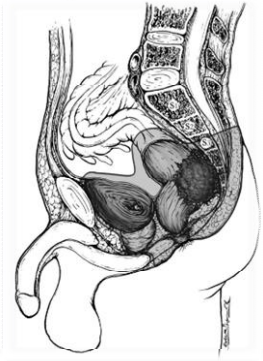
Variants	**IORT**	**EBRT**	χ^2	***P***
Age				
Median	58	63	—	—
Mean	58.04	60.82		
Range	35-73	35-71		
Sex			3.034	0.09
Male	41 (57.7%)	55 (71.4%)		
Female	30 (42.3%)	22 (28.6%)		
Pathology				
Adenocarcinoma	71 (100%)	77 (100%)		
pT classification			0.462	0.833
T1	0	0		
T2	4 (5.6%)	5 (6.5%)		
T3	39 (54.9%)	38 (49.4%)		
T4	28 (39.4%)	34 (44.2%)		
pN classification			0.883	0.653
N0	16 (22.5%)	13 (16.9%)		
N1	37 (52.1%)	41 (53.2%)		
N2	18 (25.4%)	23 (29.9%)		
2002 AJCC, TNM stage			0.783	0.869
IIb	16 (22.5%)	13 (16.9%)		
IIIa	3 (4.2%)	4 (5.2%)		
IIIb	32 (45.1%)	37 (48.1%)		
IIIc	20 (28.2%)	23 (29.9%)		
Residual disease			0.985	1.000
R0	67 (94.4%)	72 (93.5%)		
R1	4 (5.6%)	5 (6.5%)		

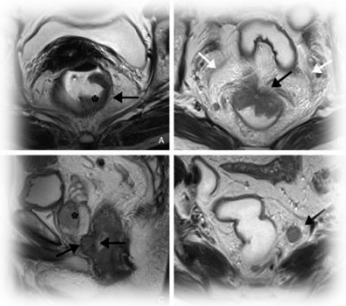
Original Article

Results of intraoperative electron beam radiotherapy containing multimodality treatment for locally unresectable T4 rectal cancer: a pooled analysis of the Mayo Clinic Rochester and Catharina Hospital Eindhoven

J Gastrointest Oncol. 2016 Dec;7(6):903-916.

Fabian A. Holman[1], Michael G. Haddock[2], Leonard L. Gunderson[3], Miranda Kusters[1,4], Grard A. P. Nieuwenhuijzen[4], Hetty A. van den Berg[5], Heidi Nelson[6], Harm J. T. Rutten[4,7]





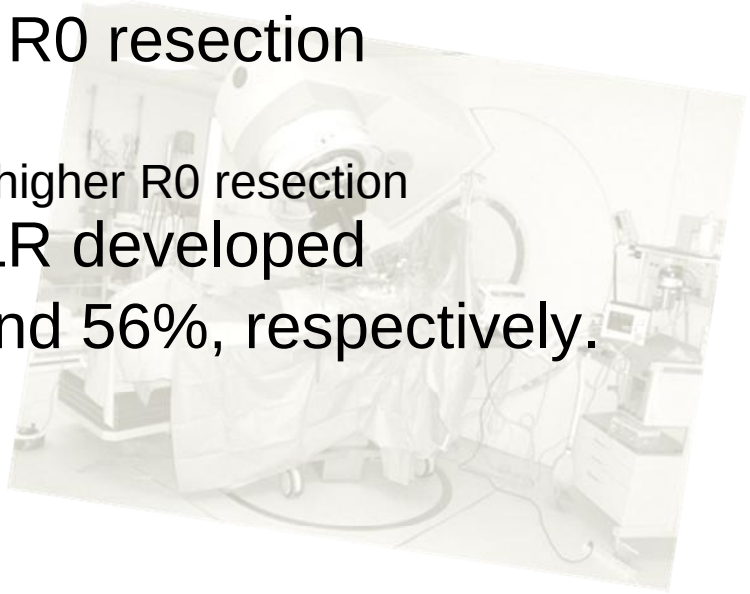
1981 to 2010, 417 patients

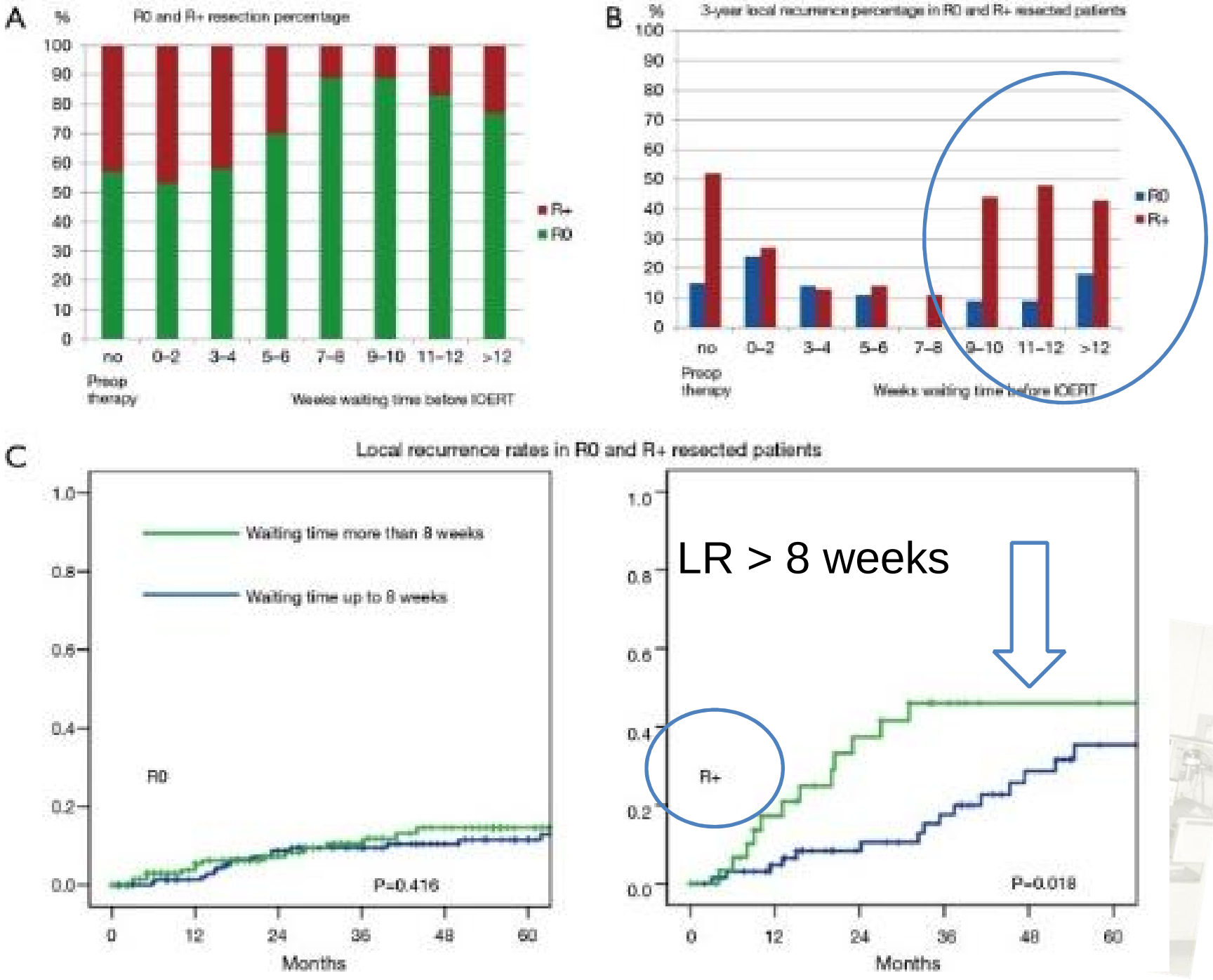
306 patients (73%) R0 resection

preop CRT associated higher R0 resection

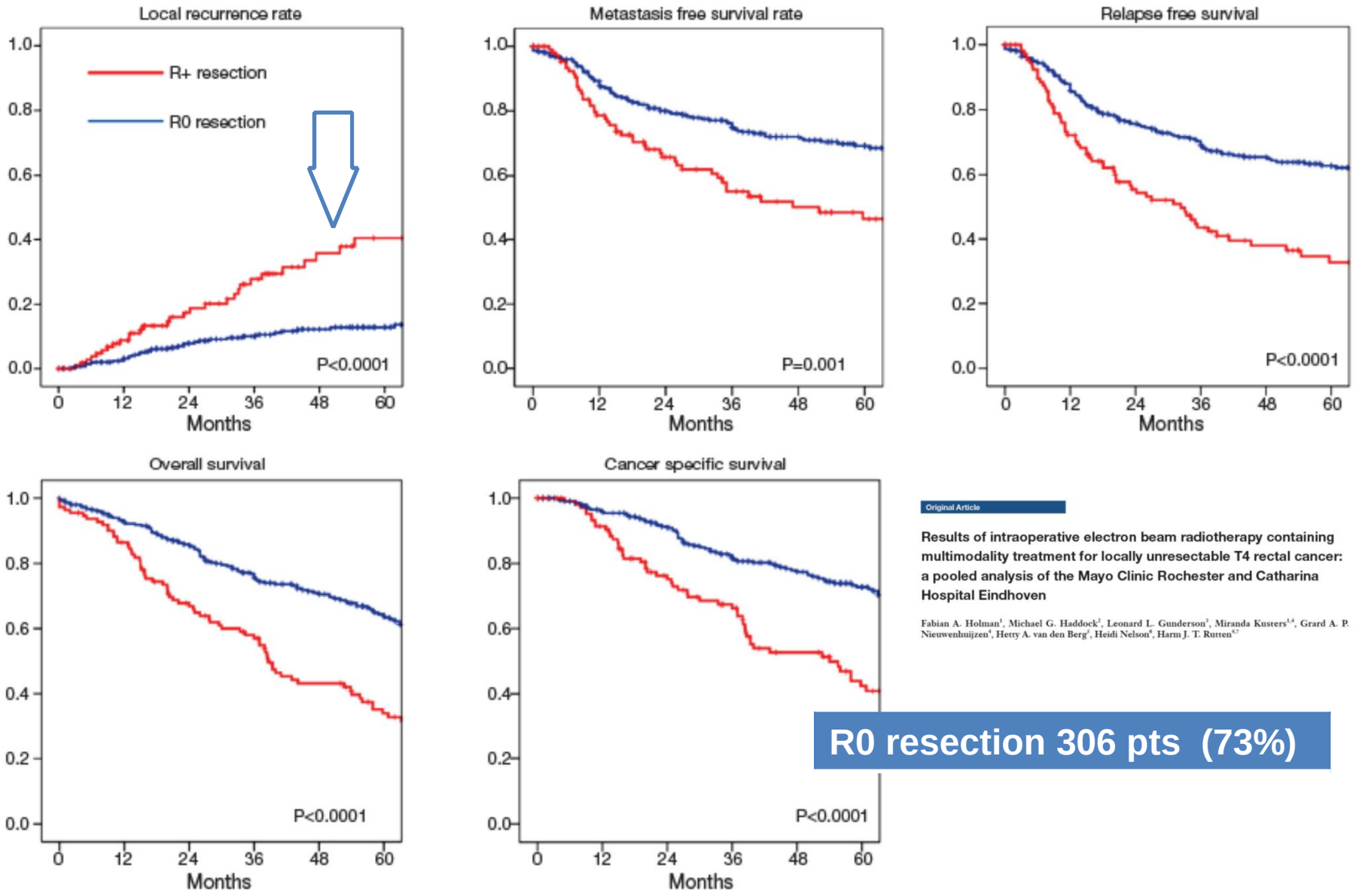
16% of all cases a LR developed

5y DFS and OS: 55% and 56%, respectively.




A
%
R0 and R+ resection percentage
100
90
80
70
60
50
40
30
20
10
0
no
0-2
3-4
5-6
7-8
9-10
11-12
>12
Preop therapy
Weeks waiting time before IOERT
R+
R0
B
%
3-year local recurrence percentage in R0 and R+ resected patients
100
90
80
70
60
50
40
30
20
10
0
no
0-2
3-4
5-6
7-8
9-10
11-12
>12
Preop therapy
Weeks waiting time before IOERT
R0
R+
C
Local recurrence rates in R0 and R+ resected patients
1.0
0.8
0.6
0.4
0.2
0.0
Waiting time more than 8 weeks
Waiting time up to 8 weeks
R0
P=0.416
0
12
24
36
48
60
Months
LR > 8 weeks
R+
P=0.018

R0 *vs* R+ outcomes



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R0 resection 306 pts (73%)

Figure 2 Influence of radicality of resection (R0 *vs.* R+) on all oncological outcome parameters.

29 studies,3.003 pts, 1792 primary LARC, 1211 recurrent

Surgical Oncology

journal homepage: www.elsevier.com/locate/suronc

Review

Intraoperative radiotherapy in colorectal cancer: Systematic review and meta-analysis of techniques, long-term outcomes, and complications

Reza Mirnezami [a], George J. Chang [b], Prajnan Das [c], Kandiah Chandrakumaran [d], Paris Tekkis [a], Ara Darzi [a], Alexander H. Mirnezami [e,*]

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[b] Department of Surgical Oncology, University of Texas, MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA
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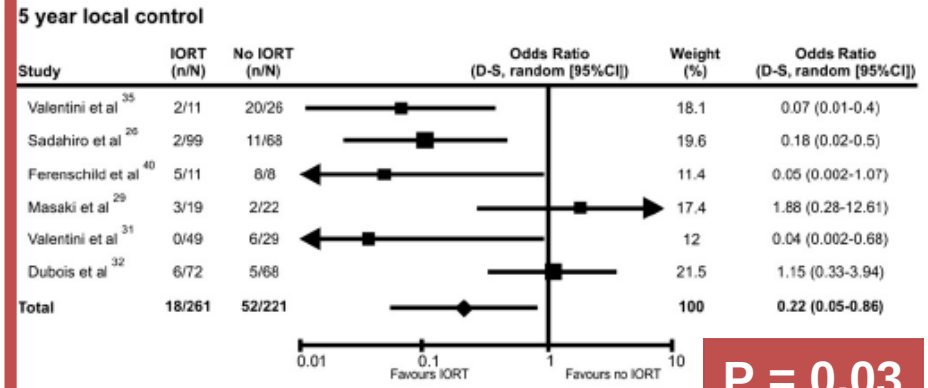
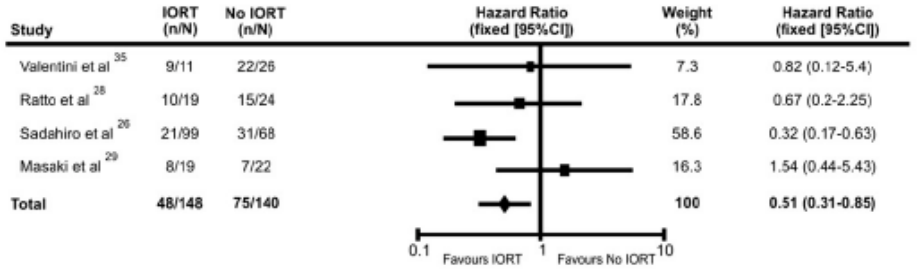
[e] Somers Cancer Research Building, University of Southampton Cancer Sciences Division, Southampton University Hospital NHS Trust, Tremona road, Southampton SO166YD, UK

A 5 year local control

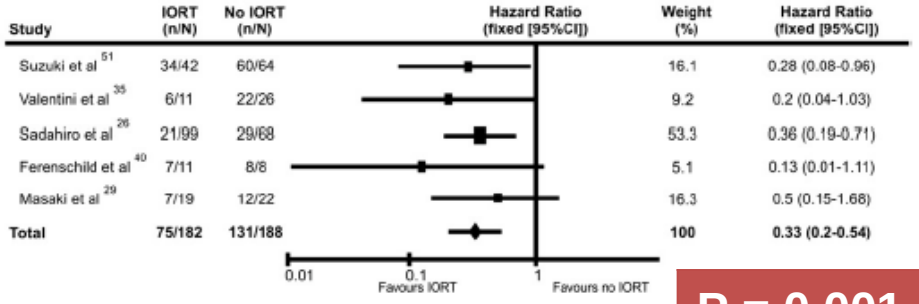


P = 0.03

B 5 year disease free survival



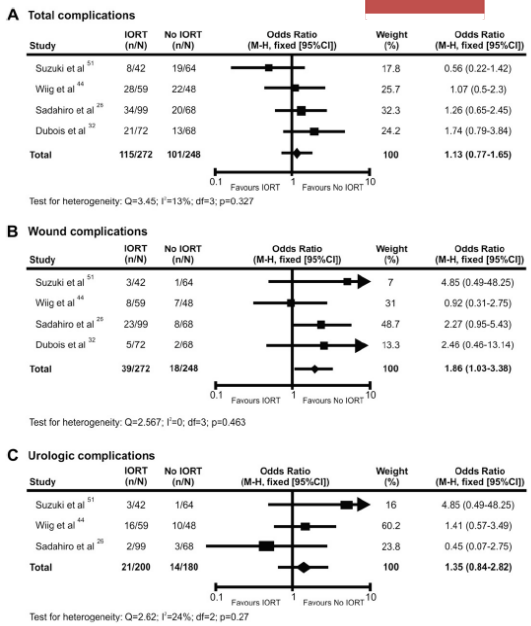
C 5 year overall survival



P = 0.001

toxicity

NS



IORT Results: colo-rectal recurrent cancer Mayo Clinic

3 decades… a summary

Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 1, pp. 143–150, 2011

0360-3016/$–see front matter

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doi:10.1016/j.ijrobp.2009.10.046

CLINICAL INVESTIGATION **Large Bowel**

COMBINED MODALITY THERAPY INCLUDING INTRAOPERATIVE ELECTRON IRRADIATION FOR LOCALLY RECURRENT COLORECTAL CANCER

MICHAEL G. HADDOCK, M.D.,* ROBERT C. MILLER, M.D.,* HEIDI NELSON, M.D.,†
JOHN H. PEMBERTON, M.D.,† ERIC J. DOZOIS, M.D.,† STEVEN R. ALBERTS, M.D.,‡
AND LEONARD L. GUNDERSON, M.D.§

*Department of Radiation Oncology, †Division of Colon and Rectal Surgery, and ‡Division of Medical Oncology, Mayo Clinic, Rochester, MN, and §Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ

1981-2008, Mayo Clinic (>25 years experience)

607 patients (rectal 70%), recurrent 45% previous RT, R0 85%

LC 68% @ 5-y, 30% OS
Central-recurrence *vs* prior EBRT (18% vs 14%)
R0/R+ (11% vs 9%)

