Brachytherapy in Rectal and Anal Cancers (Evidences)

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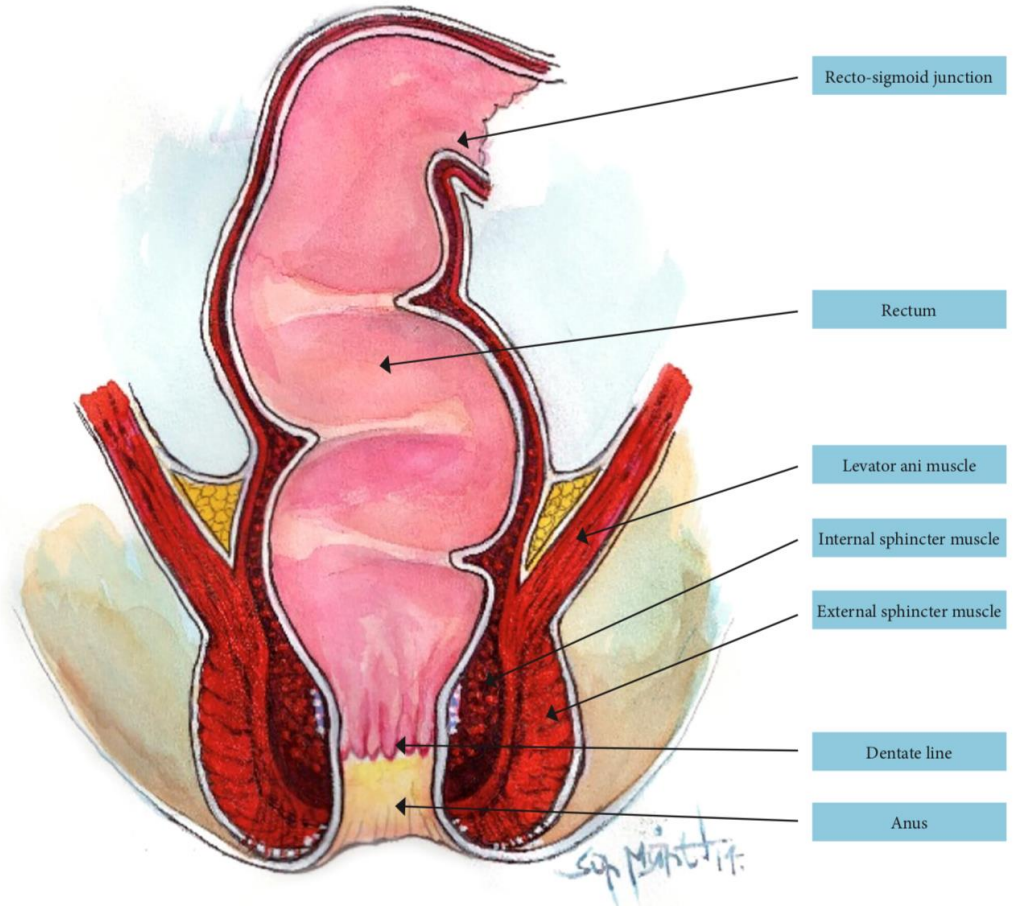
Rectal Cancer



Introduction

- Neoadjuvant radiotherapy has an established role in the management of operable rectal cancer
- Short-course or as long-course with concurrent chemotherapy
- improves local control and better tolerance

Dose Escalation

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Original article

Impact of radiotherapy boost on pathological complete response in patients with locally advanced rectal cancer: A systematic review and meta-analysis

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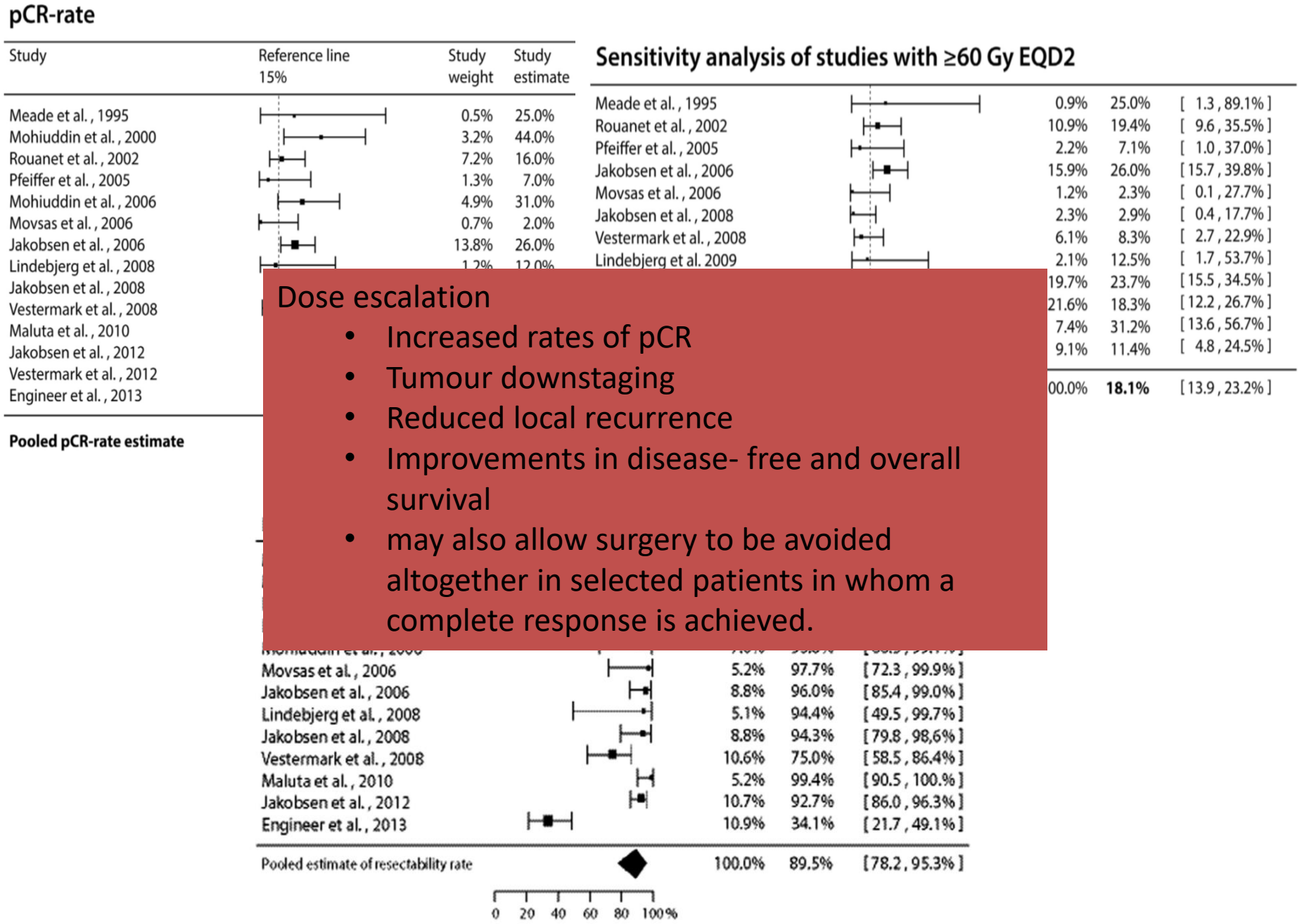
[a] *Department of Radiation Oncology;* [b] *Department of Radiology; and* [c] *Trial Bureau Imaging Division, University Medical Center, Utrecht, The Netherlands*



Dose escalation

- Increased rates of pCR
- Tumour downstaging
- Reduced local recurrence
- Improvements in disease- free and overall survival
- may also allow surgery to be avoided altogether in selected patients in whom a complete response is achieved.

Fig. 3. Forest plot of available acute grade ⩾3 toxicity and resectability with pooled estimate.

- Radiotherapy dose escalation can be achieved by intensity-modulated radiotherapy (IMRT) boost or endorectal brachytherapy
- IMRT : Dose above 60Gy is difficult without side effects

Brachytherapy:

- Highly conformal dose distribution around the tumour
- Steep dose-gradient
- Higher doses to be delivered to the tumor without increasing dose to normal tissue
- Radiobiological advantage of delivery at a high dose rate
  - Contact Brachytherapy
  - Interstitial/Endorectal Brachytherapy

- Recommendations on Brachytherapy boost is based on individual studies
- No meta-analysis.
- Systematic Reviews to guide

Endorectal brachytherapy boost after external beam radiotherapy in elderly or medically inoperable patients with rectal cancer: primary outcomes of the phase I HERBERT study

E.C. Rijkmans, MD, A. Cats, MD, Phd, R.A. Nout, MD. Phd, H.J.G.D. van den Bongard, MD, Phd, M. Ketelaars, Phd, J. Buijsen, MD, Phd, T. Rozema, MD, J.H. Franssen, MD, L.A. Velema, MD, B. van Triest, MD, Phd, C.A.M. Marijnen, MD, Phd

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Reference: ROB 24016

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Clinical investigation

High-dose rate brachytherapy in the management of operable rectal cancer: A systematic review

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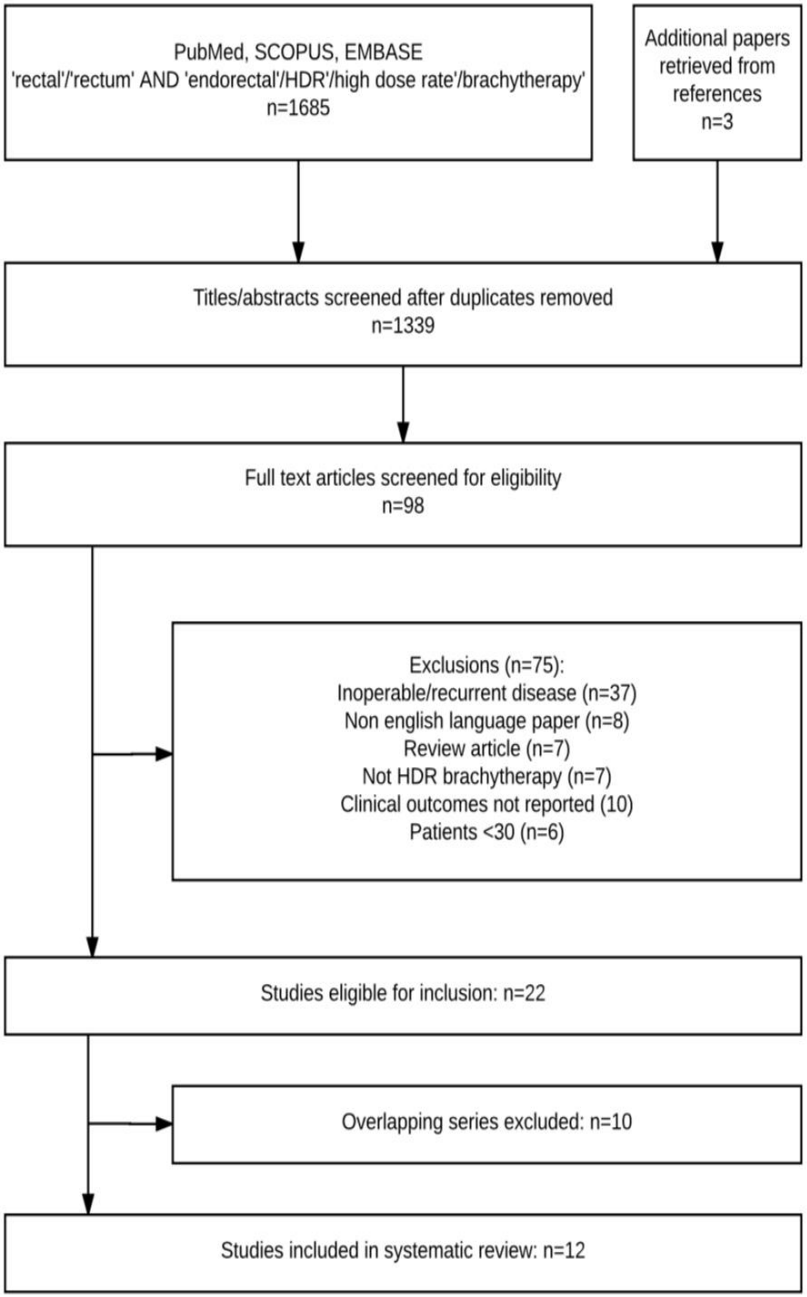


