DETERMINING THE OPTIMAL RT REGIMEN IN THE MANAGEMENT OF RECTAL CANCER

Radiation Oncology

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Objectives

1. Evidence: Short course vs Long course RT
2. The Optimal interval of RT to Surgery
3. Role of RT after Local Excision of Rectal Cancer

I: SHORT VS LONG RT

Evidence and BCCA guidelines

I: Short vs Long RT

"Short course" pre-op RT

- **25 Gy/5** fractions over 5 days, followed by surgery **"within 1 week"**

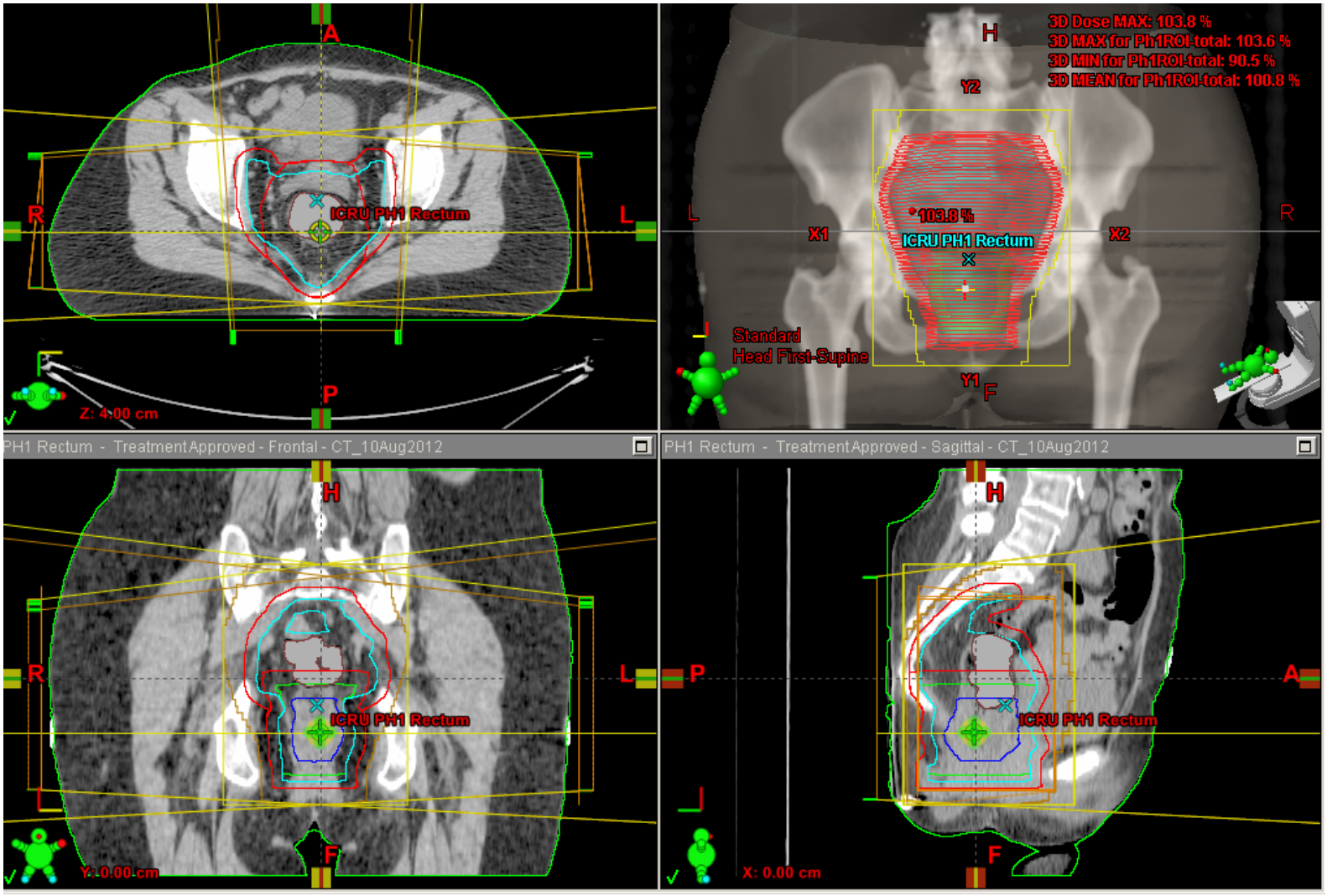
Biologically equivalent doses to fractionation given with 2 Gy per fraction in three most commonly use schedules of preoperative radiotherapy for rectal cancer

