Radiotherapy dose escalation in rectal cancer: meaningful or not?

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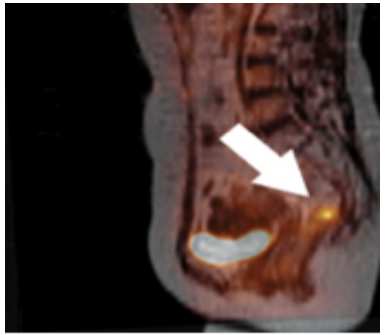
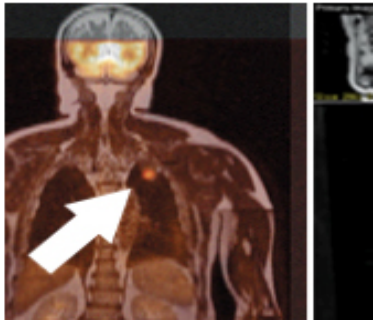
Where do we go with rectal cancer management?





Escalation Strategies

- Radiotherapy dose escalation
- Total Neoadjuvant Therapy (TNT)
- Molecular targeted therapies

De-escalation Strategies:

- Selective RT: TN-, MRT-criteria
- Selective Surgery: Organ preservation

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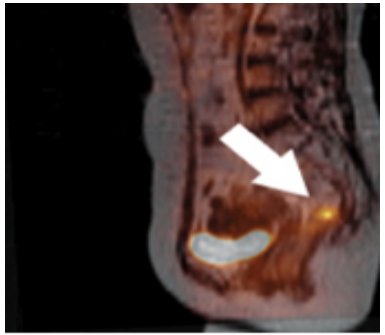

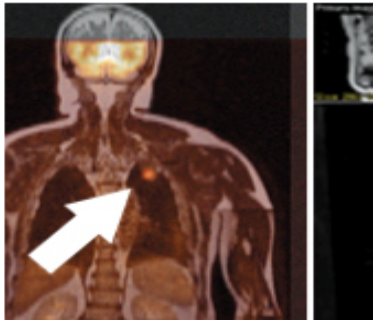

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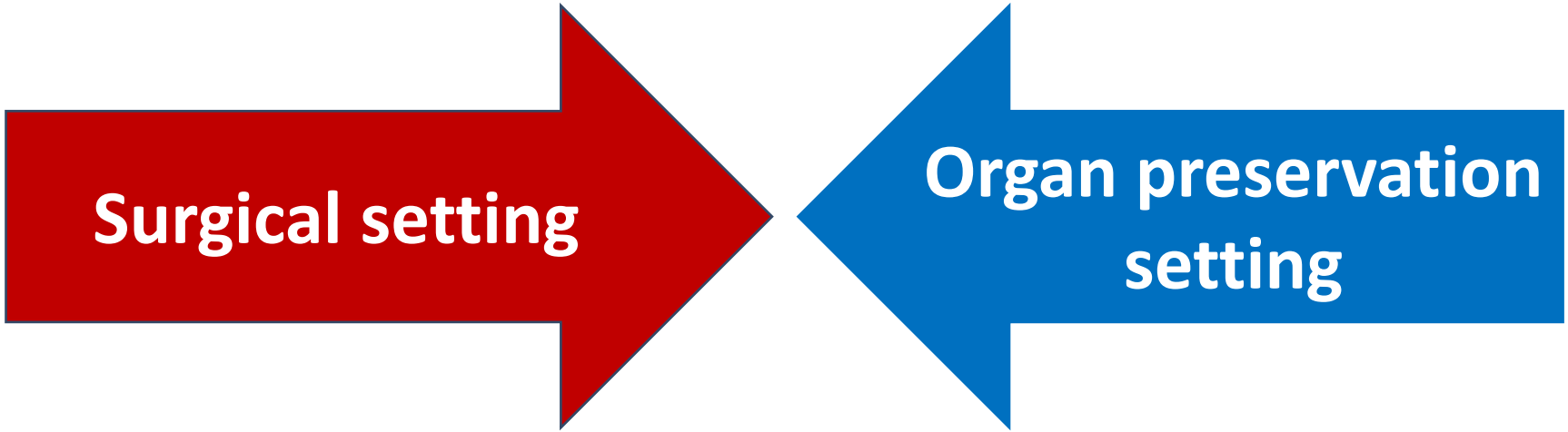
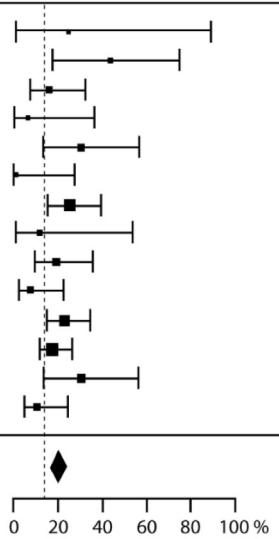
RT dose escalation meaningful? Treatment setting is key!



