Emerging Paradigms in the Treatment of Localized Rectal Cancer

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National Comprehensive Cancer Network®

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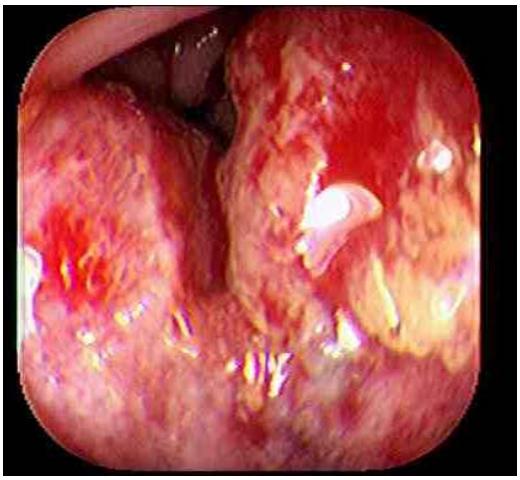
Case Presentation

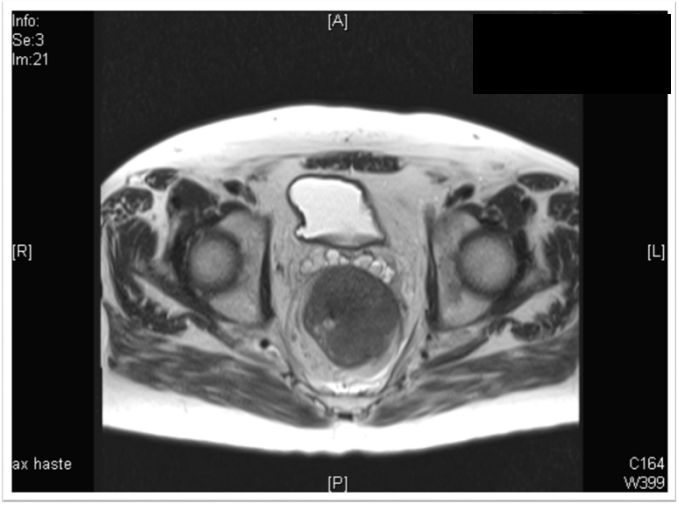
- 65 year old man in good health developed rectal bleeding and narrowing of stools
- Rigid sigmoidoscopy
- Pelvic MRI
- Colonoscopy/Abdominal and Thoracic Imaging

Rigid sigmoidoscopy

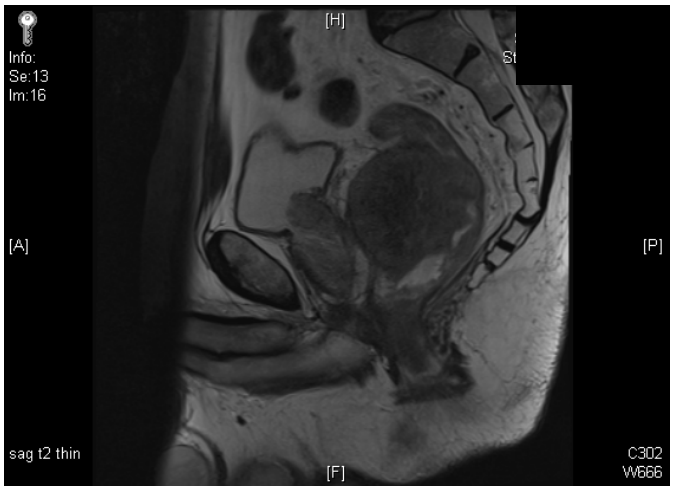


- 7 cm from anal verge
- Bulky and nearly circumerential
- Bx- MD Adenoca

MRI Axial Image



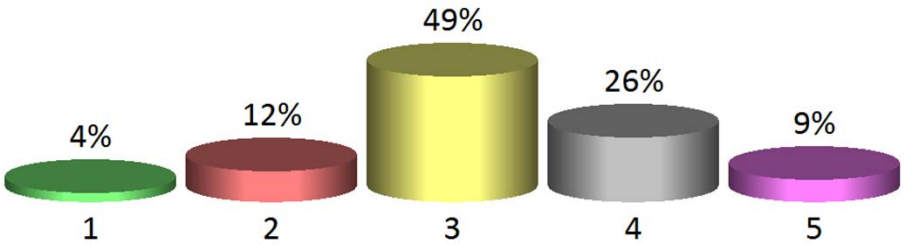
MRI Sagittal Image



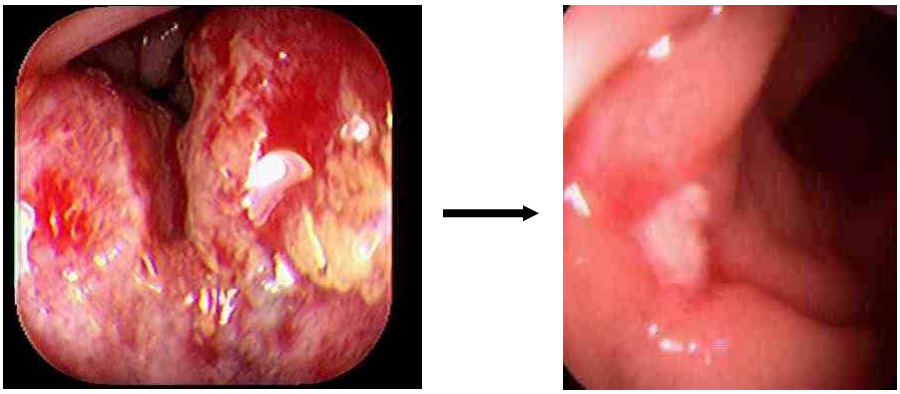
Audience Polling Results

Treatment Recommendations: Next Step?

1. Total Mesorectal Excision
2. FOLFOX Chemotherapy
3. US Style ChT/RT (50.4 Gy with capecitabine)
4. Above --> FOLFOX (6 cycles)
5. Short Course Radiation Therapy (25 Gy in 5 Fractions)



Pre- and Post- Radiation Therapy and Chemotherapy



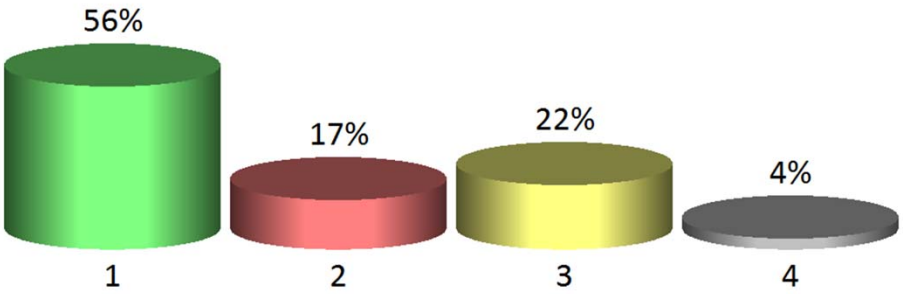
Pre-Treatment

Post-Treatment

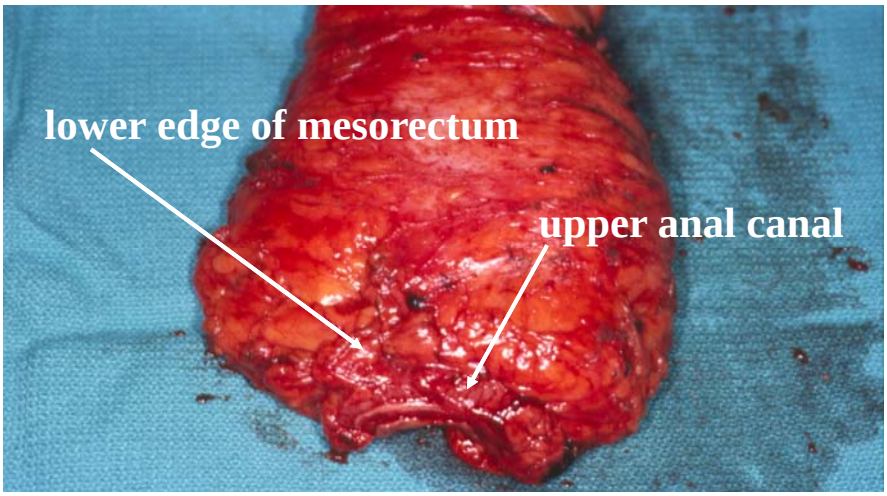
Audience Polling Results

Treatment Recommendations: Next Step?