	Biologically equivalent doses to fractionation given with 2 Gy per fraction (Gy)[a]		
	25 Gy in five fractions of 5 Gy	45 Gy in 25 fractions of 1.8 Gy	50.4 Gy in 28 fractions of 1.8 Gy
Tumour control, $\alpha/\beta = 5$ Gy [23], time correction [8][b]	35.7	28.1	30.4
Late damage, $\alpha/\beta = 3$ Gy	40.0	43.2	48.4

"Long course" pre-op RT

- 45-54 Gy/20-30 fractions over 4-5 weeks, followed by planned **break of 6-10 weeks before resection**
- Can be given with concurrent Chemotherapy

RT treatment volume:



BCCA Guidelines 2012

Stage1 T1-T2N0MO

Transabdominal resection (AR, LAR, APR): no adjuvant RT

Stage 2 T3N0: Referral to Radonc/ MedOnc: preop RT +- chemo

- Upper 2/3: non-fixed = 25Gy/5# and Sx **within 10 days from D1RT**

(upper 1/3 with "predicted clear margins" may not benefit from RT)

- *FIXED tumors*
- CLOSE MARGIN mesorectum } 45Gy/25+5.4Gy/3 + chemo + **Sx (6-10wks)**
- LOWER 1/3

Stage 3 T4 or any N1+M0: Referral to Radonc/ Medonc: preop RT+- chemo

- Upper 2/3: non-fixed = 25Gy/5# and Sx within **10 days from D1RT or CHRT**
- FIXED
- CLOSE MARGIN mesorectum } 45Gy/25+5.4Gy/3 + chemo + **Sx (6-10wks)**

Neo- adjuvant short RT vs Sx

Study	Eligibility	Stages-Sx	Arms	Results
Swedish NEJM 1997 Update 2005 FU = 13 yrs	Resectable 0-16 cm N = 1168	I-35% II-34% III-31%	5Gy x 5 +sx vs Sx	**LRR 9% vs 26%** (p 0.001) (HR 0.4) **CSS 72% vs 62%** (p 0.03) **OS 38% vs 30%** (p0 0.008)
Dutch Ann Sx 2007 TME (no chemo) FU = 6 yrs	Mobile 0-16 cm N = 1861	I-33% II-30% III-36%	5 Gy x 5 +TME Vs TME **BUT** R1CRM postopRT (50.4/ 30 given 52 / 96 pts R1	**LRR = 5.6 vs 10.9%** (HR0.49) **CSS 75.4% VS 72.4% (NS)** **OS 64.2% VS 63.5% (NS)** Mets 25.8% VS 28.3%

Neo- adjuvant short RT vs Sx

Dutch Trial Kusters, EJSO 2010

- Multivariate Cox regression **LRR: randomization arm, tumor location, TNM stage, and CRM**
- **CRM +ve 16% both arms;** 89% in T3/T4; CRM + 30% APR vs 11% LAR

DISTANCE FROM AV	TME	LRR RT+SX	LRR SX	P VALUE
0-5CM	65%	**10.7%**	**12%**	**0.122**
5-10CM	85%	3.7%	13.7%	0.001
10-15 CM	100%	**3.7%**	**6.2%**	**0.578**

CRM	5 yr LRR Sx	LRR RT+Sx	P value
+ve	**23.5**	**19.7**	**0.393**
-ve	8,7	3.4	< 0.001

In RT Arm: 56% of all LRR occurred in T < 5cm

Neo- adjuvant short RT vs Sx

Dutch Trial; Peeter Ann Sx 2007

- CRM +ve: the most important predictors for LRR

"Discrepancies between colonoscopy measurements, CT and MRI and Intraoperative findings …indicate the difficulty of determining exact tumor position and the a priori chance of local failure.