Survival affected by Rstatus, CT, before/after 1997

2011

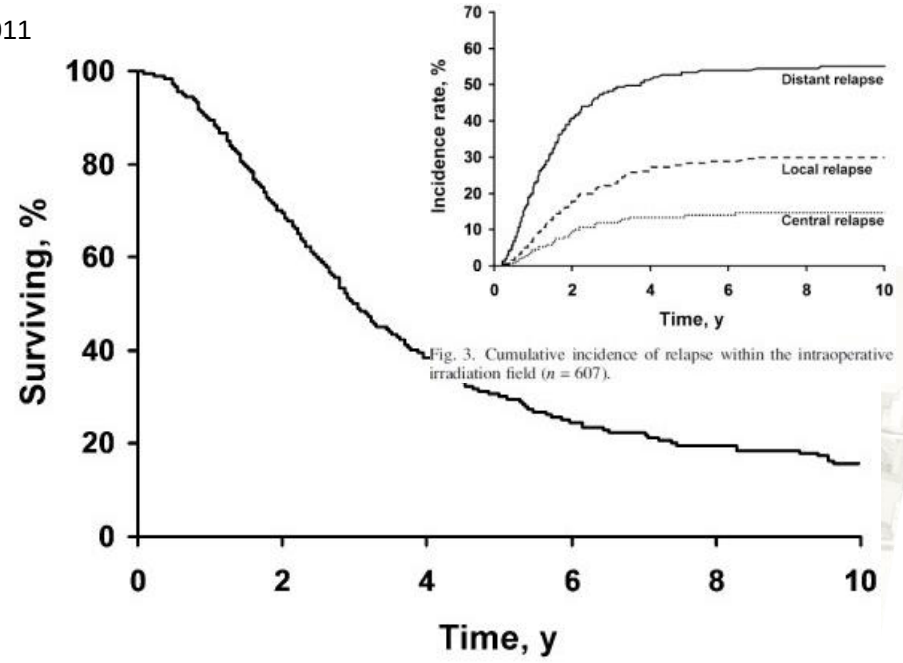
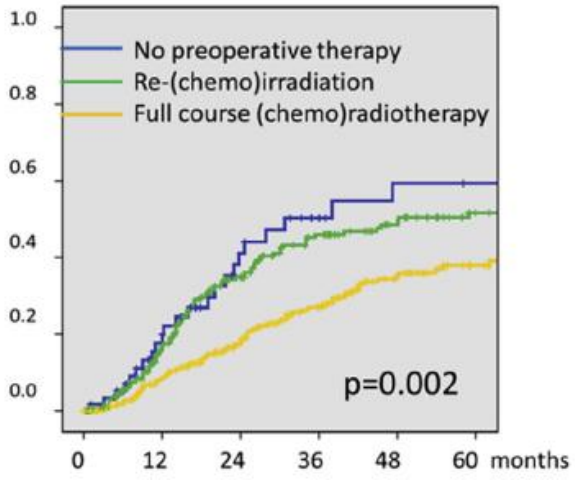


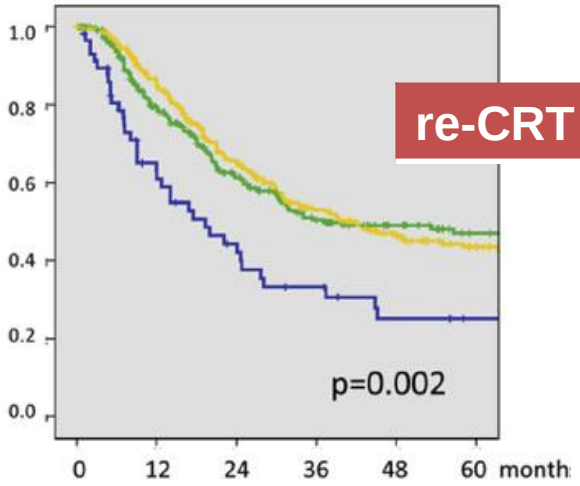
Fig. 3. Cumulative incidence of relapse within the intraoperative irradiation field ($n = 607$).

Fig. 1. Kaplan-Meier survival curve ($n = 607$).

Re local recurrence rate

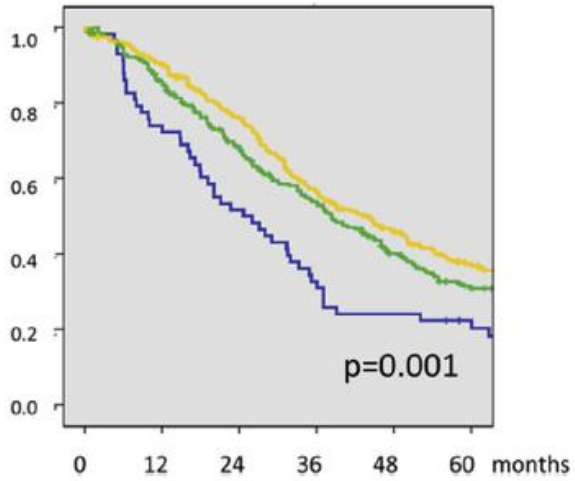


Metastasis free survival



re-CRT ! outcome

Overall survival



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Results of a pooled analysis of IOERT containing multimodality treatment for locally recurrent rectal cancer: Results of 565 patients of two major treatment centres

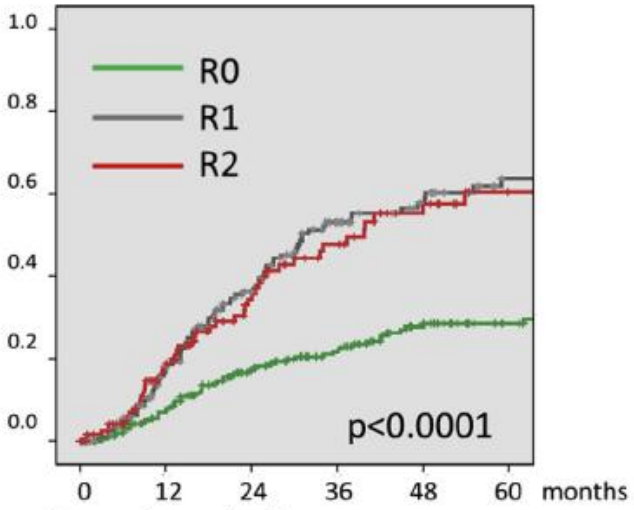
F.A. Holman [a], S.J. Bosman [b], M.G. Haddock [c], L.L. Gunderson [d], M. Kusters [a,b], G.A.P. Nieuwenhuijzen [b], H. van den Berg [e], H. Nelson [f], H.J. Rutten [b,g,*]

[a] Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands
[f] Department of Colon and Rectal Surgery, Mayo Clinic, Rochester, MN, USA
[g] GROW: School of Oncology and Developmental Biology, University of Maastricht, Maastricht, The Netherlands

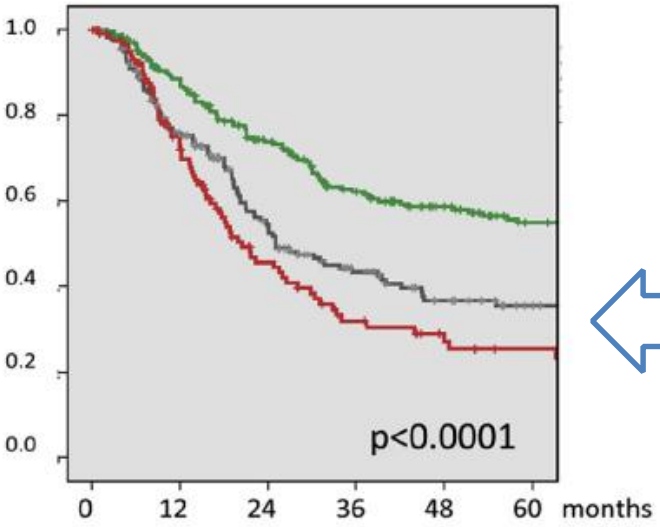
Mayo Clinic + Catherina Hospital

565 pts; before 2010; R0 44% (re-CRT 43% vs full-CRT 50%)
no preCRT R0 26%

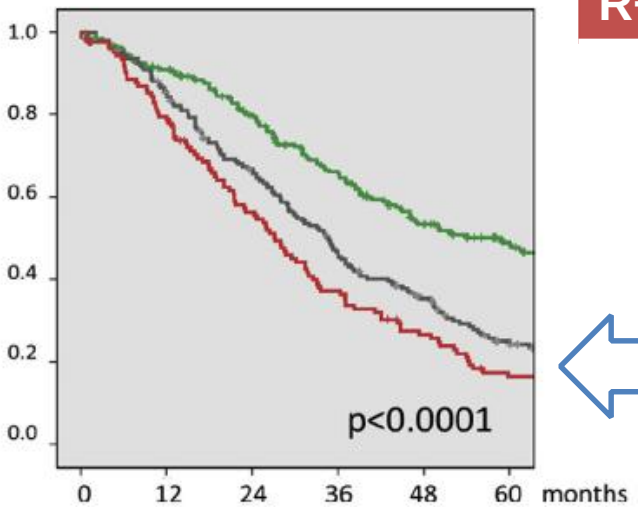
Re local recurrence rate



Metastasis free survival



Overall survival



R+ (R1 or R2) has a local + systemic impact!

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Results of a pooled analysis of IOERT containing multimodality treatment for locally recurrent rectal cancer: Results of 565 patients of two major treatment centres

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[f] Department of Colon and Rectal Surgery, Mayo Clinic, Rochester, MN, USA
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Table 1
Patient characteristics of the Mayo Clinic Rochester and the Catharina Hospital Eindhoven.

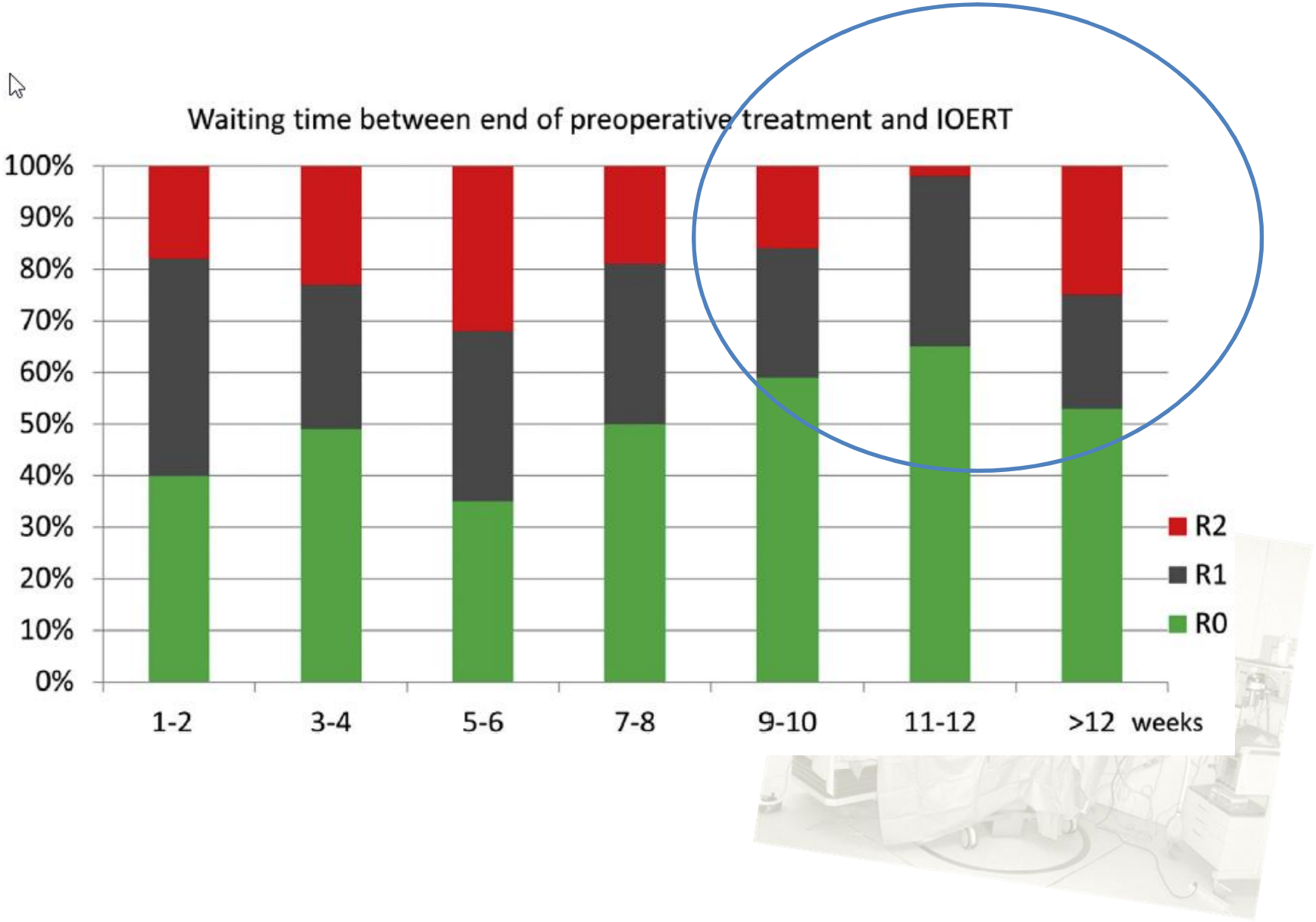
Characteristic	All N = 565	CHE N = 207	MAYO N = 358	p-Value
Mean age, yrs (range)	61.5 ± 11.0 (21–87)	62.8 ± 9.9 (39–87)	60.8 ± 13.7 (21–87)	**0.029**
Mean FU, mo (range)	44.8 ± 42.6 (1–240)	48.4 ± 43.7 (1–227)	42.6 ± 41.8 (1–240)	0.120
Gender				0.190
Male	346 (61%)	123 (59)	223 (62)	
Female	219 (39%)	84 (41)	135 (38)	
Preop Rx				0.455
None	58 (10.3%)	23 (11.1)	35 (9.8)	
Re (chemo)RT	256 (45.5%)	87 (42.0)	169 (47.5)	
Full course (Chemo)RT	249 (44.2%)	97 (46.9)	134 (42.7)	
Waiting time between end of preoperative radiotherapy and IORT				**< 0.0001**
0.1–2 weeks	138 (28.5%)	1 (0.6)	137 (43.8)	
2.1–4 weeks	53 (10.9%)	4 (2.3)	49 (15.7)	
4.1–6 weeks	92 (19.0%)	10 (5.8)	82 (26.2)	
6.1–8 weeks	74 (15.3%)	49 (28.5)	25 (8.0)	
8.1–10 weeks	56 (11.5%)	47 (27.3)	9 (2.9)	
10.1–12 weeks	40 (8.2%)	36 (20.9)	4 (1.3)	
>12 weeks	32 (6.6%)	25 (14.5)	7 (2.2)	
Total	485 (100%)	172 (100)	313 (100)	
Postoperative Chemotherapy				**< 0.0001**
No	516 (91.3%)	207 (100)	309 (86.3)	
Yes	49 (8.7%)	0	49 (13.7)	
Postoperative external beam radiotherapy				**< 0.0001**
No	537 (95.0%)	207 (100)	330 (92.2)	
Yes	28 (5.0%)	0	28 (7.8)	

Yr = year, Preop Rx = preoperative treatment, ChemoRT = chemoradiotherapy.
Waiting time = interval from end of preoperative therapy to surgery.
Postop = postoperative, Chemo = chemotherapy.

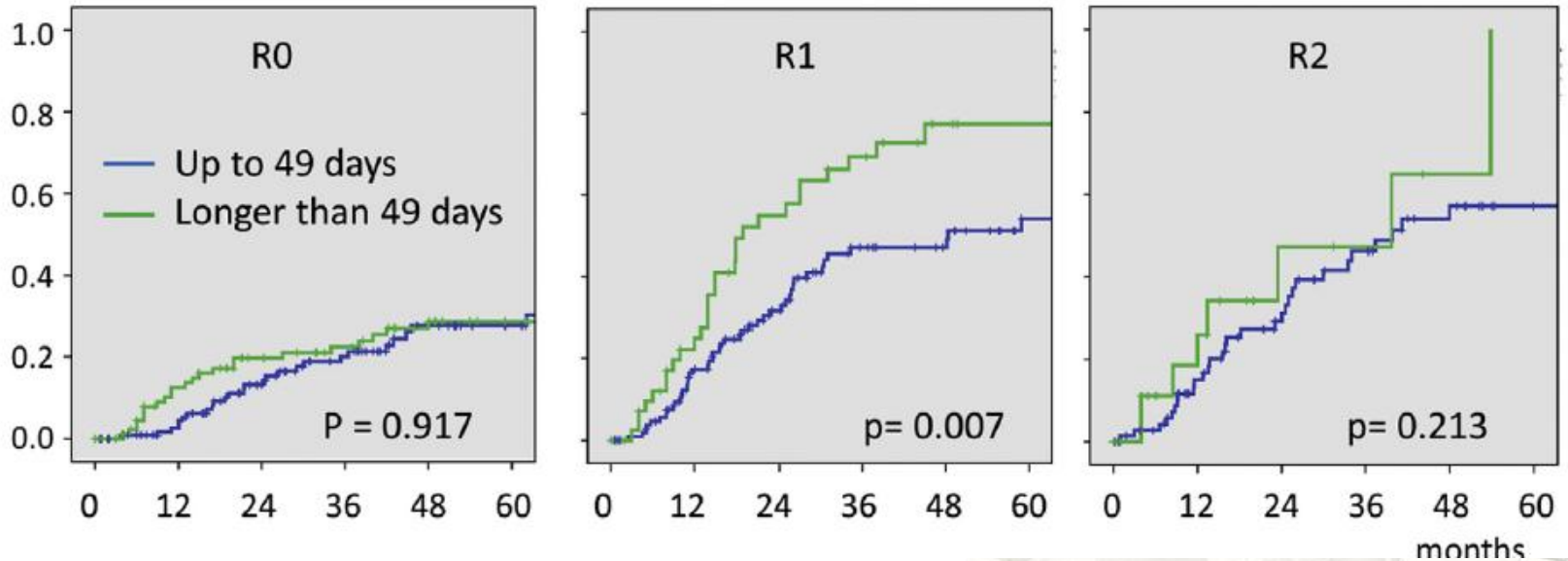
Table 2
Influence of patient and preoperative parameters on radicality of resection.

