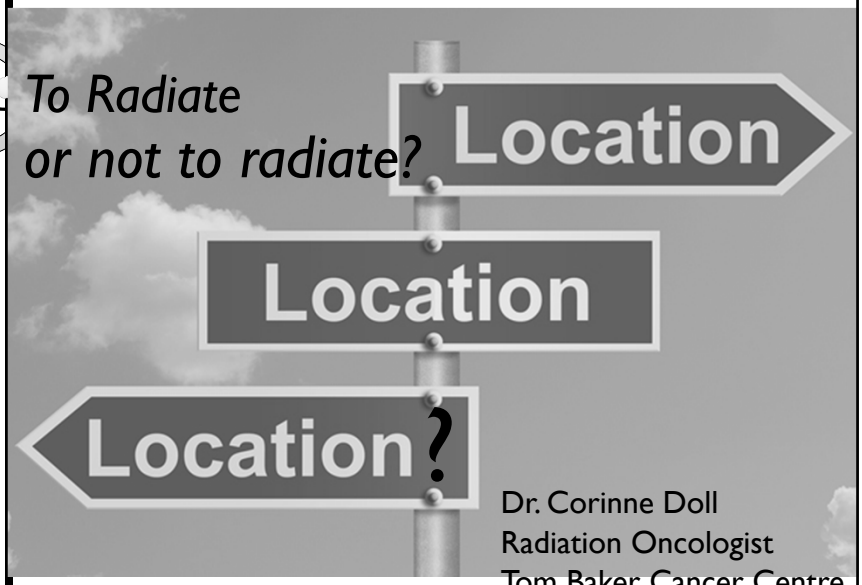
Rectal Cancer

To Radiate
or not to radiate?



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Q: Should rectal cancer RT/CRT decisions be based solely on *stage?*

Q: Can RT/CRT be *omitted* in some T3N0 cases?

Objectives

- Clinical cases
- Overview of rationale for RT/CRT
- Brief review of literature of results of neoadjuvant therapy based on tumour features and location

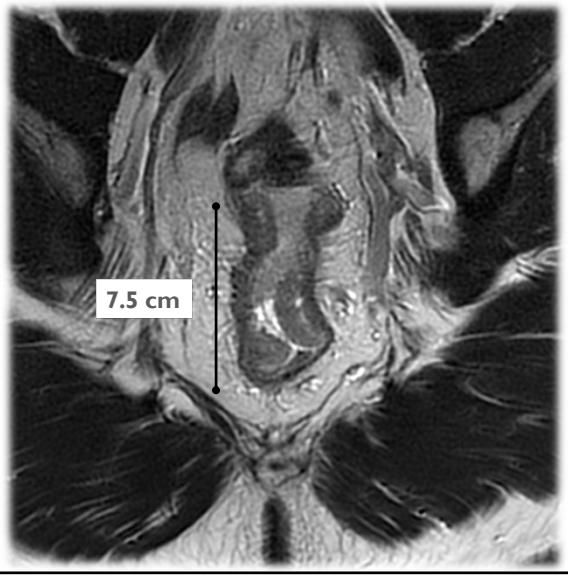
Clinical scenario:
Presentation

- 47 yo male, Mr. T
  - Otherwise healthy
- Presents with 3 month history bowel problems
  - Decrease calibre stool → BRBPR
  - Tenesmus

Clinical scenario:
Work-up

- Rectal mass at 5 cm from anal verge
- Sigmoidoscopy
  - Rectal mass extending from 5 cm above anal verge, to approx 10 cm
- Biopsy → adenocarcinoma

Work-up: *MRI*



Patient case #2:
Mr. D

- 48 yo male
- Married, healthy
- Intermittent BRBPR x 4 months, FIT test positive

Patient case #2:
Mr. D

- Examined
  - No palpable rectal mass
- Referred
  - Scope/biopsy
    - adenocarcinoma, upper rectum at 11 cm
- MRI – 3 cm tumour, upper rectum,
  - T3, N0, CRM not threatened (>5mm)