1339 papers considered
99 Full Text
22 Studies included
12 studies included in the review

Patient Selection

Table 1: Complete pathological response and R0 resection rates after HDREBT for operable rectal cancer

Study	Design	Patient s eceivi g DR n)	Inclusion criteria	reatment details	Total radiotherapy BED (Gy)[§]	Stage: T (%), N (%)	Distance from anal verge	Tumour size (cm)	Interval to surgery (weeks)	R0 resectio n (%)	pCR % (Assessme nt method)
			HDREBT wi CRT								
Jakobsen et al, 2006[33]	Prospective	8	T3 tumour, CRM \<5mm on MRI \<10cm from anal verge, OR where no MRF T3 tumour \<5mm distance to muscle/other organs	***EBRT:*** 0Gy/30 ***Concomitant hemotherapy:*** FT 100mg/m^2 TDS & V 7.5mg TDS eatment days ***DR brachytherapy:*** Gy/1 (at 10mm from pplicator surface)	79.5	T2: 0 T3: 48 (100%) T4: 0 N+: 35 (70%) N1: 30 (60%) N2: 5 (10%)	<10cm	Mean 4.7 (2.3-8)	NR	98%	27% (Mandard
Jakobsen et al, 2008[34]	Prospective	1	T4 tumour or T3 tumour CRM \<5mm on MRI \<10cm from anal verge OR where no MRF tumour \<5mm distance to muscle/other organs	***EBRT:*** 0Gy/30 ***Concomitant hemotherapy:*** FT 100mg/m^2 TDS & V 7.5mg TDS eatment days, elecoxib 400mg BD ***DR brachytherapy:*** Gy/1 (to tumour bed)	79.5	T2: 0 T3: 77% T4: 23% N: NR		11)			(Mandard TRG1)
Jakobsen et al, 2012[18]	Phase III	14 120 andom sed)	T4 tumour or T3 tumour <10cm from anal verge with a CRM <5mm on MRI OR in distal rectum any T3 tumour if distance between intestinal wall and MRF<5mm	***EBRT:*** 0.4Gy/28 ***Concomitant hemotherapy:*** enmark: FT100mg/m^2 TDS & V 7.5mg TDS eatment days (n=224) anada: 5FU 25mg/m^2/day (n=24) ***DR brachytherapy:*** 0Gy/2 (at 10mm from applicator surface), weeks 4&6	74.5	T2:0 T3: 102 (85%) T4: 18 (15%) N1: 57 (47.5%) N2: 51 (42.5%) N+: 108 (88%)	<10cm	Median diameter 3.6	8	T3=99% (not reported for T4/whole study)	18% (Mandard TRG1)

T3 (majority of studies
CRM <5mm on MRI
<10cm from the Anal Verge

Dose and Fractionations

Table 1: Complete pathological response and R0 resection rates after HDREBT for operable rectal cancer

Study	Design	Patients receiving HDR (n)	Inclusion criteria	Treatment details	Total radiotherapy BED (Gy)[$]	Stage: T (%), N (%)	Distance from anal verge	Tumour size (cm)	Interval to surgery (weeks)	R0 resection (%)	pCR % (Assessment method)
				HDREBT with CRT							
Jakobsen et al, 2006[33]	Prospective	48	T3 tumour, CRM \<5mm on MRI \<10cm from anal verge, OR where no MRF T3 tumour \<5mm distance to muscle/other organs	***EBRT:*** 60Gy/30 ***Concomitant chemotherapy:*** UFT 100mg/m^2 TDS & LV 7.5mg TDS treatment days ***HDR brachytherapy:*** 5Gy/1 (at 10mm from applicator surface)	79.5	T2: 0 T3: 48 (100%) T4: 0 N+: 35 (70%) N1: 30 (60%) N2: 5 (10%)	<10cm	Mean 4.7 (2.3-8)	NR	98%	27% (Mandard TRG1)
Jakobsen et al, 2008[34]	Prospective	31	T4 tumour or T3 tumour CRM \<5mm on MRI \<10cm from anal verge OR where no MRF tumour \<5mm distance to muscle/other organs	***EBRT:*** 60Gy/30 ***Concomitant chemotherapy:*** UFT 100mg/m^2 TDS & LV 7.5mg TDS treatment days, Celecoxib 400mg BD ***HDR brachytherapy:*** 5Gy/1 (to tumour bed)	79.5	T2: 0 T3: 77% T4: 23% N: NR					
Jakobsen et al, 2012[18]	Phase III	114 (120 randomised)	T4 tumour or T3 tumour \<10cm from anal verge with a CRM \<5mm on MRI OR in distal rectum any T3 tumour if distance between intestinal wall and MRF\<5mm	***EBRT:*** 50.4Gy/28 ***Concomitant chemotherapy:*** Denmark: UFT100mg/m^2 TDS & LV 7.5mg TDS treatment days (n=224) Canada: 5FU 225mg/m^2/day (n=24) ***HDR brachytherapy:*** 10Gy/2 (at 10mm from applicator surface), weeks 4&6	74.5	T2:0 T3: 102 (85%) T4: 18 (15%) N1: 57 (47.5%) N2: 51 (42.5%) N+: 108 (88%)					

- EBRT 50-60Gy
- Brachytherapy 5Gy /1fr or 10Gy in 2 fr (HDR)
- Prescribed at 10mm from surface of applicator/tumor bed
- Total BED 74.5-79Gy

Sun Myint et al, 2010[21]	Pilot study	34	Bulky low T2 (cm verge) or T3 w CRM threaten, or multiple suspic us lymph nodes (Definition of 'b ky' not stated)	***EBRT:*** 45Gy/25 ***Concomitant chemotherapy:*** 5FU 750-1000mg/m^2 over 4 days, week 1,5, or Capecitabine 625-825mg/m^2 treatment days ***HDR brachytherapy:*** 10Gy in 1 fraction (at 10mm), if good response at 4 weeks	73.1	T2: 5 (15%) T3: 32 (68%) T4: 6 (18%) N1: 21 N2: 11 N+: 32 (94%)	<6cm for T2 (NR for T3)	NR	6-8	80%	31% (Mandard TRG1)
				HD EBT alone							
Yanagi et al, 2000[17]	Retrospective series	115	T2-T4, N0-N3 Lower/middle tal tumour (Defini n of 'lower/middle' t stated) (UICC 1992, 4 edition)	***HDR brachytherapy:*** 16-80Gy (in 4-40Gy per fraction)		NR					
Vuong et al 2015[23,]	Phase I/II	483	T3 and low T2 ith positive CRM (definition of 'l ' not stated)	***HDR brachytherapy:*** 26Gy/4 (to CTV) *Pre-2005: adjuvant EBRT 45Gy/25 if N+ (n=43)[$] with 5-FU 225mg/m^2 continuous infusion (n=43)[$] Post-2005: adjuvant FOLFOX (clinician discretion)[$]*	42.9	N	NR	NR	6-8	NR	27% (NR)
Hesselager et al*, 2013[27]	*Matched control, retrospective*	*318*	*Resectable re l cancer <15cm nal verge)*	***HDR brachytherapy:*** *26Gy/4 (to CTV)*	*42.9*	*NR*	*<16cm*	*NR*	*4-8*	*96.5%*	*23.6% (ypT0N0)*

- HDR Brachy alone
  - 16-80Gy in 4-40Gy /fraction
  - 26Gy in 4 fr prescribed to CTV

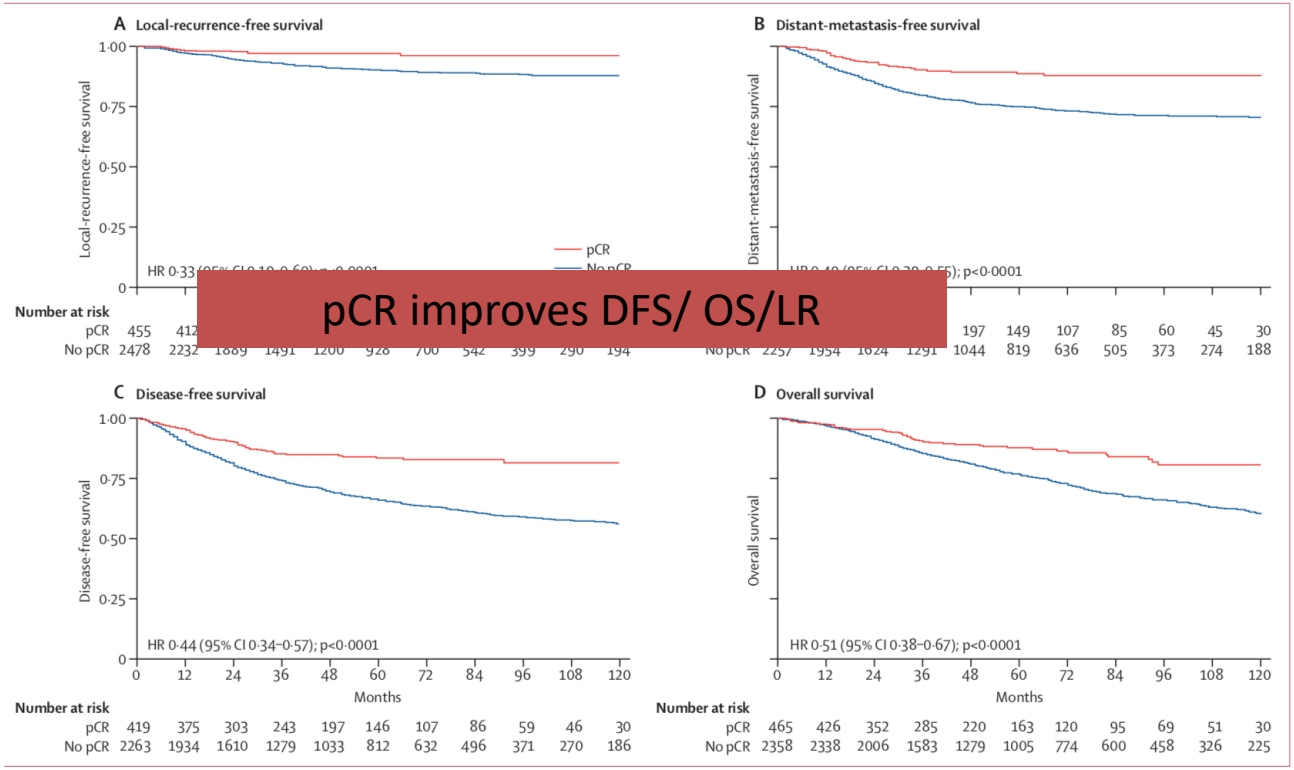
Clinical Outcomes

- Pathological Complete Response (pCR)
- Progression Free Survival (PFS)
- Overall survival (OS)
- Locoregional Relapse (LRR)
- Sphincter Preservation
- Radiation Toxicity
- Surgical Complications