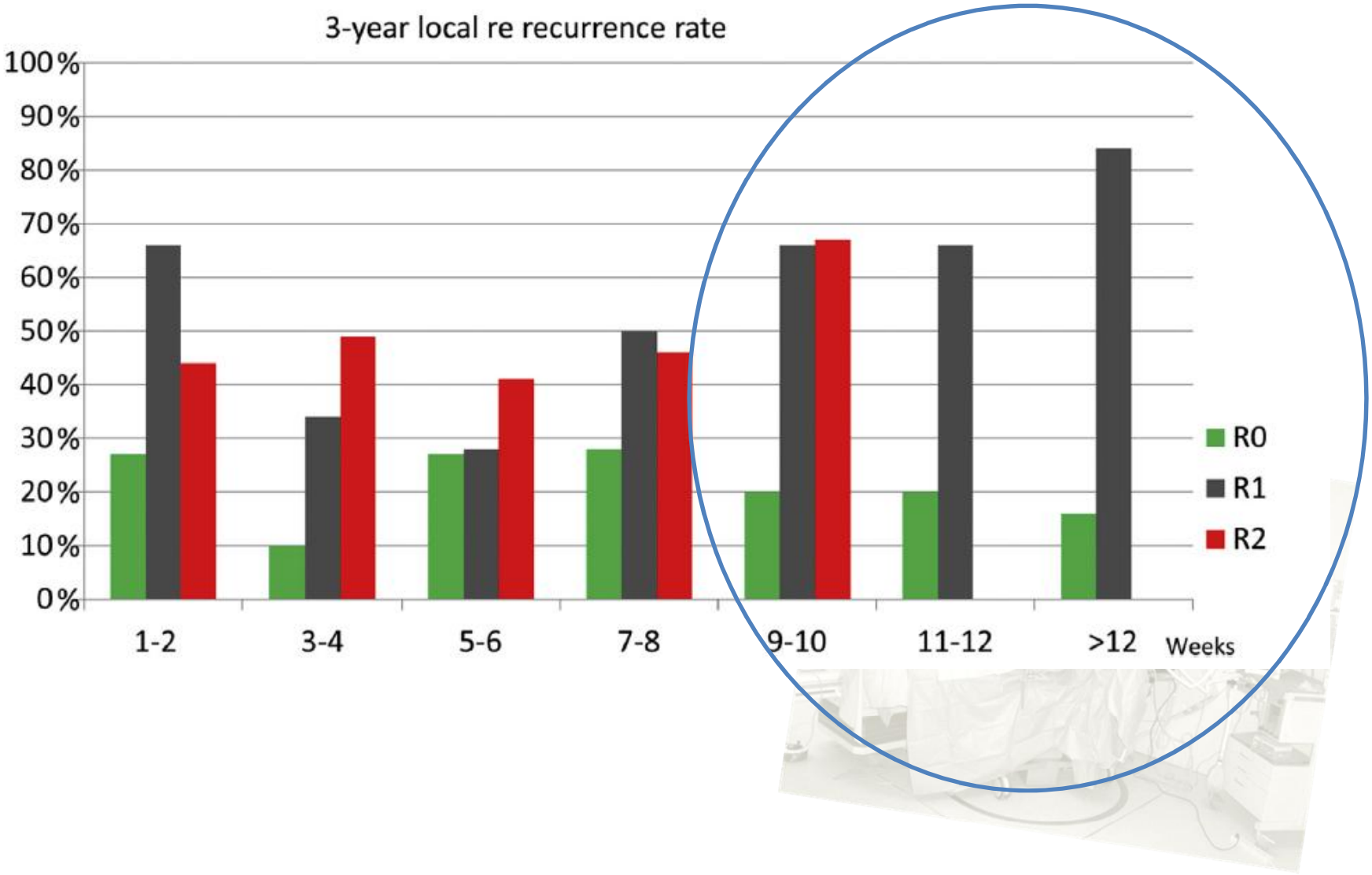
Characteristic	Resection					
	R0 No. (%)	R1 No. (%)	R2 No. (%)	Total No. (%)	Uni-variate p-value	Multi-variate (R0 vs R1/R2)
Age					**0.044**	0.108
≤69 yrs	180 (41.9)	146 (34.0)	104 (24.2)	430 (100)		
≥70	71 (52.6)	43 (31.9)	21 (15.6)	135 (100)		
Gender					0.408	
Male	147 (42.5)	117 (33.8)	82 (23.7)	346 (100)		
Female	104 (47.5)	72 (32.9)	43 (19.6)	219 (100)		
Preop Rx					**< 0.0001**	0.169
None	15 (25.9)	20 (34.5)	23 (39.7)	58 (100)		
Re (chemo)RT	110 (43.0)	100 (39.1)	46 (18.0)	256 (100)		
Full course (chemo)RT	125 (50.2)	68 (27.3)	56 (22.5)	249 (100)		
Waiting time					**0.007**	**< 0.0001**
0.1–2 weeks	54 (39.1)	58 (42.0)	26 (18.8)	138 (100)		
2.1–4 weeks	26 (49.1)	15 (28.3)	12 (22.6)	53 (100)		
4.1–6 weeks	33 (35.9)	31 (33.7)	28 (30.4)	92 (100)		
6.1–8 weeks	37 (50.0)	23 (31.1)	14 (18.9)	74 (100)		
8.1–10 weeks	33 (58.9)	14 (25.0)	9 (16.1)	56 (100)		
10.1–12 weeks	26 (65.0)	13 (32.5)	1 (2.5)	40 (100)		
>12 weeks	17 (53.1)	7 (21.9)	8 (25.0)	32 (100)		

*For multivariate analyses, the most significant cut-off point of 7 weeks was used.
Yr = year, Preop Rx = preoperative treatment, EBRT = external beam irradiation.
ChemoRT = chemoradiotherapy, Waiting time = interval from end of preoperative therapy to surgery.


Waiting time between end of preoperative treatment and IOERT
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1-2
3-4
5-6
7-8
9-10
11-12
>12 weeks
R2
R1
R0

Re local recurrence rates up to and longer 49 days waiting time




3-year local re recurrence rate
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1-2
3-4
5-6
7-8
9-10
11-12
>12
Weeks
R0
R1
R2

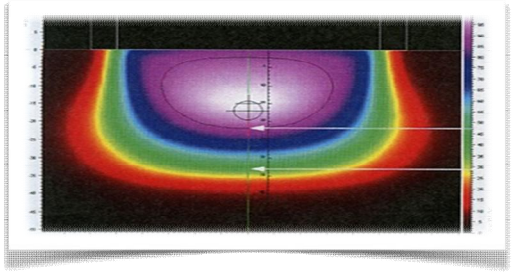
Boost Treatment Strategy: Dose–escalation & Cancer sites

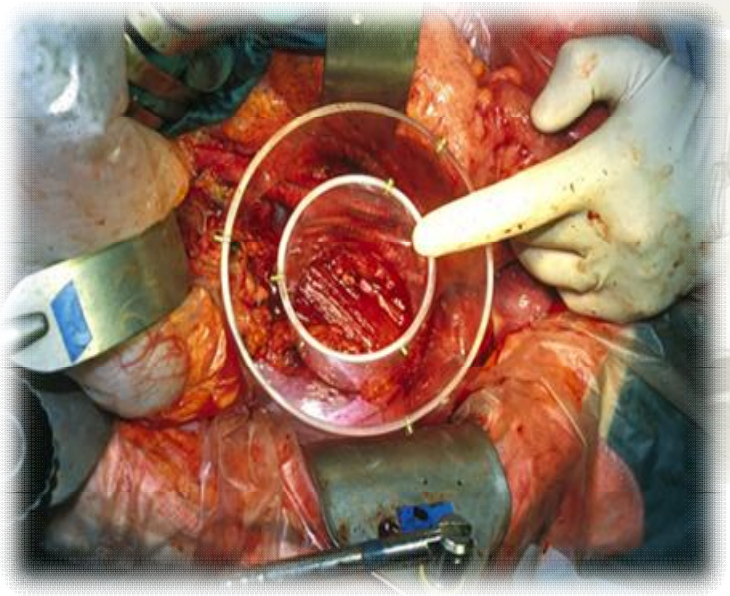
GI: pancreas, colo-rectal, esophago-gastric

Sarcomas: retroperitoneal, extremity, bone

Breast: unselected and post-neoadjuvant CT

Prostate: exclusive and post-prostatectomy





Int J Clin Oncol
DOI 10.1007/s10147-016-1086-6 2017

ORIGINAL ARTICLE

Effect of intraoperative radiotherapy in the treatment of retroperitoneal sarcoma

Liz B. Wang[1] · David McAneny[1] · Gerard Doherty[1] · Teviah Sachs[1]

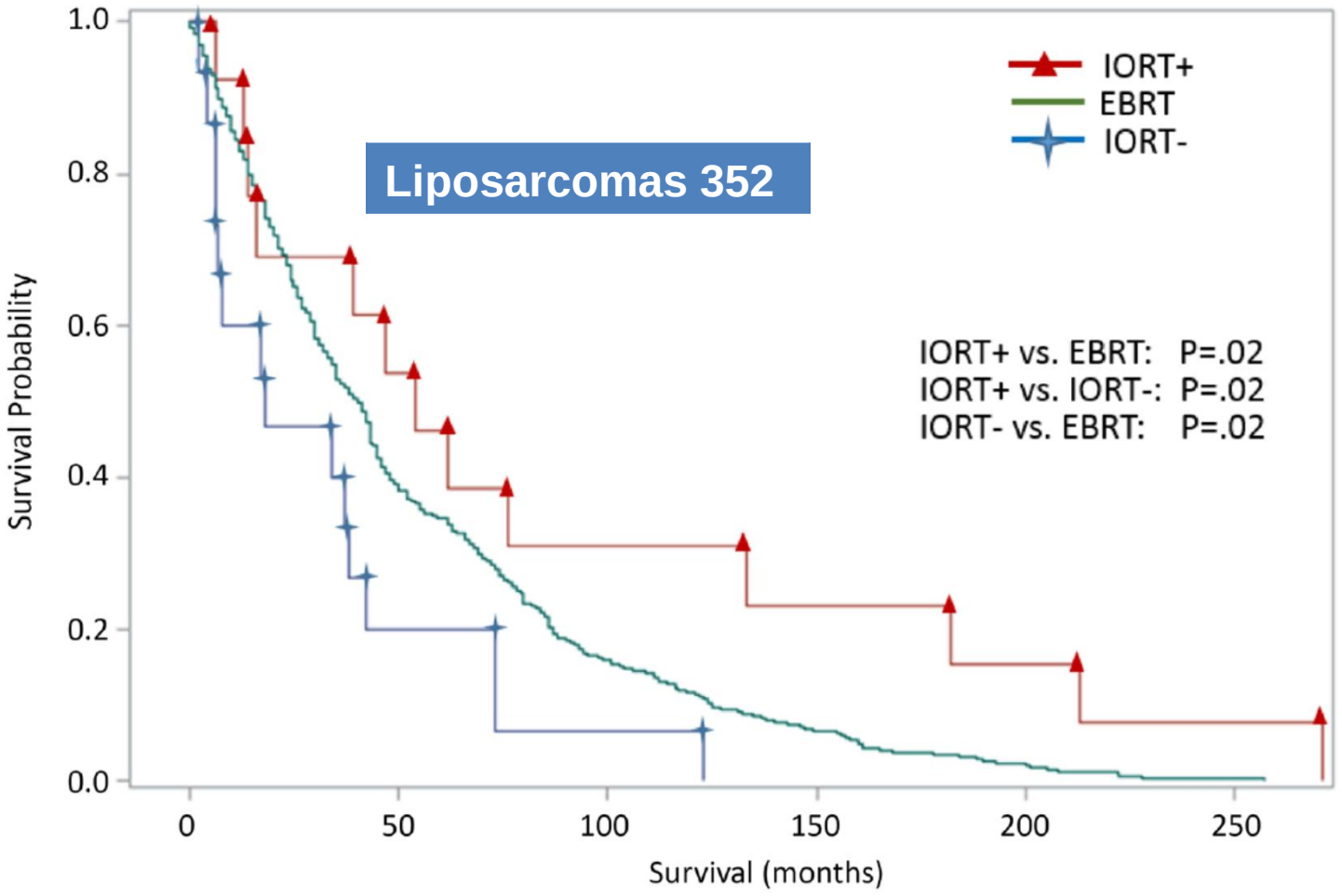
908 patients 1988-2013

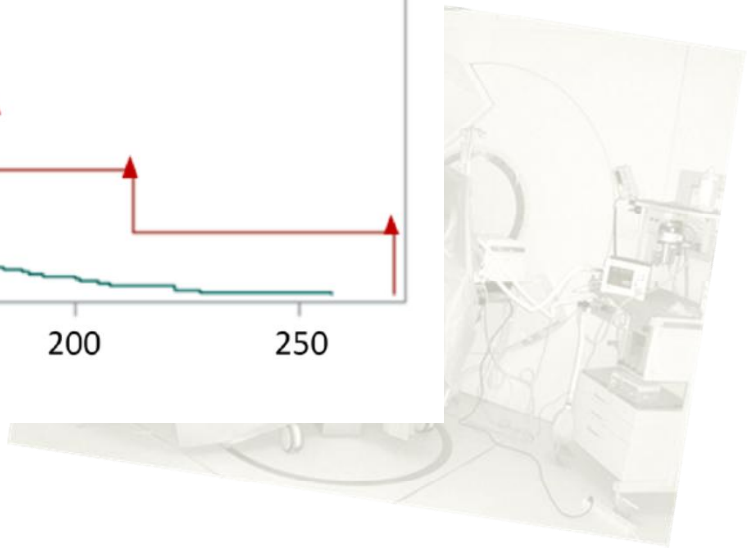
352 liposarcomas

843 EBRT
32 EBRT + IOERT
33 IORT + S

but those undergoing IORT in this study were more likely to have larger tumors and local tumor extension. A survival benefit for surgically resected patients with liposarcoma may exist with combination IORT and EBRT, but further investigations will be necessary to establish this observation.

IOERT + EBRT+ S best combination (survival)





Hager *et al. Radiation Oncology* (2017) 12:29
DOI 10.1186/s13014-017-0769-0

Radiation Oncology

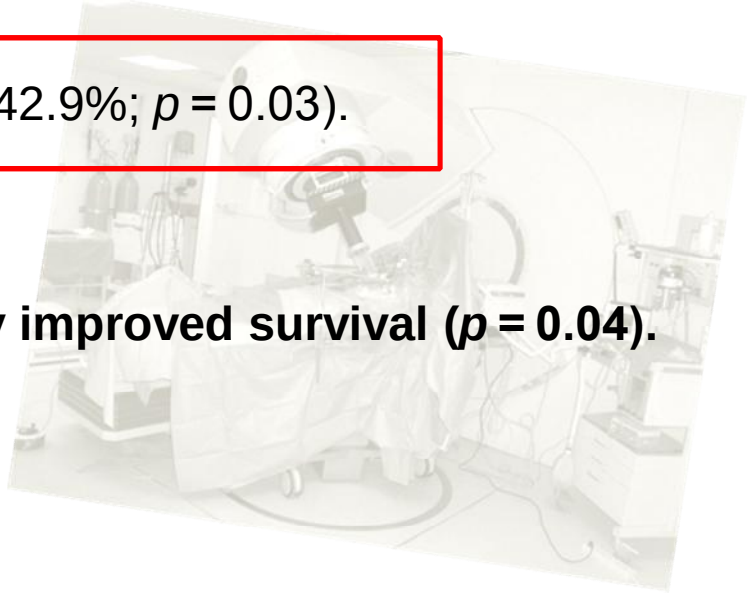
RESEARCH Open Access

Significant benefits in survival by the use of surgery combined with radiotherapy for retroperitoneal soft tissue sarcoma

Departments of General- and Visceral Surgery, Radiation Oncology
Universitätsklinik Freiburg, Germany.

23 (50%) surgery + radiotherapy (EBRT + IOERT), 23 (50%) surgery only

(R0: 77.6%; R1: 70.0%; R2: 42.9%; $p = 0.03$).



Surgery plus radiotherapy led to significantly improved survival ($p = 0.04$).

Hager et al. Radiation Oncology (2017) 12:29
DOI 10.1186/s13014-017-0769-0

Radiation Oncology

RESEARCH Open Access

Significant benefits in survival by the use of surgery combined with radiotherapy for retroperitoneal soft tissue sarcoma

R0 + R1

R2

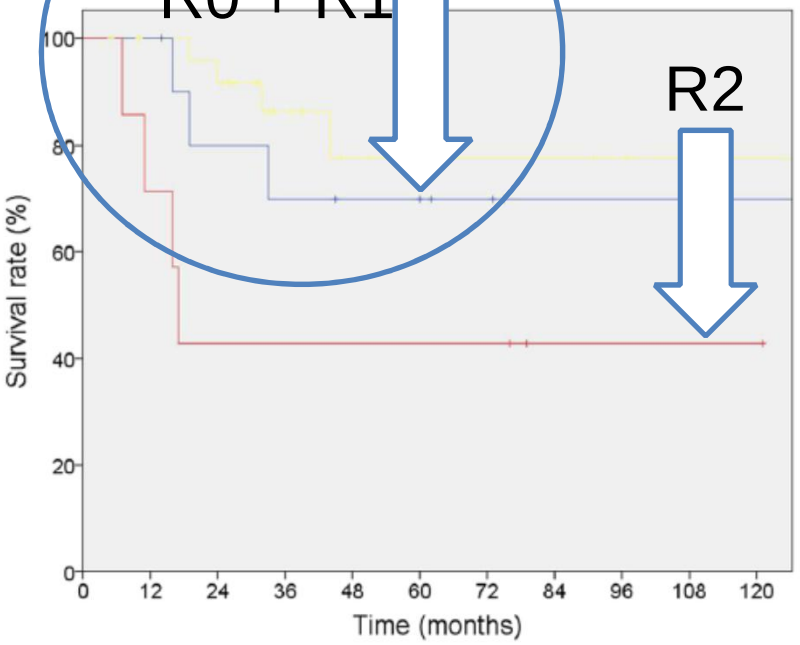


Fig. 1 Sarcoma specific 5 year-survival of 46 patients with RSTS who underwent surgical resection divided by R-status (R0-margin [*yellow*] 77.6% vs. R1-margin [*blue*] 70.0% vs. R2-margin [*red*] 42.9%; $p = 0.03$)

S + IOERT + EBRT

S alone

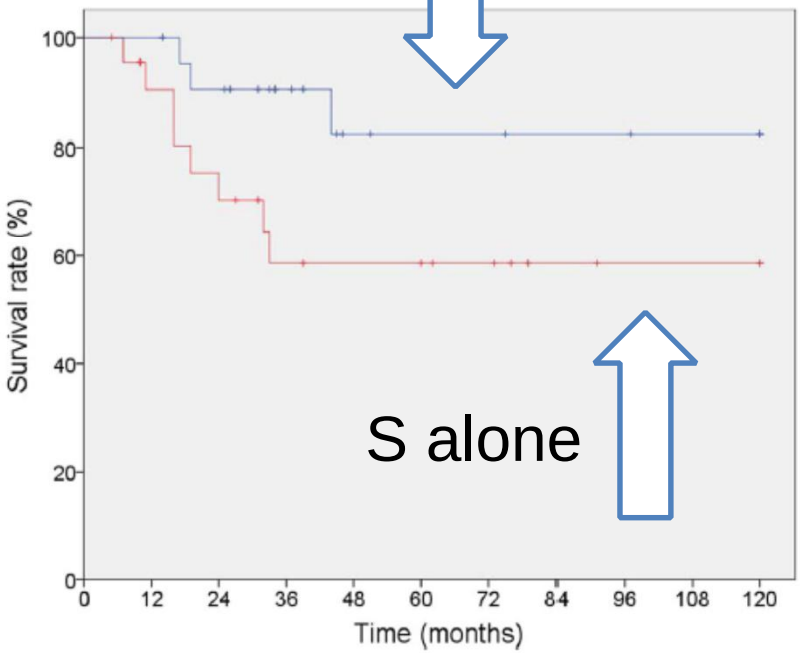


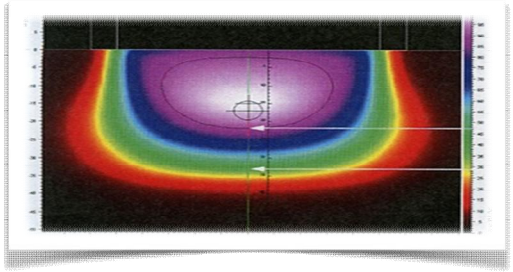
Fig. 3 Sarcoma specific 5-year-survival of 46 patients with RSTS who underwent surgical resection with or without radiotherapy (SO = surgery only [*red*] 58.6% vs. S + RT = surgery plus radiotherapy [*blue*] 82.3%, $p = 0.043$)