Same staging investigations

- CT abdomen and pelvis
- CT chest or CXR
- Complete colonic exam
- CEA
- MRI pelvis (high resolution)
  - T, N stage
  - CRM assessment

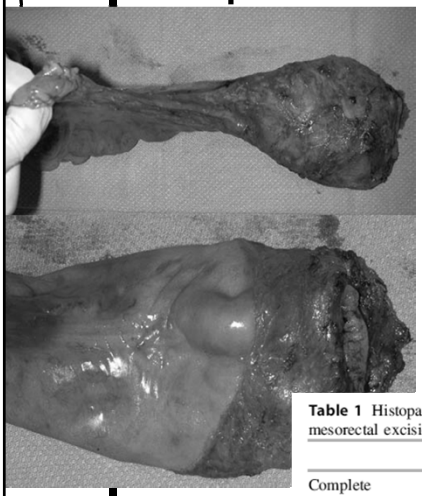
CCO Guidelines, Jan 2014

Management?

Goals of therapy

- Reduce local recurrence
- Maximize safety/minimize toxicity
  - QOL
- Prolong survival
- Preserve function (if possible)

Complete TME is key



- To achieve pelvic control, an R0 resection is essential
- Complete TME (grade 3), Quirke et al 2009
- <pelvic recurrences
  - Metastatic disease becoming a more predominant issue

Table 1 Histopathological grading of the quality and completeness of the mesorectum in a total mesorectal excision specimen

	Mesorectum	Defects	Coning	CRM
Complete	Intact, smooth	Not defects deeper than 5 mm	None	Smooth, regular
Nearly complete	Moderate bulk, but irregular	No visible muscularis propria	Moderate	Irregular
Incomplete	Little bulk and very irregular	Down to muscularis propria	Moderate–marked	Irregular

Rectal cancer: adjuvant therapy selection – how to choose?

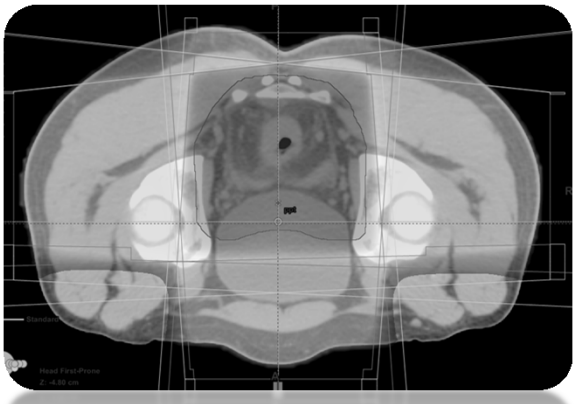
- Movement to *preoperative* therapy in the 1990s, many path variables no longer easily assessed
  - all patients with cT3 and/or N+ rectal cancer offered preoperative CRT
- The most common preoperative imaging techniques in the 1990s were transrectal ultrasound and CT
- This has led to both *underuse* and *overuse* of preoperative therapy

Neoadjuvant chemoradiotherapy

Pros	Cons
• "Downstage" disease • Enhances sphincter sparing • Less toxic than post-op • Fewer anastomotic complications? • Better outcomes?	• Pathologic staging not available ◦ May be overtreating some? • Delays primary surgery • Toxicity ◦ Radiation/CRT induced complications

The RT

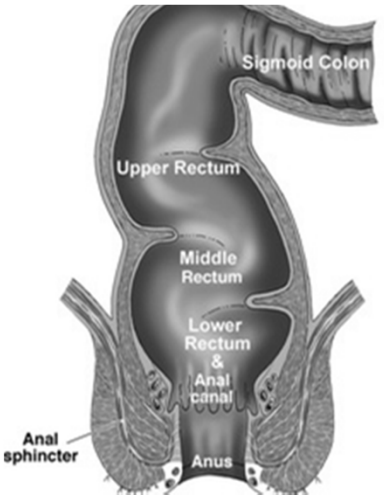
- Dose/fractionation
  - Long: 45 Gy +/- 5.4 Gy boost/25-28#
  - Short: 5 Gy x 5#
- Pelvis
  - 4-field, occ IMRT