"These subgroup analyses provide limited support to withhold radiotherapy from patients with proximal rectal cancer or to apply a prolonged radiotherapy schedule for patients with distal rectal cancer"

Short course Pre-op RT

- Reduces the LRR by approximately 50%
- With TME: no difference DFS, OS
- Hypothessis:
  - most useful in mid-rectal tumors (imaging accuracy)
  - Enough in distal rectal tumors?
  - Enough with close surgical margins?

Neo- adjuvant Long course RT+- Ch

Study	Eligibility	Arms	Results
EORTC 22921 Bosset NEJM 2006 JCO 2007 FU 5.4 yrs TME advocated 1999 onward	N = 1011 Ressectable T3/T4 0-15 cm	I RT (45Gy/25) II CRT (+5FU/LVwk1/5) II: RT alone III: RT+adj chemo IV: CRT+adj chem Poor compliance post op CT (42%)	**ChT: ↓LF, ↑ pCR,** **No chg DFS,OS** **Strongest predictor OS = CRM+** **LRR** **17% RT vs 8%-10% ChRT p 0.002** **DFS** **RT 54% vs 56% chemoRT NS** **ChemoRT: APR 48% (NS)** ChemoRT +CRM 5.4 vs 4.9% **(NS)** In ypT0-2: greater effect of adjuvant ChRT on DFS and OS

Neo- adjuvant Long course RT+- Ch

Study	Eligibility	Arms	Results
FFCD 9203 Gerard et a; JCO 2006 FU 6.75 yrs (81mths)	N = 762 Ressectable T3/T4 Accessible DRE (mid-distal)	RT (45Gy/25#) vs ChRT (5FU/LV wk1+5) All had adjt RT (4 x q4wks 5FU/LV) Sx 3-10 wks post RT	**pCR 11.4% ChRT *v* 3.6% RT p 0.001** **LRR 8.1% ChRT *v* 16.5% RT p< 0.05** PFS: 59.4% ChRT vs 55.5% RT **NS** 5-year OS rate 67.9% *v* 67.4% **NS** **Grd3/4 acute 14.6 vs 2.7 p < 0.05** No diff APR No diff in distant mets

- ChRT greater pCR and improved LRR
- No difference in APR rates, metastasis, PFS or OS
- Increased acute toxicity with ChRT

Overall Addition of Chemo (5FU/LV bolus) to Long Course RT Ressectable Ca

- Chemotherapy effect: observed if concurrent or adjuvant
- **Increases Downstaging** effect: T stage, N stage, PNI, LVI
- **Increases Local Control**

- May not affect frequency of CRM + (not all TME)
- No effect on APR rates
- Did not affect metastatic rates, DFS, OS (pooled analysis 2 trials: EurJCa2012)

- Addition of Chemotherapy increases acute toxicity not long term

Short vs Long-Course RT

Study	Eligibility	pCR/Sx and Toxicity	Results
Polish Bujko BJS 2006 Median FU 4yrs Endpoint: sphincter preservation If mobile: ERUS or MRI or CT exclude T1/T2	N = 312 Ressectable T3/T4 Distal DRE Preop 20Gy/5 + Sx(7d) vs ChRT 50.4Gy/28# (bolus5Fu/LV wk1+5) + Sx 4-6wks Adjt (5Fu/LV) - 6 mths - 4 mths	Compliance 97·9 SRTvs 69.2%ChRT pCR 0.7 vs 16.1(0.001) **CRM+ 12·9 vs 4.4%** **(p = 0.017)** **Acute Toxicity** **Grd III-IV 3.2% vs 18.2** **(<0.001)** Late Toxicity 28·3%vs27% *(*0·810)	**No stat diff LRR, DFS,** **OS or APR rates** LRR SRT 9vs CRT14%NS APR: 38.8 vs 42 NS Dist mets:23 vs 26% NS DFS 58·4 *vs* 55·6 % NS 4yrOS SRT 67v 66%2NS