Pathological complete Response

Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data

Monique Maas, Patty J Nelemans, Vincenzo Valentini, Prajnan Das, Claus Rödel, Li-Jen Kuo, Felipe A Calvo, Julio García-Aguilar, Rob Glynne-Jones, Karin Haustermans, Mohammed Mohiuddin, Salvatore Pucciarelli, William Small Jr, Javier Suárez, George Theodoropoulos, Sebastiano Biondo, Regina G H Beets-Tan, Geerard L Beets



pCR improves DFS/ OS/LR

Figure 2: **Kaplan-Meier survival curves for patients with and without pathological complete response (pCR)**
(A) Local-recurrence-free survival. (B) Distant-metastasis-free survival. (C) Disease-free survival. (D) Overall survival. Not all study centres provided data for all four outcome measures, which explains the differences in numbers at risk between outcome measures. p values were determined by log-rank test. HR=hazard ratio.

pCR

Table 1: Complete pathological response and R0 resection rates after HDREBT for operable rectal cance

Study	Design	Patients receiving HDR (n)	Inclusion criteria	Treatment details	Total radiotherapy BED (Gy)[$]	Stage: T (%), N (%)	Distance from anal verge	Tumour size (cm)	Interval to surgery (weeks)	R0 resection (%)	pCR % (Assessment method)
				HDREBT with CRT							
Jakobsen et al, 2006[33]	Prospective	48	T3 tumour, CRM \<5mm on MRI \<10cm from anal verge, OR where no	***EBRT:*** 60Gy/30 ***Concomitant chemotherapy:*** 5Gy/1 (at 10mm from applicator surface)	79.5	T2: 0 T3: 48 (100%) T4: 0 N+: 35 (70%) N1: 30 (60%) N2: 5 (10%)	<10cm	Mean 4.7 (2.3-8)	N	98%	27% (Mandard TRG1)
Jakobsen et al, 2008[34]	Prospective	31	T4 tumour or T3 tumour CRM \<5mm on MRI \<10cm from anal verge OR where no MRF tumour \<5mm distance to muscle/other organs	***EBRT:*** 60Gy/30 ***Concomitant chemotherapy:*** UFT 100mg/m^2 TDS & LV 7.5mg TDS treatment days, Celecoxib 400mg BD ***HDR brachytherapy:*** 5Gy/1 (to tumour bed)	79.5	T2: 0 T3: 77% T4: 23% N: NR	<10cm	Median 5.2 (1.3-11)	8	97%	21% (n=33) 22.6%(n=31) (Mandard TRG1)
Jakobsen et al, 2012[18]	Phase III	114 (120 randomised)	T4 tumour or T3 tumour <10cm from anal verge with a CRM <5mm on MRI OR in distal rectum any T3 tumour if distance between intestinal wall and MRF<5mm	***EBRT:*** 50.4Gy/28 ***Concomitant chemotherapy:*** Denmark: UFT100mg/m^2 TDS & LV 7.5mg TDS treatment days (n=224) Canada: 5FU 225mg/m^2/day (n=24) ***HDR brachytherapy:*** 10Gy/2 (at 10mm from applicator surface), weeks 4&6	74.5	T2:0 T3: 102 (85%) T4: 18 (15%) N1: 57 (47.5%) N2: 51 (42.5%) N+: 108 (88%)	<10cm	Median diameter 3.6	8	T3=99% (not reported for T4/whole study)	18% (Mandard TRG1)

HDR with CRT improved pCR

pCR

Sun Myint et al, 2010[21]	Pilot study	34	Bulky low T2 (<6cm verge) or T3 with CRM threatened, or multiple suspicious lymph nodes (Definition of 'bulky' not stated)	***EBRT:*** 45Gy/25 ***Concomitant chemotherapy:*** 5FU 750-1000mg/m^2 over 4 days, week 1,5, or Capecitabine 625-825mg/m^2 treatment days ***HDR brachytherapy:*** 10Gy in 1 fraction (at 10mm), if good response at 4 weeks	73.1	T2: 5 (15%) T3: 32 (68%) T4: 6 (18%) N1: 21 N2: 11 N+: 32 (94%)	<6cm for T2 (NR for T3)	NR	6	80%	31% (Mandard TRG1)
HDREBT alone											
Yanagi et al, 2000[17]	Retrospective series	115	T2-T4, N0-N3 Lower/middle rectal tumour (Definition of 'lower/middle' not stated) (UICC 1992, 4th edition)	***HDR brachytherapy:*** 16-80Gy (in 4-40Gy per fraction)		NR	NR	NR	2	NR	10.4% (ypT0)
Vuong et al 2015[23]*	Phase I/II	483	T3 and low T2 with positive CRM (definition of 'low' not stated)	***HDR brachytherapy:*** 26Gy/4 (to CTV) *Pre-2005: adjuvant EBRT 45Gy/25 if N+ (n=43)$ with 5-FU 225mg/m^2 continuous infusion (n=43)$* *Post-2005: adjuvant FOLFOX (clinician discretion)$*	42.9	N	NR	NR	6	NR	27% (NR)
Hesselager et al*, 2013[27]	*Matched control, retrospective*	*318*	*Resectable rectal cancer <15cm anal verge)*	***HDR brachytherapy:*** *26Gy/4 (to CTV)*	*42.9*	*NR*	*<16cm*	*NR*	*4*	*96.5%*	*23.6% (ypT0N0)*

Table 6: Comparison of results of HDR EBT in rectal cancer with Cochrane meta-analysis

	pCR	10	Sphincter preservation	2yr local recurrence	5yr local recurrence	2yr PFS/DFS	5yr PFS/DFS	2yr OS	5yr OS
Pre-operative HDR & CRT	26.1% (n=267)	5.5% (n=215)	51.4% (n=261)	6% (n=144)	NR	68.1% (n=144)	52% (n=110)	81.5% (n=144)	63.6% (n=110)
Pre-operative HDR	23.8% (n=598)	6.5% (n=318)	59.4% (n=318)	7.5% (n=115)	5.8% (n=598)	NR	66.6% (n=598)	74.9% (n=598)	70.8% (n=598)
Definitive HDR & CRT	-		-	25.9% (n=51)	NR	NR	NR	100% (n=51)	NR
Cochrane[3]									
RT	3.5%	NR	48.3%	NR	16.5%	NR	54.9%	NR	65.2%
CRT	11.8% (n=1142)	NR	50.4%	NR	9.4% (n=1007)	NR	57.5% (n=881)	NR	63.9% (n=1007)

pCR=pathological complete response, PFS=progression free survival, DFS=disease free survival, OS=overall survival, HDR=high dose rate, CRT=chemoradiotherapy, NR=Not reported

High pCR after brachytherapy doesn't seem to translate into PFS or OS

But why

- Brachytherapy being a local treatment
- Cannot control microscopic regional node or distant metastatic disease.

Way to go

Chemoradiation or Brachytherapy for Rectal Cancer (CORRECT)

ClinicalTrials.gov Identifier: NCT02017704

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

Recruitment Status : Active, not recruiting
First Posted : December 23, 2013
Last Update Posted : November 26, 2019

Sponsor:

Future ongoing studies could bring more info

Study Description

Go to

Brief Summary:

This research is being done to compare the effectiveness of high dose endorectal brachytherapy (END-HDR) and the standard treatment option of chemoradiation with Capecitabine in the treatmer of cancer of the lowest part of the bowel (rectum).

Condition or disease	Intervention/treatment	Phase
Rectal Cancer	Radiation: Endo-HDR (if randomized to this arm) Drug: capecitabine and IMRT (if randomized to this arm) Radiation: IMRT (intensity modulated radiation therapy) Drug: FOLFOX6 Procedure: Surgery	Phase 2

Do we really have a long term result

Int J Radiat Oncol Biol Phys. 2014 September 1; 90(1): 110–116. doi:10.1016/j.ijrobp.2014.05.025

Long term results of a randomized trial in locally advanced rectal cancer: No benefit from adding a brachytherapy boost

Ane L Appelt, PhD[1,2], Ivan R Vogelius, PhD[3], John Pløen, MD[4], Søren R Rafaelsen, MD[4], Jan Lindebjerg, MD[4], Birgitte M Havelund, MD, PhD[4], Søren M Bentzen, PhD, DSc[5], and Anders Jakobsen, DMSc[2,4]

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[5]Division of Biostatistics and Bioinformatics, University of Maryland Greenebaum Cancer Center, and Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, USA

Table 3: Recurrence and survival after HDREBT for operable rectal cancer

Study (Period)	Design	No of patients (n)	Patients receiving HDR (n)	Median age (yrs)	Inclusion	Treatment details	BED (Gy)[$]	T&N stage	Interval to surgery (weeks)	Local recurrence	DFS/PFS	2yr OS	5yr OS	Median F/U months
HDREBT with CRT														
Appelt 2014[19] (2005-2008)	Phase III	221	110 randomised (90 received HDR boost as planned)	64	T4 tumour or T3 tumour <10cm from anal verge with a CRM <5mm on MRI OR in distal rectum any T3 tumour if distance between intestinal wall and MRF<5mm	***EBRT:*** 50.4Gy/28 ***Concomitant chemotherapy:*** UFT100mg/m^2 TDS & LV 7.5mg TDS treatment days ***HDR brachytherapy:*** 10Gy/2 (at 10mm from applicator surface), weeks 4&6	74.5	T2:0 T3: 93 (85%) T4:17 (15%) N0:13 (12%) N1-2 95 (86%) Not determined :2	8	NR[$] *Locoregional* *2yr: 7.8%* *5yr: 14.3%*	2yr PFS: 68.7% 5yr PFS: 52 %	84.5 %	63.6 %	65
et al 2010[21] (NR)					(<6cm verge) or T3 with CRM threatened, or multiple suspicious lymph nodes	45Gy/25 ***Concomitant chemotherapy:*** 5FU 750-1000mg/m^2 over 4 days, week 1,5, or Capecitabine 625-825mg/m^2 treatment days ***HDR brachytherapy:*** 10Gy in 1 fraction (at 10mm), if good response at 4 weeks		T3: 32(68%) T4: 6(18%) N1: 21 N2: 11 N+: 32(94%)		recurrences.	79% 2yr PFS: 66%			
HDREBT alone														

221pts
90 pts received HDR
EBRT : 50.4 Gy followed by
HDR 10Gy /2 fr BED 74.5Gy

Disease Relapse

Mortality

OS

PFS

Freedom from Metastasis

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **221 (110 vs 111)** **Disease relapse** • HDR brachytherapy boost=35.5% (39/110) • Standard chemoradiotherapy=32.4% (36/111), p value not reported **Mortality** • HDR brachytherapy boost=32.7% (39/110) • Standard chemoradiotherapy=38.7% (43/111), p value not reported **Overall survival at 2 years** • HDR brachytherapy boost=84.5% • Standard chemoradiotherapy=82.0%, p value not reported **Overall survival at 5 years** • HDR brachytherapy boost=63.6% • Standard chemoradiotherapy=70.6%, p=0.34 **Progression-free survival at 2 years** • HDR brachytherapy boost=68.7% • Standard chemoradiotherapy=73.0%, p value not reported **Progression-free survival at 5 years** • HDR brachytherapy boost=52.0% • Standard chemoradiotherapy=63.9%, p=0.32 **Freedom from locoregional failure at 5 years** • HDR brachytherapy boost=85.7% • Standard chemoradiotherapy=93.9%, p=0.06 **Freedom from distant metastases at 2 years** • HDR brachytherapy boost=77.6% • Standard chemoradiotherapy=76.8%, p value not reported **Freedom from distant metastases at 5 years** • HDR brachytherapy boost=68.4% • Standard chemoradiotherapy=68.7%, p=0.85 **5-year risk of secondary cancer** • HDR brachytherapy boost=8.9% • Standard chemoradiotherapy=7.8%, p=0.61 There was no difference in the prevalence of stoma between the groups (66.1% among 2-year survivors and 64.5% among 5-year survivors).	No safety outcomes were reported.