RT dose escalation in the surgical setting

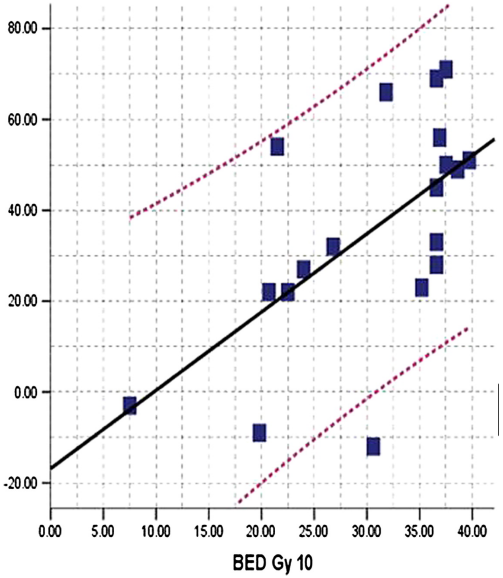
RT ≥ 60 Gy can increase pCR rates

Study	Reference line 15%	Study weight	Study estimate	95% Confidence Interval
Meade et al. , 1995		0.5%	25.0%	[1.3 , 89.1%]
Mohiuddin et al. , 2000		3.2%	44.0%	[17.7 , 74.9%]
Rouanet et al. , 2002		7.2%	16.0%	[7.7 , 32.5%]
Pfeiffer et al. , 2005		1.3%	7.0%	[1.0 , 37.0%]
Mohiuddin et al. , 2006		4.9%	31.0%	[13.6 , 56.7%]
Movsas et al. , 2006		0.7%	2.0%	[0.1 , 27.7%]
Jakobsen et al. , 2006		13.8%	26.0%	[15.7 , 39.8%]
Lindebjerg et al. , 2008		1.2%	12.0%	[1.7 , 53,7%]
Jakobsen et al. , 2008		8.0%	20.0%	[9.8 , 36.4%]
Vestermark et al. , 2008		3.9%	8.0%	[2.7 , 22.9%]
Maluta et al. , 2010		19.8%	23.0%	[15.5 , 34.5%]
Jakobsen et al. , 2012		23.6%	18.0%	[12.2 , 26.7%]
Vestermark et al. , 2012		4.9%	31.0%	[13.6 , 56.7%]
Engineer et al. , 2013		6.4%	11.0%	[4.8 , 24.5%]
Pooled pCR-rate estimate		100.0%	**20.4%**	[16.8 , 24.5%]



Burbach et al, Green J 2015

RT >30 Gy improves LC



Viani GA et al, IJROBP, 2010

Historical pCR rate after standard chemoradiotherapy (CRT 50 Gy): 10-15%

RT dose escalation fails to improve LC in the surgical setting

Randomized trials (phase)	N	Control arm	Experimental arm	3-year LC	pCR (or cCR)
Brachy-boost (II) cT3-4N0-2	248	CRT 50.4 Gy	CRT 50.4 Gy + Brachy Boost 2x 5 Gy	86% vs 94%, p=0.06	18% vs 18%
INTERACT (II) cT2-3N0-2	534	CRT 50.4 Gy	CRT 50.4 Gy + SIB 4.6 Gy	93% vs 93%, p=0.51	pCR: 24% vs 24%
RECTAL-BOOST (II) cT2-4N0-2	128	CRT 50 Gy	CRT 50 Gy + SIB 3x 5 Gy	not reported	pCR/cCR: 36% vs 38%