Cochrane Meta-Analysis 2009
Preoperative ChRT vs RT alone Stg II/III ressectable rectal cancer

- 4 RCT (EORTC Bosset, FFCD 9203 Gerard, Polish Bujko, **Boulis-Wassif 1984)**

No difference in DFS or OS

Chemotherapy improved

- **pCr**, ChRT 11.8% vs 3.5% (OR 3.65, p < 0.001)
- **LC** 16.5 vs 9.4%; (OR 0.53, p < 0.001)

No difference in Sphincter preservation

- ChRT 49.6% vs RT 47.6% (P = 0.29)

No diff Distant mets = 30% all arms; no systemic effect with current RT regimen

Morbidity:

- No difference peri- op risk 30 day mortality, postoperative morbidity, or anastomotic leak
- Higher acute toxicity: Grade III or IV ChRT 14.9% vs 5.1% (OR 4.1, P = 0.002)

TROG 2012: Short vs Long RT

Study	Eligibility	pCR & Toxicity	Results
TROG **Ngan** JCO Sep 24, 2012 Median FU 5.9 yrs ALL had MRI or EUS Minimum FU 3 yrs **Endpoint: 3 yr LRR**	N = 326 T3N0-N2 0-12cm Preop 20Gy/5 + Sx(3-7d) vs ChRT 50.4Gy/28# (inf5Fu/LVwk1+5) + Sx 4-6wks Adjt (5FU/FA) 6 courses (85%) & 4 (86%)courses	**SIGN DWNSTG** **28 vs 45% (0.002)** pCR 1 vs 15% **Mrg+ve 5 vs 4% (NS)** Complications (w/i 3 mths) 53 vs 50% NS Late II/IV toxicity: 5.8 vs 8.2% NS	**No stat diff LRR, DFS, OS or APR rates** **3yr CumLRR SRT 7.5%** **Vs ChRT 4.4% NS** <5cm: LRR 6/48 vs 1/31NS <5cm; **APR 79 vs 77% NS** **5 yr dist 27 vs 30% NS** (p 0.89) **5 yr OS 74 vs 70% NS**

Conclusions from TROG 2012 Short vs Long RT

- **Small difference in LRR (3.1% at 3 yrs) in favour of ChRT BUT** not statistically significant (trial required 8%)
- **Distal Cancer (<5cm**) despite a large observed difference LRR (favour LChRT); **no statistical difference in LRR according to treatment arm**
- **Significant predictors of LRR: Resection Margin +ve; Lymph Node +; CEA level at diagnosis**
- **Greater pathologic downstaging with ChRT;** but no effect on APR rate for distal tumors; no effect on margin status
- No significant difference in late toxicity at 3 yrs (grd ¾); no reports of severe neuropathy

II: DEFINING THE OPTIMAL INTERVAL FROM RT TO SX

Short Course RT:

BCCA : "Surgery **within 10 days from D1RT**

Long Course ChemoRT

BCCA: " Surgery **within 6-10 wks post complete RT**

Interval short course RT to Sx
Stockholm III trial

Stockholm III	Arms and Characteristics	Toxicity	Subgroup analysis
Petterson, BJS; 2010 Interim analysis: -SE's, compliance -CT or MRI	N = 303 Locally ressectable; 0-15cm All Sx = TME RCT: 1. SRT(25/5); 1 wk Sx (118) 2. SRTds; 4-8 wks Sx (120) 3. LRTds(50/25);4-8wkSx (65)	**No diff acute tox** SRT = 0 SRTds 4.2% LRTds 5% No diff pst comp 46.6 vs 40 vs 32% (0.164)	**SRT (118)post op complications:** p= 0.036 < 10D (29/75) 39% **11-17d (24/37) 65%** >17d (2/6) 33% **APR 30 vs 33.3 vs 20% (p = 0.07)**