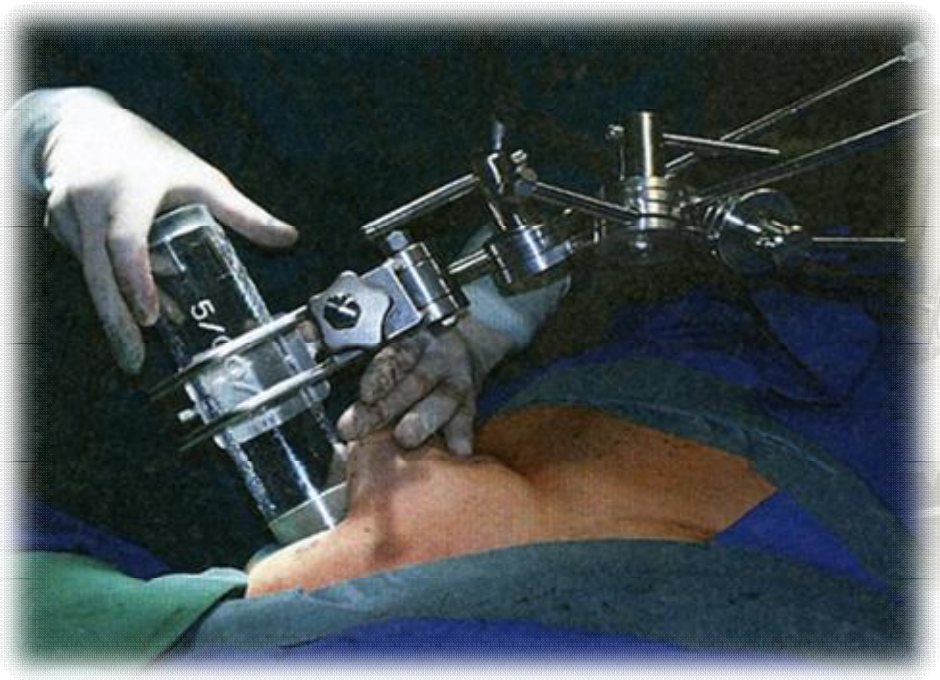
Boost Treatment Strategy: Dose–escalation & Cancer sites

GI: pancreas, colo-rectal, esophago-gastric

Sarcomas: retroperitoneal, extremity, bone

Breast: unselected and post-neoadjuvant CT





Radiotherapy and Oncology 108 (2013) 279–286

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Breast cancer radiotherapy

IORT with electrons as boost strategy during breast conserving therapy in limited stage breast cancer: Long term results of an ISIORT pooled analysis

Gerd Fastner [a,*,1], Felix Sedlmayer [a,1], Florian Merz [a,1], Heinrich Deutschmann [a,1], Roland Reitsamer [b,c,1], Christian Menzel [b,1], Christoph Stierle [b,c,1], Armando Farmini [b,c,1], Torsten Fischer [b,c,1], Antonella Ciabattoni [d,1], Alessandra Mirri [d,1], Eva Hager [e,1], Gabriele Reinartz [f,1], Claire Lemanski [i,1], Roberto Orecchia [g,1], Vincenzo Valentini [h,1]

[a] Department of Radiotherapy and Radio-Oncology; [b] Department of Special Gynecology; [c] Department of Gynecology, Paracelsus Medical University, Salzburg, Austria; [d] Department of Radiotherapy, San Filippo Neri Hospital, Rome, Italy; [e] Department of Radiotherapy, Landeskrankenhaus Klagenfurt, Austria; [f] Department of Radiotherapy, University Clinic Münster, Germany; [g] Department of Radiotherapy, European Institute of Oncology, Milano, Italy; [h] Department of Radiotherapy, Università Cattolica S. Cuore, Rome, Italy; [i] Department of Radiotherapy, Montpellier, France

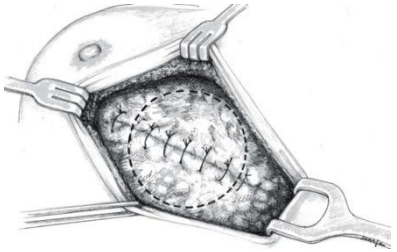


Table 3
Local-recurrences depending on age separated in four groups.

LR	Age	Pts/%	FUP: median/range (mths)	LR: pts/%	Annual
IB					
	<40	53/4.8	74.48 (16.50–126.00)	2/3.7	0.64%
	40–49	234/21.1	75.89 (4.80–187.90)	5/2.1	0.34%
	50–59	326/29.3	72.90 (3.80–208.50)	4/1.2	0.21%
	⩾60	496/44.6	73.03 (3.48–215.00)	5/1.0	0.16%
IQ					
	<40			2/3.7	0.64%
	40–49			2/0.85	0.14%
	50–59			2/0.61	0.10%
	⩾60			2/0.40	0.06%
OQ					
	<40			0/0	0
	40–49			3/1.27	0.21%
	50–59			2/0.61	0.10%
	⩾60			3/0.60	0.09%

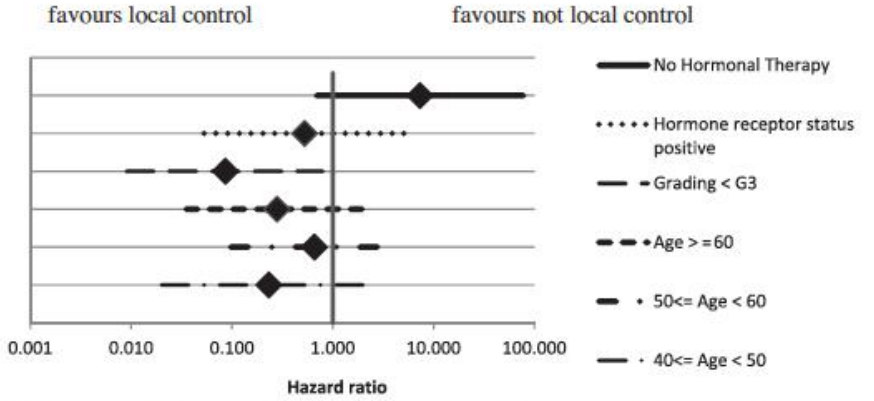


Fig. 2. Forrest – Plot: negative predictive factors for development of in-quadrant local recurrences.

ISIORT e, 1109 p (unselected), 10 Gy, 72 MFT

16 in-breast (1,4%), 99.2% LC @ 5y, grade 3 (0.03 multiv)

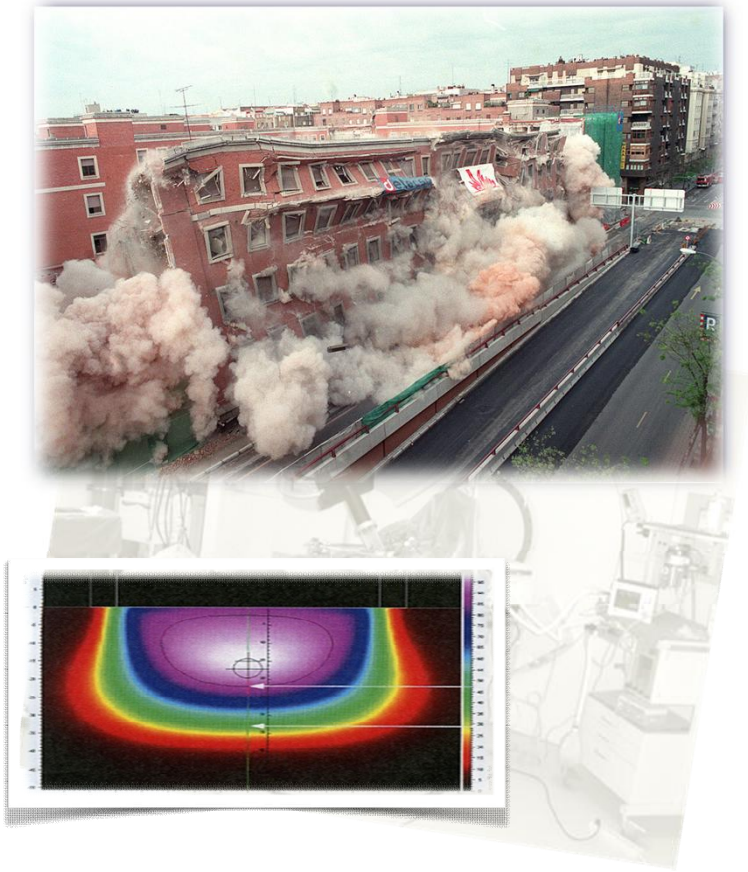
Boost Treatment Strategy HGUGM: Dose–escalation & Cancer sites

GI: pancreas, colo-rectal, esophago-gastric

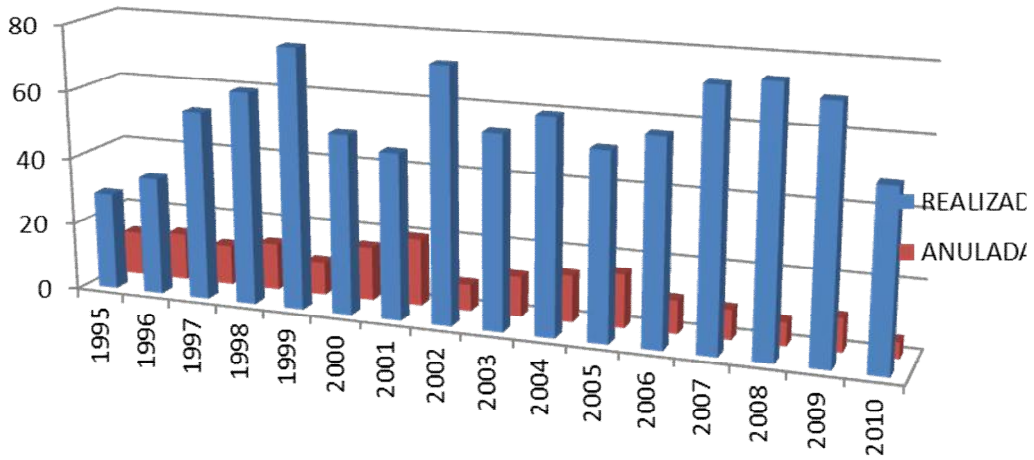
Sarcomas: retroperitoneal, extremity, bone

Oligo-recurrences: gyne, sarc, rectal

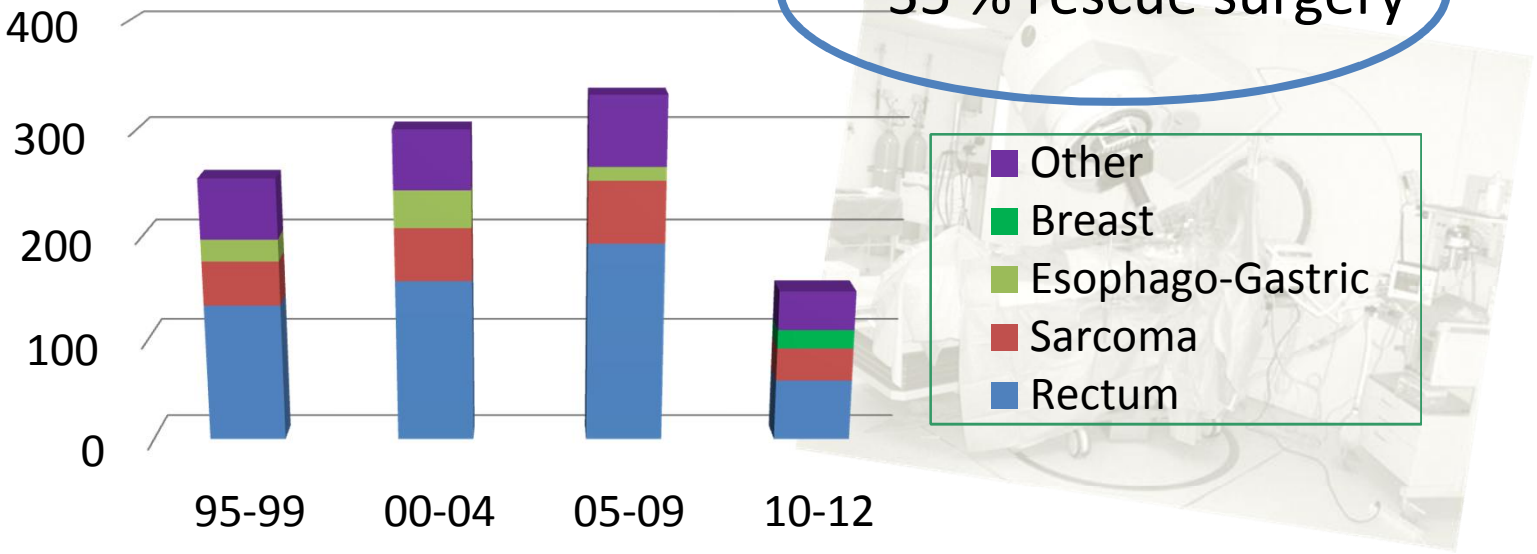
Pediatric: Ewing, rabdo, miscellaneous



10 to 20 Gy boost + EBRT 45-55 Gy



35 % rescue surgery



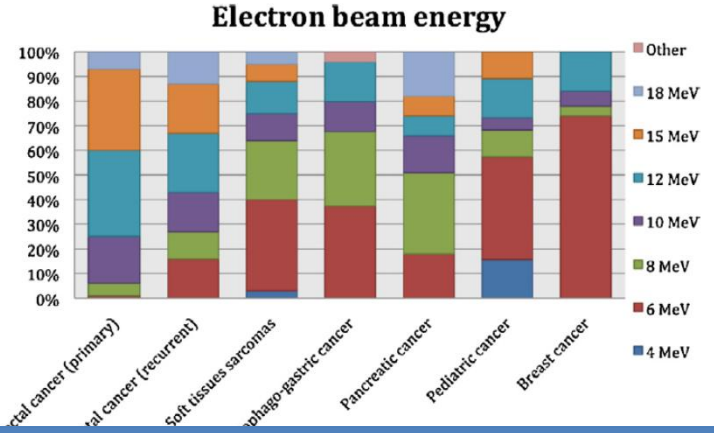
Available online at www.sciencedirect.com
SciVerse ScienceDirect
journal homepage: http://www.elsevier.com/locate/rpor

Original research article

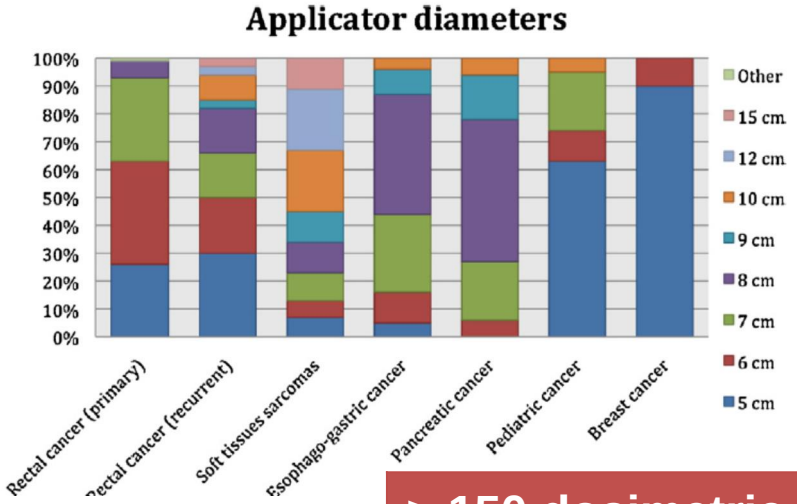
Intraoperative radiation therapy opportunities for clinical practice normalization: Data recording and innovative development☆

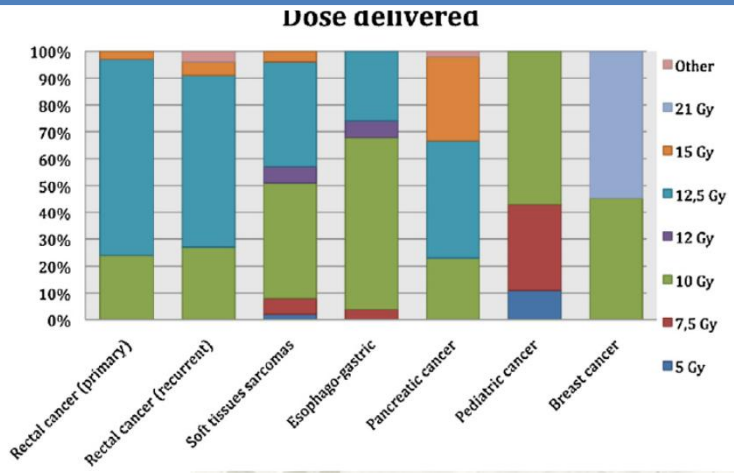
Felipe A. Calvo[a,b,d], Morena Sallabanda[b], Claudio V. Sole[a,b,d,*], Carmen Gonzalez[b,c], Laura Alonso Murillo[b], Javier Martinez-Villanueva[b], Juan A. Santos[c,d], Javier Serrano[c], Ana Alavrez[c], Jose Blanco[c], Ana Calin[c], Marina Gomez-Espi[c], Miguel Lozano[c], Rafael Herranz[c]

[a] Department of Oncology, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[b] School of Medicine Complutense University, Madrid, Spain
[c] Service of Radiation Oncology, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[d] Institute for Sanitary Research, Hospital General Universitario Gregorio Marañón, Madrid, Spain



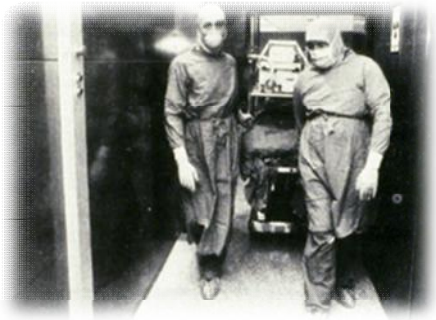
8 applicator diameter 5-15 cm; 4 beveled end 0-45º;7 e- enegies 4-8 MeV





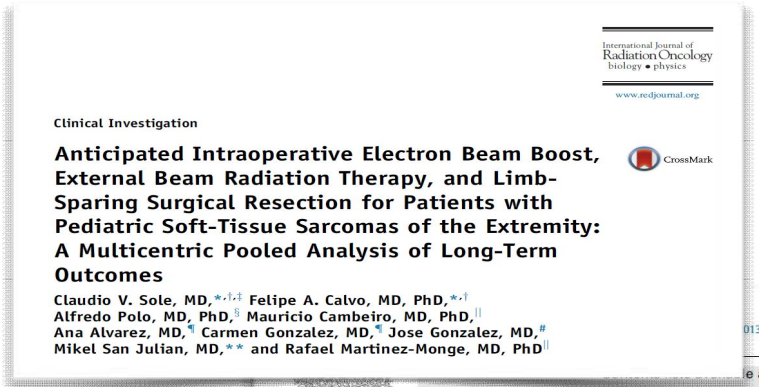
> 150 dosimetric configurations available