Appelt et al. IJROBP 2014; Valentini et al. Radiother Oncol 2019; Couwenberg et al. IJROBP 2020

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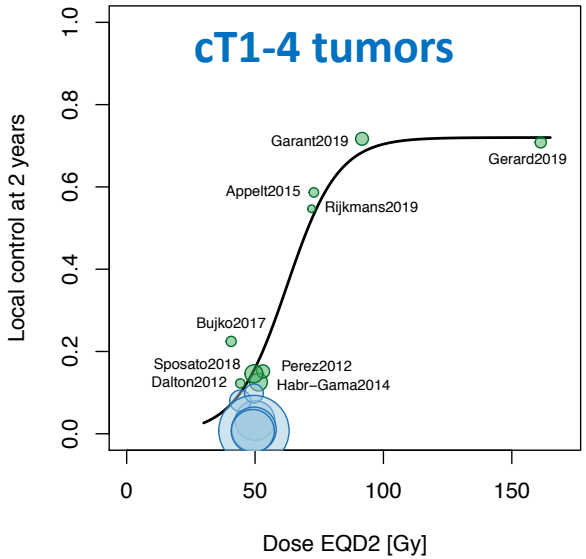
Lyon R96-02 (randomized) cT2-3N0x	88	**EBRT 13x3 Gy**	**EBRT 13x3 Gy + Brachy Boost (35/30/20 Gy)**	2-year LRFS: 88% vs 92%	2% vs 26%; sterilized specimen/ few residual cells: 34% vs 57%

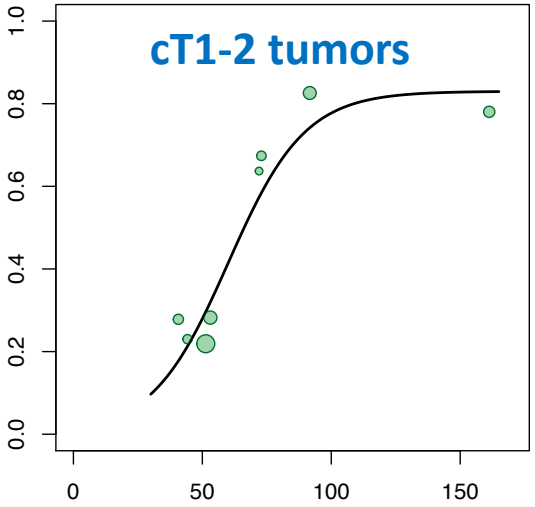
Appelt et al. IJROBP 2014; Valentini et al. Radiother Oncol 2019; Couwenberg et al. IJROBP 2020; Gerard et al. JCO 2004

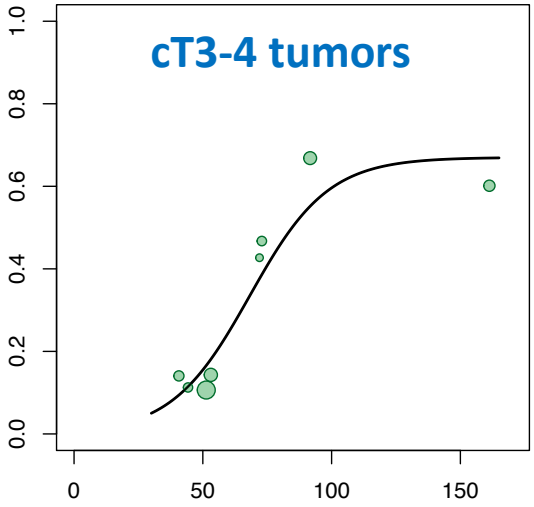
RT dose escalation in the organ preservation setting

