Associazione Italiana Radioterapia Oncologica

Società Italiana di Radiobiologia

Farmaci innovativi
e ipofrazionamento

PALACONGRESSI DI RIMINI
30 settembre, 1-2 ottobre 2016

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Preoperative Radiotherapy with a Simultaneous Integrated Boost compared to Chemoradiotherapy for cT3-4 Rectal Cancer: *a multicentric randomized trial*

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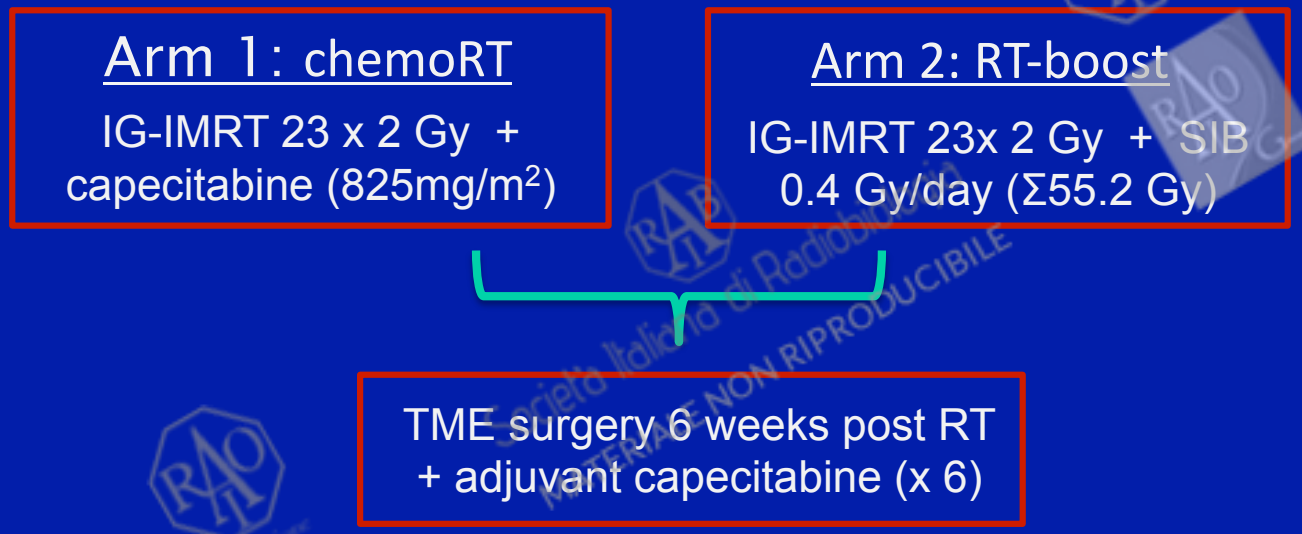
CRO-IRCCS Aviano, IRCC Candiolo, IST- IRCCS Genova, IRCCS Reggio Emilia
Università Torino, NCI-Vilnius (LT), ICO Nantes (F), UZ Brussel (BE)

