MADRID 2023 ESMO congress

Controversy session:

Can we avoid preoperative (chemo) radiotherapy in locally advanced rectal cancer patients?

Against the motion

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Disclosures

- Research funding from Cancer Research UK and Yorkshire Cancer Research

Can we avoid pre-operative (chemo) radiotherapy in locally advanced rectal cancer patients?

NO!

In **locally advanced** rectal cancer **we should NOT**:

- **Omit the use** of pre-operative (chemo) radiotherapy
- **Replace** pre-operative (chemo) radiotherapy with chemotherapy alone
- **Remove** the opportunity for organ preservation

http://joannemattera.blogspot.com/2011/06/marketing-mondays-red-flags.html

What do we mean by “locally advanced” rectal cancer?

- **Definitions vary widely** internationally **and this need to change** – we are not using a common language - this is both confusing and is **likely to impair optimal patient care**

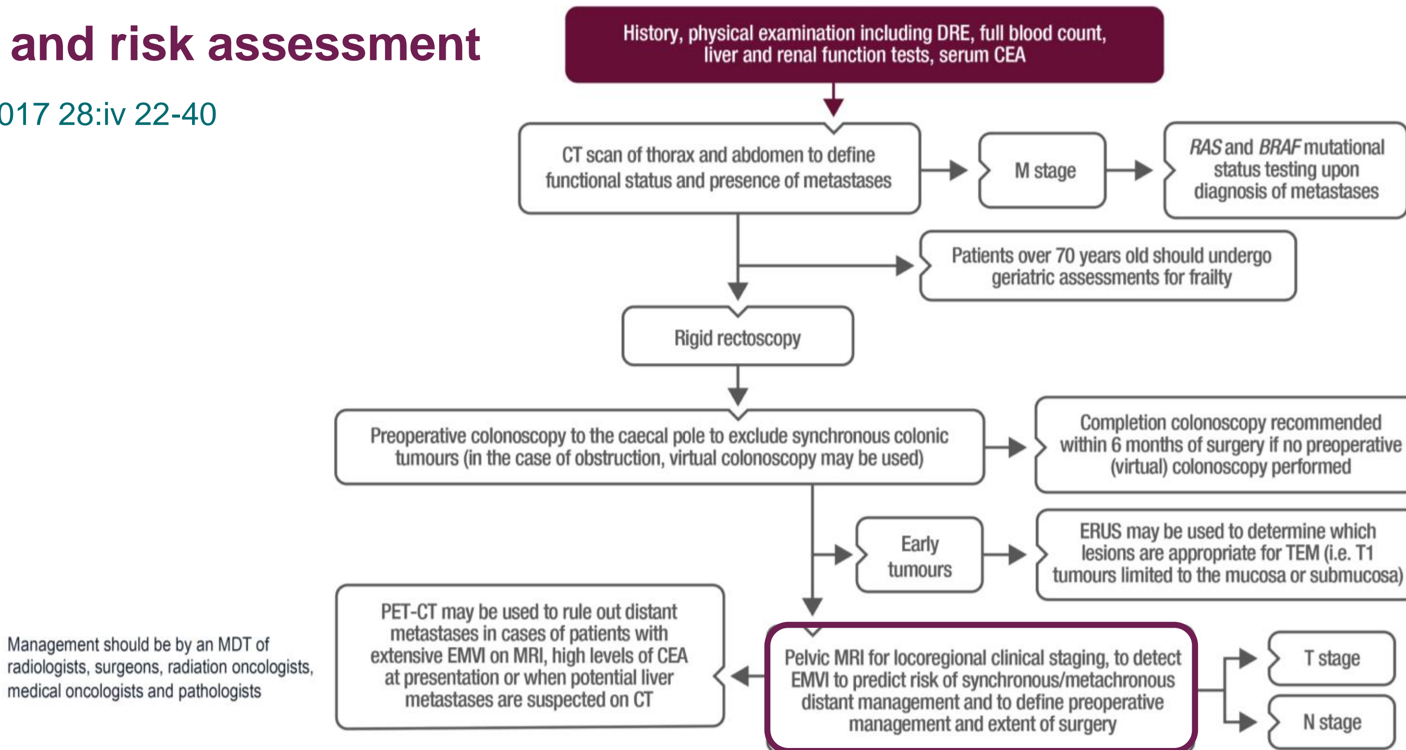
- Rectal cancer management in 2023 should be **appropriately risk-stratified** to determine the appropriate selection of neoadjuvant therapy strategies

- In my opinion, the evidence **based ESMO rectal cancer guidelines currently provide the best risk-stratified guidelines** to guide these decisions

ESMO rectal cancer clinical practice guidelines

Staging and risk assessment

Ann Oncol 2017 28:iv 22-40



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Pelvic MRI is the essential diagnostic staging tool to enable risk stratification