LC after (C)RT for Watch & Wait



LC is tumor size-dependent after CRT for Watch & Wait





Appelt et al. ESTRO 2020

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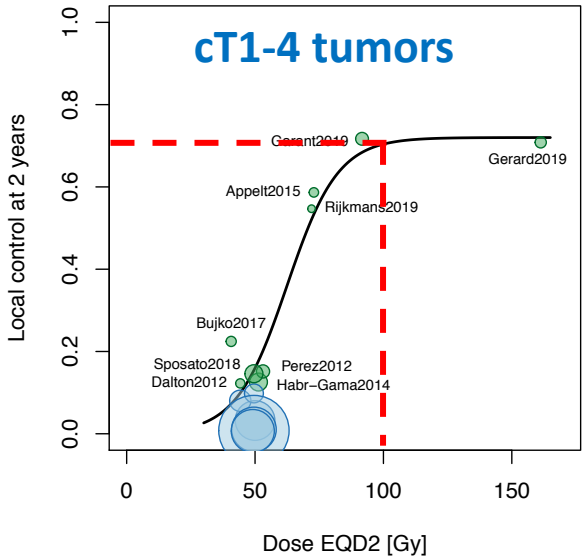

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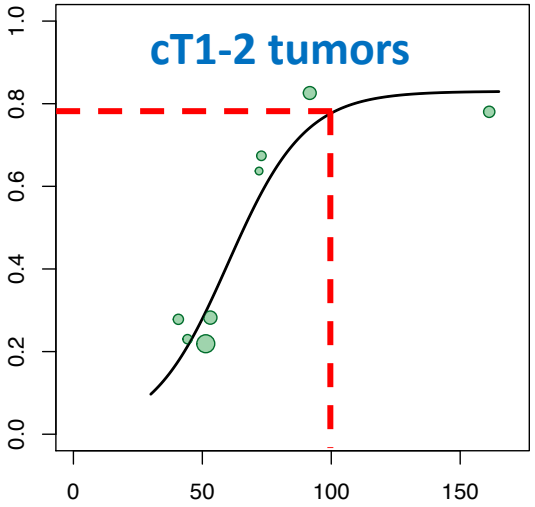
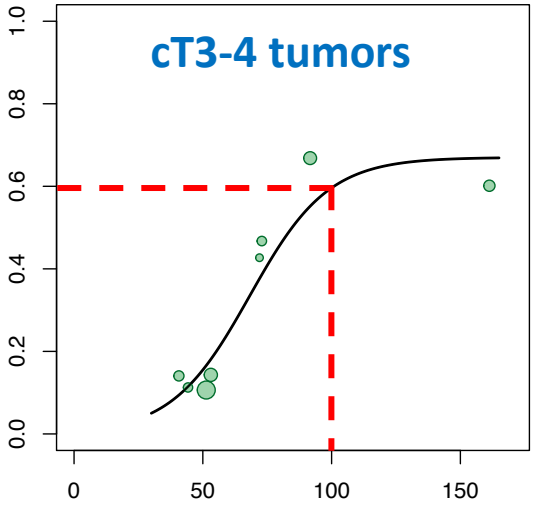




Appelt et al. ESTRO 2020

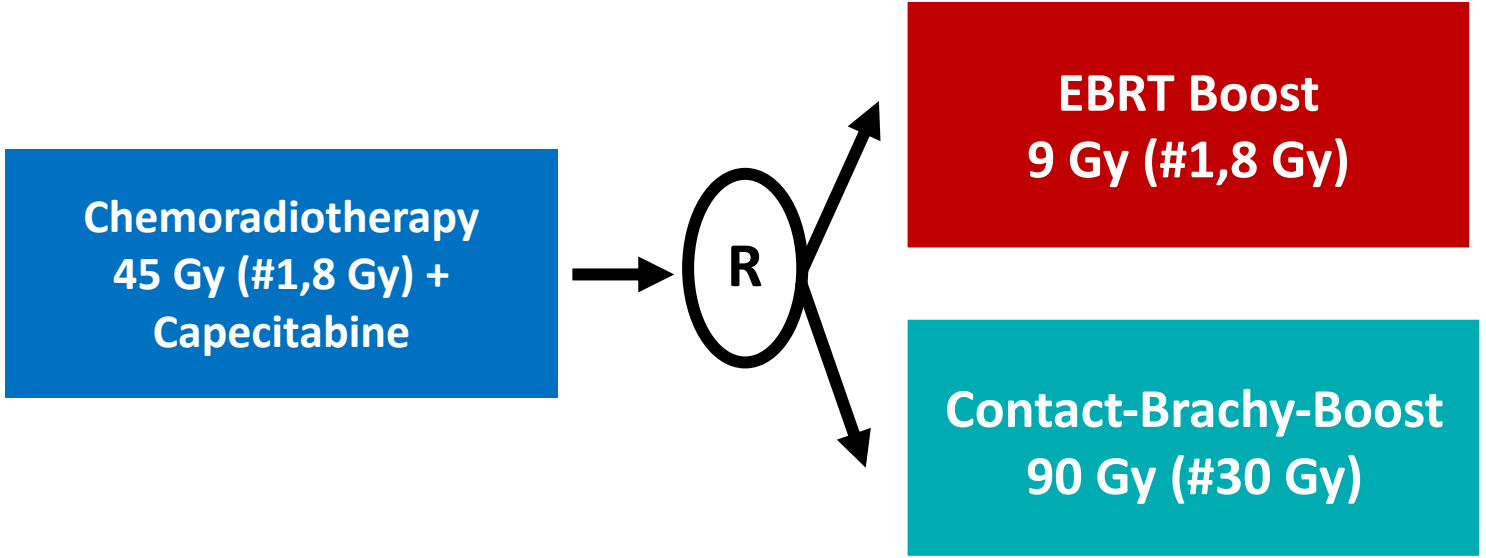
RT dose escalation in the organ preservation setting