Study design

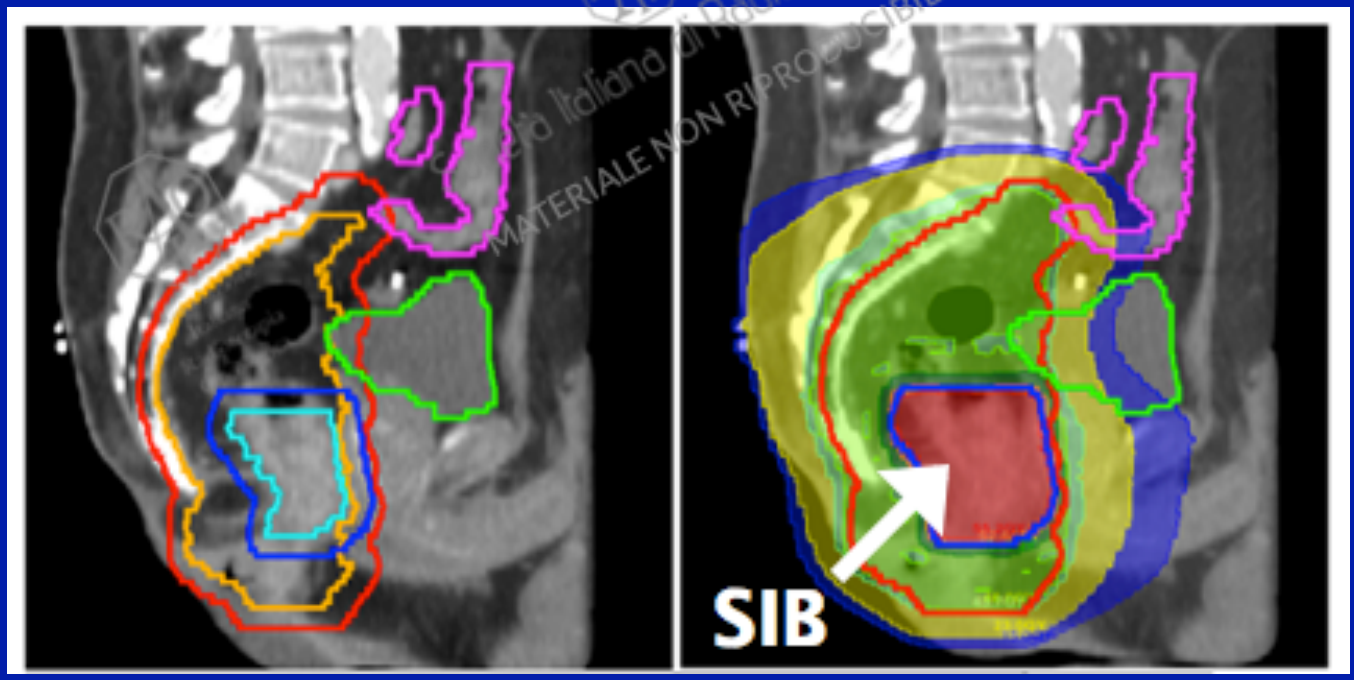
- **cT3-4 rectal cancer** (MRI, EUS, <15cm AV)



- **Primary endpoint: reduction in metabolic tumor activity**
  - SUV_{max} on 18FDG-PET imaging
  - Non-inferiority: difference in metabolic response ≤ 10%
  - Sample size: 156,78 in both arms (α: 0.05, power: 80%)

Background

- Phase II study* of preoperative image-guided and intensity-modulated radiotherapy (IG-IMRT) with a simultaneous integrated boost (SIB) in locally advanced rectal cancer:
  - Limited acute toxicity (1% grade 3+)
  - High local control rate of (97% at 5 years)