1. Total Mesorectal Excision
2. Transanal Excision
3. Careful observation with Surgery reserved for Salvage
4. Brachytherapy application

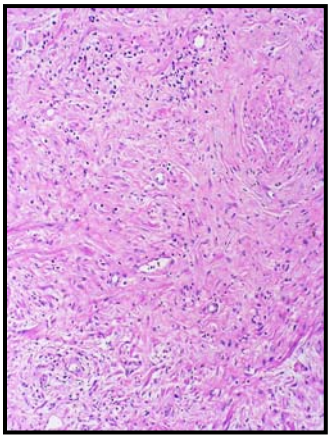


TOTAL MESORECTAL EXCISION



Distal resection margin after TME is about 2cm above dentate line.

Pathology of Resected Specimen

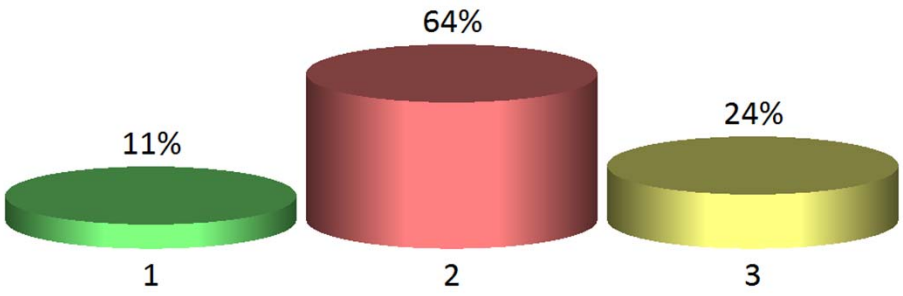


ypT0N1 (1/15 sampled mesorectal LN)

Audience Polling Results

Treatment Recommendations: Next Step?

1. No further therapy
2. FOLFOX (8 cycles)
3. FOLFOX (6 cycles) should have been administered neoadjuvantly after SC or LC before surgery



Paradigms in Treatment of Resectable Rectal Cancer

- Short Course vs. Long Course
- Neoadjuvant ChT ± RT
- Cure and Organ Preservation without Surgery

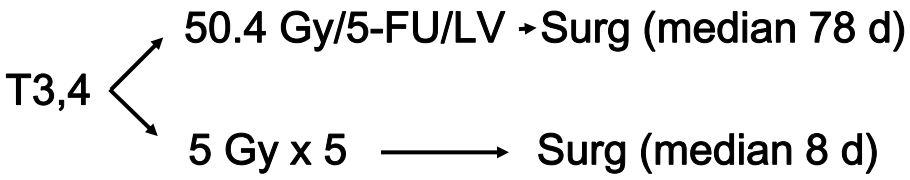
Rectal Cancer: Short-Course (SC) vs Long-Course (LC) Radiation

European SC: 25 Gy/ 5Fx	U.S. LC: 50.4 Gy + ChT
• Immediate Surgery	• Delayed Surgery
• No Δ in Preop Stage	• Improved Path Resp Rates
• Lower Cost	• More Tumor Regression
• Excellent Compliance	• Sphincter Preservation
• ? Less Acute Toxicity	• ? Improved Late Effects
	• ? Watch and Wait

Phase III Trials: SC vs LC

1. Polish (2004)
2. TROG (2012)
3. Stockholm III (2015)
4. Polish II (2016)

Polish Preoperative Phase III Trial



- 316 Pts with T3-4 Resectable Distal Cancers
- No Involvement of the Sphincter
- Total mesorectal excision (TME) Only for Distal Tumors
- No Central QA

Bujko et al.: Radiother Oncol 2004

Polish Trial: Results

Preoperative Schedule	Path CR (%)	Sphincter Preservation Rate (%)	LF (%)	4 yr OS (%)
25 Gy (155 Pts)	1	61	9	67.2
50.4 Gy + 5-FU (157 Pts)	16*	58	14.2	66.2

Bujko et al: BJS 2006

Polish Trial: Results

Preoperative Schedule	Acute G3-4 Toxicity (%)	Compliance (%)	Late Toxicity (%)	Severe Late Toxicity (%)
25 Gy (155 Pts)	3.2*	97.9*	28.3	10.1
50.4 Gy + 5-FU (157 Pts)	18.2 (2 Cardiac deaths)	69.2	27	7.1

Bujko et al: BJS 2006

TROG Trial

	Pelvic RT	Resection	Adjuvant chemotherapy
SC	25 Gy/5 fx/ 5d	within 1 wk	5FU 425 mg/m^2 + FA 20 mg/m^2 for 5 days 6 cycles
Randomize			
LC	50.4 Gy/28 fx/ 5w3d + 5FU CI 225 mg/m^2/day 7d/wk	in 4 - 6 wk	5FU 425 mg/m^2 + FA 20 mg/m^2 for 5 days 4 cycles

Main eligibility criteria:

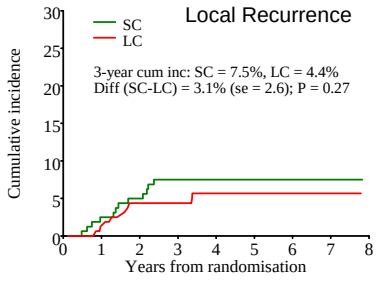
- localized adenocarcinoma of the rectum
- ultrasound or MRI staged clinical T3N$_{any}$M0

Ngan et al: J Clin Oncol 2012

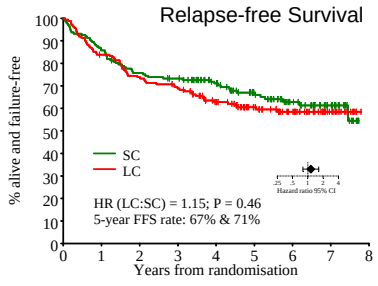
Compliance

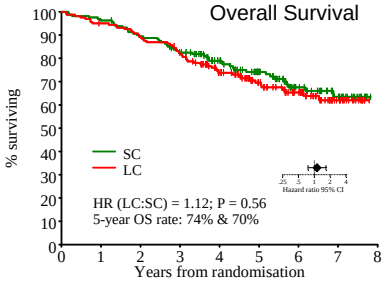
- Short Course (25 Gy/5 Fxs): 100%
- Long Course (50.4 Gy/28 Fxs): 93%
- Concurrent 5-FU: 84% (within 10% of prescribed dose)
- Adjuvant ChT: 85% Short Course and 86% Long Course

Ngan et al: J Clin Oncol 2012



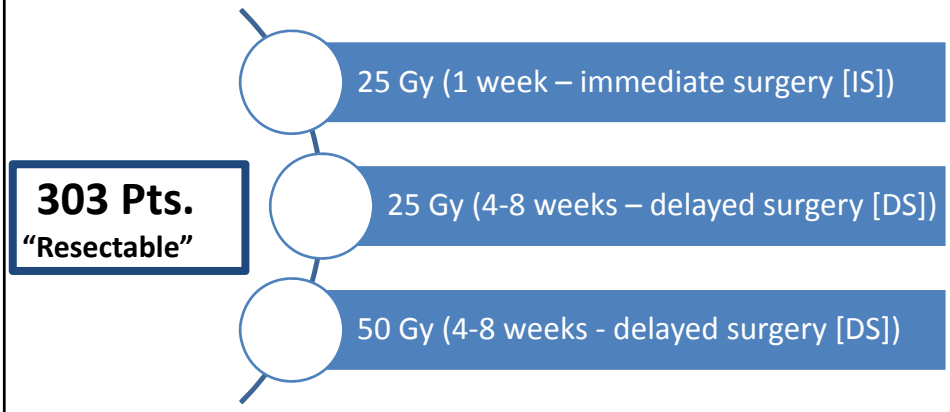
- Three-year LR rates between SC and LC were not statistically significantly different
- No differences in rates of distant recurrence, relapse-free survival, overall survival
- Comparison of QOL has become a clinically important issue in assessing their relative merits