- Post op complications NOT increased in SRT vs LRT with delayed Sx

- SRT immediate Sx: inc post op complications: > 10d from start RT
  (= wait > 3-5d to Sx) = Sx < 10 DAYS FROM START RT

Interval short course RT to Sx

Retrospective Series Stockholm

Study	Patients and	Ouctomes	Path response
Petterson; BJSx 2012 Retrospect Jan 02-08 MRI pre & post	N = 112 Ressectable + Unressectable Stg I 8% II 35%; III 45.5 IV 7% 25Gy/5# CRM +ve of <=1mm Median time RT to Sx 7 wks (4-17wks)	Post op compl 38.4% (= Stock III) Severe RT toxicity 5.4%	95% pre MRI MRI vs PATH T2 11% vs 22% T3 42.2% vs 56% T4 45.9% vs 14.7% N0 45.8% vs 63.6% N1 26.2% vs 16.8% N2 28% vs 19.6 **CRM+ 50 vs 14.3%**

- **Signif diff in preMRI T stg vs pT < 0.001 and N stg 0.014 and margin < 0.001**
- Acceptable toxicity = agrees with Stockholm III

Longer interval SRT

- Stockholm III will offer RCT evidence of effectiveness and safety of prolongued interval to SRT
- Prolongued Interval with SRT: increase path. downstaging
- Interval may predict complications: highest if 10-17 days from D1RT; > 17 days did not appear to increase morbidity
- ? Role of chemotherapy if prolong the interval with SRT

Interval Long course RT to Sx: STANDARD

Lyon Trial (BJS, 2003)

RCT RT followed by variable interval to Surgery (2 wks vs 6-8 wks)

N= 201

FU 6.3 yrs

- 1991-95: T2-T3N+ accessible by DRE
- RCT: 39Gy/13# Short Interval (2wks Sx) vs Long Interval (6-8 wks Sx)
- **Long Interval 6-8 wks: ↑ clinical response, ↑ path dwnstg**
- No diff morbidity, APR 68 vs 76%, LRR, (13 vs 10%) or survival (66 vs 69%)
- **STANDARD INTERVAL following ChRT = 6-8 wks**

Interval Long course RT to Sx: +ve studies

Study	Characteristics	Outcome
De Campos-Lobato; JGISx 2011 FU 4.21 yrs Retrosp Rev All MRI or ERUS	N = 177 II/III Neo-adj ChRT (50.4Gy/28#) +5FU **< 8 wks (83) vs** **> 8 wks (94)**	**Increased pCR and LRR; No dif DFS or OS** **pCR 16.5% vs 30.8% (p = 0.03)** No diff morbidity or complications; APR same **3yr LRR 10.5 % vs 1.2% (p = 0.04)** 3 yr DFS 75.3 vs 84.7 (0.26) NS 3 yr OS 85.5 88.2 (0.74) NS
WoolthuisAnn Sx Onc 2012 FU 4.9yrs Prosp database Retrospective Review	N = 356 Stg II/III Neo-adjt ChRT (45Gy/25#) +inf 5FU **SI < /= 7 wks (201)vs** **LI > 7 wks (155)**	**Increased pCR and LRR and CSS** **pCR SI 16% vs LI 28% (p = 0.0006)** No diff in morbidity or APR rates **5 yr FFRR: 73% vs 83% (p = 0.026)** **5 yr CSS SI 83% vs LI 91% (p = 0.046)**

Interval Long course RT to Sx: -ve studies

Study	Characteristics	Outcomes
Lim Ann Sx 2008 2002-2006 FU 2.58 yrs All MRI+EUS Most TME (2% LE)	N = 397 0-9cm T3-T4orN+ ChRT: 50.4Gy+5.4bst Ch: 1)bolus5FU/LV (185) 2) Cape (140) 2) IC (72) GrpA: 4-6 wk(217) GrpB 6-8 wk (180)	**No diff in dwnstg, CR, APR, LRR, or morbidity** T-level dwnstg: A: 47.5% vs. B: 44.4%, *NS* pCR: A: 13.8% vs. B: 15.0%, *NS* 2 yr LRFS 95% vs 92% (0.116) Morbidiity 17 vs 15% (0.501)
Moore DisCRect 2004 All EUS	N = 155 T3TrN+ ChRT 50.4Gy+5FU Grp A < 6.3 wks (82) Grp B > 6.3 wks (73)	**No diff pCR, dwnstg, trend inc complications** pCR 12% vs 19% (P = 0.27) Dowstaging: 6 vs 15% (P = 0.11) **More anastomotic compl (0 vs 7%) (0.05)**