*De Ridder, Engels et al IJROBP and R&O 2008 - 2013

3D-CRT vs IMRT

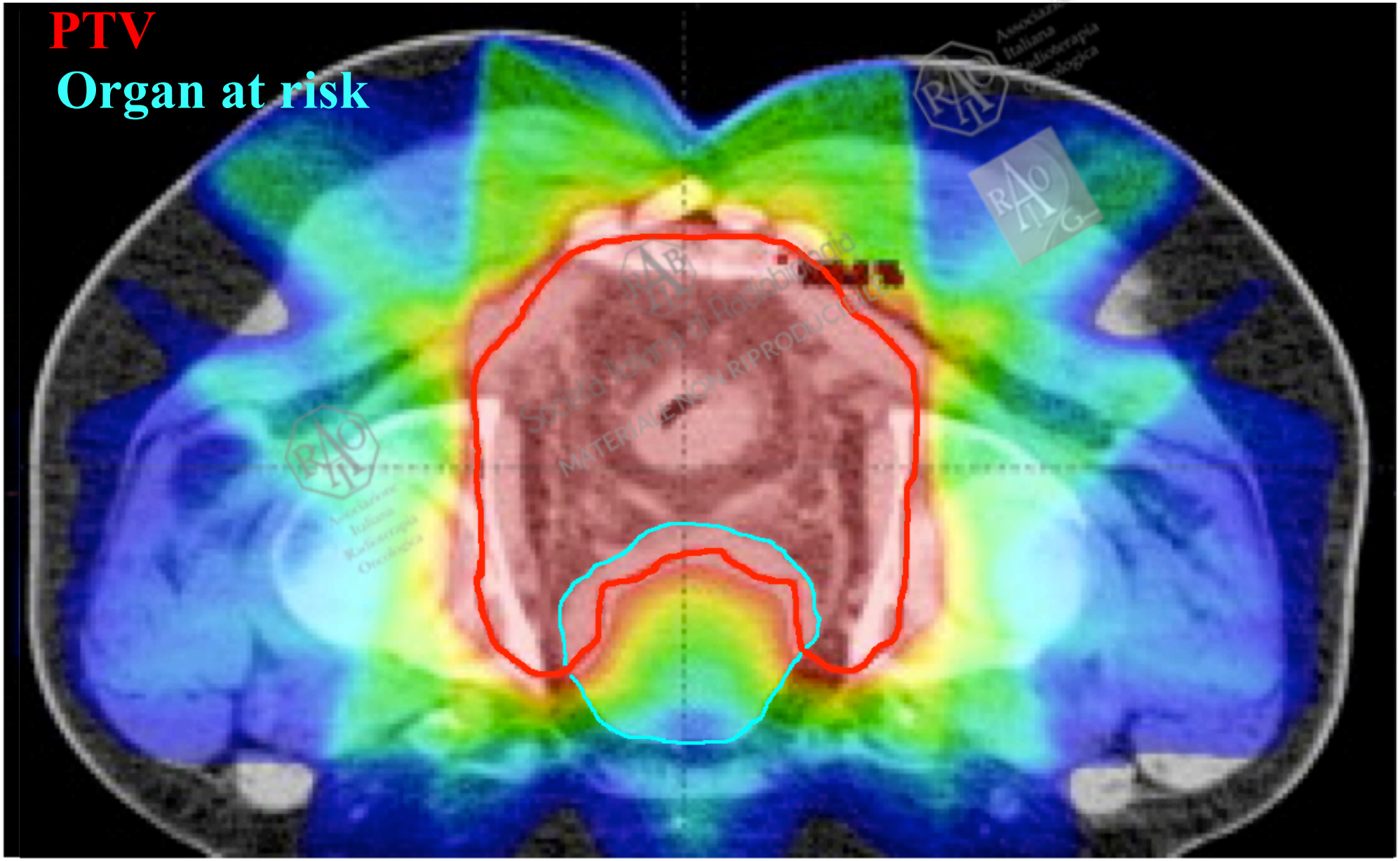
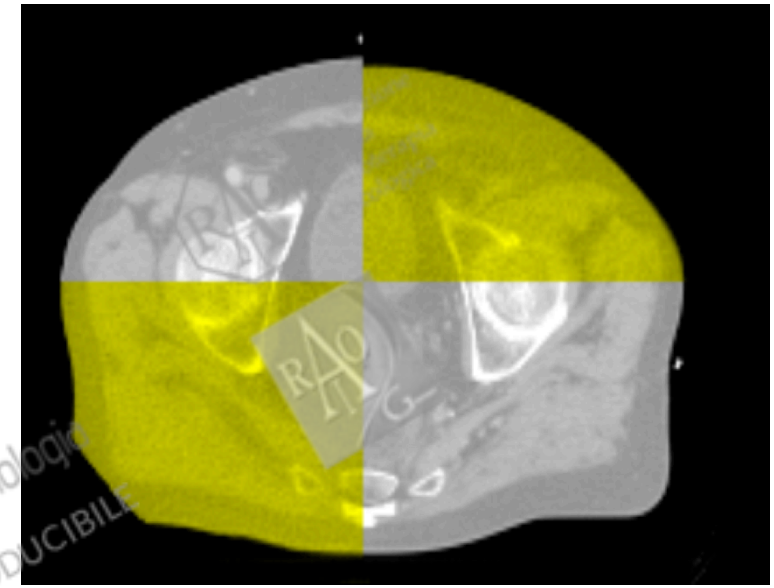


Image-guided RT (IG-IMRT)

