Supplementary Figure 1

A) German Rectal Cancer Trial

- 827 patients <75 years of age with T3, T4 or node-positive rectal cancers
- Preoperative ChemoRT 50.4 Gy with concurrent continuous infusion 5-FU during first and fifth weeks of RT
- Postoperative ChemoRT 30.4 Gy with 5.4 Gy boost with continuous concurrent 5-FU
- TME = total mesorectal excision, 5-FU = 5-fluorouracil

Results:
- 10 year local recurrence: 7% vs 10% favoring preoperative ChemoRT (p=0.048)
- Likelihood of Sphincter Preservation: 39% vs 19% favoring preoperative ChemoRT (p=0.004)
- Acute Grade 3-4 Toxicity: 27% vs 40% favoring preoperative ChemoRT (p=0.001)
- Late Grade 3-4 Toxicity: 10% vs 24% favoring preoperative ChemoRT (p=0.01)
Supplementary Figure 2

B) NSABP R-03

267 patients with clinical T3, T4, or node positive disease

Preoperative ChemorT with 5-FU and Leucovorin and 45 Gy in 25 fractions with 5.4 Gy boost

Within 8 weeks

Surgery

Within 4 weeks

Postoperative ChemorT with 5-FU and Leucovorin and 45 Gy in 25 fractions with 5.4 Gy boost

Surgery

Results

5-year DFS significantly improved in preoperative group (54.7% vs 53.4%, p=0.01)

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CS trended towards significance favoring preoperative ChemorT (74.5% vs 65.6%, p=0.06)

5-FU = 5-fluorouracil
Supplementary Figure 3

C) MRC CR07 and NCIC-CTG C016

1,350 patients with operable rectal cancer

Short-Course preoperative RT to a dose of 22.5 Gy in 5 fractions

Within 7 days of last RT fraction

Surgery

Selective Postoperative Chemotherapy to a dose of 45 Gy with concurrent 5-FU only in patients with involvement of circumferential resection margin

Medial follow-up 4 years

Results

Three Year LR: 4.4% vs. 16.6% favoring preoperative treatment (p<0.0001)

Three Year DFS: 77.5% vs. 71.5% favoring preoperative treatment (p=0.013)

5-FU = 5-Fluorouracil
A) Swedish Rectal Cancer Trial

1168 rectal cancer patients <80 years of age with resectable disease

S08 patients ultimately deemed to have curative treatment

RT to a dose of 5 x 5 Gy

Within 1 week

Surgery

Surgery

Results

Median follow up of 13 years

Overall Survival improved favoring RT group (38% vs 30%), p<0.001

Cancer-Specific Survival improved favoring RT group (72% vs 62%), p<0.001

Decreasing Local Recurrence Rate favoring RT group (9% vs 24%), p<0.01

*Not all patients had a TME
B) Dutch CKVO 95-04

- 1861 patients with resectable rectal cancer
- 1805 were eligible to participate
- Radiation to a dose of 5 Gy x 5
- Total Mesorectal Excision
- Results
  - Decrease in local recurrence favoring RT group (5% vs 11%), p<0.0001
  - No difference in Overall Survival (48% vs 49%), p=0.66
  - Stage III patients with negative circumferential margins had overall survival benefit favoring RT group (50% vs 49%), p=0.012

Medium follow up of 24.9 months
Supplementary Figure 6

A) Bujko et al 2006

312 patients with clinical T3 rectal cancers

Radiation to a dose of 5 Gy x 5

Within 1 week

Total Mesorectal Excision

ChemoRT to a dose of 50.4 Gy with bolus 5-FU and leucovorin

Within 4-6 weeks

Total Mesorectal Excision

Median follow up of 48 months

Results

No significant differences in:
- Crude Local Recurrence (9% vs 14.2%, p=0.70)
- Disease free survival (58.4% vs 55.6%, p=0.820)
- Overall Survival (67.2% vs 66%, p=0.364)
- Late Toxicity (30.1% vs 7.2%, p=0.062)

Early Radiation Toxicity significantly increased in the ChemoRT group (18.2% vs 3.2%, p<0.001)

S-FU = 5-fluorouracil
Supplementary Figure 7

**B) TROG Intergroup Trial**

- 128 patients with T3N0-2 rectal cancers
- Radiation to a dose of 25 Gy in 5 fractions
- Chemotherapy to a dose of 50.4 Gy in 28 fractions with continuous infusion 5-FU
- Surgery within 3-7 days
- 4-6 weeks after surgery
- Six cycles of 5-FU and folinic acid
- Median follow-up of 5.9 years

**Results**

- No significant differences in:
  - 3-year overall survival (74% vs 70%, p=0.62)
  - 5-year distant recurrence rates (27% vs 30%, p=0.32)
  - 8-year overall survival (78% vs 70%, p=0.32)
  - 3-year disease-free survival (58% vs 84%, p=0.03)

5-FU = 5-fluouruouracil
Supplementary Figures

Supplementary Figure 8

C) Bujko et al 2016, Polish II

- 541 patients with fixed clinical T3 or T4 rectal cancers
- Radiation to a dose of 35 Gy in 5 fractions and three cycles of FOLFOX4
- Median 12.4 weeks
- Surgery