Ngan et al: J Clin Oncol 2012

Stockholm III Rectal Cancer Trial



Pettersson et al: British J Surgery 2010

Stockholm III: Preliminary Results

	p CR (%)	APR (%)	Severe Acute Toxicity (%)	Anastomotic Leak (%)
25 Gy (118 pts) IS	0.8	30	0	13
25 Gy(120 pts) DS	12.5	33.3	4.2	11
50 Gy (65 pts) DS	5.0	20	5	4

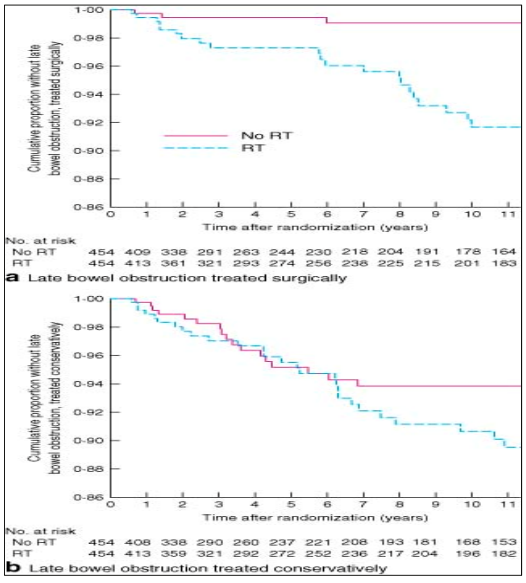
Pettersson et al: British J Surgery 2010

Stockholm III: Interim Results

	# Pts.	pCR (%)	Dworak G 4 (%)
25 Gy IS	234	1.7	1.7
25 Gy DS	228	11.8	10.1

Pettersson et al: British J Surgery 2015

Swedish Rectal Cancer Trial: Late Toxicity



Birgisson et al: British J Surgery 2008

Bowel Function of TME Trial Patients 14 Years Post-Treatment

Low Anterior Resection Syndrome	Preoperative RT + TME (n=118)	TME (n=124)
Severe	55.9	35.5
Minor	19.5	25.0
None	24.6	39.5 p<0.01

Chen et al: Clinical Colorectal Cancer 2015

Long-term Quality of Life Analysis

- Primary objective
  - To compare long-term quality of life (QOL) between short course and long course preoperative radiotherapy for rectal cancer
- Eligibility criteria
  - Participants of the TROG 01.04 trial
  - Completed a baseline QOL
  - Completed at least one other QOL at or after 12 months

McLachlan et al: Eur J Cancer 2016

Endpoints

- Changes from baseline of nine QOL scales were nominated, prior to data analysis, as the major endpoints
  - global health status/QoL
  - sexual functioning
  - sexual enjoyment

  Function scales

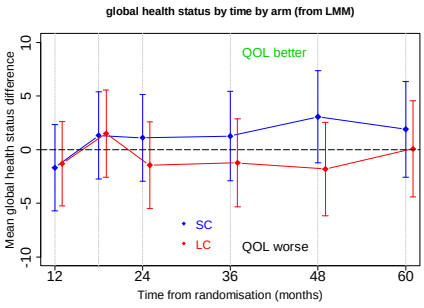
  - micturition
  - gastrointestinal tract
  - male sexual problems
  - constipation
  - diarrhea
  - defecation problems

  Symptom scales
- An area-under-curve (AUC) statistic (from 12 to 60 months) was used to assess the major endpoints

McLachlan et al: Eur J Cancer 2016

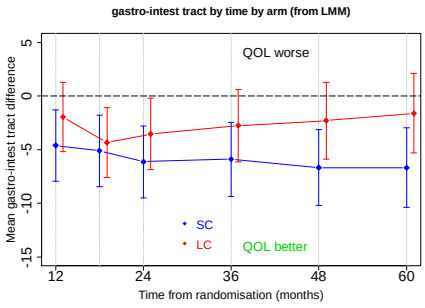
Results

Global Health Status/QOL



AUC analysis indicated there was little difference in global health status between arms. Mean diff = -2.5
P = 0.33 [95% CI: -7.48 to 2.48]

Gastro-intestinal Tract

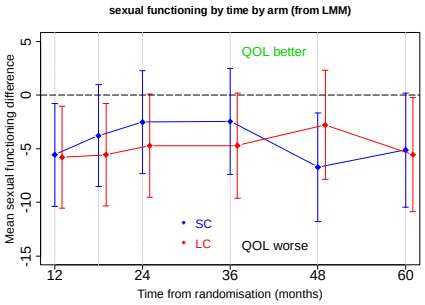


Difference in mean QOL = 3.3
P = 0.13 [95% CI: -0.96 to 7.48]

McLachlan et al: Eur J Cancer 2016

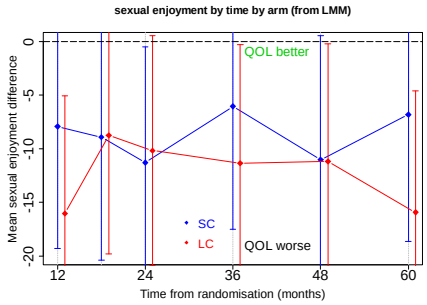
Results

Sexual functioning



Difference in mean QOL = -0.3
P = 0.93 [95%: -6.26 to 5.70]

Sexual enjoyment

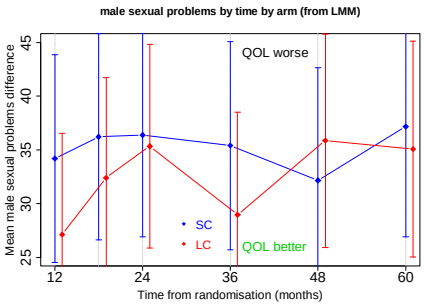


Difference in mean QOL = -2.8
P = 0.67 [95%: -15.54 to 9.98]

McLachlan et al: Eur J Cancer 2016

Results

Male sexual problems



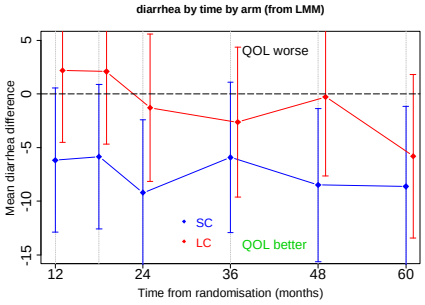
Difference in mean QOL = -2.1
P = 0.73 [95% CI: -13.83 to 9.72]

Female sexual problems was not analysed due to lack in response to this question (n=11)

McLachlan et al: Eur J Cancer 2016

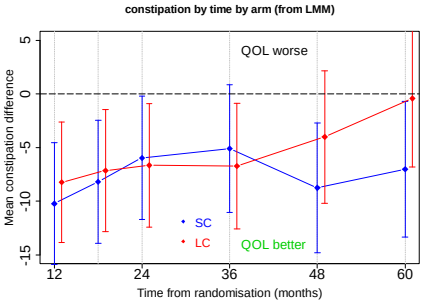
Results

Diarrhea



Difference in mean QOL = 6.2
P = 0.17 [95% CI: -2.59 to 15.03]