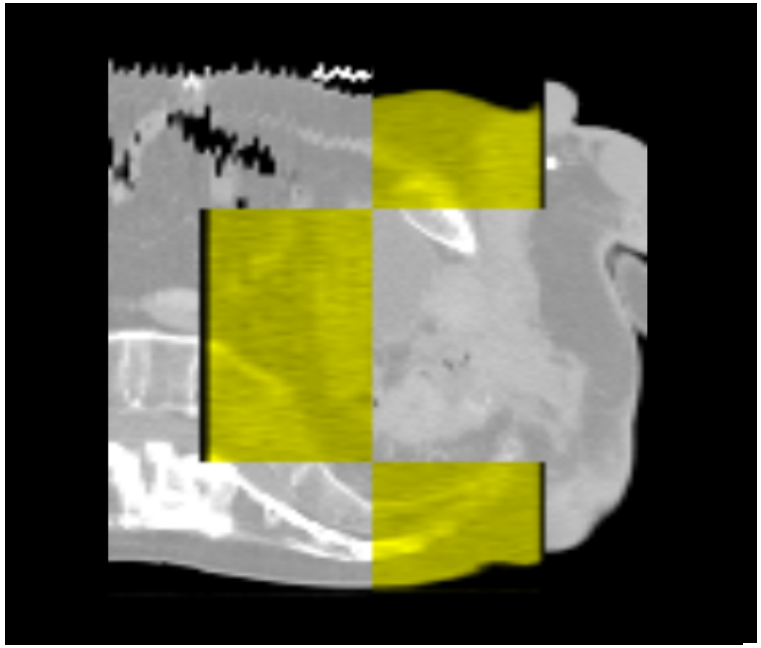
The dose distribution is delivered at the exact location within the patient by image guidance



Planning CT

CT prior to treatment

co-registration



Margins

IMRT/IGRT: margins based on daily MVCT

Lat	Ant	Post	Cran	Caud
8	11	7	10	10

IMRT, 3D-CRT: margins based on lasers (NO IGRT)

Lat	Ant	Post	Cran	Caud
15	16	14	10	10

Int J Radiat Oncol Biol Phys. 2008 Jul 1;71(3):934-9.

Patient/Tumour Charactheristics (April 2010- May 2014; 169 pts)

Table 1. Patients Characteristics at Baseline

Characteristics	CRT (n=86) No. of Patients	%	RTSIB (n=83) No. of Patients	%	p-value
Age, years					
Average	66		65		
Range	48-83		37-87		.67
Sex					
Male	55	64	56	67	
Female	31	36	27	33	.63
ECOG performance status					
0	73	85	68	82	
>/=1	13	15	15	18	.27
Distance from anal verge					
< 5 cm	40	46	35	42	
5 - 10 cm	42	49	44	53	
> 10 cm	4	5	4	5	.85
T stage					
T2	2	2	0	0	
T3 - CRM > 1 mm	48	56	45	54	
T3 - CRM ≤ 1 mm	31	36	29	35	
T4	5	6	9	11	.35
N stage					
node-negative	9	10	15	18	
node-positive	77	90	68	82	.16
Tumor biopsy					
Grade 1 adenocarcinoma	8	9	7	8	
Grade 2 adenocarcinoma	36	42	39	47	
Grade 3 adenocarcinoma	4	5	4	5	.93
Grade not stated	38	44	33	40	
M1	0	0	2	2	.15

Acute Toxicity (CTAE V. 3)

Table 2. Early Adverse Events

	CRT (n=86)		RTSIB (n=82)		p-value
Grade	**2**	**3**	**2**	**3**	
	No. of Patients (%)	No. of Patients (%)	No. of Patients (%)	No. of Patients (%)	
Gastrointestinal	36 (42)	1 (1)	35 (43)	2 (2)	.91 (.53)
Diarrhea	17 (20)	0	17 (21)	1 (1)	.88 (.30)
Enteritis (abdominal pain)	18 (21)	0	10 (12)	0	.13
Proctitis	13 (15)	1 (1)	18 (22)	1 (1)	.25 (.97)
Urinary	7 (8)	0	11 (13)	0	.27
Dysuria	4 (5)	0	10 (12)	0	.08
Urinary frequency	5 (6)	0	4 (5)	0	.79
Haemathology	3 (3)	1 (1)	2 (2)	0	.69 (.33)
Anemia	0	1 (1)	1 (1)	0	.30 (.33)
Leucopenia	3 (3)	1 (1)	0	0	.09 (.33)
Thrombopenia	0	0	1 (1)	0	(.30)
Other					
Hand-foot syndrome*	0	0	0	0	
Radiation dermatitis	14 (16)	2 (2)	10 (12)	1 (1)	.45 (.59)
Vaginal mucositis	2 (2)	2 (2)	1 (1)	0	.59 (.16)
Overall toxicity score	43 (50)	5 (6)	46 (56)	3 (4)	.43 (.51)