Pelvic RT

- To reduce risk of local relapse
  - By approximately 50%
- Not without risks
  - Loss of fertility
  - Radiation enteritis/cystitis
  - Delayed wound healing
  - Bone changes
  - (Second malignancies)
- *Location* of primary tumour can determine toxicity

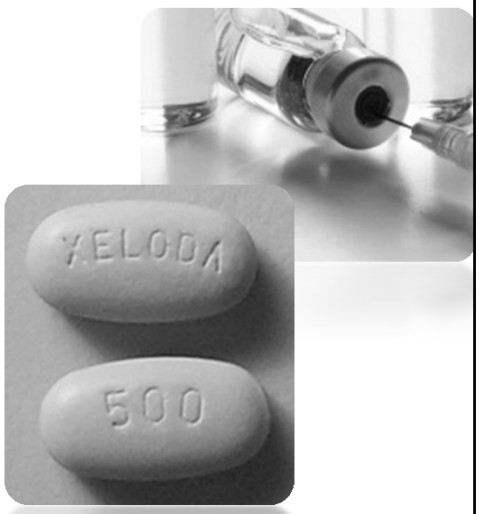
Rectum anatomy – location



- Upper rectum
  - ≥10 cm -15 cm
- Mid rectum
  - ≥5-10 cm
- Low rectum
  - <5 cm

The Chemo

- Oral capecitabine
  =
- Infusional 5-FU



Chemotherapy with RT

- To enhance local control, improve survival
- Not without risks
  - GI
    - NVD
    - mucositis
  - Hematologic
  - DPD deficiency- yikes!

T3 Rectal cancer – CRM matters

- Norwegian Rectal Cancer Group
  - 1,676 pts with T3 rectal cancer + TME, without pre-op RT
  - Multivariate analysis: CRM status and LN status assoc with local recurrence, distant mets, and OS
    - 5-year local rec 19.4% with CRM ≤ 1mm vs 11.1% with CRM >3mm
    - Recommend pre-op MRI and pre-op CRT for tumours with mrf ≤ 3mm

MRC CR07 – CRM status matters

Table 3 Summary of the 3-Year Local Recurrence Rates in MRC CR07/NCIC-CTG-CO16 Study of Preoperative Short-Course Radiotherapy Compared with Selective Postoperative CRT[24]

	Preoperative RT (n = 674) (%)	Selective Postoperative CRT (n = 676) (%)	HR (95% CI)*
3-year local recurrence	4.4	10.6	0.39 (0.27-0.58)
3-year disease-free survival	77.5	71.5	0.76 (0.62-0.94)
3-year overall survival	80.3	78.6	0.91 (0.73-1.13)
3-year LR by CRM			
Involved	13.8	20.7	0.64 (0.25-1.64)
Uninvolved	3.3	8.9	0.36 (0.23-0.57)
3-year LR by tumor position			
<10-15 cm	1.2	6.2	0.19 (0.07-0.47)
>5-10 cm	5.0	9.8	0.50 (0.28-0.90)
0-5 cm	4.8	10.4	0.45 (0.23-0.88)
3-year LR by plane of dissection†			$P = .0039$
Muscularis propria	10	16	
Intramesorectal	4	10	
Mesorectal	1	7	

RT, radiation therapy; CRT, chemoradiotherapy; HR, hazard ratio; CRM, circumferential margin; LR, local recurrence.
*Compared with preoperative RT as baseline.
†HRs not provided.