Constipation

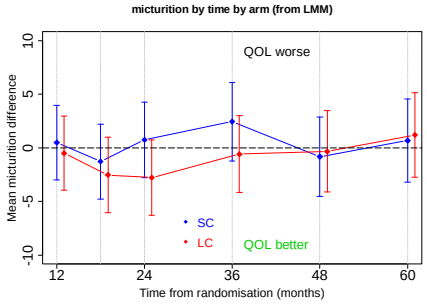


Difference in mean QOL = 1.7
P = 0.65 [95% CI: -5.66 to 9.10]

McLachlan et al: Eur J Cancer 2016

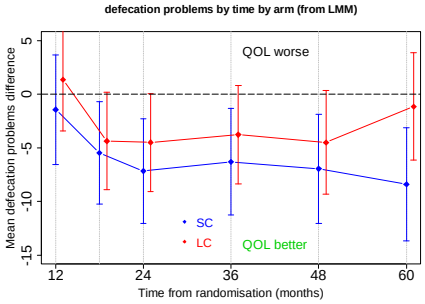
Results

Micturition



Difference in mean QOL = -1.4
P = 0.52 [95% CI: -5.86 to 2.97]

Defecation problems



Difference in mean QOL = 3.0
P = 0.34 [95% CI: -3.16 to 9.09]

McLachlan et al: Eur J Cancer 2016

Conclusion

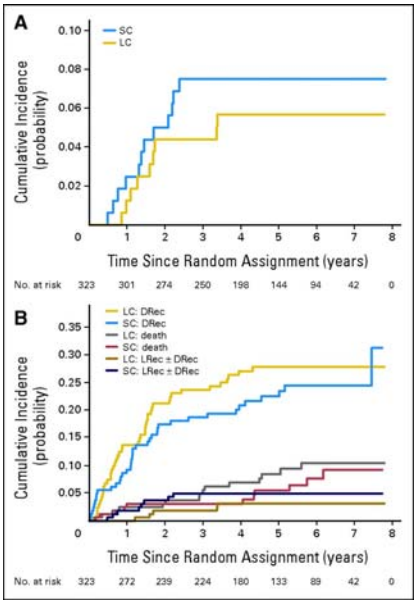
Assuming >10 points difference in QOL is clinically important, during the period from 12-60 months following registration for the trial, in patients alive and without having relapsed, results suggest that:

- There is no important difference between SC and LC for global health status, constipation, sexual functioning, micturition, GIT, and defecation;
- Possible important differences have not been ruled out in:
  - diarrhoea [95% CI: -2.59 to 15.03]
  - sexual enjoyment [95%: -15.54 to 9.98] and
  - male sexual problems [95% CI: -13.83 to 9.72].

Resectable Rectal Cancer: SC vs. LC

- Similar rates of local control, distant metastases, and overall survival
- Similar rates of late (intermediate time) toxicity
- Similar impact on QOL (intermediate time)
- Watch late effects with SC (> 5years!) – Swedish and TME trials (no comparable data – Long Course)
- Time after treatment is important for tumor regression.

(A) Cumulative incidence curves of any local recurrence (LRec) by allocated treatment arm: competing risks analysis for events, LRec, and death (not shown).



Samuel Y. Ngan et al. JCO 2012;30:3827-3833

Survival data from randomised clinical trials: Adjuvant chemotherapy vs. Observation

Study	Objective	Adjuvant chemotherapy arm	Observation arm	*P* value
EORTC 22921	10-year OS	*n* = 506 51.8%	*n* = 505 48.4%	0.32
I-CNR-RT Italian trial	5-year OS (in resected patients only)	*n* = 296 69%	*n* = 294 70%	0.77
PROCTOR SCRIPT	5-year OS	*n* = 216 79.2%	*n* = 221 80.4%	0.77
CHRONICLE	3-year DFS	*n* = 54 72.5%	*n* = 59 71.3%	0.56

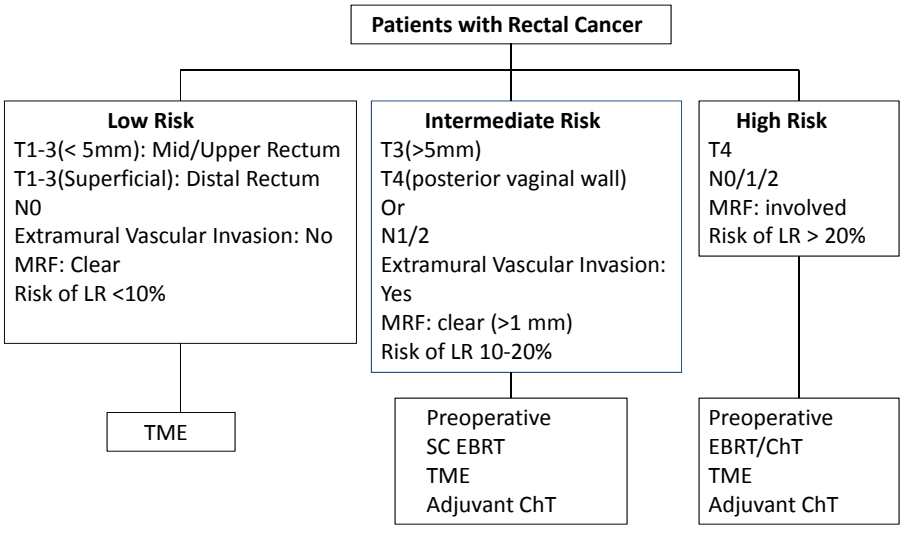
Boustani et al: Clinical Onc 2016

Survival data from randomised clinical trials: 5-fluorouracil (5-FU)- or oxaliplatin-based adjuvant chemotherapy

Study	Objective	5-FU-based adjuvant chemotherapy	Oxaliplatin-based adjuvant chemotherapy	*P*value
PETACC 6 (phase III)	3-year DFS	*n* = 547 74.5%	*n* = 547 73.9%	0.78
CAO/ARO/AIO-04 (phase III)	3-year DFS	*n* = 637 71.2%	*n* = 628 75.9%	0.038
ADORE (phase II)	3-year DFS	*n* = 149 62.9%	*n* = 146 71.6%	0.047

Boustani et al: Clinical Onc 2016

European/Scandinavian Treatment Algorithm of SC and LC



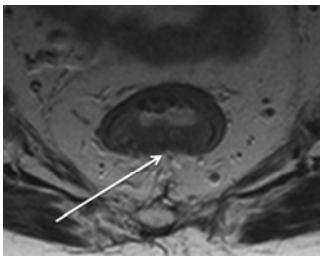
Smith and Garcia-Aguilar: J Clin Oncol 2015

Neoadjuvant Chemotherapy for Resectable Rectal Cancer

- 3 Small single arm phase II trials
- 1 Retrospective report (abstract only)
- 1 Pilot study

MSKCC cT3N0

- Pooled analysis 6 high volume centers
- 188 cT3N0 by EUS/MRI
- CRT-> Surgery



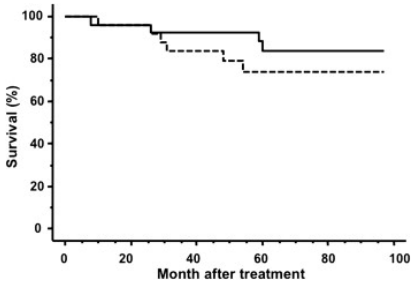
- Results
  - 22% pathologically positive mesorectal LN
  - Many patients understaged by preoperative imaging

Guillem et al: J Clin Oncol 2008

Japanese Single Arm Trial

- 2001-2004, RT availability limited in Japan + 'toxicity unfavorable'
- 26 patients, T3-4 N0-2, mid/lower rectum
- IFL chemo x 2 cycles

-R0: 100%
-downstaging in 58%
-pCR: 1 patient
-5y DFS: 74%
-5y OS: 84%



Ishii et al: Eur J Surg Oncol 2010

Rectal Cancer: Neoadjuvant Chemotherapy

GEMCAD 0801 Trial

- 46 pts with CS II-III Rectal Ca
- 4 cycles capecitabine + oxaliplatin + bevacizumab → Surgery
- 44 Pts Surgery: All R0 Resection, 20% pCR
- Anastomotic Leaks: 13%; G5 Toxicity: 3 pts.