Longer Interval with ChRT > 8wks

- No RCT
- Hypothesis:
  - May increase pathologic downstaging
  - May improve LRR, no effect on DFS or OS
  - May not affect morbidity; possibility > 10 wks increases post- RT fibrosis

III: ROLE OF RT FOLLOWING LOCAL EXCISION OF EARLY STAGE RECTAL CANCER

Evidence and BCCA recommendations

BCCA Policy

"Local, TAE of rectal cancer (including T1 lesions) has increased risk of recurrence compared to major resection"

"LE may be considered pts medical comorbidities or where pts fully informed of negative oncologic aspects of LE"

BCCA "Low Risk T1N0 lesions":

- Grd 1-2
- No LVI or perineural invasion
- Negative margins (at least 3 mm)
- < 3 cm size
- Mobile (non- fixed)
- Node negative on pre-op imaging

Rectal Cancer Staging

CT Chest (or CXR) CT A/P

Measurement: Rigid sig> flex sig/colon> EUS> DRE> MRI or CT

Local stage: ERUS or MRI (sensitivity/ specificity %)

Modality	T stg accuracy	N stg accuracy
CT	50-74%	50-70%
MRI	66-91%	65-88%
EUS	80-95%	70-75%

CRM +VE PREDICTION: "threatened CRM" = within 2 mm~ MRI 90-95% accuracy

- 149 pts: (49% EUS; 41% EUS + MRI; MRI 10%): if "free imaging" = 92% clear path
- If not assessed = 33% involved or threatened 44% CRM +ve

Stage 1

T1No- occult nodes 10-13%

T2N0- occult 17-22%

Guillem, Clin CloCa 2005; Puli, AnnSOnc 2009; You, SemRadonc 2011

T1N0 Rectal Cancer: Local excision alone

- Surgical technique: Transanal local excision (TAE) vs Transanal Endoscopic Microsurgery (TAEMS)
- T1N0: no Level I prospective randomized trials of local excision (LE) vs Standard Ressection (SR = AR, LAR, APR) or T1+-RT
- T1No- occult nodes 10-13% **High Risk: LVSI +ve** 23% ; middle 1/3 11% vs **distal 1/3 30%**; Sm 1 8% vs **Sm3 23% = depth of m. inv** (Nascimbeni)
- Salvage Rates 20-60%

Author, year	Pts SR ;TAE	FU yrs	5 yr LRR (%) SR vs TAE	5 yr OS (%) SR vs TAE
Nascimbeni, 2004	74; 70	8.1	**2.8 vs 6.6***	**90 vs 72* (OS)**
Bentrem, 2005	168; 152	4.3	**3 vs 15 ***	93 vs 89 (OS)
Nash, 2009	145; 137	5.6	**2.7 vs 13.2 ***	**96 vs 87 (DSS)***
You, Nat Ca Database, 2007	493; 601	6.3	**6.9 vs 12.5***	82 vs 77 (OS)

You, SemRadonc 2011

T1N0 Rectal Cancer: High risk Features +- RT

Trends T1N0 nodal risk:

- **High : Grade 3; +ve LVI; =PNI; +ve margins; >4 cm = ↑ LRR, ↓ DFS, ↓ OS**
- Technical: < 40% circumference, < 10 cm from AV

Addition of RT to LE in T1N0

- LIMITED: Retrospective bias, variable RT volume, RT dose, selection criteria
- **Trend RT in high risk T1; trend RT ↑ LC and ↑ DFS ~ low risk T1 LE alone**
- Late LRR in RT, no plateau in DFS, LRR associated mets, poor salvage rates