NS

Conclusion

In conclusion, despite a statistically significant improvement in pathological tumor response from the addition of a brachytherapy boost to preoperative CRT for locally advanced rectal cancer, a corresponding improvement in OS, PFS or locoregional control was not seen. Thus, an increase in pathological tumor regression at the time of surgery did not indicate a benefit on late clinical outcome. TRG score and R0 resection are well-established prognostic factors, but their utility as surrogate endpoints for long-term patient benefit remains to be defined.

Sphincter preservation

Table 2: Sphincter preservation surgery after HDREBT for operable rectal cancer

Study	No. patients undergoing surgery after HDR (%)	Sphincter preservation rate (%)	No. patients undergoing other surgery (%)
HDREBT with CRT			
Jakobsen et al, 2008[34]	33 (94%)	16(45.7%)* *LAR	APR 15 (42.9%) Hartmann's procedure 2 (5.7%) No surgery 2 (5.7%) (reason not reported)
Jakobsen et al, 2006[33]	48 (96%)	19 (39.6%)* *LAR	APR 27 (56.3%) Hartmann's procedure1 (2.1%) Other 1 (2.1%) No surgery 2 (4.2%) (1 refused, 1 developed metastases)
Jako 2012	No study had sphincter preservation as a prespecified endpoint		
Sun Myint et al, 2010[21]	29 (85.3%)	10 (29.4%)* *LAR	APR 18 (53%) Hartmann's procedure 1 (2.9%) No surgery 5 (14.7%) (2 refused, 1 developed metastases, 1 unresectable at laparotomy)
HDREBT alone			
Yanagi et al, 2000[17]	115 (100%)	14 (12.2%)* *LAR	CAA 72 (62.6%) APE 28 (24.4%) TPE 1 (0.87%)
Hesselager et al, 2013[27]	318 (100%)	171 (53.8%)* *LAR	APR 141 (44.3%) Hartmann's procedure 6 (1.9%)

LAR=low anterior resection, APR=abdomino-perineal resection, CAA=ano-abdominal rectal resection with colo-anal anastomosis,

Sphincter preservation following HDREBT and CRT (Cochrane meta-ananlysis) was similar.

Table 6: Comparison of results of HDREBT in rectal cancer with Cochrane meta-analysis

	pCR	R0	Sphincter preservation	2yr local recurrence	5yr local recurrence	2yr PFS/DFS	5yr PFS/DFS	2yr OS	5yr OS
Pre-operative HDR & CRT	26.1% (n=267)	95.5% (n=215	51.4% (n=261)			1% (n=144)	52% (n=110)	81.5% (n=144)	63.6% (n=110)
Pre-operative HDR	23.8% (n=598)	96.5% (n=318	59.4% (n=318)	7.5% (n=115)	5.8% (n=598)	NR	66.6% (n=598)	74.9% (n=598)	70.8% (n=598)
Definitive HDR & CRT	-	-	-	25.9% (n=51)	NR	NR	NR	100% (n=51)	NR
Cochrane[3]									
RT	3.5%	NR	48.3%	NR	16.5%	NR	54.9%	NR	65.2%
CRT	11.8% (n=1142)	NR	50.4%		(n=1007)		57.5% (n=881)	NR	63.9% (n=1007)

pCR=pathological complete response, PFS=progression free survival, DFS=disease free survival, OS=overall survival, HDR=high dose rate, CRT=chemoradiotherapy, NR=Not reported

Radiation Toxicity

Table 5: Radiation toxicities after HDREBT in operable rectal cancer

Study	Patients receiving HDR (n)	Treatment details	EBRT	HDR	Chemotherapy	Acute toxicity	Assessment method
HDREBT with CRT							
Jakobsen et al, 2008[34]	31	***EBRT:*** 60Gy/30 ***Concomitant chemother*** UFT 100mg/m^2 TDS & LV TDS treatment days, Cele 400mg BD ***HDR brachytherapy:*** 5Gy/1 (to tumour bed)					NS
Jakobsen et al, 2006[33]	48	***EBRT:*** 60Gy/30 ***Concomitant chemotherapy:*** UFT 100mg/m^2 TDS & LV 7.5mg TDS treatment days ***HDR brachytherapy:*** 5Gy/1 (at 10mm from applicator surface)				G4=0	NS
Jakobsen et al, 2012[18]	114	***EBRT:*** 50.4Gy/28 ***Concomitant chemotherapy:*** Denmark: UFT100mg/m^2 TDS & LV 7.5mg TDS treatment days (n=224) Canada: 5FU 225mg/m^2/day (n=24) ***HDR brachytherapy:*** 10Gy/2 (at 10mm from applicator surface), weeks 4&6	50.4Gy/ 28	10Gy/2	Denmark: UFT/LV Canada:5FU	>/G2: diarrhoea 23(19%) skin 21 (17%) dysuria 8 (7%) proctitis 18 (15%). G3 not reported sep	CTC
HDREBT alone							
Yanagi et al, 1997[18]	115	***HDR brachytherapy:*** A16-40Gy (n=96) B:40-80Gy (n=19)	No	A: 16-40Gy (n=96) B: 40-80Gy (n=19)	No	Peri-anal skin: 21 (18.3%) Ileitis/pouchitis: 5 (4.3%) (grade NS)	NS
Vuong et al, 2007[25]	100	***HDR brachytherapy:*** *26Gy/4 (to CTV)*	Post-op if N+ (n=27)	26Gy/4	none	G2: proctitis 99 (99%) G3: proctitis 1 (1%)	NS

NO alarming Toxicity was reported in studies with brachytherapy

Clinical Investigation: Gastrointestinal Cancer

Dose-Effect Relationship in Chemoradiotherapy for Locally Advanced Rectal Cancer: A Randomized Trial Comparing Two Radiation Doses

Anders Jakobsen, DMSc,*,† John Ploen, MD,† Té Vuong, MD,‡ Ane Appelt, MSc,*,† Jan Lindebjerg, MD,* and Soren R. Rafaelsen, MD*

*Danish
Denmark;

Received S

- 248 Pts
- CRT VS CRT + EBCRT : No increase in radiation related toxicity with addition of Brachytherapy

Toxicity	Arm A (*n*)	Arm B (*n*)
Thrombocytopenia	0 (0)	0 (0)
Neutropenia	1 (1)	1 (1)
Nausea	5 (4)	7 (6)
Vomiting	3 (2)	2 (2)
Stomatitis	0 (0)	2 (2)
Diarrhea	23 (19)	23 (19)
Skin	21 (17)	24 (20)
Dysuria	8 (7)	7 (6)
Proctitis	18 (15)	22 (18)

Data in parentheses are percentages.

Post operative Complications

Table 3 Surgery type and postoperative complications

Variable	Arm A (*n*)	Arm B (*n*)
Surgery type		
LAR	52 (48)	57 (54)
APR	47 (43)	40 (38)
Postoperative complications		
None	61 (56)	71 (67)
Reoperation	9 (8)	5 (5)
Ileus	5 (5)	0 (0)
Infection (related to wound)	12 (11)	16 (15)
Death	0 (0)	1 (1)
Anastomotic leakage	4 (4)	0 (0)
Fistula	2 (2)	1 (1)
Stenosis	0 (0)	0 (0)
Urinary problems	9 (8)	3 (3)
Other	7 (6)	9 (8)

Abbreviations: APR = abdominoperineal resection; LAR = lower anterior resection.
Data in parentheses are percentages.

No difference in surgical complication with brachytherapy with CRT vs CRT

Organ preservation

Special Review: Rectal Cancer-current Therapies and Emerging Concepts

Predicting complete response: is there a role for non-operative management of rectal cancer?

T. Jonathan Yang, Karyn A. Goodman

Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA

Correspondence to: Karyn A. Goodman, MD, MS. Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA. Email: goodmank@mskcc.org.

High chance of pCR following HDREBT could be promising

Future studies to guide

Watchful Waiting. An Observational Study of Patients With Rectal Cancer After Concomitant Radiation and Chemotherapy

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT00952926

Recruitment Status : Completed
First Posted : August 6, 2009
Last Update Posted : February 5, 2020

PV-0139 Endorectal HDR brachytherapy boost with MRI guidance for non operative management of rectal cancer

R. Engineer[1], A. Saklani[2], A. D'Souza[2], A. Baheti[3], M. Patil[1], S. Chopra[1], P. Patil[4]

[1]Tata Memorial Hospital, Radiation Oncology, Mumbai, India; [2]Tata Memorial Hospital, Surgical Oncology, Mumbai, India; [3]Tata Memorial Hospital, Radlogy, Mumbai, India ; [4]Tata Memorial Hospital, Gastrointestinal Oncology, Mumbai, India

Purpose or

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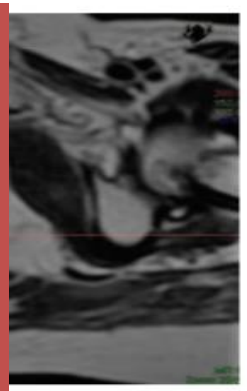
those with a residual ulcerative disease and no greater than three-fourth circumferential involvement were considered for further boost. A planning MRI scan with a multiple channel surface applicator in place was taken within 3 weeks of NACTRT completion. Residual tumour / fibrotic regions were contoured (CTV), dose prescribed at periphery of the residual tumor (7 - 10 mm) depending on depth of invasion and isodose distribution generated for 2-3 channels in closest proximity to the CTV. Plan evaluation consisted of ensuring that the CTV is completely covered by the 85% isodose cloud, while trying to limit the opposing rectal wall from being covered by the 50% isodose line (Fig. 1). High dose rate brachytherapy was delivered with iridium-192 source to a dose of 4 to 6 Gy in 2 fractions one week apart. Patients were assessed for tumor response at 6 weeks from radiation completion with DRE, rectal MRI scan and direct endoscopic visualization a 12 weeks. Patients with incomplete clinical response at 6 to 12 weeks were sent for immediate surgery. Patients with complete (CR) or near complete clinical response (NCR) were observed.

- Pilot study : TMH Mumbai
- T2-T4, N0-2 M0
- Within 6 cm from Anal Verge
- Oct 2017-May 2018
- EBRT 50.4Gy
- MRI after 3 weeks of EBRT
- Residual tumor : HDR 4-6Gy in 2fr
- Incomplete response at 6-12 weeks >> Surgery
- Complete response or Near Complete response were observed
- 75% had CR or NCR at 12 weeks
- Dose escalation can be achieved with brachytherapy leading to oragan preservation



in the given period
be suitable for
ulted immediately
Four (20%) patients
abdominoperineal
esection. Of these 1
ponse.
) had CR to NCR at
d for the wait and
CR underwent local

ange16 – 44 weeks)
wth and all15 (75%)
. No rectal toxicity

Dose escalation with MRI guided endorectal brachytherapy for non operative management of rectal cancer is feasible and can lead to a larger number of patients to achieve complete clinicoradiological response leading to organ preservation.

Longer follow up and a larger sample size would be required to weigh the potential benefits of dose escalation with regard to local response, progression free interval, successful salvage and against risk of long term toxicity.