IOERT Program HGUGM Madrid Spain 1995 – 2015: colective maximal effort



- **1.326 procedures … (7th May 2015)**

- **> 2.200 surgical-room hours in primary disease**
- **> 1.200 surgical-room hours for rescue of oligo-recurrent disease**
- **> 95% of cases transported to a fixed non-dedicated linac**
- **20 years of sustined clinical activity (no discontinuity)**
- **> 200 profesional involved (20 generations of residents)**
- **> 100 visitors, 17 countries, 22 hospitals**



Clinical Investigation

Anticipated Intraoperative Electron Beam Boost, External Beam Radiation Therapy, and Limb-Sparing Surgical Resection for Patients with Pediatric Soft-Tissue Sarcomas of the Extremity: A Multicentric Pooled Analysis of Long-Term Outcomes

Claudio V. Sole, MD,*,†,‡ Felipe A. Calvo, MD, PhD,*,† Alfredo Polo, MD, PhD,§ Mauricio Cambeiro, MD, PhD,‖ Ana Alvarez, MD,¶ Carmen Gonzalez, MD,¶ Jose Gonzalez, MD,# Mikel San Julian, MD,** and Rafael Martinez-Monge, MD, PhD‖

Clinical Investigation: Genitourinary Cancer

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*

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Original article

Chemoradiation for resected pancreatic adenocarcinoma wit
therapy boost: Long-term o

1, Freddy Atahualpa [b,e], Miguel A. L
cía-Alfonso [g], Luis Gonzalez-Bayon [
,e

www.redjournal.org

Clinical Investigation

Intraoperative Electron-Beam Radiation Therapy for Pediatric Ewing Sarcomas and
utcomes

PhD,†,‡
hD,‖
,#
ago, Chile; †School of
logy, Hospital General
logy, Clínica Universidad de
neral Universitario Gregorio
Medicine, Hospital General

Limb-sparing management with surgical resection, external-beam and intraoperat radiation th patients wit sarcoma of

A multicentric p

Felipe A. Calvo[1,2] · Claudio V. S
Angel Montero[4] · Ana Alvarez
Rafael Martinez-Monge[9]

Strahlentherapie

2012-2017; 7 pub (1q/ >48 IF)
primary locally advanced disease
8 cancer sites/histologies
757 pts

Radiotherapy and Oncology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

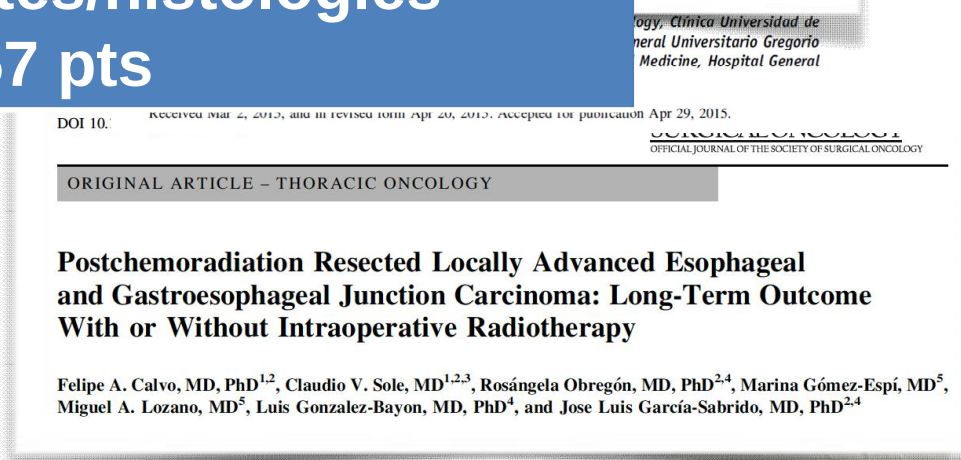
Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Post-chemoradiation intraoperative electron-beam radiation therapy boost in resected locally advanced rectal cancer: Long-term results focused on topographic pattern of locoregional relapse

Claudio V. Sole [a,b,i,*], Felipe A. Calvo [c,d,i], Javier Serrano [d,e,i], Emilio del Valle [f,i], Marcos Rodriguez [f,i], Alberto Muñoz-Calero [d,f,i], Fernando Turégano [f,i], Jose Luis García-Sabrido [d,f,i], Pilar Garcia-Alfonso [d,g,i], Isabel Peligros [h,i], Sofia Rivera [b,j,k], Eric Deutsch [b,j,k], Emilio Alvarez [d,h,i]



DOI 10.
Received Mar 2, 2015; and in revised form Apr 20, 2015. Accepted for publication Apr 29, 2015.

OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – THORACIC ONCOLOGY

Postchemoradiation Resected Locally Advanced Esophageal and Gastroesophageal Junction Carcinoma: Long-Term Outcome With or Without Intraoperative Radiotherapy

Felipe A. Calvo, MD, PhD[1,2], Claudio V. Sole, MD[1,2,3], Rosángela Obregón, MD, PhD[2,4], Marina Gómez-Espí, MD[5], Miguel A. Lozano, MD[5], Luis Gonzalez-Bayon, MD, PhD[4], and Jose Luis García-Sabrido, MD, PhD[2,4]

Ann Surg Oncol (2013) 20:1962–1969
DOI 10.1245/s10434-012-2810-8

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – THORACIC ONCOLOGY

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Felipe A. Calvo, MD, PhD[1,2], Claudio V. Sole, MD[1,2,3], Rosángela Obregón, MD, PhD[2,4], Marina Gómez-Espí, MD[5], Miguel A. Lozano, MD[5], Luis Gonzalez-Bayon, MD, PhD[4], and Jose Luis García-Sabrido, MD, PhD[2,4]

53 patients

NAT CRT vs NAT CRT + IOERT

IOERT improved local control

5,4% vs 25% local relapse
cN and cT compensation

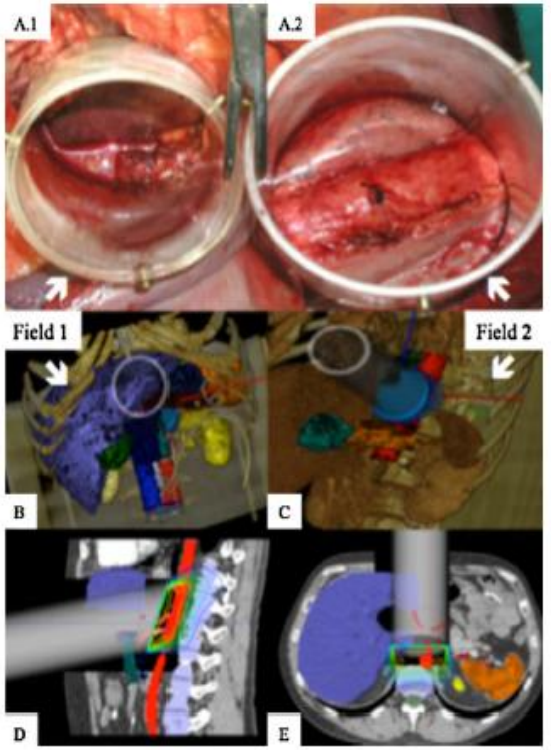


FIG. 1 Intrasurgical target volume view (**a**), 3D (**b** and **c**) and 2D (**d** and **e**) CT scan-based IOERT planning technology. Planning treatment volume (PTV) encompasses the upper abdominal lymph node area (**a.1** and **b**), including lymph node groups of the right/left cardia, left gastric artery, celiac artery, and abdominal para-aorta (*Field 1*), and tumor bed plus inferior mediastinum (**a.2** and **c**) (*Field 2*)

Pancreatology 13 (2013) 576–582

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Original article

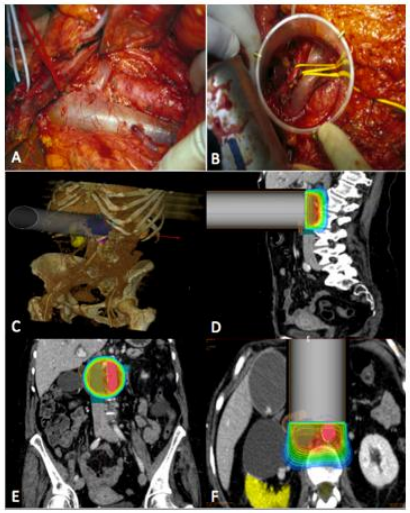
Chemoradiation for resected pancreatic adenocarcinoma with or without intraoperative radiation therapy boost: Long-term outcomes

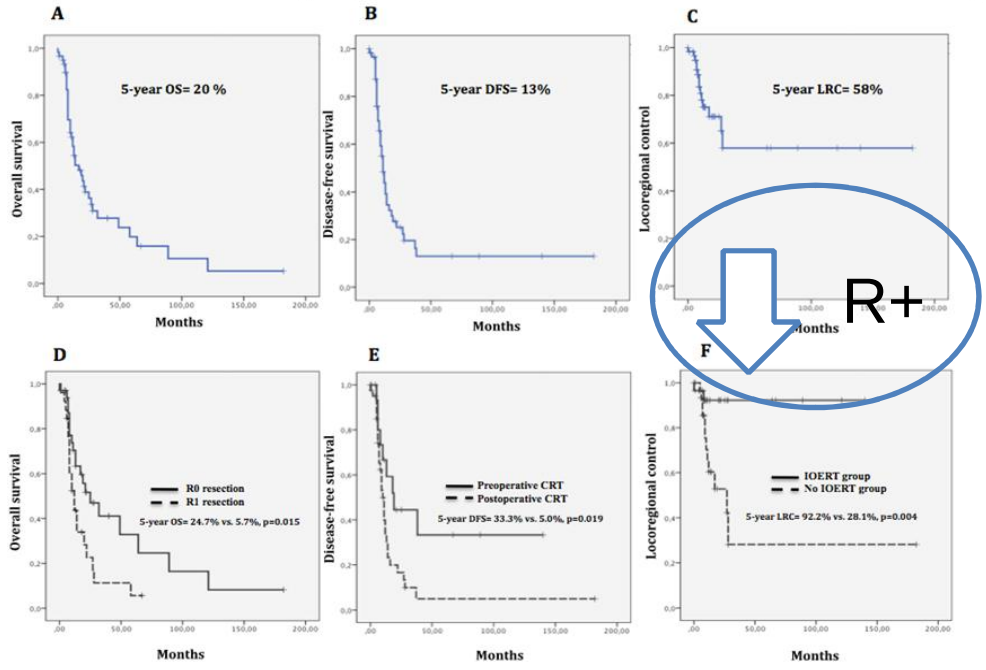
Felipe A. Calvo [a,b,1], Claudio V. Sole [a,b,c,d,*,1], Freddy Atahualpa [b,e], Miguel A. Lozano [f], Marina Gomez-Espi [f], Ana Calin [f], Pilar García-Alfonso [g], Luis Gonzalez-Bayon [e], Rafael Herranz [f], Jose Luis García-Sabrido [b,e]

60 pts resected + EBRT
1995-2010
29 non-IOERT pts
vs
31 IOERT pts

Vascular resection 17 %

Supplemental figure. Intrasurgical target volume view (A, B), 3D (C) and 2D (D, E, F) CT scan-based IOERT planning technology.





Radiotherapy and Oncology xxx (2014) xxx–xxx

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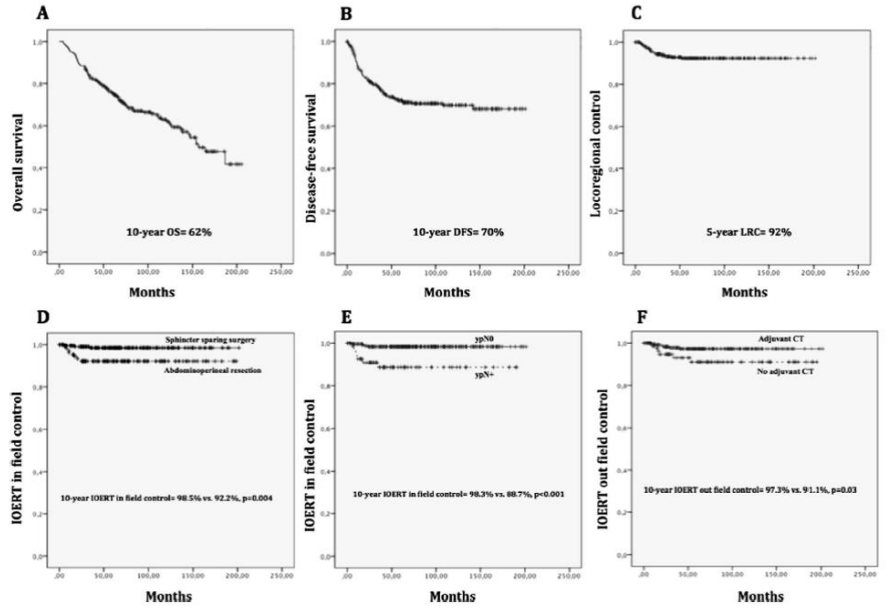
Post-chemoradiation intraoperative electron-beam radiation therapy boost in resected locally advanced rectal cancer: Long-term results focused on topographic pattern of locoregional relapse

Claudio V. Sole [a,b,i,*], Felipe A. Calvo [c,d,i], Javier Serrano [d,e,i], Emilio del Valle [f,i], Marcos Rodriguez [f,i], Alberto Muñoz-Calero [d,f,i], Fernando Turégano [f,i], Jose Luis García-Sabrido [d,f,i], Pilar Garcia-Alfonso [d,g,i], Isabel Peligros [h,i], Sofia Rivera [b,j,k], Eric Deutsch [b,j,k], Emilio Alvarez [d,h,i]

The index score was defined as weighted sum of the risk factors (distal margin < 10 mm, 1 point; R1 resection, 2 points; tumor histological grade 3, 3 points). Risk groups were defined by comparing



Radiotherapy and Oncology xxx (2014) xxx–xxx

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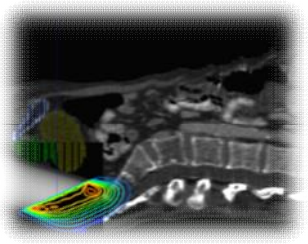


Table 2
Factors associated with locoregional control, IOERT in field control and IOERT out field control in multivariate analyses.

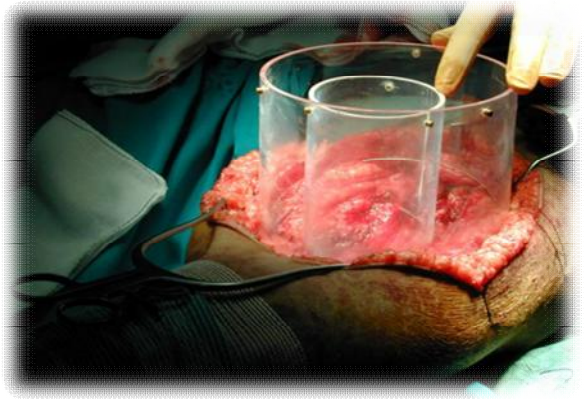
Parameter	Variable	Locoregional control			IOERT in field control			IOERT out field control		
		HR	CI 95%	*p* value	HR	CI 95%	*p* value	HR	CI 95%	*p* value
Microscopic surgical specimen										
Distal margin status	⩾10 mm	1.0	1.09–5.57	0.03	–	–	–	1.0	1.16–8.45	0.024
	<10 mm	2.46						3.13		
Margin resection status	R0	1.0	1.40–18.26	0.013	1.0	2.07–34.23	0.003	1.0	1.27–12.69	0.018
	R1	5.06			8.42			4.02		
Primary tumor histologic grade	I–II	1.0	2.74–22.12	<0.001	–	–	–	1.0	2.53–22.10	<0.001
	III	7.79						7.65		
Tumor Regression Grade	TRG 3–4	1.0	1.03–6.67	0.05	–	–	–	–	–	–
	TRG 1–2	2.63								
Re-staging ypN	N0	–	–	–	1.0	1.60–21.38	0.008	–	–	–
	N+				5.84					
Surgery										
Resection	Sphincter sparing resection	–	–	–	1.00	1.17–14.29	0.02	–	–	–
	Abdominoperineal resection				4.33					
Treatment										
Adjuvant CT	Yes	–	–	–	–	–	–	1.0	1.02–7.14	0.05
	No							2.70		

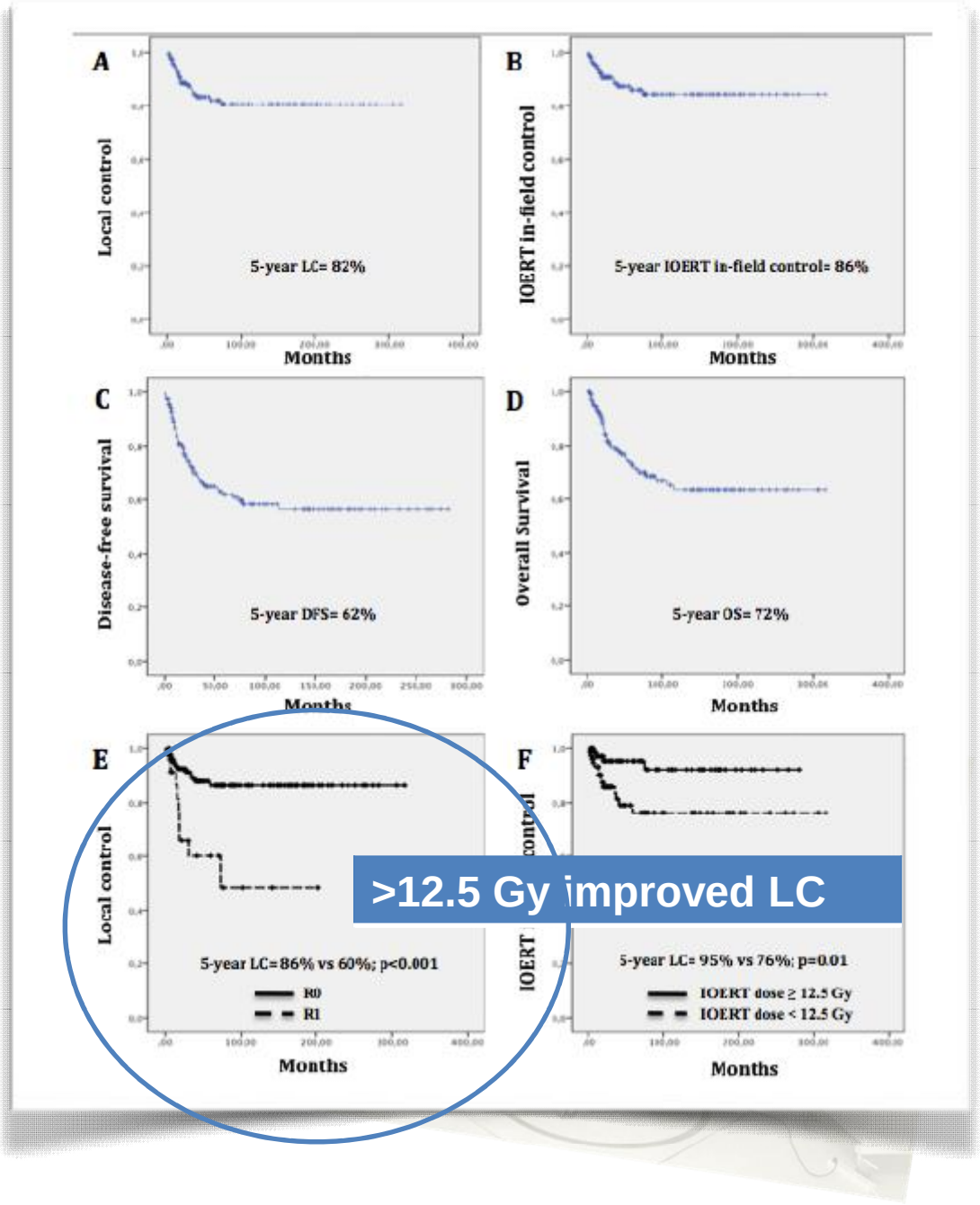
Limb-sparing management with surgical resection, external-beam and intraoperative electron-beam radiation therapy boost for patients with primary soft tissue sarcoma of the extremity