Fernandez-Martos, The Oncologist 2014

Japanese Phase II Trial

- CAPOX plus bev prior to TME
- 32 patients, poor-risk per MRI

- R0: 90%
- downstaging in 37%
- pCR: 13%
- post-op complications: 43% (attributed to bev? anastamotic leakage, perforation)

Uehara et al: Jpn J Clin Oncol 2013

MSKCC Retrospective

- Pts receiving chemo alone because of suspected metastatic disease, contraindications/refusal of XRT
- 20 patients, 6 rectal
- FOLFOX +/- bev

- overall pCR 35%

Rectal patients n=6:
- pCR: 3 patients
- tumor regression: 5 patients

Cercek et al: JCO 2010; 28(15S) abst 3511

MSKCC Pilot Study

- Clinical stage II/III rectal
- non-T4 tumors
  - Sphincter-sparing candidates (LAR with TME)
  - Nonthreatened CRM by MRI
- FOLFOX+ bev x 6
- 32 patients (2 had preop XRT)

-R0: 100%
- downstaging in 100%
- pCR: 25%
- 4y local recurrence: 0%
- 4y DFS: 84%
- 4y OS: 91%

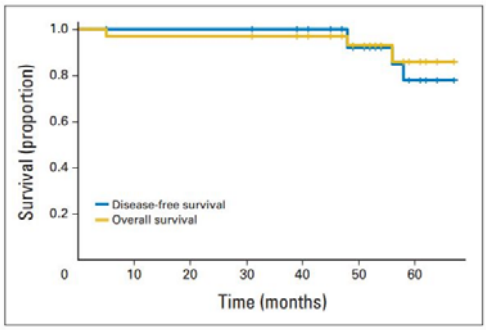


Fig 2. Disease-free and overall survival for the 32 study participants. A single patient who died as a result of postoperative complications but without disease is not censored, but is considered to have had an event.

Schrag et al: J Clin Oncol 2014

PROSPECT

Preoperative Radiation Or Selective Preoperative radiation and Evaluation before Chemotherapy and TME

An Alliance Phase II/III Trial of Neoadjuvant FOLFOX with Selective Use of Combined Modality Chemoradiation for Locally Advanced Rectal Cancer Patients Undergoing Low Anterior Resection with Total Mesorectal Excision

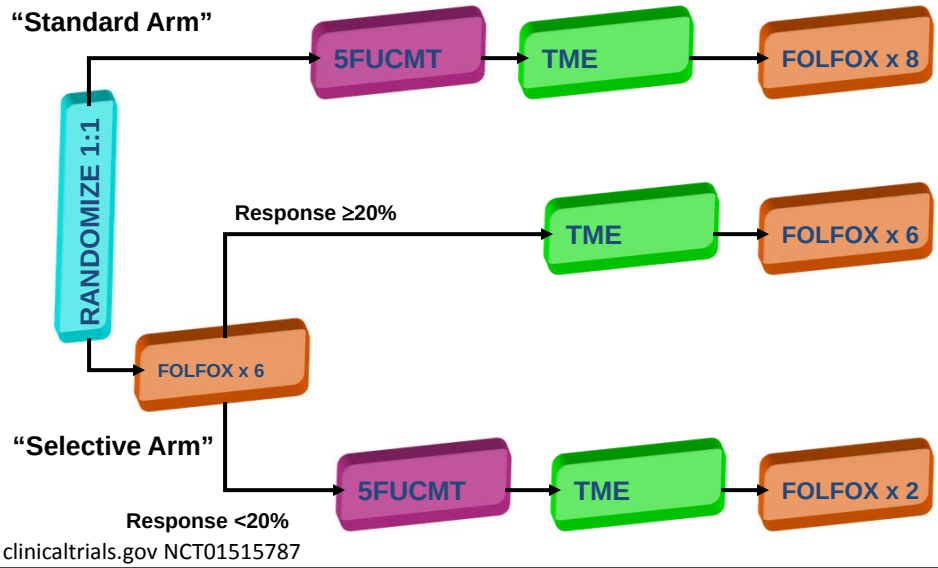
clinicaltrials.gov NCT01515787

Inclusion Criteria

- Biopsy proven rectal adenocarcinoma
- Tumor tissue located at **5-12 cm** from the anal verge
- Candidate for sphincter sparing surgery
- ECOG Performance Status 0, 1 or 2
- Surgeon is TME credentialed
- Baseline Clinical staging: T2N1, T3N0, T3N1
  - Physical exam by primary surgeon
  - Proctoscopy
  - MRI or ERUS (MRI preferred)
  - CT scan of Chest/Abdomen/Pelvis

clinicaltrials.gov NCT01515787

Study Schema



clinicaltrials.gov NCT01515787

Caution with Neoadjuvant Chemotherapy

- Inclusion relies on imperfect preoperative imaging

Variable	Preoperative Chemoradiotherapy (N=415)	Postoperative Chemoradiotherapy (N=384)
Histopathological finding (%)		
Complete response	8	0
TNM stage		
I	25	18
II	29	29
III	25	40
IV	6	7

Sauer et al: NEJM 2004

Chemotoxicity

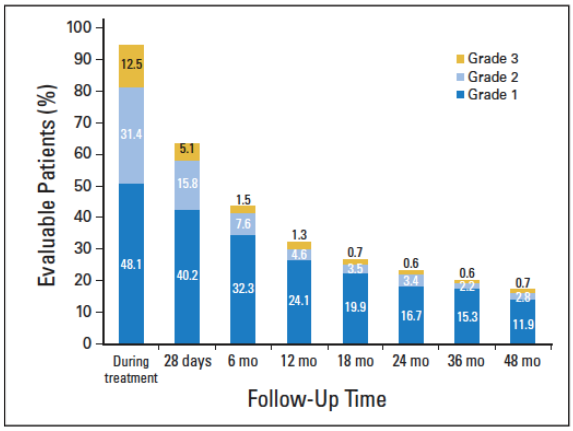


Fig 5. Proportion of patients treated with oxaliplatin plus fluorouracil and leucovorin with grade 1, 2, or 3 peripheral sensory neuropathy during treatment and after follow-up to 4 years.

Second cancer

- 5.5% FOLFOX4 group
- 6.1% LV5FU2 group

André et al: J Clin Oncol 2009

Intensification of Neoadjuvant Treatment

- Chemotherapy → LC → Surgery
- SC or LC → Chemotherapy → Surgery

Royal Marsden: Neoadjuvant Chemotherapy + RT/Chemotherapy

105 pts: "poor risk" rectal ca:

- Capecitabine + oxaliplatin (12 wks)
- 45 Gy with capecitabine
- TME (6 wks)
- Capecitabine (12 wks)

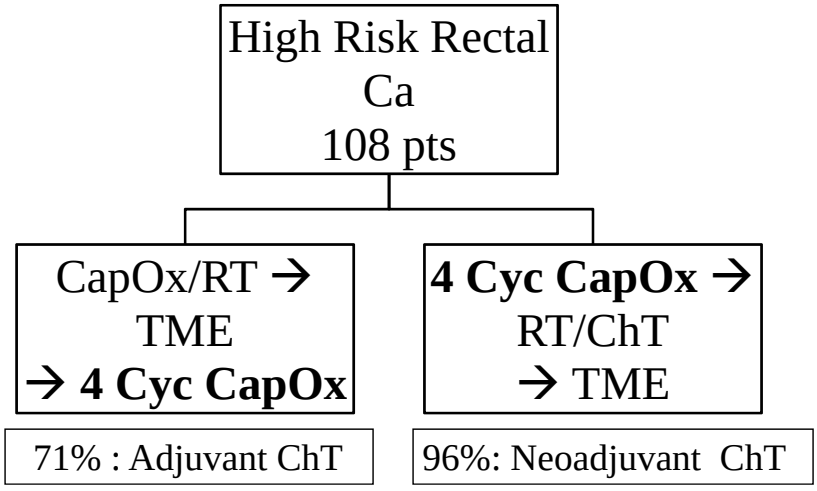
Chau et al: Lancet Oncol 2010

Royal Marsden: Neoadjuvant Chemotherapy + RT/Chemotherapy

- ChT not completed: 12/105 (11%)
- 5 Deaths During Neoadjuvant ChT
- MR scan: 74% RR after ChT
- TME: 95/105 (90%)
- pCR: 21/105 (20%)