LR worse with CRM involved; worse in selective post-ops
LR lowest for upper rectal cancers; worse in selective post-ops

MRI: imaging advanced

- High-resolution MRI
  - opportunity to identify relevant variables preoperatively
  - Allows potentially more *selective* use of preoperative therapies
- Better than ERUS for evaluation of distance from tumour to mesorectal fascia
  - Mercury study, 92.5% positive correlation with T-stage

MRI

- CRM assessment
  - has important prognostic value re: local/distant recurrence
- Nodal involvement inside and outside the mrf
- Depth of penetration thru muscularis propria
- Extramural venous invasion
- Can assist surgical decisions – plane of surgery

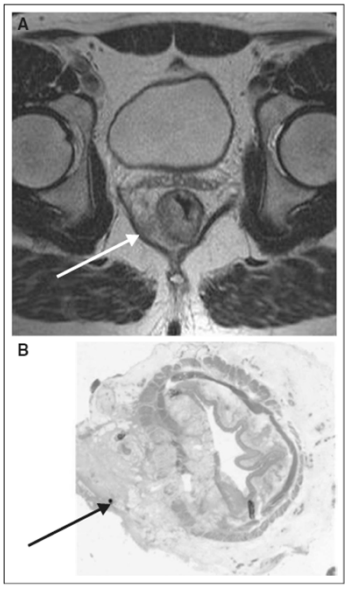


Fig 2. (A) T2-weighted axial thin section magnetic resonance imaging scan and (B) the corresponding histology section stained with hematoxylin and eosin. This scan and the corresponding histology section depict a low rectal tumor with involvement of the potential circumferential resection margin (white arrow) confirmed on corresponding histology (black arrow).

Usefulness of old TNM T3 subclassification?

TNM	Stage	Extension to	
Tis N0 M0	0	Carcinoma *in situ*: intraepithelial or invasion of lamina propria	
T1 N0 M0	I	Submucosa	
T2 N0 M0	I	Muscularis propria	
T3 N0 M0	IIA	Subserosa/perirectal tissue	
	Substaging[a]	T3a	<1 mm
		T3b	1–5 mm
		T3c	5–15 mm
		T3d	15+ mm
T4 N0 M0	IIB	Perforation into visceral peritoneum (b) or invasion to other organs (a)[b]	
T1–2 N1 M0	IIIA	1–3 regional nodes involved	
T3–4 N1 M0	IIIB	1–3 regional nodes involved	
T1–4 N2 M0	IIIC	≥4 regional nodes involved	
T1–4 N1–2 M1	IV	Distant metastases	

NB: based on TNM 5 and pre-treatment MRI (and/or histopathologic classification). NOT validated/incorporated in TNM versions 6 and 7.

Mercury: Identification of good prognosis stage I/II/III rectal ca pts: surgery alone?

TABLE 3. Outcomes for MRI-predicted Good Prognosis Patients and Effect of Univariate and Multivariate Analysis Local Recurrence, 5-year Overall Survival and Disease-free Survival

MERCURY—MRI-predicted Good Prognosis Patients	Local Recurrence	5-Year Overall Survival	5-Year Disease-free Survival
Total patients (n = 122)	3.3%	68.2% (95% CI, 60.3%–7.0%)	84.7% (95% CI, 76.0%–90.4%)
T3a/b N0, N1, and N2 (n = 58)	1.7%	67.9% (95% CI, 53.9%–78.5%)	81% (95% CI, 66.1%–89.8%)
T1,2, or, 3b, N positive disease (n = 22)	0%	81% (95% CI, 48.7%–78.2%)	95% (95% CI, 69.5%–99.3%) .