Contact X RAY Brachytherapy

Supplement article

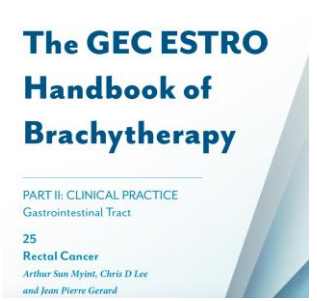
doi:10.1111/codi.14507

Treatment: the role of contact X-ray brachytherapy (Papillon) in the management of early rectal cancer

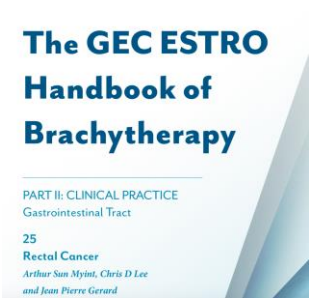
A. Sun Myint*†, A. Stewart‡§, J. Mills¶, R. Sripadam*, K. Whitmarsh*, R. Roy, A. Franklin‡, A. Dhadda** and on behalf of the UK Papillon team**

*Papillon Suite, Clatterbridge Cancer Centre, Bebington, Wirral, UK, †Translational Medicine Department, University of Liverpool, Liverpool, UK, ‡St Luke's Cancer Centre, Royal Surrey County Hospital, Guildford, UK, §University of Surrey, Guildford, UK, ¶Nottingham University Hospital, Nottingham, UK, and **Queen's Centre for Oncology and Haematology, Hull, UK

Contact X Ray Brachytherapy



- Rectal adenocarcinoma cT1 or cT2 (confined to the bowel wall)
- Well to moderately differentiated cancer
- Mobile exophytic tumour
- Size less than 3 cm in all dimensions
- Location not higher than 12 cm
- Patient must agree to long term follow up



- Patients with rectal cancer more than 3 cm in size and stage cT3a or T3b can be offered initial EBCRT or EBRT alone to down size and down stage the tumour.
- The use of contact X-ray brachytherapy boost can be considered for good responders (>80% regression) with residual exophytic tumours less than 2 cm which penetrate only a few millimetres from the rectal wall.

Not candidate for contact X-ray radiotherapy are:

The GEC ESTRO Handbook of Brachytherapy
PART II: CLINICAL PRACTICE
Gastrointestinal Tract
25
Rectal Cancer
Arthur Sun Myint, Chris D Lee and Jean Pierre Gerard

- Poorly differentiated adenocarcinoma
- Presence of lympho- vascular invasion
- Deeply infiltrative ulcerative fixed cancer
- Tumours involving more than half of the circumference
- Tumours extending into the anal canal below the dentate line

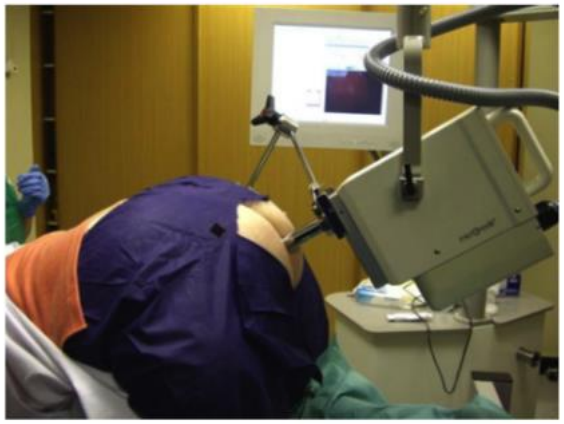
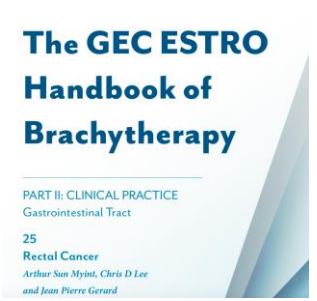
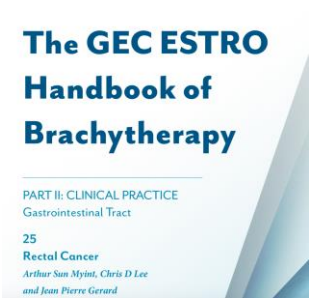


Fig 25.2. Treatment position for contact x-ray brachytherapy

DOSE, DOSE RATE AND FRACTIONATION



- Contact x-ray brachytherapy (Papillon
- Radical : 30 Gy in 3 fractions at 2weeks interval
- If residual tumor is visible or palpable during last fraction 4th fraction of 20 Gy after 2 weeks



- Boost following EBCRT: Contact X RAY Brachytherapy
  - 45 Gy in 25 fr or 25 Gy in 5 fr followed by 30Gy x 3 fractions over 4 week total dose of 100Gy /Fr
  - Total local dose to tumor bed becomes 344Gy (45 Gy) or 331Gy for 25 Gy

Endoluminal and interstitial brachytherapy

- Infiltrative cancers
- Bulky
- Residual lesion involving more than half of circumference

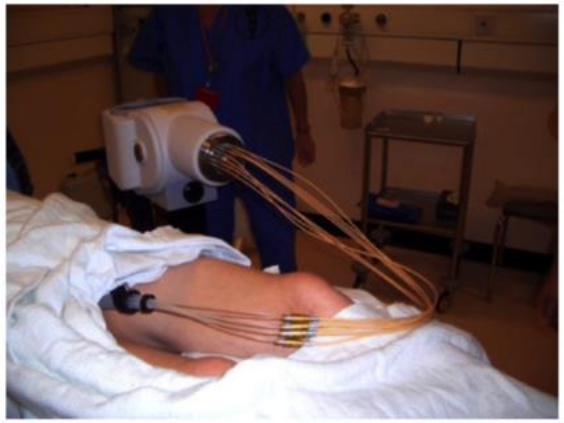


Figure 25.5g. Showing rectal HDR endoluminal brachytherapy applicator in treatment position

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PART II: CLINICAL PRACTICE
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Rectal Cancer
Arthur Sun Myint, Chris D Lee and Jean Pierre Gerard

Fig 25.5a Radiograph of rectal endoluminal applicator wi seeds indicating tumor borders

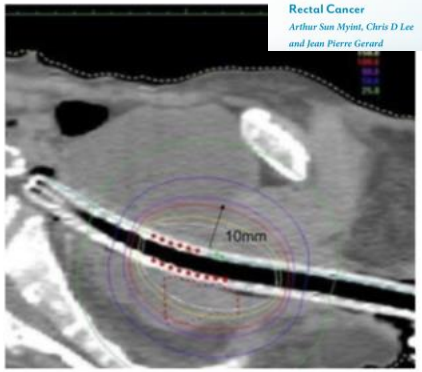


Fig 25.5b Sagittal CT with endoluminal applicator, target volume, dwell positions and isodose lines

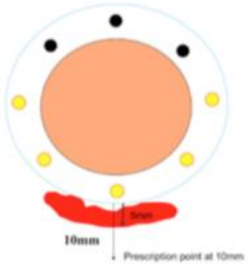


Fig 25.5c Diagram of multi-channel intraluminal rectal brachytherapy with loading positions in posterior part of the applicator for the posterior residual tumour. No loading on the contra lateral side to reduce dose to the non-involved normal rectal mucosa not involved by the tumour. Balloon can also be used to push the normal rectal mucosa away from the loaded positions.

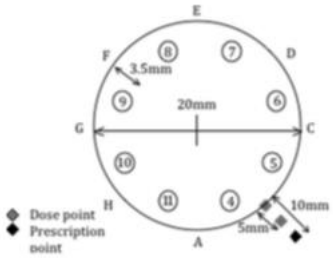
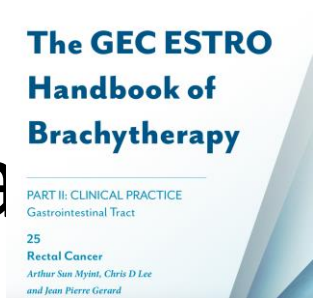


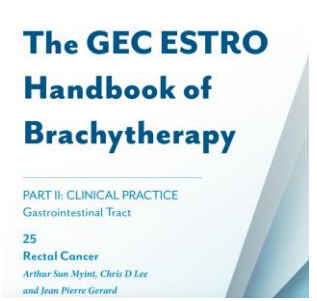
Fig 25.5d Cross section of flexible rectal applicator showing the dimensions, the catheter numbering (4-11) and the calculation points (A-H) midway between each catheter, 10 mm from the applicator surface

HDR Endoluminal Brachythera



- Preop Brachytherapy alone (Monotherapy) is given in daily 4 fractions with 6.5 Gy (4 Consecutive days) Surgery is carried out within 6-8 weeks
- Boost: 7-10 Gy 10mm depth from surface of appicator in 2-3 fractions at weekly interval

Interstitial Brachytherapy



- 4.5Gy in 3 fraction over 24hr
- Delivers 20Gy (EQD2) as boost following EBRT

- Palliative Brachytherapy
- Single line sourse with cylinder (Post operative Vaginal type POVA) or endobronchial tube 10Gy at 10mm from surface of applicator to control bleeding

NICE National Institute for Health and Care Excellence

NICE guidance

Preoperative high dose rate brachytherapy for rectal cancer

Interventional procedures guidance
Published: 26 August 2015
nice.org.uk/guidance/ipg521

1.1 Current evidence on the safety of preoperative high dose rate brachytherapy for rectal cancer and its efficacy in reducing tumour size appears adequate. However, there is no evidence that the procedure provides additional benefit when used as a boost to external beam radiotherapy. Evidence on the clinical efficacy of the procedure if used without external beam radiotherapy is inadequate in quantity. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

Foot Prints

- Dose Escalation is feasible with Brachytherapy following CRT
- pCR rate is increased but doesn't correlate with longterm survival advantage
- Brachytherapy is an option but need more to be emphasized in future studies.

Anal Canal

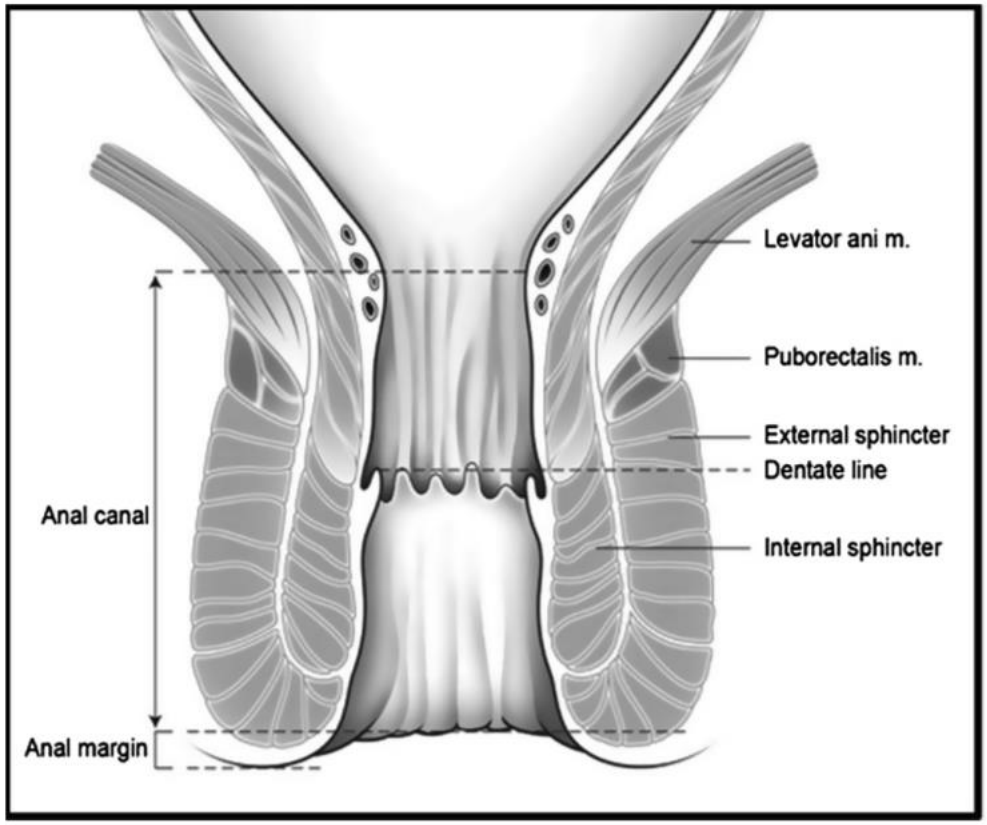


Fig. 1. Anatomy of the anal region.