Surgical parameters

Table 3. Surgery characteristics	CRT (n=84)		RTSIB (n=77)		p-value
	No. of Patients	%	No. of Patients	%	
Surgery					
Abdominoperineal resection	20	24	23	30	
Anterior resection	58	69	50	66	
Hartmann's resection	1	1	2	2	
Local excision	5	6	2	2	.55
Colostoma					
Permanent	21	25	25	32	
Protective	55	65	43	56	
None	8	10	9	12	.46
Leakage anastomosis					
<30 days post surgery	7	8	8	10	
>30 days post surgery	4	5	0	0	.60
Other post-operative complications	22	26	14	18	.22
Pulmonary	3	4	2	3	
Urinary	3	4	3	4	
Fistula	4	5	1	1	
Stoma (prolaps/necrosis)	2	2	3	4	
Abdominal wall hernia	2	2	1	1	
Perineal wound infection	2	2	1	1	
Ileus	1	1	3	4	
Peritonitis	1	1	1	1	
Heart failure	1	1	0	0	
Duration of hospital stay (days)					
median	11		12		
range	4 - 77		4 - 43		
Post-operative mortality (< 60days)	2	2	1	1	.61

Pathological parameters

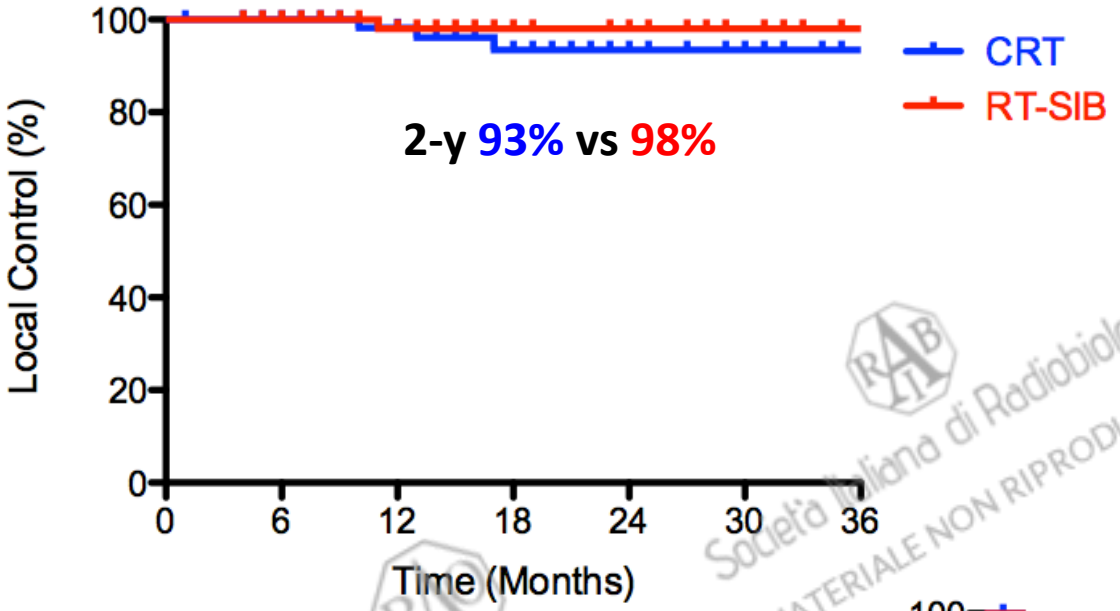
Table 4. Pathological characteristics

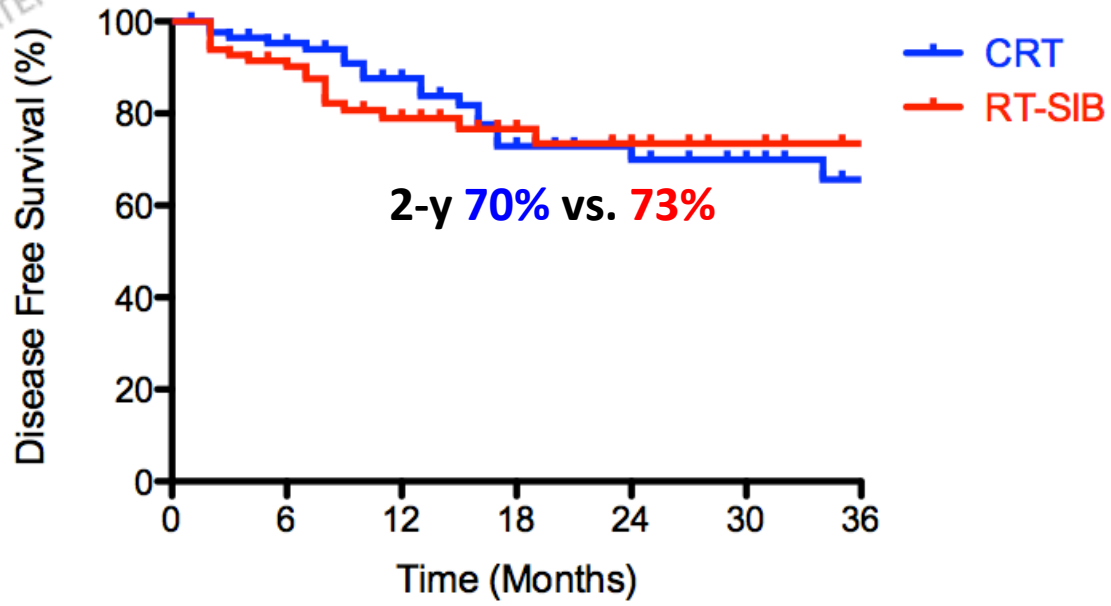
	CRT (n=84)		RTSIB (n=77)		p-value
	No. of Patients	%	No. of Patients	%	
Resection status					
R0	82	98	75	97	
R1	2	2	2	3	.93
R2	0	0	0	0	
Dworak regression					
Grade 0	1	1	0	0	.34
Grade 1	25	30	17	22	.27
Grade 2	17	20	25	33	.08
Grade 3	21	25	24	31	.38
Grade 4 (pCR)	20	24	11	14	.13
Pathological stage					
ypT0	20	24	11	14	.13
ypTis	0	0	1	1	.29
ypT1	7	8	4	5	.43
ypT2	16	19	30	39	.005
ypT3	37	44	29	38	.41
ypT4	4	5	2	3	.47