Multivariate analysis

Preoperative Factor	Local recurrence		Overall Survival		Disease-free Survival	
	Hazard Ratio	*P*	Hazard Ratio	*P*	Hazard Ratio	*P*
Height of tumor (low)	2.580 (0.268–24.829)	0.412	0.457 (0.171–1.220)	0.118	1.917 (0.598–6.152)	0.274
Type of operation (APE)	No events	n/a	2.128 (1.049–4.317)	0.036	1.031 (0.270–3.936)	0.964
Age (>65), y	0.821 (0.114–5.899)	0.845	2.967 (1.407–6.255)	0.004	0.968 (0.375–2.501)	0.947
Sex (male)	0.244 (0.025–2.374)	0.224	1.120 (0.585–2.146)	0.733	0.955 (0.376–2.428)	0.923

APE indicates abdominoperineal excision

Hypothesis: optimal MRI staging enables identification of a group of stage II and III patients with good prognosis rectal cancer and therefore the ability to avoid the need for pre-operative therapy.

Tumour height ≤5 cm vs > 5 cm was not associated with LR or DFS on multivariate analysis. Age and APR were associated with worse OS.

Low local recurrence rates in MRI-defined T3a/b, regardless of nodal status and *location* of tumour.

Taylor et al, Ann Surg 2011

Tumour location and benefit from RT or CRT

- Upper rectal tumours vs other
  - not bound by physical limitations of mid-lower tumours low in pelvis
  - Technically less challenging to get clear margins
  - Provided CRM not at risk, do these patients really benefit from neoadjuvant RT or CRT….?

Local recurrence in rectal cancer with neoadjuvant and adjuvant therapy

Trial (year results published)	Design	N	Upper rectal ca subset, distance from anal verge (cm), (%)	Follow-up (months)	Treatment	Local recurrence, overall	Local recurrence, effect, upper rectal
Swedish Rectal Cancer Trial (1997)	RCT	1168	>11 (27)	60	Neo short course RT vs surgery alone	11% vs 27% (p<0.001)	**NS p=0.30**
Dutch TME Trial (2001)	RCT	1861	10.1-15 (30)	24	Neo short-course RT (standard TME) vs surgery alone	2.4% vs 8.2% (p<0.001) 10-year 5% vs 11% (p<0.001)	**NS P=0.17**
German Rectal Cancer Study Group (2004)	RCT	799	>10 (15)	60	Neo long course RT + chemo vs adj long course RT + chemo	6% vs 13% (p=0.006)	**NS**

Adapted from Popek et al, Clin Colorec Ca 2012

Valentini et al, JCO 2011

- "Nomograms for Predicting Local Recurrence, Distant Metastases, and Overall Survival for Patients With Locally Advanced Rectal Cancer on the Basis of European Randomized Clinical Trials"
- Purpose: develop accurate models and nomograms to predict local recurrence, distant metastases, and survival for patients with locally advanced rectal cancer treated with long-course CRT followed by surgery

Valentini et al, Rectal cancer nomograms

- All data (N = 2,795) from five major European clinical trials for rectal cancer were pooled and used to perform an extensive survival analysis and to develop multivariate nomograms based on Cox regression
- The variables: sex, age, clinical tumor stage stage, *tumor location*, radiotherapy dose, concurrent and adjuvant chemotherapy, surgery procedure, and pTNM stage

Valentini et al, Rectal cancer nomograms

Table 1. Characteristics of the Five European Randomized Trials (N = 3,458) for Training the Prediction Models