- Radiochemotherapy is standard of care
- EBRT 45 Gy with MMC and 5Fu most commonly used
- followed by IMRT boost or Brachytherapy boost
- High dose can be delivered with brachytherapy

- Gerard et al. showed the feasibility of using pulsed-dose-rate (PDR) brachytherapy to treat anal carcinoma, and patient tolerance

Falk *et al. Radiation Oncology* 2014, **9**:240
http://www.ro-journal.com/content/9/1/240

RADIATION ONCOLOGY

RESEARCH Open Access

Interstitial high-dose rate brachytherapy as boost for anal canal cancer

Alexander Tuan Falk[1,2], Audrey Claren[1,2], Karen Benezery[1], Eric François[3], Mathieu Gautier[1], Jean-Pierre Gerard[1] and Jean-Michel Hannoun-Levi[1,2*]

Clin Transl Oncol (2011) 13:472-479
DOI 10.1007/s12094-011-0684-z

RESEARCH ARTICLES

Twenty-year experience in the management of squamous cell anal canal carcinoma with interstitial brachytherapy

José Luis López Guerra · Antonio José Lozano · Joan Pera · Cristina Gutiérrez · María Cambray · Ferran Ferrer · Ferran Guedea

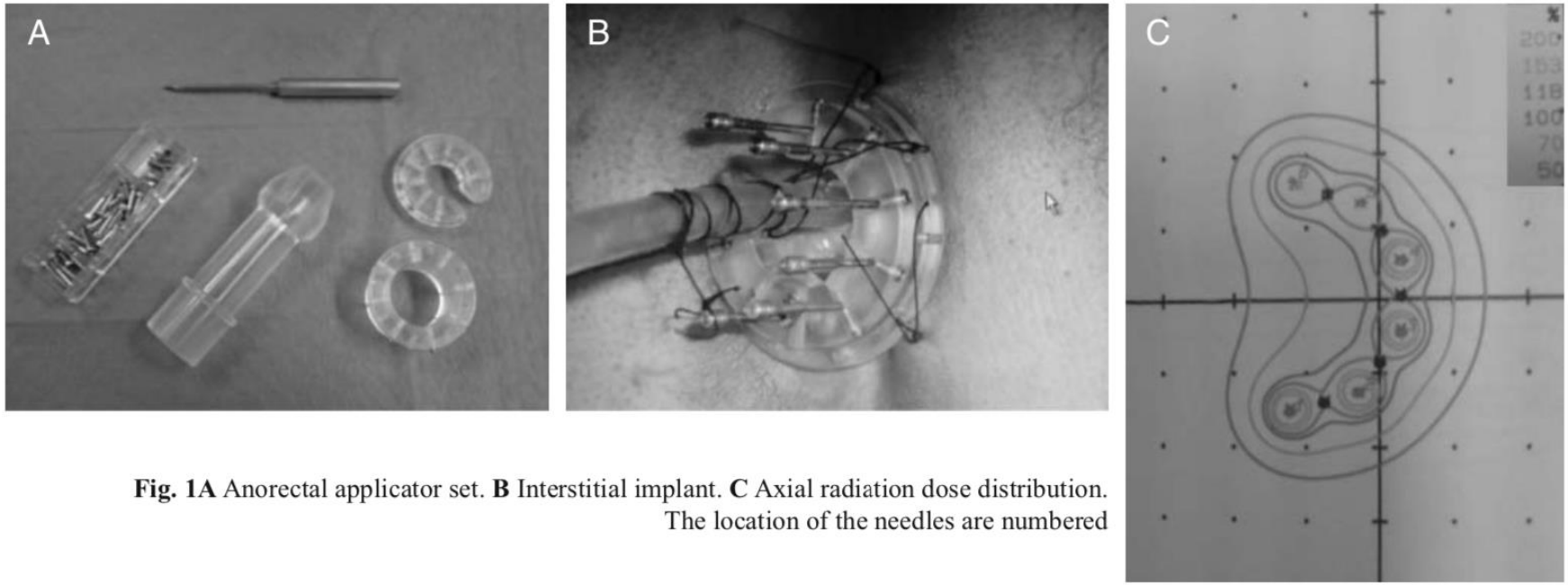


Fig. 1A Anorectal applicator set. **B** Interstitial implant. **C** Axial radiation dose distribution. The location of the needles are numbered

Retrospective study LDR and PDR as boost post EBRT in ACC

Tabla 4 Outcome of the 38 patients

	2-year		5-year	
	%	95% CI	%	95% CI
Overall survival	87	74–98	76	59–93
Disease-free survival	75	60–90	58	39–76
Local control	91	81–100	87	75–99
Distant metastasis-free survival	90	79–100	76	59–93

Received: 28 September 2010 / Accepted: 4 December 2010

Abstract
Objectives The aim of this study was to retrospectively evaluate clinical characteristics, local control, acute and late toxicity, and prognostic factors of patients with anal canal carcinoma treated with brachytherapy.
Methods From 1989 to 2009, 38 patients were treated with iridium 192 low-dose-rate (N=26) or pulsed-dose-rate (N=12) interstitial brachytherapy at a single institution. The median age was 62 years (range, 38–86 years). The TNM classification was as follows: 10 T1, 22 T2, 5 T3 and 1 T4; 32 N0, 3 N1 and 3 N2. Most patients (32/38) received either a first course of radiochemotherapy (N=22) or radiotherapy alone (N=10) consisting of a total delivered dose of 45 Gy to the pelvis (range, 32–50) followed by a boost a median of 18 days later of 15–35 Gy (median 20 Gy) to the anal canal. The remaining 6 cases were treated with brachytherapy alone (dose range, 60–65 Gy).
Results With a median follow-up of 30 months (range, 4–200), 2- and 5-year local control rates were 91% and 87%, respectively. Preservation of the anal sphincter was achieved in 32 patients (84%). Three patients experienced incontinence after brachytherapy. Only 2 patients showed chronic mucositis grade 3/4. Age proved to be a statistically significant prognostic factor for overall survival in the univariate (p=0.033) and multivariate analyses (p=0.018). Concurrent chemotherapy with external beam radiotherapy was a statistically significant prognostic factor for disease-free survival in the univariate and multivariate analyses (p=0.007 and p=0.044, respectively).
Conclusions Interstitial brachytherapy appears to be a effective and well tolerated treatment for anal carcinom offering both high local tumour control and anal sphincte preservation.

Keywords Anal carcinoma · Brachytherapy · Prognostic factor · Toxicity

Introduction

Squamous cell cancer of the anus is an uncommon malig-

Brachytherapy boost after chemoradiation in anal cancer: a systematic review

Rezarta Frakulli, MD[1], Milly Buwenge, MSc[2], Silvia Cammelli, MD[2], Gabriella Macchia, MD[3], Eleon
Alessandra Arcelli, MD[2], Martina Ferioli, MD[2], Lorenzo Fuccio, MD[5], Luca Tagliaferri, MD[6], Andrea
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Aviano, [5]Department of Medical and Surgical Sciences, S. Orsola-Malpighi Hospital, University of Bologna, [6]Departm
Policlinico Universitario "Agostino Gemelli", Catholic University, Rome, Italy

Abstract

Radio-chemotherapy (RCT) is the primary treatment of anal cancer (AC). However, the role
dose of a radiation boost is still unclear. No randomized controlled trials nor systematic reviews
to analyze the efficacy of brachytherapy (BRT) as boost in AC. Therefore, we performed this syst
on PRISMA methodology to establish the role of BRT boost in AC.

A systematic search of the bibliographic databases: PubMed, Scopus, and Cochrane library f
sible date through January 31, 2018 was performed. At least one of the following outcomes: loc
regional control (LRC), overall survival (OS), disease-free survival (DFS), or colostomy-free surv
present for inclusion in this systematic review in patients receiving a BRT boost. Data about to
function were also included.

Ten articles fulfilled the inclusion criteria. All the studies had retrospective study design. All st
to provide a level of evidence graded as 3 according to SIGN classification. Median 5-year LC/LR
were: 78.6% (range, 70.7-92.0%), 76.1% (range, 61.4-86.4%), 75.8% (range, 65.9-85.7%), and 69.4%
tively. The reported toxicities were acceptable.

RCT is the treatment cornerstone in AC. High-level evidences from studies on BRT boost in AC
studies should investigate: efficacy of BRT boost in comparison to no boost and to external beam
can benefit from this treatment intensification, and optimal radiation dose.