Meta-analysis of Addition of RT *(Sengupta, Dis ColRect, 2001)*

- LE alone (22 studies); LE +AdjtRT or Neo-adjt (19) (EUS 9/41)

Stage	LE alone (% LRR)	LE + neo/adj RT+- Ch (%LRR)
T1	9.7 (0-24)	9.5 (0-50)
T2	25 (0-67)	13.6 (0-24)
T3	38 (0-100)	13.8 (0-50)

Factors other than T-stage higher LRR after LE: Grade, LVSI, +ve margins

Local Excision +- Adjuvant ChRT

RTOG 8902	Pts	FU	Outcome
IJROBP 2000 Procto; CT (<2cm LN) 1989-1992	N = 65 < 4cm; < 40% circumf **1)Obs; grd1/2/M-ve** (14 = T1) **2)RT + 5FU: M –ve** (18) (T1 7/T2 8/T3 3) **3)HDRT +5FU: M <3mm** (33) (T1 6/T2 17/T3 10)	6.1 yrs	Overall LRR 16% % (¾ LRR) 1) LRR 0.07% 2) LRR 11% 3) LRR 15% 5 yr OS 1) 90% 2)= 3) 75%

Failure	Arm 1	Arm 2	Arm 3	Total
LRR only	1	1	1	3
Distant only	1	0	2	3
Both	0	1	4	5

- Freedom from pelvic relapse: overall 88% and 86% in ChemRT
- LRR correlated with
  - T category T1 1/27 (4%); T2 4/25 (16%); T3 3/ 13 (23%)
  - Circumference: < 20% 2/31 (6%) vs 21-40% (6/34 (18%)

Stage 1: T1T2N0 +- Adjt ChRT

Level IIa: Prospective Non-randomized single- arm Clinical Trial

CALGB 8984	Pts	FU and Pt factors	Outcome
Greenberg DisCRect 2008 T1 and T2+adjt Proctoscope; CT 1990-1995	T1= 59; M-ve 10 cm prox dentate, < 4 cm < 40% circumf -proctoscope, CT OBSERVATION	7.1 yrs No grd 3 2% Lymp; 5% vasc + Mean diam 2.2cm	**LRR = 8%** Mets = 5% 5 yr DFS = 91% **10 yr DFS = 75%** **10 yr OS = 84%**
	T2 = 51 (2-6wks) Adjt ChRT RT 54Gy + 5FU(IV D1-3, 29-3)	12% grd3; 22%Lymp+ 22%V asc +	**LRR = 18%** Mets = 12% **10 yr DFS 64%** **10 yr OS 66%**

- T stage signif OS (p = 0.04) and approached DFS (p = 0.07)
- Nat Cancer Database Stage 1 TME: 5 yr DFS 93.4% (91-95.8) ~ comparable
- Salvage rates not clearly stated: Commentary: 8/19 ~ 42% LRR salvageable

T2N0: Neo-adjuvant ChRT + LE

RCT: ChRT followed by Transanal End. MicroSx (TEM) vs Lap ressection (LR)

Lezoche et al. Italian	Pts	Recurrences	Survival
Surg Endox 2008 Median FU 7 yrs TEM vs LR	N = 70 T2N0G1-2 6 cm from AV < 3 cm All ChRT (50.4Gy/28 + cont 5FU 200mg/m2/ day)	**LRR:** **TEM 2 (5.7%) vs** **LR 1 (2.8%)** (All poor path resp) **Distant** **TEM= 2.8% = LR**	**DFS =94% equivalent** **"After ChRT; same long term probability of local control and survival in TEM vs LR"**

- Downstg: p T0 32 and 29%; pT1 17 and 20%; PT2 51% both
- TEM less operative time, blood loss, and hospital stay vs LR (p= 0.001)

" Reports shown T2 17% LRR overall after local excision alone"

THANK YOU

Questions?