- Radiation to a dose of 50.4 Gy in 28 fractions with two cycles of bolus 5-FU and leucovorin during the first and fifth weeks of RT
- Median 12.4 weeks
- Surgery

Results

3-year Overall Survival significantly increased in short course group (73% vs 65%, p<.046)

Preoperative treatment acute toxicity significantly reduced in the short course group (73% vs 89%, p<.006)

*The initial long course arm also included 5 cycles of oxaliplatin weekly but protocol was amended to forgo the oxaliplatin
**Supplementary Figure 9**

A) Habr-Gama et al 2006

- 361 patients with resectable distal rectal adenocarcinoma

  - Necadjuvant ChemorRT with 5-FU, Leucovorin, and 5040 cGy
  - Tumor Response assessed at 8 weeks

- 132 patients had initial complete response and 59 patients sustained this response at 12 months (27.4%)

- 262 patients had an incomplete clinical response (71.5%)

- Underwent pT3MDM resection

- 13 patients (13.1%) developed recurrences and five isolated endorectal recurrences were salvaged.

- Mean follow up time 59.9 months

- 5-year overall survival and disease-free survival were 93% and 85% respectively

5-FU = 5-Fluorouracil
**B) Habr-Gama et al 2013**

70 patients with T2- T4N0-1 distal rectal cancer

Necadjuvant Chemorife to a dose of 54 Gy and six cycles of 5-FU and leucovorin

Tumor Response assessed at 30 weeks

47 patients had initial complete response (88%)

Nonoperative management

8 patients (17%) developed regrowth

Median follow up 55 months

39 patients (59%) sustained complete response

>12 months of follow up

4 patients (12%) developed late recurrences

5-FU = 5-Fluorouracil
Supplementary Figure 11

C) Maas et al 2011

152 patients with MRI-staged cT3 with margins, cT4, or node-positive rectal cancer

Neoadjuvant ChemorRT with 50.4 Gy and capcitabine

Restaging MRI at 6-8 weeks after ChemorRT

21 patients with complete clinical response underwent nonoperative management

Control Group: 20 patients who had pCR after ChemorRT and total mesorectal excision

Mean follow up 25 months

Mean follow up 33 months

Results

One patient in the nonoperative group had a recurrence which was salvaged vs no patients in the control group

No significant differences in disease-free or overall survival between the nonoperative group (81% and 100%) and the control group (53% and 91%), p= .710 and p=.228 respectively

C) Maas et al 2011
D) Appelt et al 2015

- 51 patients with T2-3N0-1 distal rectal cancer
- ChemorT (60 Gy in 30 fx to tumor; 50 Gy in 30 fx to elective nodal volumes; 5 Gy endorectal boost) with oral tegafur-uracil
- CT or MRI 6 weeks after treatment
- 40 patients with complete clinical response (78.4%)
- 11 patients with incomplete response (21.6%)
- Nonoperative management
- Referred for resection
- 1-year local recurrence was 13.5%
- Sphincter function: No local incontinence in 18 patients at 1 year and 11 patients at 2 years
- Acute side effects: Grade 3 diarrhea in 4 patients
- Late side effects: Grade 3 rectal bleeding in 2 patients at 3 year and 1 patient at 2 years

Median follow-up was 13.6 months.
E) Dalton et al 2012

40 patients with rectal cancer → Neoadjuvant ChemoRT with 45 Gy and concurrent capecitabine → MRI 6-8 weeks after treatment

12 patients with complete response on MRI → Nonoperative management

37 patients with incomplete response on MRI

6 patients underwent surgery

6 patients remained clinically free of disease

Six patients with residual disease underwent surgery

30 Underwent surgery

6 had disease progression

1 patient refused surgery

Mean follow-up was 36 months

Mean follow-up was 24 months
Supplementary Figures

Supplementary Figure 14

F) Smith et al 2012

Retrospective review of rectal cancer patients who received ChemorT over 5-6 weeks with median dose of 5040 cGy with 5-FU or capecitabin

32 patients were identified with complete clinical response and were followed with nonoperative management

Median follow up was 28 months

6 patients recurred locally and all were salvaged

Control group: 57 patients who underwent ChemorT and rectal resection with pathologic complete response

Median follow up was 43 months

No local failures

No difference in 2 year distant disease-free survival (88% vs 96%, p = .27) and overall survival between the two groups (96% vs 100%, p = .56)
G) van der Valk et al 2012

- 880 patients who underwent neo-adjuvant therapy for rectal cancer for whom TME was omitted.
  - Median follow up was 3.3 years.
  - 2-year local regrowth rate 25.2% (213 patients).
  - 667 patients with sustained clinical response (75.7%).

- 46 patients (33%) treated with local excision.
  - 13 of the local excision patients ultimately underwent TME.

- 5-year disease-specific survival 84% and 5-year overall survival 75.4%.
- 5-year disease-specific survival 97.3% and 5-year overall survival 87.5%.