A multicentric pooled analysis

Felipe A. Calvo[1,2] · Claudio V. Sole[1,2,3] · Alfredo Polo[4] · Mauricio Cambeiro[5] · Angel Montero[4] · Ana Alvarez[6] · Miguel Cuervo[7] · Mikel San Julian[8] · Rafael Martinez-Monge[9]

Strahlentherapie und Onkologie X · 2014





International Journal of Radiation Oncology biology • physics
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Clinical Investigation

Anticipated Intraoperative Electron Beam Boost, External Beam Radiation Therapy, and Limb-Sparing Surgical Resection for Patients with Pediatric Soft-Tissue Sarcomas of the Extremity: A Multicentric Pooled Analysis of Long-Term Outcomes

Claudio V. Sole, MD,*,†,‡ Felipe A. Calvo, MD, PhD,*,† Alfredo Polo, MD, PhD,§ Mauricio Cambeiro, MD, PhD,|| Ana Alvarez, MD,¶ Carmen Gonzalez, MD,¶ Jose Gonzalez, MD,# Mikel San Julian, MD,** and Rafael Martinez-Monge, MD, PhD||

Size >5cm, R+ for local control compesates histology adversity

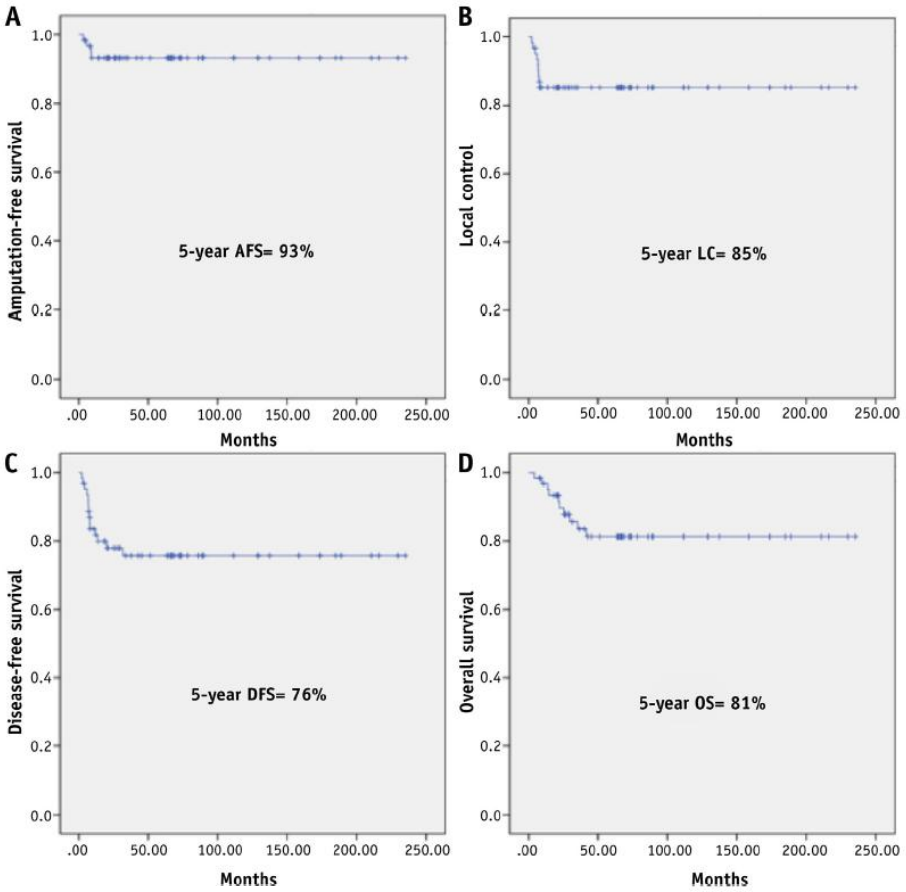

Table 3 Factors associated with local control, disease-free survival, and overall survival in multivariate analyses

Parameter	Variable	Local control HR	Local control 95% CI	Local control *P*	Disease-free survival HR	Disease-free survival 95% CI	Disease-free survival *P*	Overall survival HR	Overall survival 95% CI	Overall survival *P*
Presurgical variables										
Tumor size (cm)	≤5	1.0	1.06-11.81	.04	—	—	—	—	—	—
	>5	3.03								
Microscopic surgical specimen										
Histology subtype	NRSTS	—	—	—	1.0	1.01-8.57	.05	—	—	—
	RMS				2.88					
Surgery										
Margin status	R0	1.0	1.06-8.22	.04	1.0	1.17-8.72	.02	1.0	1.08-10.66	.04
	R1	2.32			2.47			2.71		

Abbreviations as in Table 2.

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Clinical Investigation

Intraoperative Electron-Beam Radiation Therapy for Pediatric Ewing Sarcomas and Rhabdomyosarcomas: Long-Term Outcomes

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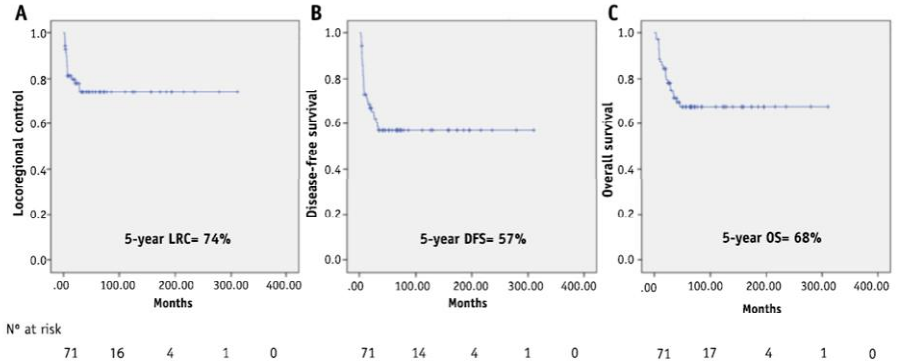

Fig. 1. Kaplan-Meir curves for all patients (n=71) for (A) locoregional control (LRC), (B) disease-free survival (DFS), and (C) overall survival (OS).

disease status (recurrent), R+ for local control compensates R1 if NAT responder

Table 3 Factors associated with locoregional control, disease-free survival, and overall survival in multivariate analyses

	Locoregional control			Disease-free survival			Overall survival		
Parameter	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Presurgical variables									
Disease status			.04			.03			.05
Primary	1.0	1.10-5.98		1.0	1.13-5.18		2.10	1.02-6.01	
Locally recurrent	2.18			2.16					
Microscopic surgical specimen									
Histologic response						.05			
Good response	—	—	—	1.0	1.01-4.72		—	—	—
Poor response				2.02					
Surgery									
Margin status			<.01			<.01			.04
R0	1.0	1.53-10.13		1.0	1.61-7.41		1.0	1.08-6.17	
R1	3.72			3.28			2.48		

Abbreviations as in Table 2.

37 Ewing / 34 RMS

Recurrent

R1

24%
LR @ 10 y

IOeRT in resected primary cancer: 2017 update HGUGM published results (toxicity)

Cancer	N Acute Late	Stage / treatment	In-field relapse	Survival	Local adversity	Local compensation
Esophago-gastric	53 **58%** **21%**	IIA-IIIB Neoadjuvant + CRT	**5,4% vs 25%**	48% (5y)	No-IORT	**cN+, cT**
Rectal	335 **30%** **10%**	cT3-4 or cN+ Neoadjuvant + CRT	2,5% (presacral)	72% (10y)	R1, ypN+	**Grade, distal margin**
Pancreas	60 **43%** **-**	IIA-IIIB R + IOeRT +/- pre/post CRT	**4% vs 65%**	20% (5y)	No-IORT, R1	**pN+, R1 (+EBRT) ypT3**
Gastric	32 **40%** **-**	IIA-III R + post CRT	0%	54% (5y)	pN+ (non in-field)	**R1, pT3 stage**
Extremity sarcoma	159 **14%** **10%**	I-III 10cm R + post RT	14%	72% (5y)		**Size >8cm histology**
Pediatric extremity sarcomas	62 **21%** **17%**	R + post RT	15%	81% (10y)	R1, >5cm	**Histology, grade deep**
Breast*	56 757 patients	T1-2Nx post-RT T1-2N0 no-ERT	0% (3y)	96% (3y)	Luminal B Margin +	**With EBRT**

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Gynecologic Oncology

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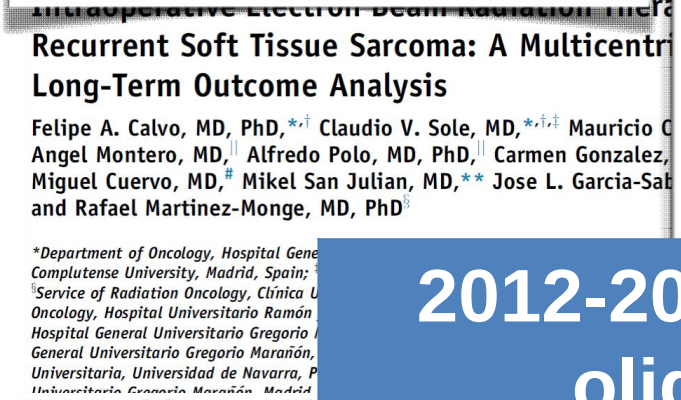
Intraoperative electron beam radiotherapy and extended surgical resection for gynecological pelvic recurrent malignancies with and without external beam radiation therapy: Long-term outcomes

F.A. Calvo [a,b,g,1], C.V. Sole [a,b,c,g,*,1], M.A. Lozano [a,d,g], L. Gonzalez-Bayon [e,g], C. Gonzalez-Sansegundo [a,d,g], A. Alvarez [d,g], J. Blanco [d,g], A. Calín [d,g], S. Lizarraga [f,g], J.L. García-Sabrido [b,e,g]



Recurrent Soft Tissue Sarcoma: A Multicentri
Long-Term Outcome Analysis

Felipe A. Calvo, MD, PhD,*,† Claudio V. Sole, MD,*,†,‡ Mauricio C
Angel Montero, MD,|| Alfredo Polo, MD, PhD,|| Carmen Gonzalez,
Miguel Cuervo, MD,# Mikel San Julian, MD,** Jose L. Garcia-Sab
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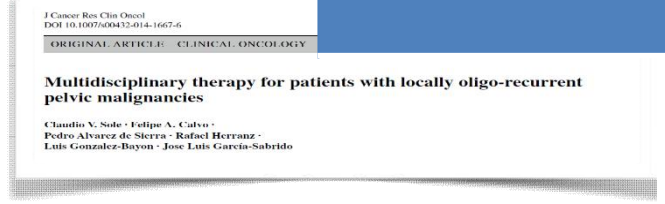
Oncology, Hospital Universitario Ramón
Hospital General Universitario Gregorio
General Universitario Gregorio Marañón,
Universitaria, Universidad de Navarra, P

External-beam radi
after surgical resec
intraoperative elec
radiation therapy f
gynecological canc

Long-term outcome

C.V. Sole[1,2,3,7] · F.A. Calvo[1,2,7] · M.A. Lozano

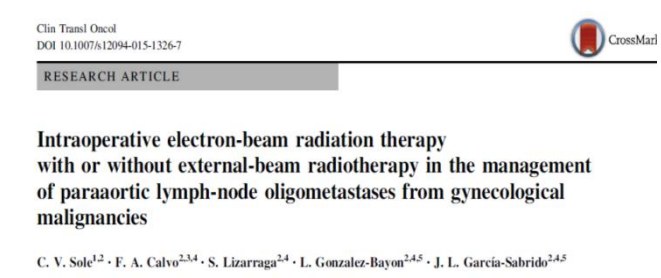


J Cancer Res Clin Oncol
DOI 10.1007/s00432-014-1667-6

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Multidisciplinary therapy for patients with locally oligo-recurrent pelvic malignancies

Claudio V. Sole · Felipe A. Calvo · Pedro Alvarez de Sierra · Rafael Herranz · Luis Gonzalez-Bayon · Jose Luis García-Sabrido



Clin Transl Oncol
DOI 10.1007/s12094-015-1326-7

RESEARCH ARTICLE

Intraoperative electron-beam radiation therapy with or without external-beam radiotherapy in the management of paraaortic lymph-node oligometastases from gynecological malignancies

C. V. Sole[1,2] · F. A. Calvo[2,3,4] · S. Lizarraga[2,4] · L. Gonzalez-Bayon[2,4,5] · J. L. García-Sabrido[2,4,5]

ELSEVIER

SciVerse ScienceDirect

EJSO 38 (2012) 955–961

EJSO the Journal of Cancer Surgery

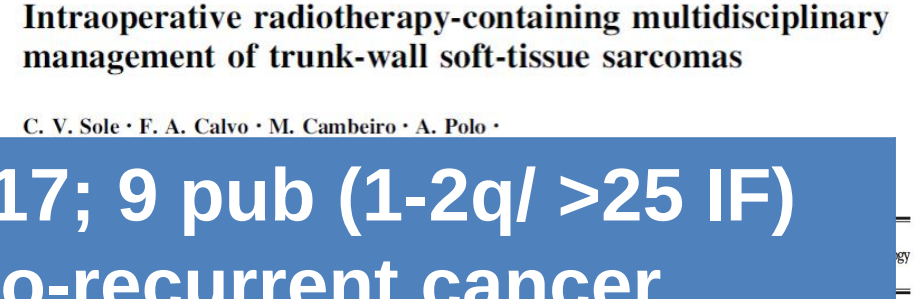
www.ejso.com

Surgery and intraoperative electron radiotherapy in recurrent or metastatic oligotopic extrapelvic cancer: Long-term outcome

F.A. Calvo [a,f,g,*], M.E. González [b,g], C. González-San Segundo [c,f], L. González-Bayón [d,f], M.A. Lozano [c], J.A. Santos-Miranda [c,f], E. Álvarez [e,f], J.L. García-Sabrido [d,f]

Clin T
DOI 1

RESEARCH ARTICLE



Intraoperative radiotherapy-containing multidisciplinary management of trunk-wall soft-tissue sarcomas

C. V. Sole · F. A. Calvo · M. Cambeiro · A. Polo ·

2012-2017; 9 pub (1-2q/ >25 IF)
oligo-recurrent cancer
6 cancer sites/histologies
332pts

ELSEVIER

Alberto Muñoz-Calero, MD,[1,3] Fernando Turegano, MD,[1,3] Rafael Herranz, MD,*[,3,||]
Luis Gonzalez-Bayon, MD, PhD,[†,§] and Jose Luis García-Sabrido, MD, PhD[†,§,||]

BRACHYTHERAPY

Salvage wide resection with intraoperative electron beam therapy or HDR brachytherapy in the management of isolated local recurrences of soft tissue sarcomas of the extremities and the superficial trunk

Mauricio Cambeiro[1,*], José Javier Aristu[1], Marta Moreno Jimenez[1], Leire Arbea[1], Luis Ramos[1], Mikel San Julian[2], Ignacio Azinovic[3], Felipe A. Calvo[4], Rafael Martínez-Monge[1]

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Clinical Investigation: Sarcoma

Prognostic Value of External Beam Radiation Therapy in Patients Treated With Surgical Resection and Intraoperative Electron Beam Radiation Therapy for Locally Recurrent Soft Tissue Sarcoma: A Multicentric Long-Term Outcome Analysis

Felipe A. Calvo, MD, PhD,*,† Claudio V. Sole, MD,*,†,‡ Mauricio Cambeiro, MD, PhD,§ Angel Montero, MD,|| Alfredo Polo, MD, PhD,|| Carmen Gonzalez, MD,†,‡,§,||,¶ Miguel Cuervo, MD,# Mikel San Julian, MD,** Jose L. Garcia-Sabrido, MD, PhD,†,†† and Rafael Martinez-Monge, MD, PhD§