Chau et al: Lancet Oncol 2010

GCR-3: Ph II Preop Trial



Fernandez-Martos et al: The Oncologist 2015

Spanish GCR-3 Trial Results

Neoadjuvant Tx	R0 Rate (%)	pCR Rate (%)	5 yr LF / DM (%)	5 yr OS/ DFS (%)
ChT/RT TME 4 Cycles CapOx (n=52)	87	13	2 /21	78/ 64
4 Cycles CapOx Ch/RT TME (n=56)	86	14	5 / 23	75/ 62

Fernandez-Martos et al: The Oncologist 2015

Polish II: Ph III Trial

Fixed cT3or cT4
515 pts

5 Gy x 5
mFOLFOX x 3
Surgery

50 Gy + FU/Leu ± Oxal
Surgery

Bujko et al: Ann Oncology 2016

Polish II Trial Results

Neoadjuvant Tx	R0 Rate (%)	pCR Rate (%)	LF / DM (%)	3 yr OS/ DFS (%)
5 Gy x 5 FOLFOX4 x 3 Surgery n=264	77	16	22 /30	**73*** / 53
50.4 Gy+FU/Leu ± Oxal Surgery n= 215	71	12	21 / 27	**65*** / 52 *p=0.046

Bujko et al: Ann Oncology 2016

Polish II Trial Results

Neoadjuvant Tx	G3/4 Toxicity Rate (%)	Toxic Deaths (%)	Postop Toxicity (%)	Late Toxicity (%)
5 Gy x 5 FOLFOX 4 x 3 Surgery n=264	23	16	29	20
50.4 Gy+FU/Leu ± Oxal Surgery n= 215	21	12	25	22

Bujko et al: Ann Oncology 2016

Rapido Trial

Locally Advanced Rectal Cancer

↓

Randomisation

Experimental arm B:	**Standard arm A:**
5x5 Gy short course RT	Chemoradiotherapy
↓	↓
6 cycles CAPOX	TME surgery
↓	↓
TME surgery	8 cycles CAPOX

Nilsson et al: BMC Cancer 2013

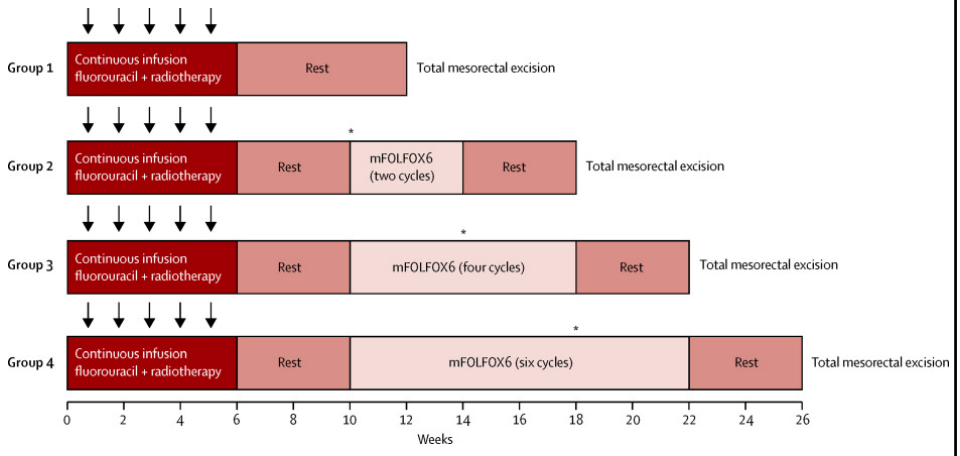
Adding mFOLFOX after Neoadjuvant Chemoradiation: Multi-site Phase II Study

292 Patients with Rectal Cancer:

- Clinical Stage II (T3-4, N0) or III (any T, N1-2)
- Cancers within 12 cm of the anal verge
- Local Staging: EUS or MRI
- Accrued Patients from 2004-2012

Garcia-Aguilar et al: Lancet Oncology 2015

Trial Protocol



Garcia-Aguilar et al: Lancet Oncology 2015

Surgical Results

	Group 1 (n=60)	Group 2 (n=67)	Group 3 (n=67)	Group 4 (n=65)	p value
Time from start of chemoradiation to surgery (weeks)	14·2 (4·3)	17·1 (2·9)	21·0 (2·7)	25·2 (4·0)	0·0001
Time from end of chemoradiation to surgery (weeks)	**8·5 (4·2)**	**11·1 (2·9)**	**15·4 (2·6)**	**19·3 (4·2)**	**0·0001**
Sphincter-saving surgery	46 (77%)	50 (75%)	50 (75%)	44 (68%)	0·68
Ileostomy	38/46 (83%)	43/50 (86%)	47/50 (94%)	38/43 (88%)*	0·33
Resection with negative margins	59 (98%)	67 (100%)	64 (96%)	64 (100%)†	0·089
Number of nodes examined	12 (2–31)	14 (2–30)	13 (2–30)	11 (1–47)	0·20
Pelvic fibrosis‡	**2·4 (1·7)**	**3·9 (2·6)**	**4·4 (2·4)**	**3·9 (2·4)**	**0·0001**
Technical difficulty§	**4·6 (2·7)**	**4·9 (2·8)**	**5·1 (2·5)**	**4·8 (2·4)**	**0·80**
Estimated blood loss (mL)	200 (50–1200)	225 (25–1500)	200 (50–1000)	150 (0–1000)	0·62

Garcia-Aguilar et al: Lancet Oncology 2015

Surgical Complications

	Group 1 (n=60)		Group 2 (n=67)		Group 3 (n=67)		Group 4 (n=65)		p value
	# of Pts*	# of events	# of Patients*	# of events	# of patients*	# of events	# of patients*	# of events	
None	36 (60%)	NA	41 (61%)	NA	44 (66%)	NA	37 (57%)	NA	..
Grade 1	11 (18%)	16	12 (18%)	18	10 (15%)	16	11 (17%)	14	0·88
Grade 2	**4 (7%)**	**6**	**10 (15%)**	**12**	**10 (15%)**	**13**	**11 (17%)**	**16**	**0·04**
Grade 3a	2 (3%)	2	1 (1%)	2	1 (1%)	1	4 (6%)	5	0·27
Grade 3b	5 (8%)	6	2 (3%)	2	2 (3%)	2	2 (3%)	2	0·11
Grade 4a	2 (3%)	2	1 (1%)	1	0	0	0	0	0·18

Garcia-Aguilar et al: Lancet Oncology 2015

Pathological Tumor Response

	Group 1 (n=60)	Group 2 (n=67)	Group 3 (n=67)	Group 4 (n=65)	p value
Path complete response	**11 (18%)**	**17 (25%)**	**20 (30%)**	**25 (38%)**	**0·0036**
Partial response	44 (73%)	50 (75%)	46 (69%)	39 (60%)	..
Stable disease	5 (8%)	0	1 (1%)	1 (2%)	..