J Contemp Brachyther
DOI: https://doi.o

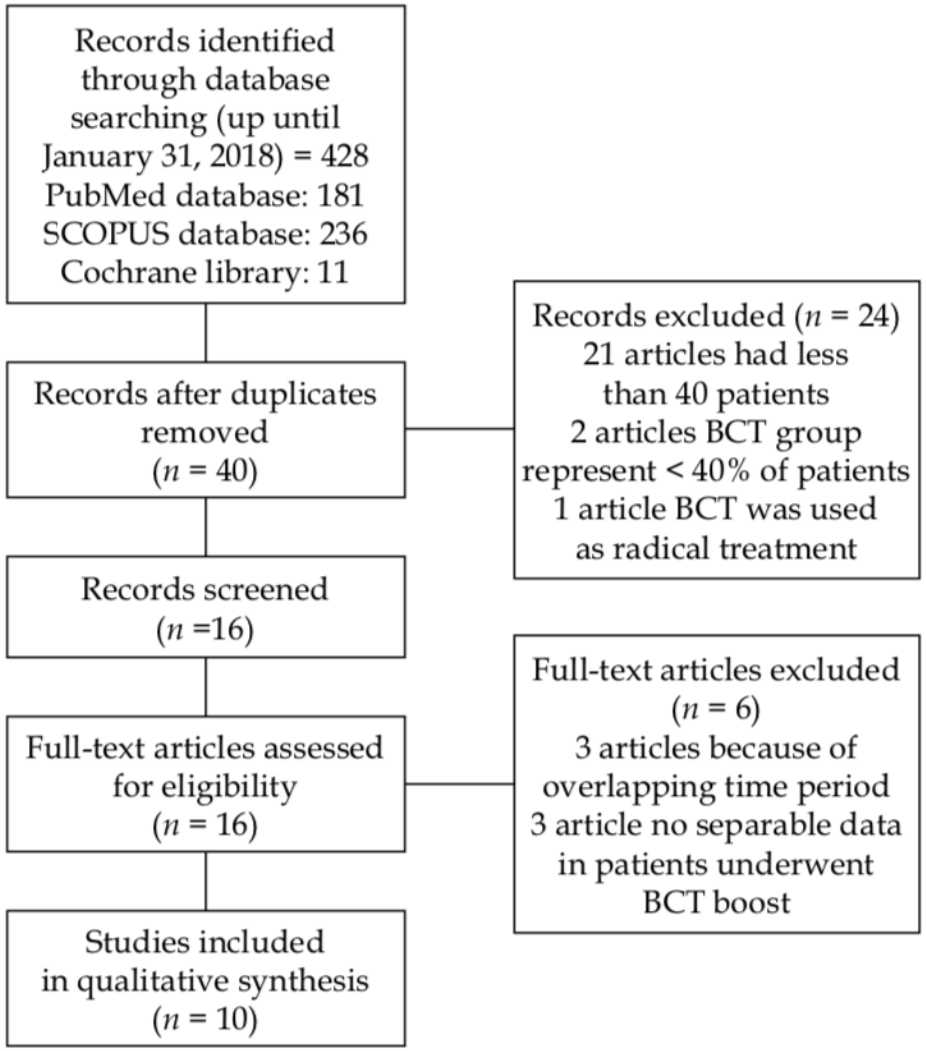

Fig. 1. Flow chart of the systematic search and review process

Table 2. Summary of treatment features

Authors (reference)	EBRT		Chemotherapy		Median gap between EBRT & boost (days)	Brachytherapy boost	
	Median dose (Gy)/ number of fractions, target	EBRT planning technique	% neoadjuvant	% pts concomitant (number of courses)		Dose rate	Total dose median (range) Gy, planning technique
Papillon *et al.* [14]	35/15 AR + PN	2D	–	5-FU + MMC: 40.3	56	LDR	15-20; 2D
[illegible]	[illegible]	2D/3D	–	[illegible]	35	LDR	20-40; 2D
[illegible]	[illegible]	2D	–	5-FU + MMC: 100 (1/2)	37.5	LDR	18 (17-20); 2D
[illegible]	[illegible]	2D	23.9	5-FU + CDDP: 56.3 (1/2)	42-56	LDR	20 (15-25); 2D
[illegible]	[illegible]	3D	–	5-FU (weekly) MMC (1st and 5th):	[illegible]	HDR	NR (8-12)/2 fr; 3D
Bruna *et al.* [19]	45.5*/25 AR + PN + IN (24%)	2D/ 3D	[illegible]	[illegible]P: 6	[illegible]	PDR	17.8 (10-25); 2D
Hannoun-Levi *et al.* [20]	45.1/25 (90%) AR + PN + IN (46%)	3D	[illegible]	[illegible]: 72	[illegible]	LDR	17.4 (10-25); 2D
Lestrade *et al.* [21]	45*/25 AR + PN + IN (19.0%)	2D/3D/IM	[illegible]	[illegible]P: 4 5-FU + MMC: 14 (2: 81.5 and 1: 11.9)	[illegible]	LDR: (72.2%)/ PDR (27.8%)	18 (10-31.7); 2D
Gryc *et al.* [22]	50.4/28 boost (T1): 5.4; boost (≥ T2): 9, AR + PN + IN	2D/3D	–	5 5-FU	[illegible]	PDR	15.5 (8-35.8); 2D, 3D
Cordoba *et al.* [23]	45/NR AR + PN-IN	2D/3D/IMRT	–	5 5-FU + CDDP: 19.5; other: 2.9 (2)	[illegible]	LDR	17.2 (10-30); 2D

AR – anal region, BRT – brachytherapy, CDDP – cisplatin, CT – chemotherapy, D – dimensional, EBRT – external beam radiotherapy, fr (s) – fraction (s), HDR – high-dose-rate, IMRT – intensity-modulated radiotherapy, IN – inguinal nodes, LDR – low-dose-rate, MMC – mitomycin C, PDR – pulsed-dose-rate, PN – pelvic nodes, pts – patients, 5-FU – 5-fluorouracil
** – mean dose, % – percentage of patients*

Gap 27-56Days

35-50 Gy
Mostly 2D /3D planning
New studies IMRT

Chemotherapy
5FU/MMC
5FU /CDDP

LDR : 904 pts in 7 Studies Median prescribed dose 10-40GY

PDR : 3 stiudies 176 pts
Median dose 8-25Gy

Outcome

- Good
  - Locoreginal control
  - Colostomy free survival
  - Disease free survival
  - Overall Survival

Table 3. Summary of 5-year outcomes

Authors (reference)	LC/LRC	CSF	DFS	OS
Papillon *et al.* [14]	NR	61.4	65.9	NR
Sandhu *et al.* [15]	78.0	NR	NR	NR
Weber *et al.* [16]	70.7	NR	NR	NR
	NR	NR	75.8	63.4
	92.0	NR	74.0	82.0
	NR	NR	NR	NR
Hannoun-Levi *et al.* 20]	88.0	71.0	78.0	NR
Lestrade *et al.* [21]	78.6	79.4	80.9	69.4
Gryc *et al.* [22]	75.0	76.1	75.0	65.0
Cordoba *et al.* [23]	89.1	86.4	85.7	73.0

CFS – colostomy-free sur ival, DFS – disease-free survival, LC/LRC – local control/loco regional control, NR – not reported, OS – overall survival

Toxicity

Table 4. Summary of toxicities and sphincter function

Authors (reference)	Toxicity/sphincter function scale	Acute toxicity %	Late toxicity (%)	Colostomy related to toxicity (%)	Sphincter function (%)
Papillon *et al.* [14]	NR/NR	necrotic ulcerations: 6.0; intermittent AR bleeding: 15.0	radionecrosis/ rectal bleeding: 2.7	radionecrosis/ rectal bleeding: 2.7	
Sandhu *et al.* [15]	NR/NR	NR	Moderate fibrosis: 6.5, stricture: 2.6, proctitis: 5.2, ulceration/	ulceration/ necrosis, incontinence: 3.9	totally continent: 71.0
					NR
					NR
Doniec *et al.* [18]	NR/NR	mild proctitis; severe sphincter necrosis: 2.0	mild continence: 4.0; sever incontinence: 4.0	severe incontinence: 4.0, severe sphincter necrosis: 2.0	NR
Bruna *et al.* [19]	LENT-SOMA/NR	NR	G3 toxicity (pain, bleeding, fecal incontinence or necrosis): 14.0, G4 radionecrosis: 2.8	G4 radionecrosis: 2.8	NR
Hannoun-Levi *et al.* [20]	NR/NR	NR	NR	3.5	NR
Lestrade *et al.* [21]	CTCAE v. 4.0/ Womack scale	G3 toxicity: 13.3 (skin: 5.7, AR: 4.3, vulvo-vaginal: 1.4, diarrhea: 1.4, urinary: 0.4); G3 toxicity related to chemotherapy: 4.6	G3-4 AR toxicity: 6.3	G4 AR toxicity: 2.8	totally continent: 82.0, incontinence to gas: 15.0, incontinence to liquid: 3.0
Gryc *et al.* [22]	NR/NR	G3-4 toxicity: diarrhea; proctitis: 42.0; skin: 26.0; urinary: 2.0; hematological: 50.0	G3-4: proctitis: 16.0; diarrhea: 3.0	NR	NR
Cordoba *et al.* [23]	CTCAE v. 4.0/NR	NR	G2-4 toxicity: proctitis: 26.2, anal incontinence: 10.7, intermittent rectal bleeding: 3.8, cystitis: 2.9, rectal ulcerations: 1.9, lymphedema: 0.9, perineal pain: 0.9	severe incontinence: 3.8	NR

AR – anorectal, BRT – brachytherapy, CTCAE – common terminology criteria for adverse event, EBRT – external beam radiotherapy, EORTC – European Organization for Research and Treatment of Cancer, LENT – late effects normal tissue task force, NR – not reported, RTOG – Radiation Therapy Oncology Group, SOMA – subjective, objective, management, analytic

No studies can correlate toxicities to the Brachytherapy
Difficult to relate sphincter function preservation with Brachytherapy

EBRT Vs Brachy

CLINICAL INVESTIGATION **Anus**

HIGH-DOSE SPLIT-COURSE RADIATION THERAPY FOR ANAL CANCER: OUTCOME ANALYSIS REGARDING THE BOOST STRATEGY (CORS-03 STUDY)

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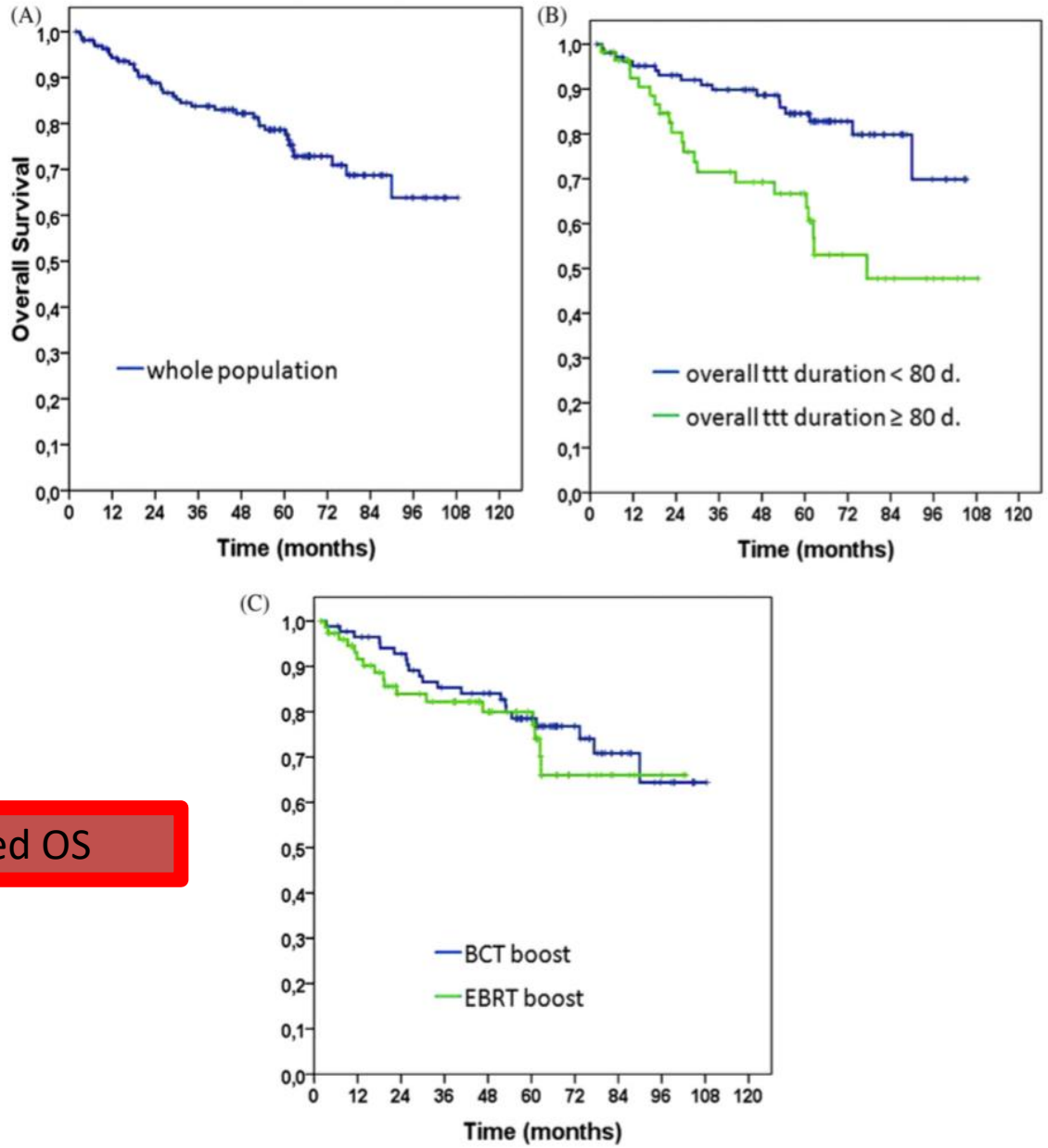
Table 2. Treatment features

Treatment feature	EBRT boost $n = 76$ (%)	BCT boost $n = 86$ (%)	p value	Whole population $n = 162$ (%)
Neoadjuvant chemotherapy				
Yes	7 (9)	10 (12)	0.80	17 (10)
No	69 (91)	76 (88)		145 (90)
Concurrent chemotherapy				
Yes	50 (66)	62 (72)	0.39	112 (69)
No	26 (34)	24 (28)		50 (31)
Field size of EBRT first course				
Small field*	5 (7)	11 (13)	0.06	16 (10)
Pelvic field	41 (54)	31 (36)		72 (44)
Pelvic field + inguinal nodes	30 (39)	44 (51)		74 (46)
Mean dose of EBRT first course (Gy) (minimum–maximum)	45.4 (39.5–50)	44.9 (40–50)	0.10	45.1 (39.5–50)
Mean boost dose (Gy) (minimum–maximum)	18.3 (8–25)	17.4 (10–25)	0.07	17.9 (8–25)
Mean overall treatment time† (days) (minimum–maximum)	82 (45–143)	69 (37–128)	<0.001	75 (37–143)
Mean gap duration‡ (days) (minimum–maximum)	39 (0–106)	30 (2–89)	0.02	36 (0–106)

Abbreviations: EBRT = external beam radiotherapy; BCT = brachytherapy.