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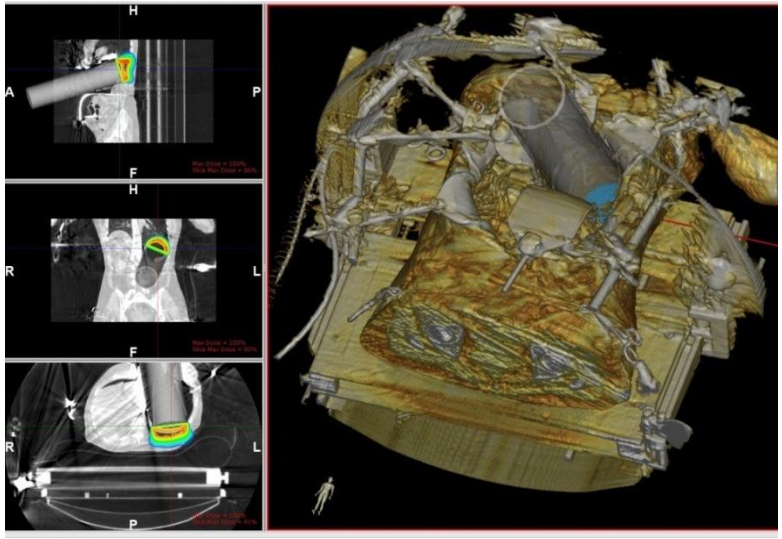
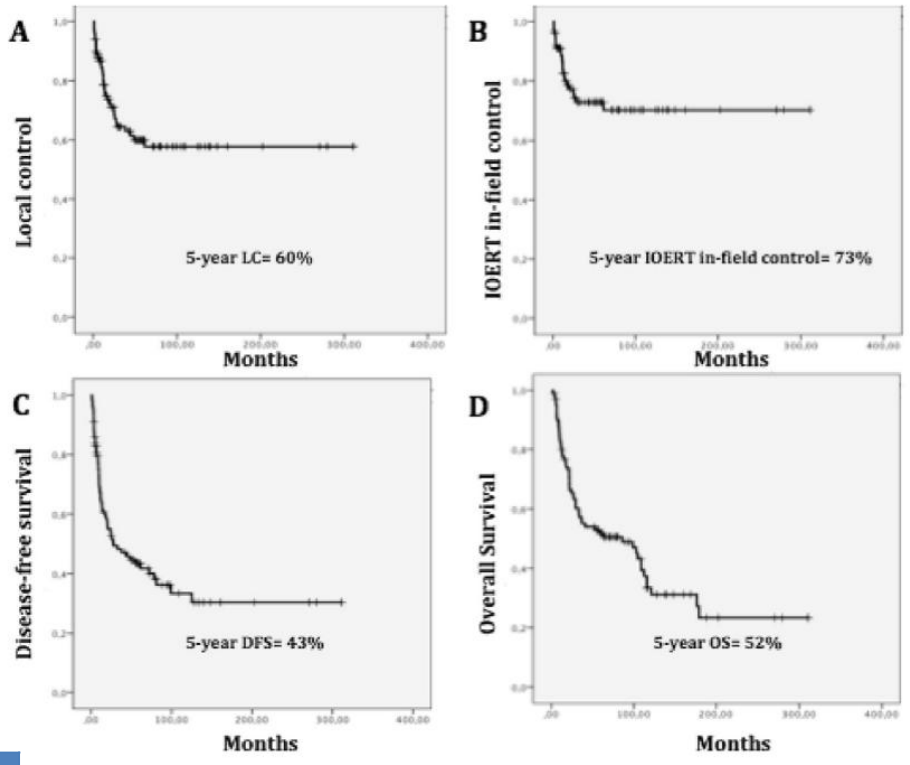
Table 4 Factors associated with local control, intraoperative electron beam radiation therapy (IOERT) in-field control, disease-free survival, and overall survival in multivariate analyses

		Local control			IOERT in-field control			Disease-free survival			Overall survival		
Parameter	Variable	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Patient variables													
Time interval from primary to LR (mo)	≥24	-	-	-	-	-	-	1.0			1.0		
	<24							3.87	1.36-7.88	.006	3.44	1.29-7.08	.008
Microscopic surgical specimen													
Histologic grade	1-2	-	-	-	-	-	-	1.0			-	-	-
	3							2.41	1.06-4.92	.04			
Surgery													
Margin status	R0	1.0	1.06-3.34	.04	-	-	-	1.0			1.0		
	R1	1.73						1.72	1.11-2.83	.03	2.41	1.21-4.21	.02
IOERT technical parameters													
CT treatment													
EBRT treatment to LR-STS	Yes	1.0			1.0			-	-	-	-	-	-
	No	2.12	1.18-3.23	.02	2.08	1.10-3.64	.03						

Abbreviations: CI = confidence interval; CT = chemotherapy; EBRT = external beam radiation therapy; HR = hazard ratio.





R+, re-recurrence for local control

Clin Transl Oncol
DOI 10.1007/s12094-014-1157-y

RESEARCH ARTICLE

Intraoperative radiotherapy-containing multidisciplinary management of trunk-wall soft-tissue sarcomas

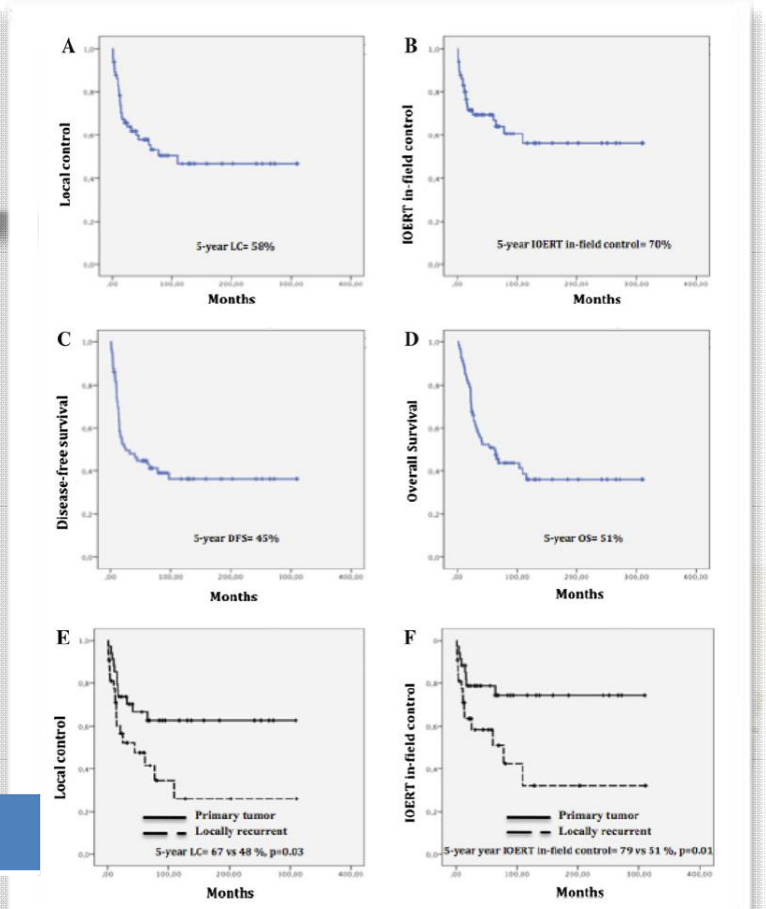
C. V. Sole · F. A. Calvo · M. Cambeiro · A. Polo · A. Montero · R. Hernanz · C. Gonzalez · M. Cuervo · D. Perez · M. S. Julian · R. Martinez-Monge

Table 4 Factors associated with local control, IOERT in-field control, disease-free survival and overall survival in multivariate analyses

Parameter	Variable	Local control			IOERT in-field control			Disease-free survival			Overall survival		
		HR	95 % CI	*p* value	HR	95 % CI	*p* value	HR	95 % CI	*p* value	HR	95 % CI	*p* value
Patients													
Age (years)	≤50	–	–	–	–	–	–	–	–	–	1.0	1.13–6.38	*0.03*
	>50										2.68		
Pre–surgical variables													
Tumor status	Primary	–	–	–	1.0	1.05–6.27	*0.04*	1.0	1.21–5.33	*0.01*	1.0	1.08–3.26	*0.04*
	Recurrent				2.52			2.54			1.75		
Microscopic surgical specimen													
Histologic grade	I–II	–	–	–	–	–	–	1.0	1.15–4.76	*0.02*	1.0	1.03–4.76	*0.04*
	III–IV							2.38			2.12		
Surgery													
Margin status	*R*0	1.0	1.90–8.30	*<0.001*	1.0	1.36–7.67	*0.008*	1.0	1.15–4.88	*0.01*	1.0	1.43–5.88	*0.003*
	*R*1	3.97			3.23			2.48			2.90		

Values in italic indicate $p < 0.05$

IOERT intraoperative electron-beam radiotherapy



R+, recurrent, histology for in-field control

Oligo-recurrent rectal cancer

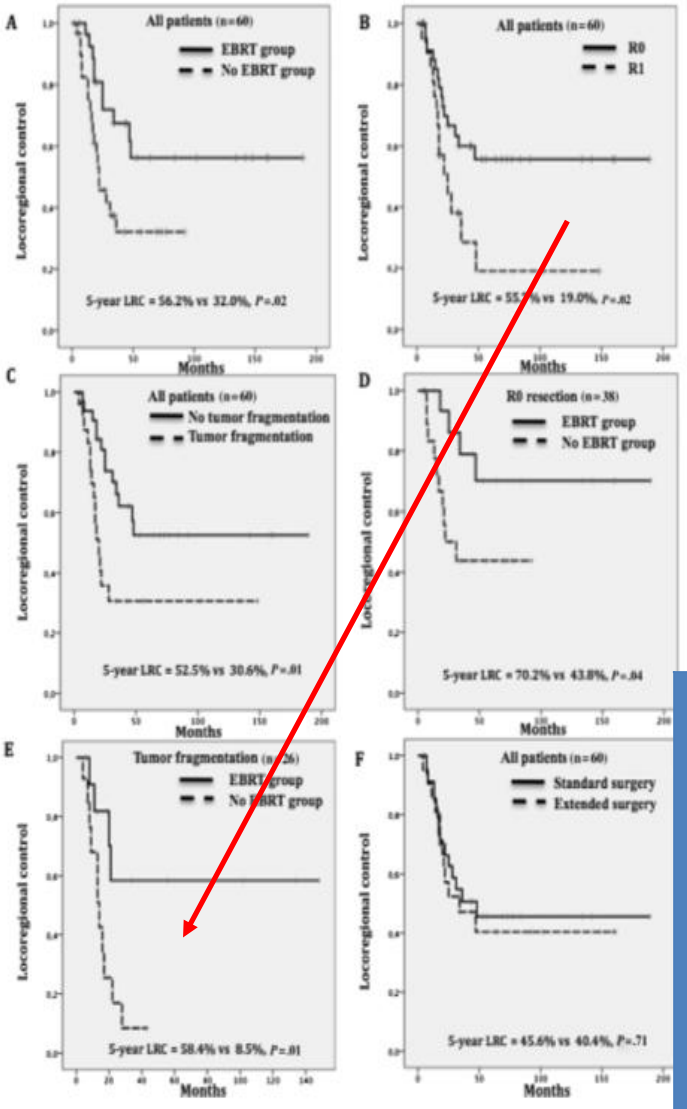


Fig. 2. Locoregional control according to external beam radiation therapy (EBRT) to the recurrent tumor (A), margin status (B), fragmentation (C), EBRT to the recurrent tumor in R0 patients (n=38) (D), EBRT to the recurrent tumor in patients with tumor mentation (n=26) (E), and surgical (standard/extended) resection (F).

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Clinical Investigation: Gastrointestinal Cancer

Prognostic Impact of External Beam Radiation Therapy in Patients Treated With and Without Extended Surgery and Intraoperative Electrons for Locally Recurrent Rectal Cancer: 16-Year Experience in a Single Institution

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60 pts (extended resection 38)
Multiorgan 26
LC 53%
5y survival 43%

Local compensation:

Tumor fragmentation
R1 if no previous EBRT

J Cancer Res Clin Oncol
DOI 10.1007/s00432-014-1667-6

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Multidisciplinary therapy for patients with locally oligo-recurrent pelvic malignancies

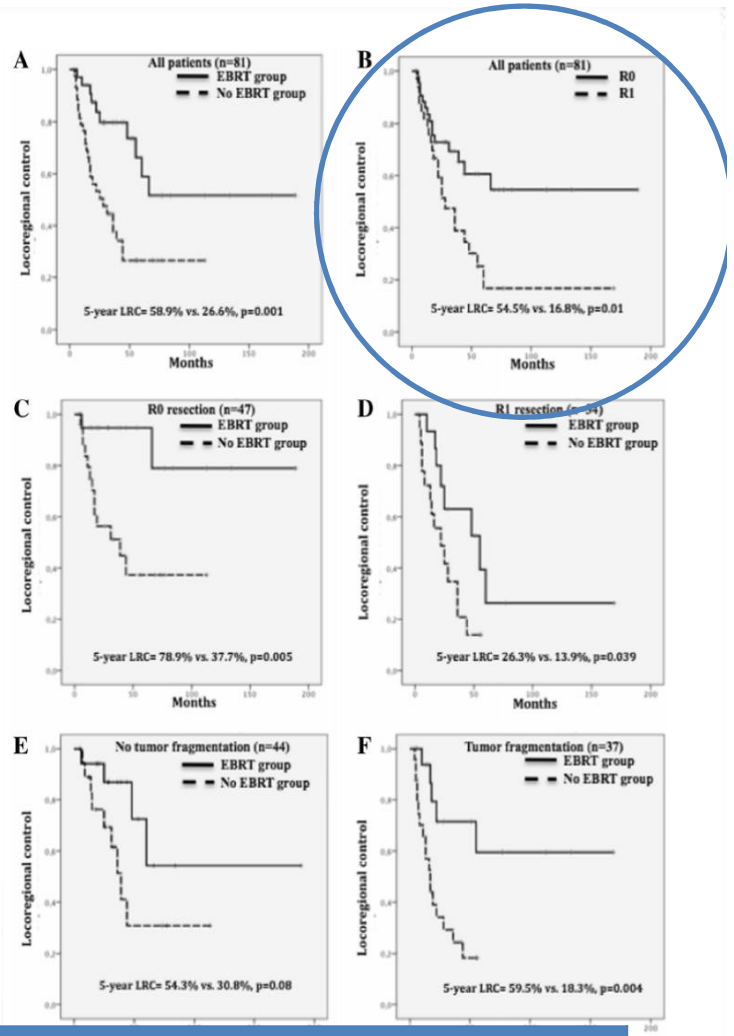
Claudio V. Sole · Felipe A. Calvo · Pedro Alvarez de Sierra · Rafael Herranz · Luis Gonzalez-Bayon · Jose Luis García-Sabrido

Table 4 Correlations between macroscopic/microscopic pathology characteristics and IOERT technical parameters

Pathology/IOERT	Surgical specimens	Applicator size Median/range	IOERT dose (Gy) Median/range	IORT energy (MeV) Median/range
Total number of fragments				
1	37	8/5–15	12.5/10–15	10/6–15
2	16	9/5–12	12.5/10–15	12/6–18
3	15	7/5–12	12.5/10–15	12/6–18
4	5	8/6–15	12.5/10–12.5	12/6–12
5	3	7/5–10	12.5/12.5–15	15/10–18
6	5	8/6–15	12.5/12.5–15	10/8–18
T_{max} size (cm)				
1–3	22	7/5–9	12.5/10–15	9/6–15
3.5–6	35	8/5–12	12.5/10–15	12/6–15
6.5–24[a]	26	10/7–15	12.5/10–15	12/6–18

[a] 1-Field PTV, 13 patients; 2-field PTV, 13 patients



81 pts
Extended surgery
5y LC 41%

R+ EBRT + IOERT 5y OS 27%

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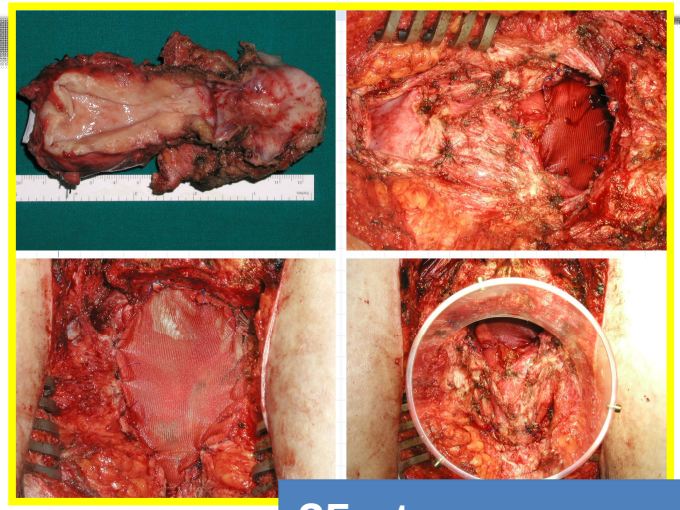
Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Intraoperative electron beam radiotherapy and extended surgical resection for gynecological pelvic recurrent malignancies with and without external beam radiation therapy: Long-term outcomes

F.A. Calvo [a,b,g,1], C.V. Sole [a,b,c,g,*,1], M.A. Lozano [a,d,g], L. Gonzalez-Bayon [e,g], C. Gonzalez-Sansegundo [a,d,g], A. Alvarez [d,g], J. Blanco [d,g], A. Calin [d,g], S. Lizarraga [f,g], J.L. García-Sabrido [b,e,g]



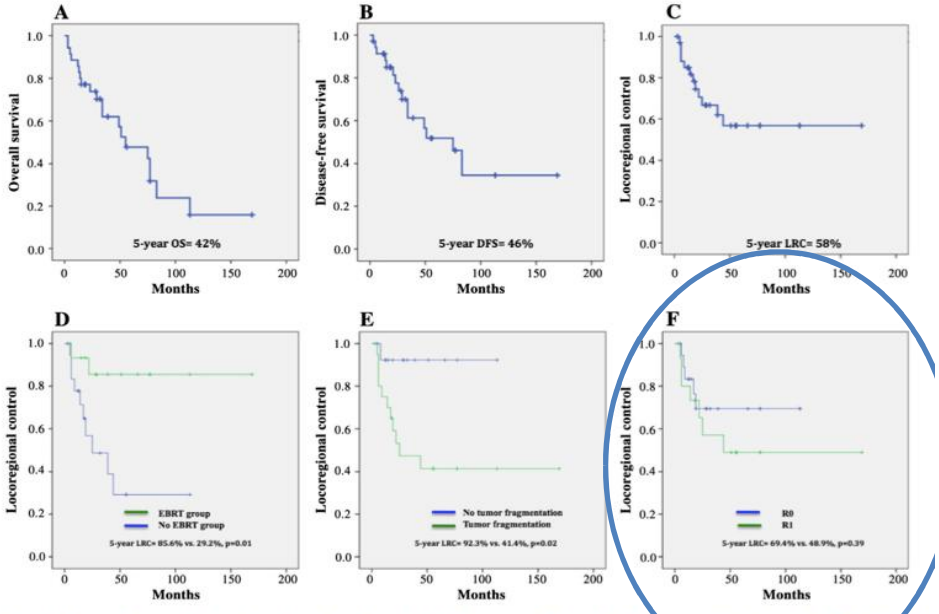


Fig. 1. Kaplan–Meier curves for all 35 patients for overall survival (A), disease-free survival (B), local-regional control (C), locoregional control according to EBRT to the recurrent tumor (D), tumor fragmentation (E) and margin status (F).