Garcia-Aguilar et al: Lancet Oncology 2015

Univariable and Multivariable Regression for Pathological CR

		Univariable analysis		Multivariable analysis	
		OR (95% CI)	p value	OR (95% CI)	p value
Radiation dose		1·00 (0·99–1·00)	0·40	1·00 (0·99–1·00)	0·13
Clinical stage					
	II	1·22 (0·66–2·25)	0·53	1·26 (0·63–2·51)	0·52
	III	1·00	..	1·00	..
Tumour size		0·93 (0·80–1·09)	0·38	0·90 (0·76–1·07)	0·24
Distance from anal verge		1·02 (0·93–1·12)	0·65	0·98 (0·89–1·09)	0·73
Study group					
	1	1·00	0·092*	1·00	0·048*
	2	1·52 (0·64–3·56)	0·67	1·58 (0·59–4·23)	0·63
	3	1·90 (0·82–4·38)	0·61	1·95 (0·75–5·07)	0·79
	4	**2·78 (1·22–6·34)**	**0·028**	**3·49 (1·39–8·75)**	**0·011**

Garcia-Aguilar et al: Lancet Oncology 2015

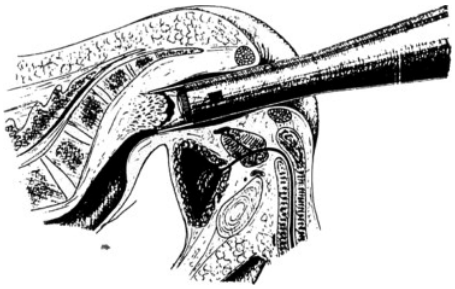
Conclusions

- Increasing cycles of mFOLFOX6 after ChT/EBRT and before Surgery: ↑ in Path CR rates
- ↑ Response: without tumor progression, ↑ technical difficulties or surgical complications.
- Support efforts to shift systemic treatments into neoadjuvant setting
- Delivering Chemotherapy after EBRT/ChT: More effective at increasing pCR rates than before
- ? Higher proportion of patients for less invasive surgery or watch and wait approaches

Garcia-Aguilar et al: Lancet Oncology 2015

Rectal Cancer: Organ Preservation

Papillon: Endocavitary Irradiation of "Early" Rectal Cancer (1951)



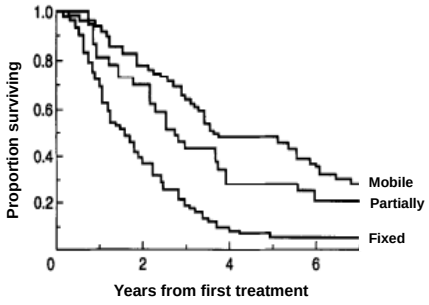
Papillon: Technique/Results

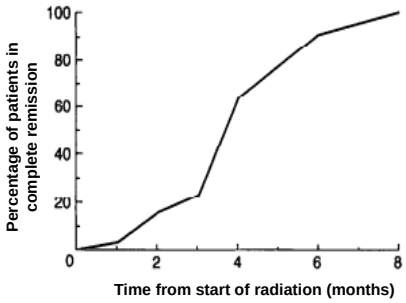
- 1951-1967: 123 Pts with minimum 5 yr follow-up
- 3-5 applications (2500-4000 R) with 50 kV unit over 4-6 weeks
- 84 Pts (68%) Disease free (>5 yrs)
- 14 pts (11%) Local Failure: *5 salvaged with surgery*
- 9 pts (7%) Distant Metastases

Papillon et al: Proc R Soc Med 1973

Non-Operative Tx

- PMH: 229 pts
- RT alone (unresectable, medically unfit, refused surgery)
- Dose 40 Gy/10 fx to 60 Gy/30 fx
- mobile tumors: cCR 50%
- cCR mobile crude LF: 38%





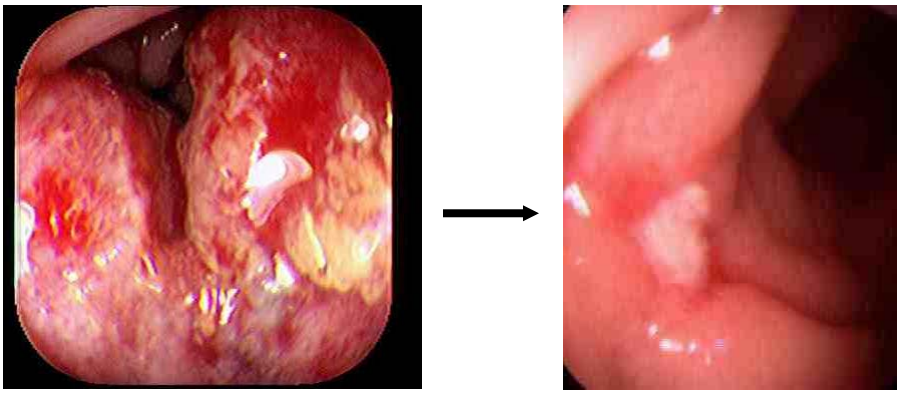
Brierley et al: IJROBP 1995

Non-Operative Treatment of Rectal Cancer after RT/Chemotherapy (50.4 Gy/5-FU/LV)

- 360 pts with low rectal cancer
  - 99 pts (28%) with clinical complete response
    - **OBSERVED**
      - Mean follow-up 60 months
        - » 7 systemic recurrences
        - » 5 local recurrences
        - » 1 sytemic and local recurrence
        - » 5 yr OS: 93%
        - » 5 yr DFS: 85%

Habr-Gama et al: J of GI Surgery 2006

T3 Rectal Cancer



Pre-Treatment

Post-Treatment

Non-Operative Treatment of Rectal Cancer after RT/Chemotherapy (50.4 Gy/5-FU/LV)

- 183 pts with distal rectal cancer (cT2-4, N 0/+)
  - 90 pts (49%) with clinical complete response at 8 weeks
    - **Watch and Wait**
      - Median follow-up 60 months
        - » 5 yr Local RFS: 69% (28 LF)
        - » Salvage therapy: 26/28 pts (4 LF)
        - » 5 yr Local RFS: 94% (including salvage)
        - » 5 yr Cancer Specific OS: 91%
        - » 5 yr DFS: 68%

Habr-Gama et al: Int J Rad Onc Bio Phy 2014

MSKCC: Non-Operative Management (NOM)

- 447 Pts (Stage I-III Rectal Ca): Neoadjuvant Tx (2006-2014)
- 73 Pts. Identified: cCR and NOM
- 72/369 Pts (20%): TME with pCR

Smith et al: ASCO GI Symposium 2015 (abstract 509)

MSKCC: Non-Operative Management Results

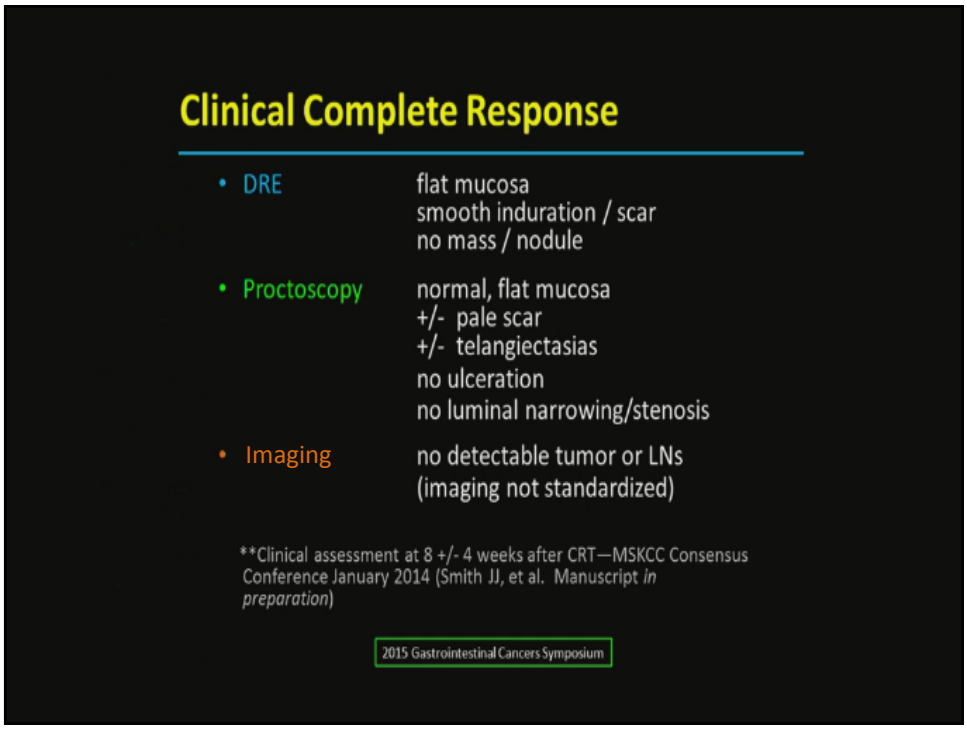
Group	Pt #	Local Regrowth	LR after resection	DM	DSS	OS	Rectal preservation
NOM	73	19	0	9	69(91%)	67(71%)	56(72%)
TME/pCR	72	0	0	5	70(96%)	68(95%)	0