Significant reduction in OTT in Brachytherapy Boost



OTT >>> improved OS

Fig. 2. Overall survival for the whole population (A), regarding the overall treatment time < 80 days vs. ≥80 days (B), according to the boost technique: brachytherapy (BCT) vs. external-beam radiotherapy (EBRT) (C).

Table 3. Univariate analysis for 5-year overall survival, cumulated rate of local recurrence, and colostomy-free survival

		5-year OS		5-year CRLR		5-year CFS	
Factors	Categories	%	*p* value	%	*p* value	%	*p* value
Gender	Male	67	0.16	21	0.95	67	0.60
	Female	82		20		82	
Age	< 67 years	82	0.32	27	0.22	70	0.13
	≥ 67 years	75		25		60	
T stage	T1–2	84	0.009	15	0.03	72	0.04
	T3–4	68		36		51	
Nodal status	N0–1	83	<0.001	19	0.07	72	0.02
	N2–3	45		28		46	
Boost technique	BCT	78	0.47	12	0.002	71	0.04
	EBRT	80	–	33		56	
OTT	< 80	84	<0.001	14	0.005	74	0.004
	≥ 80	67		34		50	

Abbreviations: OS = overall free survival; CRLR = cumulated rate of local recurrence; CFS = colostomy-free survival; OTT = overall treatment time.

LR improved with BRT

When OTT increased beyond 80 days no improvement

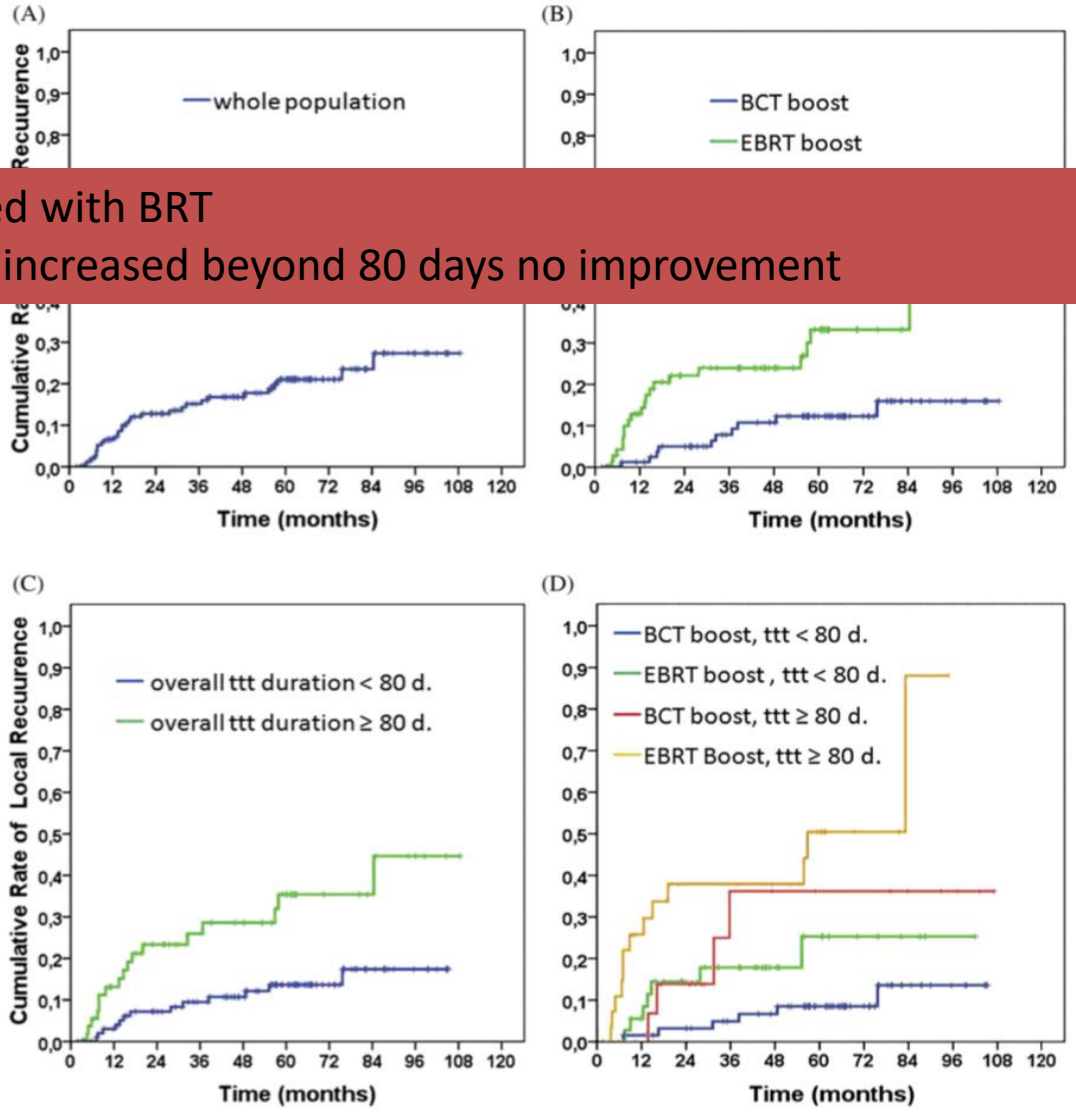


Fig. 3. Cumulative rate of local recurrence for the whole population (A), regarding the boost technique: brachytherapy (BCT) vs. external-beam radiotherapy (EBRT) (B), regarding the overall treatment time (<80 days vs. ≥80 days) (C), and combining boost technique and overall treatment time (D).

Brachytherapy boost after chemoradiation in anal cancer: a systematic review

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Abstract

Radio-chemotherapy (RCT) is the primary treatment of anal cancer (AC). However, the role and the optimal total dose of a radiation boost is still unclear. No randomized controlled trials nor systematic reviews have been performed to analyze the efficacy of brachytherapy (BRT) as boost in AC. Therefore, we performed this systematic review based on PRISMA methodology to establish the role of BRT boost in AC.

A systematic search of the bibliographic databases: PubMed, Scopus, and Cochrane library from the earliest possible date through January 31, 2018 was performed. At least one of the following outcomes: local control (LC), loco-regional control (LRC), overall survival (OS), disease-free survival (DFS), or colostomy-free survival (CFS) had to be present for inclusion in this systematic review in patients receiving a BRT boost. Data about toxicity and sphincter function were also included.

Ten articles fulfilled the inclusion criteria. All the studies had retrospective study design. All studies were classified to provide a level of evidence graded as 3 according to SIGN classification. Median 5-year LC/LRC, CFS, DFS, and OS were: 78.6% (range, 70.7-92.0%), 76.1% (range, 61.4-86.4%), 75.8% (range, 65.9-85.7%), and 69.4% (63.4-82.0%), respectively. The reported toxicities were acceptable.

RCT is the treatment cornerstone in AC. High-level evidences from studies on BRT boost in AC are lacking. Further studies should investigate: efficacy of BRT boost in comparison to no boost and to external beam boost, patients who can benefit from this treatment intensification, and optimal radiation dose.

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Original article

Anal cancer: ESMO–ESSO–ESTRO clinical practice guidelines for diagnosis, treatment and follow-up ☆

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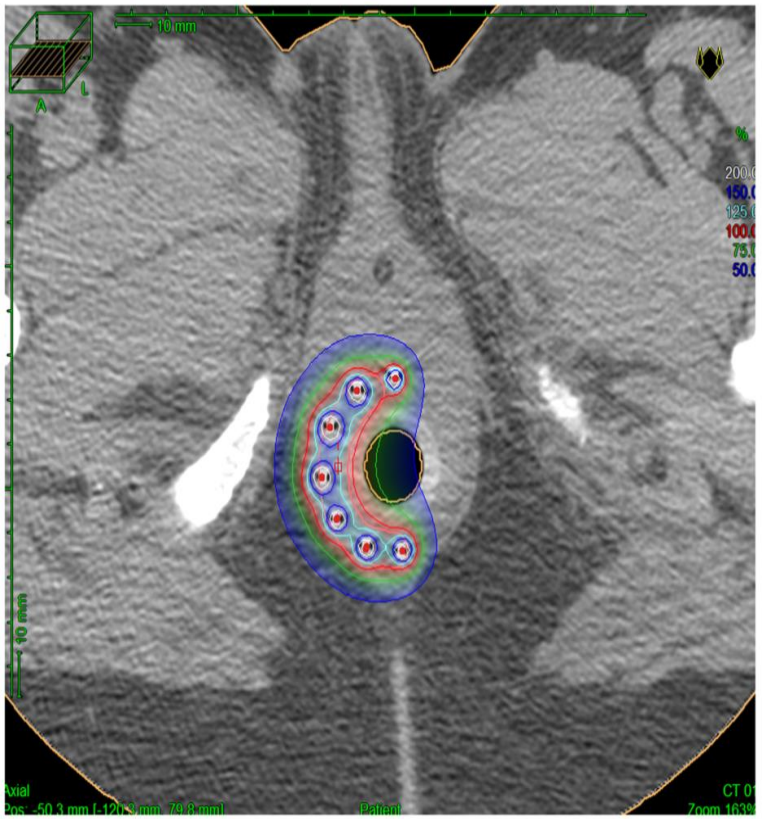
- Limited data with HDR
- Curative Brachytherapy (single Modality) is not recommended
- Boost can be considered
- Risk of late necrosis and radiation proctitis

Foot Notes Anal canal Brachytherapy

- Lesion should be less than half of circumference of the anal canal
- 5mm thickness
- 5cm in craniocaudal length for sphincer preservation
- Single or double plane of implant
- Catheters are inserted through perianal area in central plane 0.5cm away from anal or rectal mucosa.
- Peripheral planes are kept at 1-1.5cm
- EBRT 45 Gy followed by 15-20 Gy ^{192}I brachytherapy



istribution analysis on the post-implant CT-scan.

- Brachytherapy is an option in early rectal cancer but need expertise and more data.

Thank you


Apollo Cancer Hospitals
Suman Das