Trial Name	Study Design	Inclusion Criteria	Accrual	No. of Patients	Reference
European Organisation for Research and Treatment of Cancer (EORTC) 22921	Preoperative RT Preoperative CRT Preoperative RT + postoperative CT Preoperative CRT + postoperative CT	T3 or resected T4M0 No history of cancer Age < 80 years WHO performance index 0-1 Tumor within 15 cm of the anorectal verge	1993-2003	1,011	Bossett et al[1]
French (Fédération Francophone de Cancérologie Digestive [FFCD])	Preoperative RT Preoperative CRT	T3,T4, M0 Age < 75 years WHO performance index 0-1	1993-2003	733	Gérard et al[2]
German (CAO/ARO/AIO 94 [Working Group of Surgical Oncology/ Working Group of Radiation Oncology/Working Group of Medical Oncology of the Germany Cancer Society])	Preoperative CRT Postoperative CRT	cT3-4 or cN-positive No history of cancer Age < 75 years Tumor within 16 cm of the anorectal verge	1995-2002	823*	Sauer et al[13]
Polish	Preoperative RT (5 cycles of 5 Gy) Preoperative CRT (50.4 Gy)	cT3-4, resectable tumor Age < 75 years WHO performance index 0-2 No sphincter involvement	1999-2002	312*	Bujko et al[2]; Bujko et al[14]
Italian	Preoperative CRT Preoperative CRT + postoperative CT	cT3-4 No history of cancer Age < 75 years Tumor within 15 cm of the anorectal verge	1992-2001	579	Cionini et al (submitted)[15]

Abbreviations: CRT, chemoradiotherapy; CT, chemotherapy; EORTC, European Organisation for Research and Treatment of Cancer; RT, radiotherapy.
*Only the preoperative long-course radiotherapy arm was used for this study.

Valentini et al, Rectal cancer nomograms

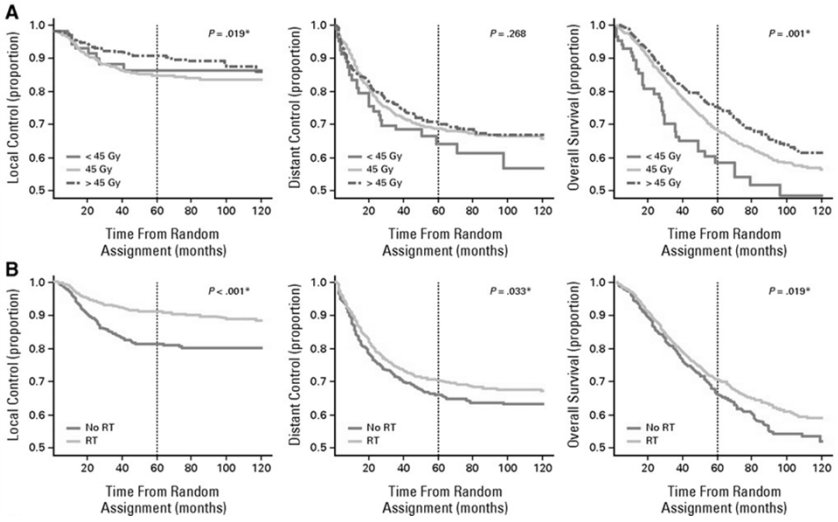
Table 2. Event-Free Rates at 5 and 10 Years for the Complete Randomized Pooled Data Set, Stratified for Each Variable

Variable	No. of Patients	Local Control			Distant Control			Overall Survival		
		5 Years	10 Years	*P*	5 Years	10 Years	*P*	5 Years	10 Years	*P*
Total No. of patients	2,795	87.1	85.7	—	69.2	65.8	—	69.6	57.3	—
Clinical diagnosis										
Sex				.466			.138			< .001*
Male	1,961	87.4	85.1		67.9	64.8		67.6	54.1	
Female	843	88.7	87.0		72.1	68.1		74.1	64.9	
Age, years				.170			.191			< .001*
≤ 49	378	84.5	83.9		68.0	64.5		71.9	63.1	
50-59	746	86.9	85.9		70.1	66.6		72.9	65.2	
60-69	1,131	88.7	85.4		67.3	64.5		67.0	54.6	
≥ 70	540	89.8	87.4		72.8	68.3		68.8	46.9	
Tumor location				.127			.001*			.001*
Low	953	86.0	84.8		64.3	60.1		64.7	52.6	
Mid	1,461	88.2	85.4		70.9	68.1		71.5	60.8	
High	369	90.8	88.6		75.4	72.5		74.3	55.6	

Tumour location (high best) predicts for distant control and overall survival

- however, not independent factor in multivariate analysis as final predictors in the nomogram

Kaplan-Meier curves stratified for the treatment factors (A) radiotherapy dose, (B) concurrent chemotherapy RT/no RT



Valentini V et al. JCO 2011;29:3163-3172

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Who should have pre-op CRT?