35 pts
Multiorgan resection 54%
5y LC 58%
5y OS 42%

EBRT and time interval influence Survival

Oligo-recurrent + / - locally advanced renal cancer

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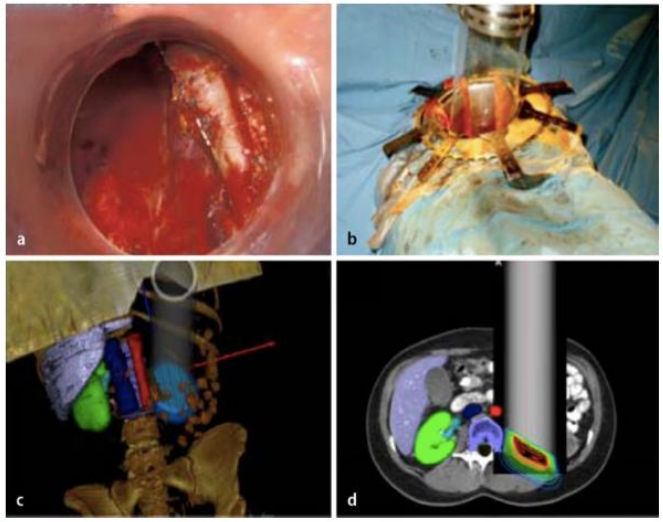

Fig. 3 ▲ **a, b** Postnephrectomy tumor bed. An IORT applicator defining the target area (12 cm diameter). Note that normal sensitive intra-abdominal tissues and structures have been displaced from the renal fossae, **c, d** Treatment planning for an IOERT procedure on the renal fossae area (radiance technology)

98 patients
MGH, CUN, Heidelberg, Marañon
Pooled analysis 2014

Clinical Investigation: Genitourinary Cancer

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

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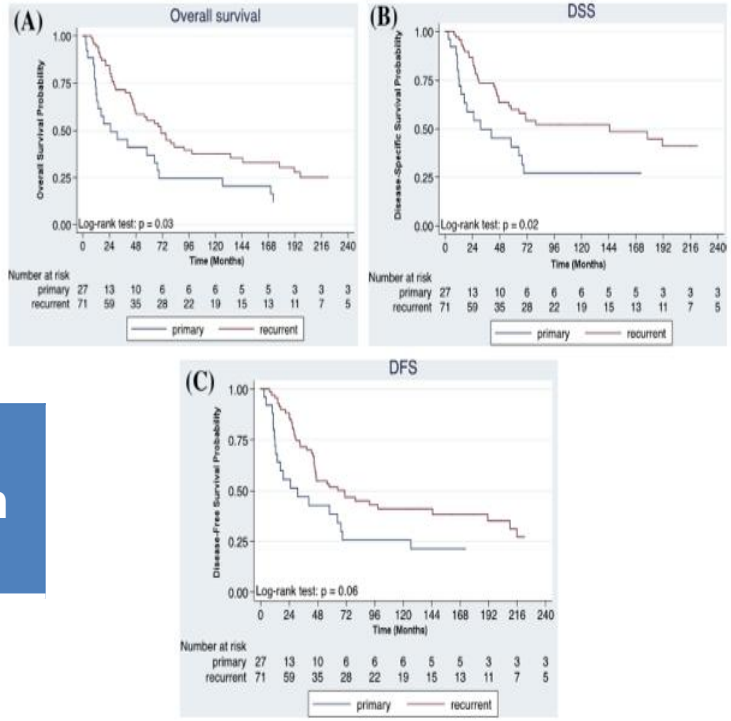

Fig. 2. (A) Overall survival after intraoperative radiation therapy (IORT). (B) Disease-specific survival after IORT. (C) Disease-free survival after IORT.

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ORIGINAL ARTICLE – RADIATION ONCOLOGY

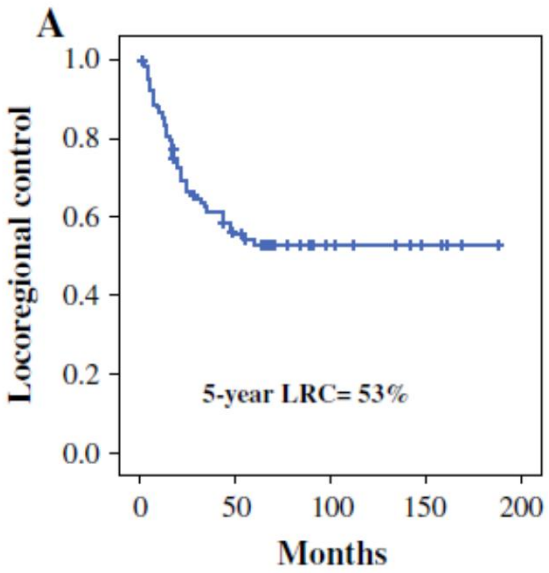
Single-Institution Multidisciplinary Management of Locoregional Oligo-Recurrent Pelvic Malignancies: Long-Term Outcome Analysis

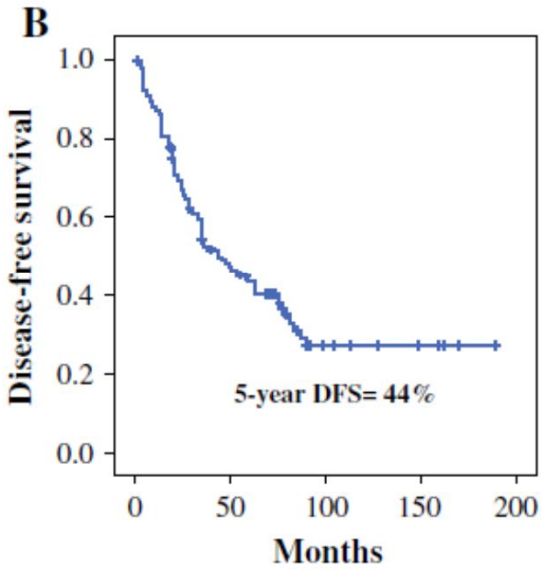
Claudio V. Sole, MD, PhD[1,2], Felipe A. Calvo, MD, PhD[2,3,4], Santiago Lizarraga, MD[2,4], Luis Gonzalez-Bayon, MD, PhD[2,4,5], Carmen Gonzalez San Segundo, MD, PhD[2,4,6], Manuel Desco, MD, PhD[2,7], and Jose L. García-Sabrido, MD, PhD[2,4,5]

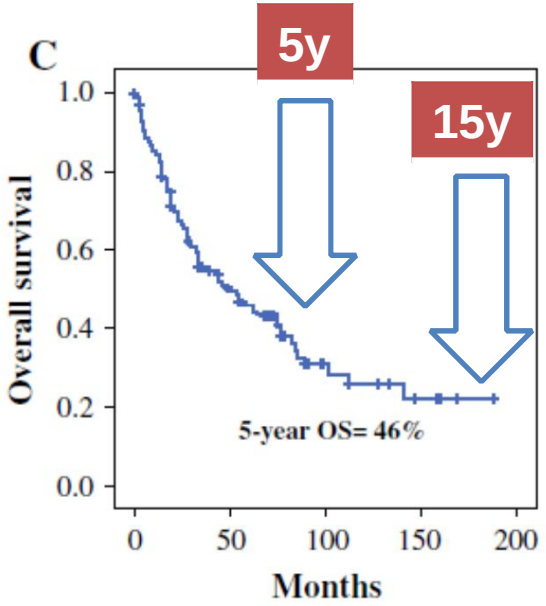
1995 – 2017
143 patients
MFT 48 months
5y LRC 53%
5y OS 46%

Local adversity:

R1
Interval
Fragmentation
Radio-resistance







IOeRT electrons: 2017 results update oligorecurrence (grade 3 toxicity)

Cancer	N		Local control % @ 5y	Survival % @ 5y	Adversity Local	Compensation Local
	Acute	Late				
Gynecologic[1]	61		69	42	No EBRT	**Para-aortic**
	43%	**21%**				
Rectal[1]	60		44	39	No EBRT R1	**Fragmentation**
	42%	**19%**				
Sarcoma [2]	103		64	52	No EBRT R1	**Fragmentation / histology grade**
	16%	**13%**				
Renal[3]	98		72	43	Recurrence N+	**R1**
	29%	**-**				

[1,] HGUGM
[2] HGUGM, HRyC, CUN
[3] HGUGM, CUN, MGH, Heidelberg

322 patients

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Radiotherapy and Oncology

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Osteosarcoma

Adjuvant radiation therapy in resected high-grade localized skeletal osteosarcomas treated with neoadjuvant chemotherapy: Long-term outcomes

Claudio V. Sole [a,*], Felipe A. Calvo [b,c], Eduardo Alvarez [d], Mauricio Cambeiro [e], Miguel Cuervo [f], Mikel San Julian [g], Sebastian Sole [a,h], Rafael Martinez-Monge [e], Luis Sierrasesumaga [i]

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72 patients

IOERT 15-20 Gy

EBRT 30% (R+)

neoCT 60%

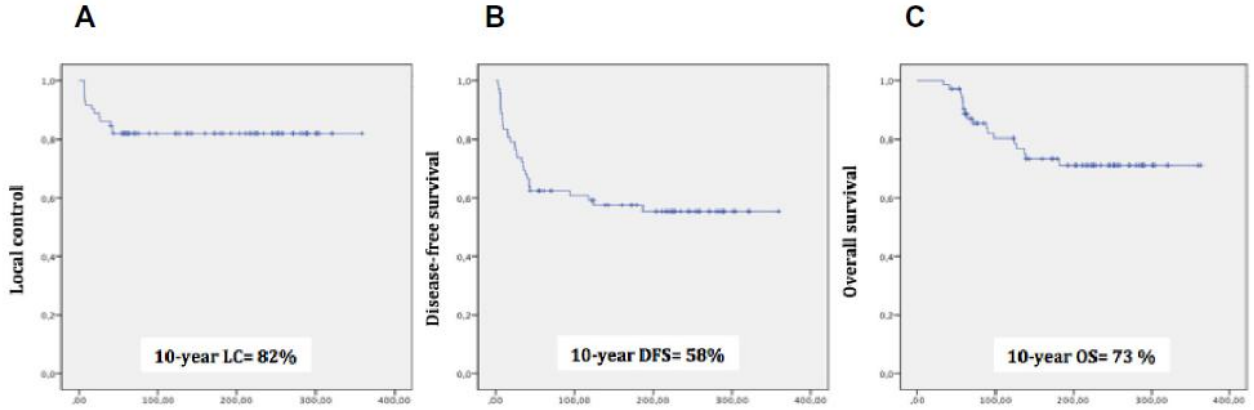


Table 3
Factors associated with local control, disease-free survival and overall survival in multivariate analyses.

Parameter	Variable	Local control			Disease-free survival			Overall survival		
		HR	CI 95%	*p* value	HR	CI 95%	*p* value	HR	CI 95%	*p* value
Microscopic surgical specimen										
Histological response	Necrosis ⩾ 90%	–	–	–	1.0	1.13–9.80	0.03	1.0	1.09–15.34	0.04
	Necrosis < 90%				3.32			3.48		
Margin status	R0	1.0	1.21–16.53	0.02	1.0	1.02–5.50	0.05	1.0	1.01–7.48	0.05
	R1	4.46			2.36			2.68		

Results for skeptics…

3 decades… a summary

IOERT & Surgical Margin

Is optimized radiotherapy… *feasible and tolerable*

Is precise radiotherapy… *able to be adapted to R0 & R+*

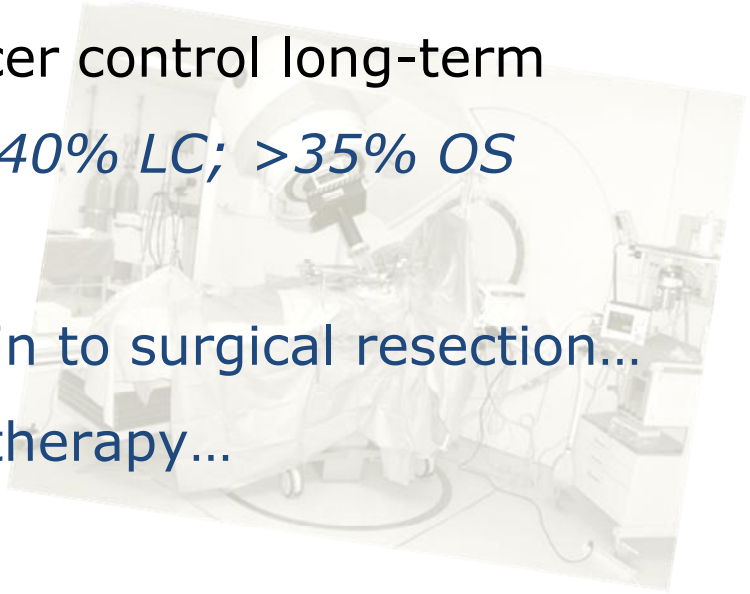
Is a precise component of RT for dose-escalation…

50Gy + 10/15Gy IORT LC >90% R0

50Gy + 10/15Gy IORT LC >40% R+

Contributes to oligo-recurrent cancer control long-term

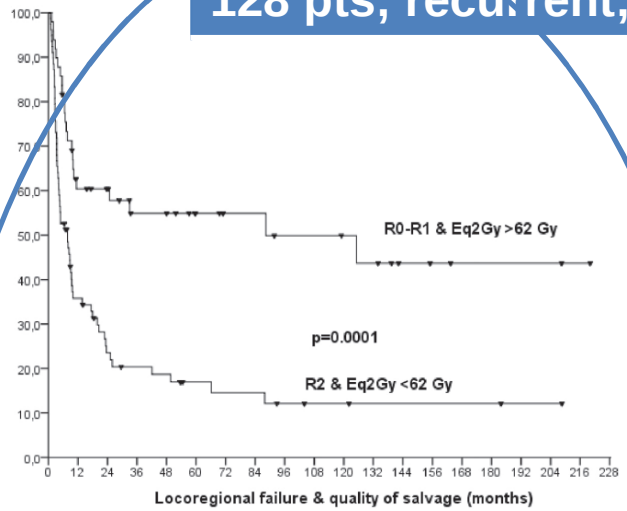
IOERT + EBRT + S: >40% LC; >35% OS

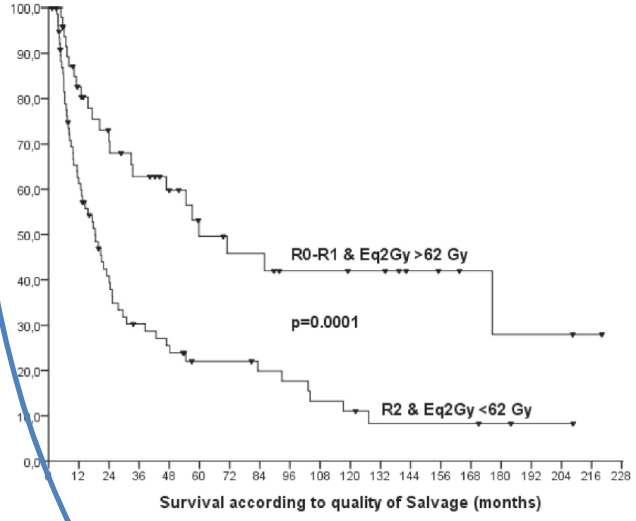


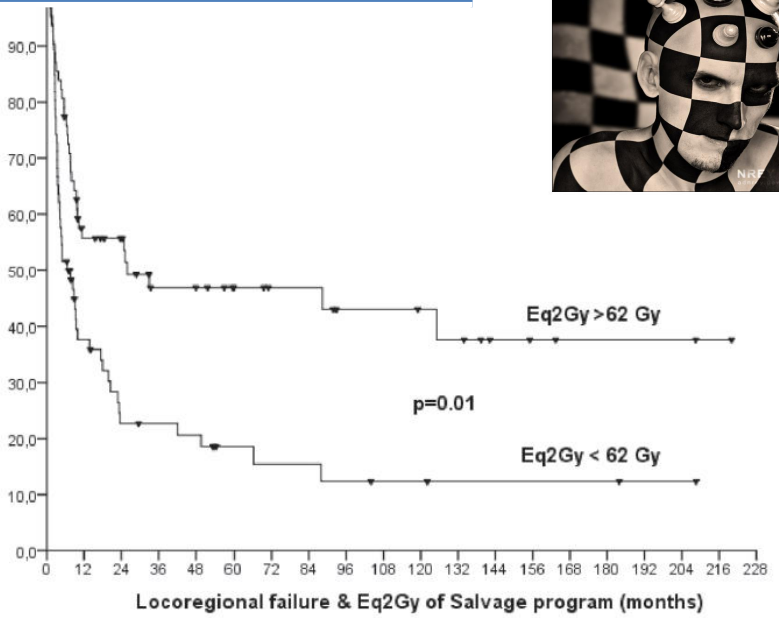
Adds a radiobiological safety margin to surgical resection…

Does not interferes with systemic therapy…

128 pts; recurrent; EBRT 60%; EqD2Gy model







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IOERT of recurrent tumors

Salvage surgery and radiotherapy including intraoperative electron radiotherapy in isolated locally recurrent tumors: Predictors of outcome

Mauricio Cambeiro [a,*], Felipe A. Calvo [f], José Javier Aristu [a], Marta Moreno Jimenez [a], Mikel San-Julian [b], Juan Alcalde [c], Jose Luis Hernandez-Lizoain [d], Matías Jurado [e], Rafael Martínez-Monge [a]

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BED-like IOERT containing biomodels for outcome

Integration of Radiation Oncology with Surgery as Combined-Modality Treatment

Leonard L. Gunderson, MD, MS[a,*], Jonathan B. Ashman, MD, PhD[a], Michael G. Haddock, MD[b], Ivy A. Petersen, MD[b], Adyr Moss, MD[c], Jacques Heppell, MD[d], Richard J. Gray, MD[e], Barbara A. Pockaj, MD[e], Heidi Nelson, MD[f], Christopher Beauchamp, MD[g]

Surg Oncol Clin N Am 22 (2013) 405–432
http://dx.doi.org/10.1016/j.soc.2013.02.003 surgonc.theclinics.com

- Combined modality treatment–related morbidity: In patients with locally advanced primary or locally recurrent malignancies, the issue of morbidity following aggressive treatment is placed into clearer perspective by a comparison with tumor-related morbidity. For instance, when EBRT is used as the only radiation modality for patients with residual disease following surgical resection of locally advanced rectal cancer or those with locally recurrent colorectal cancers, more than 90% of patients have local persistence or relapse of disease, and most are dead within 2 to 3 years (end result is nearly 100% tumor-related morbidity and/or mortality).

100 % toxicity in local persistance or relapse…

2016 IOERT recomendations

National Comprehensive Cancer Network®

Cervix: marginal resection

Rectal: T4 & recurrent

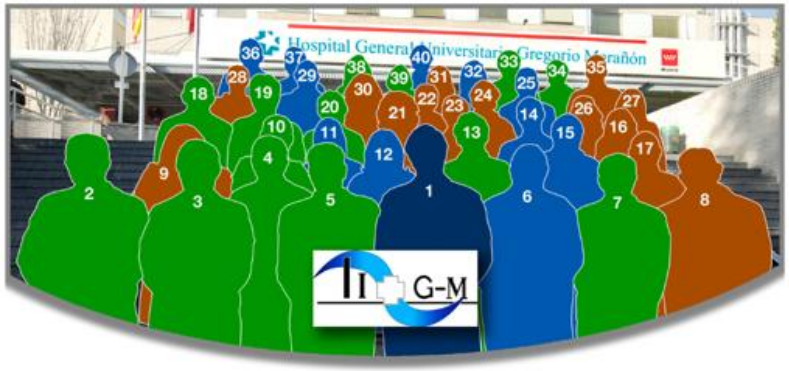
Pancreas: close/positive margins

Sarcomas: extremity, trunk,H &N, retroperitoneal

Endometrial: recurrent

Anal canal: recurrent

BIOTECHNOLOGICAL INTERDISCIPLINAR ONCOLOGY



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IOERT & Surgical Margin: intensification context

Surgical margin… *influences local control (…no question)*

R1 status in primary locally advanced cancer
may be compensated by IOERT intensification… *gastric, pancreas*

R+ in primary/recurrent cancer compromishes local and systemic outcomes… *rectal, sarcoma, gynecologic*

Re-irradiation or further dose-escalation (intra-boost) are developmental available alternatives … *rectal model*