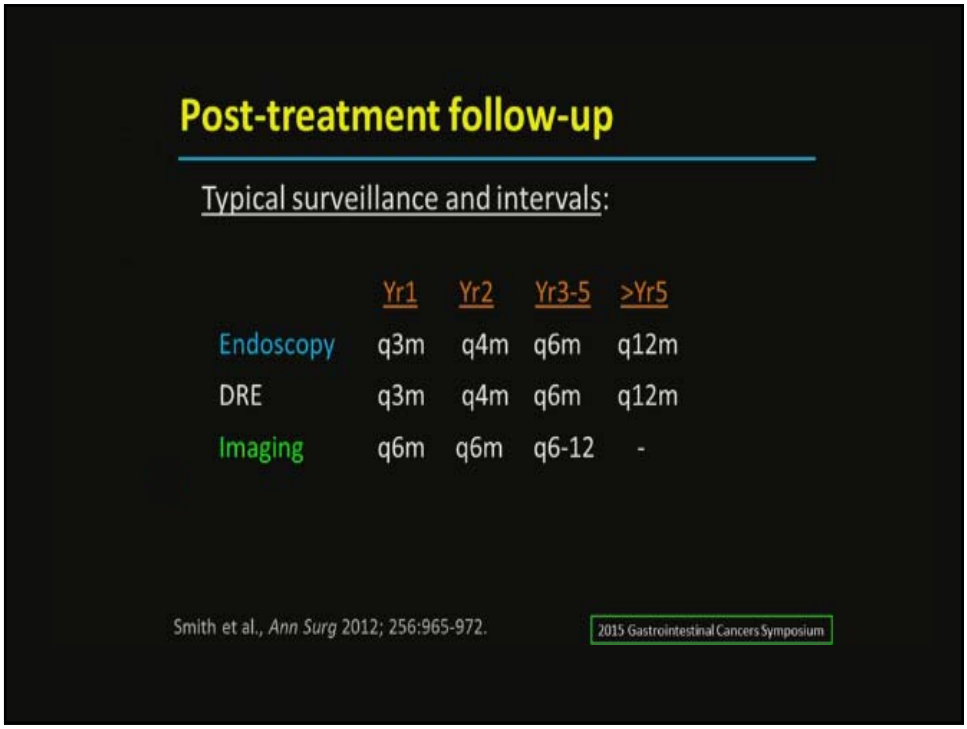
Smith et al: ASCO GI Symposium 2015 (abstract 509)

MSKCC Non-Operative Management: Conclusions

- Highly selected pts (cCR) to Neoadjuvant Tx:
- NOM with surgical salvage of local tumor regrowth achieved local control in all pts.
- 4 yr oncologic outcome for NOM pts was comparable to pts with pCR after resection
- NOM does not compromise oncologic outcome and rectal preservation is achieved in a majority of patients.

Smith et al: ASCO GI Symposium 2015 (abstract 509)





"Wait-and-See"

- **Netherlands trial**
- 21 pts cCR after chemoradiotherapy prospectively followed
- 3 to 6 monthly MRI, endoscopy, and CT
- Mean f/u 25 months
- 1 LR undergoing surgical salvage; others disease free

Maas et al: J Clin Oncol 2011

"Wait-and-See"

- Conclusion: Wait-and-see with strict selection criteria, up-to-date imaging techniques and follow-up is feasible and results in promising outcomes

"Watchful Waiting"

- Danish Prospective Trial
- 55 pts cT2-3,N0-1 (1999-2013)
- Tx: 60 Gy IMRT + 5 Gy endorectal brachytherapy + tegafur-uracil
- 40 pts cCR after chemoradiotherapy prospectively followed
- 3 to 6 monthly MRI, endoscopy, and CT
- Median follow-up 23.9 months
- 9 LR undergoing surgical salvage; 3 DM
- G3 Bleeding – 3 pts and sphincter function – excellent

Appelt et al: Lancet Oncology 2015

"Wait-and-See" Trials

- MSKCC Randomized Phase II Trial
- Royal Marsden Hospital
- Instituto do Cancer do Estado de São Paulo (Randomized Phase II)
- CMT with > 80% regression: (OPERA) trial standard CRT (45 Gy + 5.4 Gy boost) versus (45 Gy) contact X-ray radiotherapy boost (UK-phase III)
- European expert panel-cCR pts should be given option

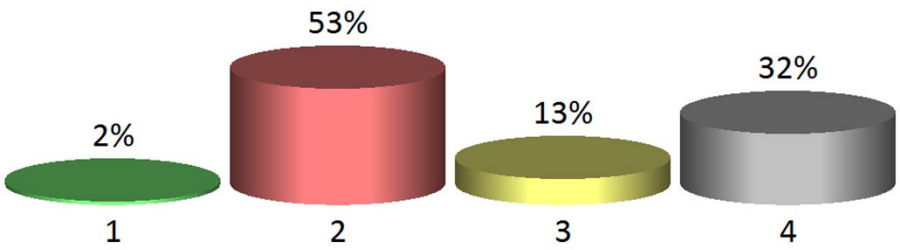
Summary

- Short Course vs. Long Course Treatment
- Neoadjuvant ChT ± RT
- Cure and Organ Preservation without Surgery

Audience Polling Results

What is the Optimal Neoadjuvant Therapy for Clinical Stage II and III Rectal Cancer?

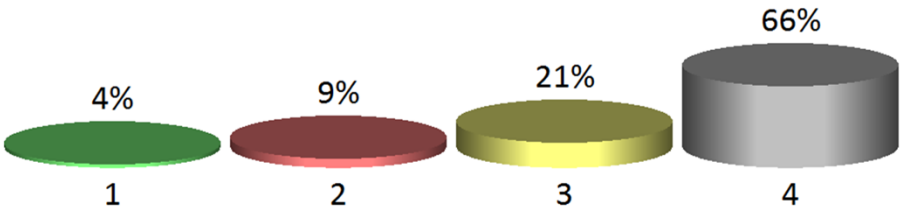
1. ChT Only (FOLFOX)
2. Long Course Radiation Therapy + Concurrent Fluoropyrimidine
3. Short Course Radiation Therapy
4. Radiation Therapy Followed by ChT (FOLFOX)



Audience Polling Results

Randomized Trials Have Shown that Short Course Radiation Therapy:

1. Inferior DFS and OS Rates Vs. Long Course RT + ChT
2. Higher Acute and Late Complication Rates Vs. Long Course RT + ChT
3. Superior Quality of Life Vs. Long Course RT + ChT
4. Pathological CR Rates Depend on Time from Completion of Radiation Therapy



Audience Polling Results

For Patients Having a Complete Clinical Response After Long Course RT + ChT: Next Step?

1. Total Mesorectal Excision
2. Transanal Excision
3. Observation with Careful Follow-up
4. Chemotherapy (FOLFOX)