- Advanced tumours at *any location*:
  - "The ugly"
- T3, mrf + (CRM breached or threatened)
- T4;
- Sacral +
- Node + (esp lateral LN+)

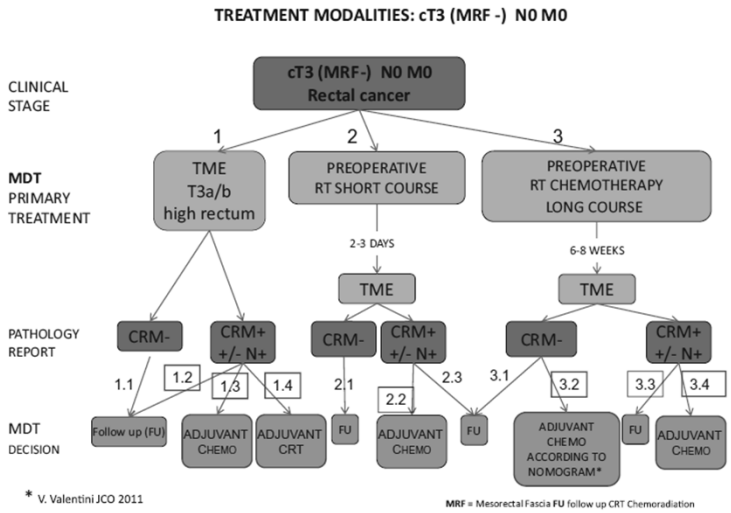
Who doesn't need pre-op CRT?

- "The good"
- T1/T2
- Mrf clear (CRM not threatened)
- N0
- Very low local recurrence rates, and high cure rates after TME surgery

What about the in-betweeners?

- T3, esp upper rectum
- Mrf clear (CRM not threatened, predicted ≥ 2mm)
- N0

Treatment algorithm, cT3 N0 rectal ca



Valentini et al European Registration of Cancer Care 2014

Are there clearly distinguishable intermediate T3 groups who do not need RT?

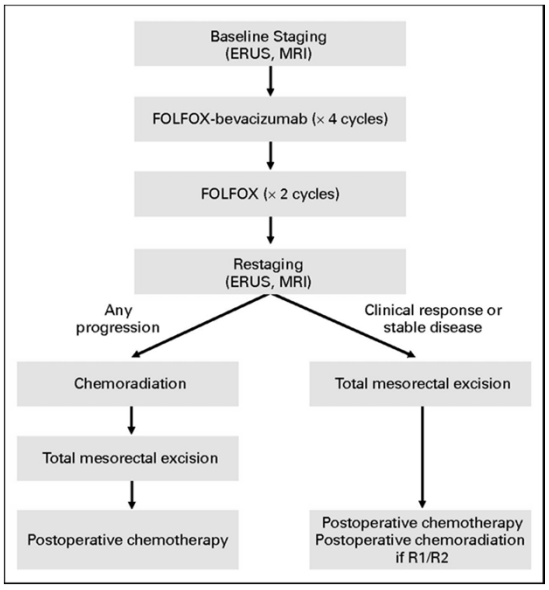
- Based on MRI and clinical risk factors
- T3a/b, <4 mm extension into muscularis propria, CRM not threatened (predicted ≥ 2mm), cN0, M0
- Overall – chance of R0 resection and good quality in mesorectal plane, no shrinkage required

Glynne-Jones, 2014

Schrag et al, JCO 2014

- MSKCC07-021
- Single institution phase II trial
- Thirty-two patients with clinical stages II to III rectal cancer
- All were candidates for low anterior resection with total mesorectal excision (TME)

Patient flow diagram.