Randomized trials (phase)	N	Control arm	Experimental arm	Primary endpoint
OPERA (III) cT2-T3bN0-1	148	CRT 45 Gy + EBRT Boost 9 Gy	CRT 45 Gy + Brachy Boost 3x 30 Gy	3y-organ preservation: 60% vs 81%, p=0.005
MORPHEUS (III) cT2-T3bN0	40	CRT 50 Gy + EBRT Boost 9 Gy	CRT 45 Gy + Brachy Boost 3x 10 Gy	2y-TME-free survival: 40% vs 80%, p=0.006
HERBERT 2 (III) cT1-3N0-1	106	EBRT 13 x 3 Gy	EBRT 13x 3 Gy + Brachy Boost 3x 7 Gy	recruitment ongoing
APRHODITE (II) cT1-T3bN0	104	CRT 50.4 Gy	CRT 50.4 Gy + SIB 11.6 Gy	recruitment ongoing

Myint et al. ASCO 2021; Garant et al. ESTRO 2021; Appelt et al. BMJ Open 2022

OPERA randomized phase III trial

cT2-T3bN0-N1 < 8mm; <50% circumference, <5 cm, < 10 cm from AV



Primary endpoint: Organ preservation

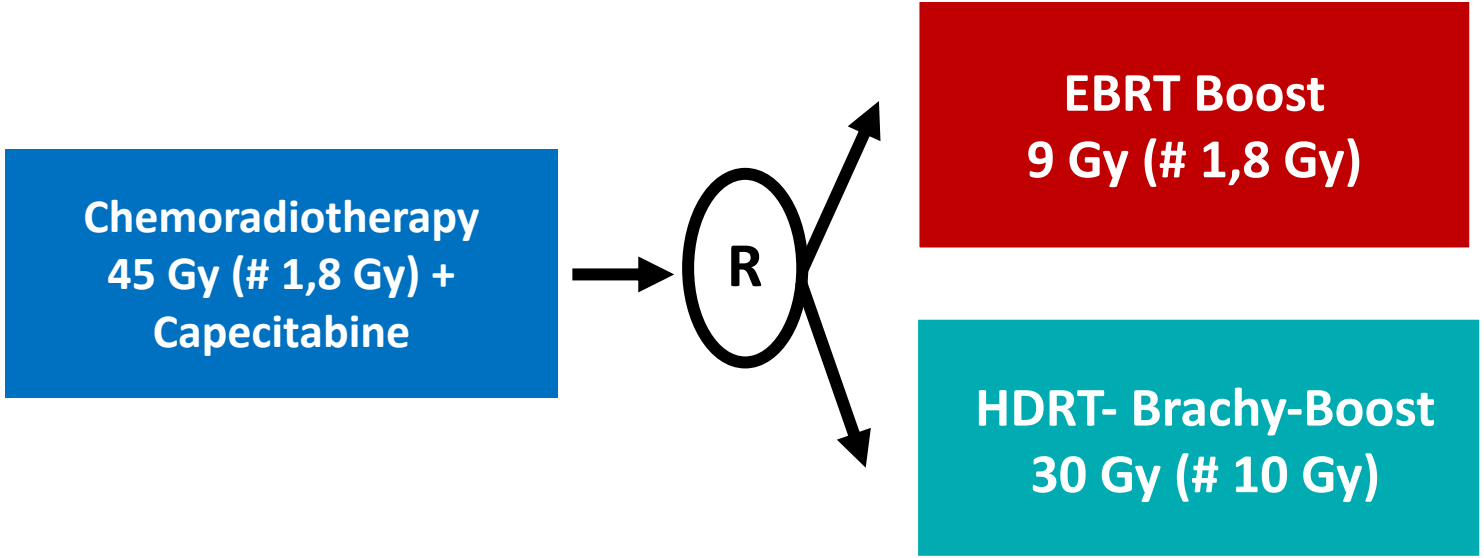
OPERA randomized phase III trial

Median F/u: 34 months	CRT+EBRT N=69	CRT+Brachy N=71	p-value
3-year organ preservation (all pts)	60%	81%	**.005**
3-year organ preservation(T<3cm)	65%	97%	**.02**
Poor LARS (score >30)	21%	17%	NS
Rectal bleeding (telangiectasia)	12%	63%	<.001

Myint S, ASCO 2021 & 2022

MORPHEUS randomized phase III trial

cT2-T3aN0M0; < 2/3 circumference, length < 5 cm, < 10 cm from AV



Primary endpoint: TME-free survival

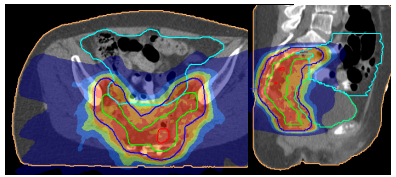
MORPHEUS randomized phase III trial (interim analysis)

Median F/u: 26 months	CRT+EBRT N=20	CRT+Brachy N=20	p-value
2-year TME-free Survival	40%	85%	.006
cCR	10/20 (50%)	18/20 (90%)	-