Number of resected lymph nodes					
median	12		11		
range	2 - 25		1 - 55		
Nodal stage					
ypN0	62	74	55	71	
ypN1	11	13	12	16	
ypN2	6	7	8	10	
No lymph node dissection	5	6	2	3	.63

Results (n = 169)

	chemo-RT	RT-boost	
Metabolic response	-55,8% (±24,0%)	-52,9% (±21,6%)	95% CI: -10.1% to +4,3% p=0.06
Dworak grade 4 (ypCR)	24%	14%	p = 0,13
Dworak grade 3 + 4	49%	45%	
Sphincter preservation	75%	68%	p = 0,29
R0	98%	97%	
Acute grade 3 toxicity	6/86 patients	3/82 patients	
Gastrointestinal	*1*	*2*	
Haemotology	*1*	*0*	
Dermatitis/mucositis	*4*	*1*	

Local Control - Disease Free Survival





..in summary

- Preoperative IG-IMRT results in limited acute grade 3 toxicity in both arms (6% vs 4%), no grade 3+ diarrhea
- pCR rates appeared in favour of CRT(24% vs 14% in RTSIB), even if remarkable TRG (Dworak grade 3-4) in both arms (49% vs 45%) was reported
- Preop IMRT-SIB marginally failed to prove non-inferiority to CRT in terms of Metabolic Response (p=0.06), Primary Endpoint
- So far no differences in LC, PFS and OS between both arms

Conclusions

- Preoperative chemo-RT is well tolerated when IG-IMRT are used. Eliminating chemotherapy in preop setting appears not to be an appropriate research direction.

- RT-SIB represents an attractive alternative to chemo-RT for frail patients no candidates for concomitant chemotherapy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