Schrag D et al. JCO 2014;32:513-518

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Schrag et al, JCO 2014

Table 1. Summary of Study Outcomes With Mean of 53 Months of Follow-Up Since Enrollment

Study Outcome	No.	%	95% CI
R0 resection rate	32	100	89 to 100
Pathologic complete response rate	8	25	11 to 43
Completion of neoadjuvant FOLFOX/bevacizumab	30	93.8	79 to 99
Preoperative chemoradiation	2	6.3	1 to 21
Postoperative radiation	1	3.1	1 to 16
4-year local recurrence rate	0	0	0 to 11
4-year disease-free survival	27	84	67 to 94
4-year overall survival rate	29	91	75 to 98

Abbreviation: FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin.

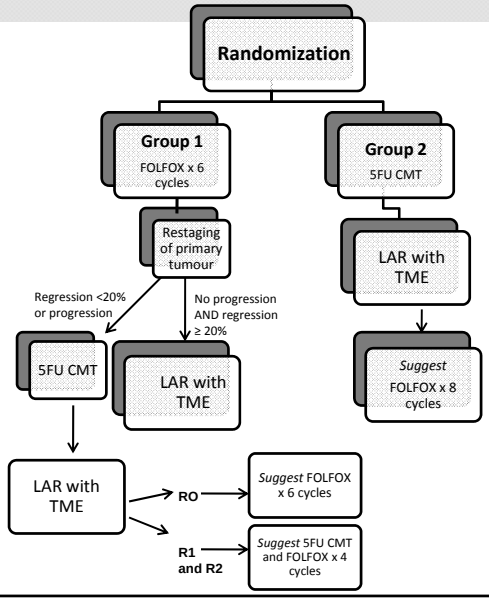
Schrag et al, JCO 2014

- For selected patients with clinical stages II to III rectal cancer, neoadjuvant chemotherapy and *selective radiation* does not seem to compromise outcomes
- Preoperative Radiation or Selective Preoperative Radiation and Evaluation Before Chemotherapy and TME (PROSPECT), a randomized phase III trial to validate this experience, is now open in the US cooperative group network…

A phase II/III trial of neoadjuvant FOLFOX with selective use of combination XRT in locally advanced rectal cancer

- N1048: NCCTG through Alliance for Clinical Trials in Oncology **"NCIC CRC7" – PROSPECT TRIAL**
- **Can RT be safely omitted in some patients and still achieve RO and good local control?**
- Eligibility: clinical T2N1, T3N0, T3N1 (stage IIA, IIIA, or IIIB) adenocarcinoma of the rectum where standard treatment recommendation would be combined modality neoadjuvant chemoradiation followed by curative intent surgical resection
  - Tumour >5 cm to 12 cm from anal verge; Tumour not within 3 mm of mrf on pre-op MRI or ERUS/pelvic CT
- Objectives: Primary Outcomes: Pelvic R0 resection rate (phase II) DFS (Phase III) Time to local recurrence (TLR)

A phase II/III trial of neoadjuvant FOLFOX with selective use of combination XRT in locally advanced rectal cancer (NCIC CRC7): Draft Schema



Summary

- Paucity of data evaluating outcomes of locally advanced upper rectal cancer, or location-based analyses, treated with and without neoadjuvant RT
- Adequate CRM appears to be the major variable shown to correlate with local recurrence rates in
  - Accurate pre-treatment staging is key
- *Some* patients with T3N0 rectal cancer may have little/no benefit with RT
  - Esp if CRM is not threatened
  - However, CRM status likely *more important* than location

Summary…

- Re-think pre-op CRT for "all T3/4 and/or N+"
- Await results of CRC7/Prospect Trial for more definitive results
  - …update coming up!
- Weigh risks/benefits of CRT
  - Multidisciplinary discussion
  - Patient and tumour factors