Local regrowth at 2 years	3/10 (30%)	3/18 (17%)	-
≥ G3 proctitis	-	10%	

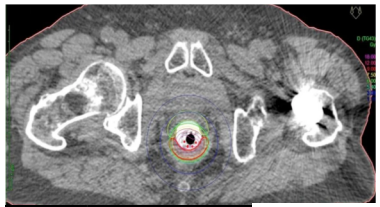
Garant A, ESTRO abstract 2021

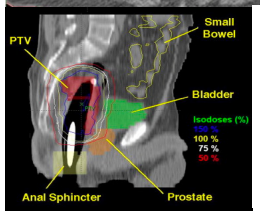
ACO/ARO/AIO-22 Phase-II-Studie bei älteren und gebrechlichen Patient:Innen mit Rektumkarzinom

Hypofraktionierte Radiotherapie 13 x 3 Gy



Endorektale Brachytherapie 3 x 8 Gy





RESTAGING

Komplett-remission → „Watch and Wait“

Keine Komplett-remission → Palliative Therapie / OP*

Ko-Primäre Endpunkte:

- Klinische Komplettremission
- Lebensqualität (EORTC QLQ-ELD14)

N=80; DKH Förderantrag gestellt

≥70 Jahre alt:

- von Chirurg:innen als inoperabel eingeschätzt
- ***und/oder*** Geriatrische 8 (G8)-Frailty-Score ≤ 14
- ***und/oder*** ASA PS ≥ 3

*Reevaluation der Operabilität

Conclusion

Is RT dose escalation meaningful in rectal cancer? It depends on the clinical setting:

- **Surgical setting → No:** lack of significant LC benefit
- **Organ preservation setting → Yes:** high cCR rates can be achieved after high RT doses, especially with endorectal brachytherapy in early / intermediate-stage

The OPERA and MORPHEUS randomized phase III trials provide Level I evidence in support of endorectal brachytherapy for organ preservation in rectal cancer

The planned ACO/ARO/AIO-22 phase II trial will assess the efficacy and tolerability of the percutaneous radiotherapy plus endorectal brachytherapy in elderly frail patients with rectal cancer that are unsuitable for radical surgery