MRI provides the essential information to risk stratify

T stage

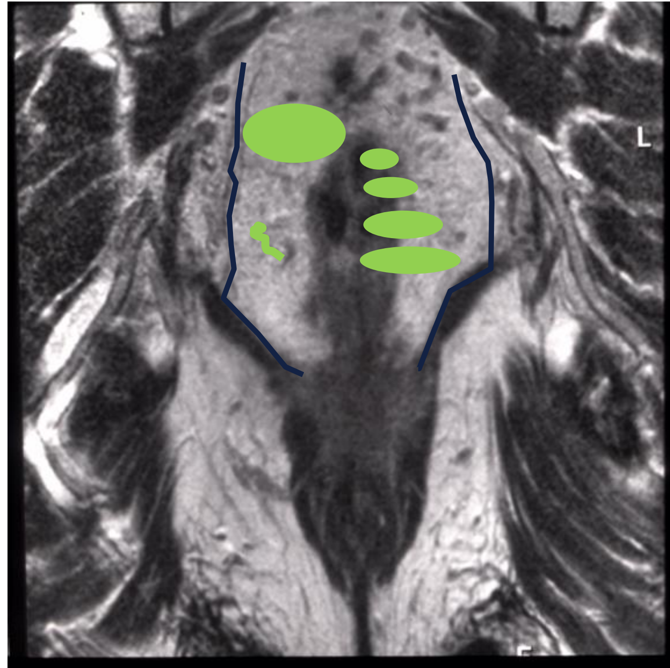
- Studies have validated the sub-classification of T stage predicting risk of loco-regional failure

EMVI

- Clearly identifies EMVI

CRM

- 88% - 90% accuracy of MRI prediction of pathological clear circumferential margin (defined as >=1mm) – MERCURY study



T stage

- T3a (<1mm)
- T3b (1-5mm)
- T3c (>5-15mm)
- T3d (>15mm)

EMVI

N stage

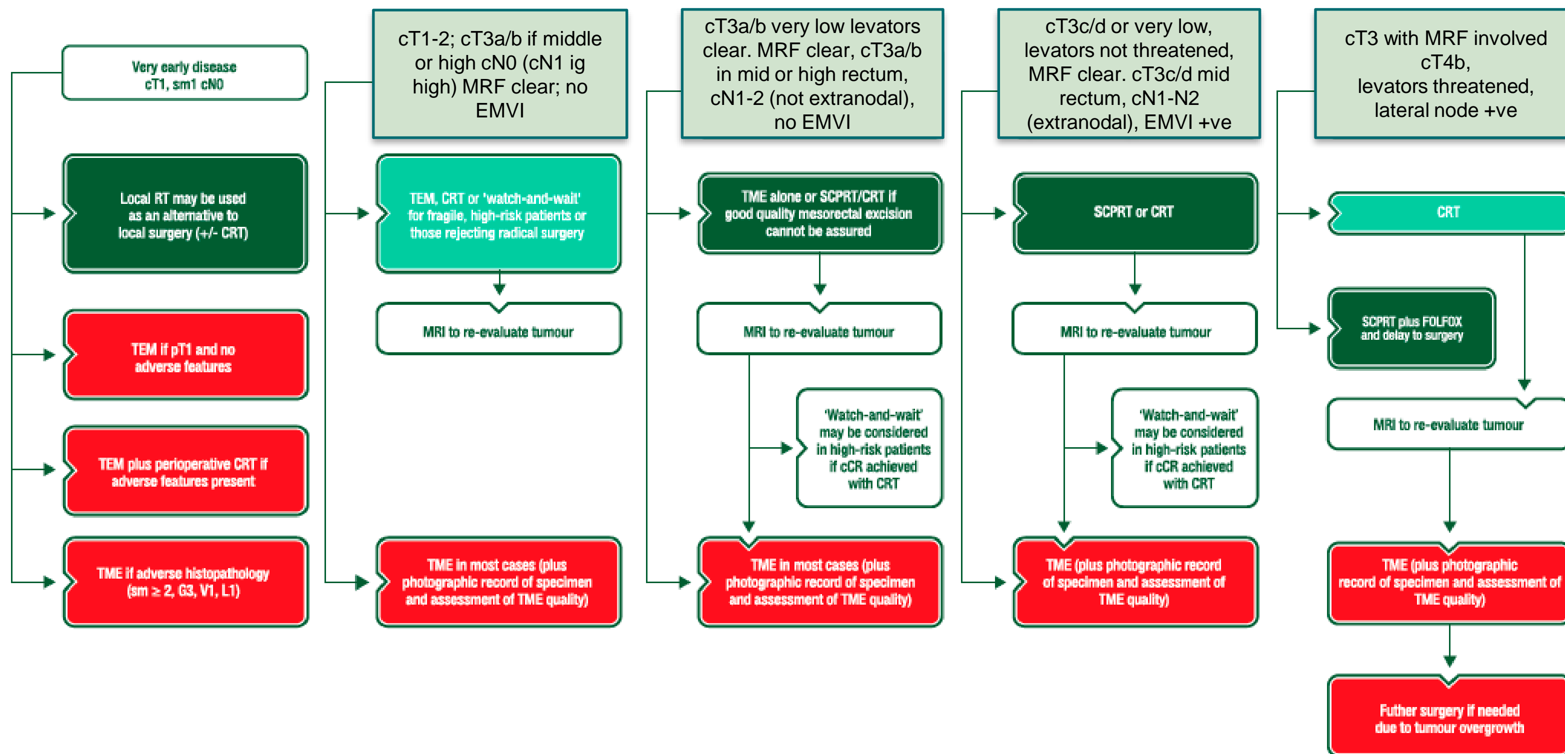
- N0/X/N+

Mesorectal fascia

- <=1mm

MERCURY Study Group BMJ 2006

ESMO rectal cancer clinical practice guidelines



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Quality of surgery excision and the added benefit of radiotherapy

Mesorectal plane (good plane of surgery achieved)

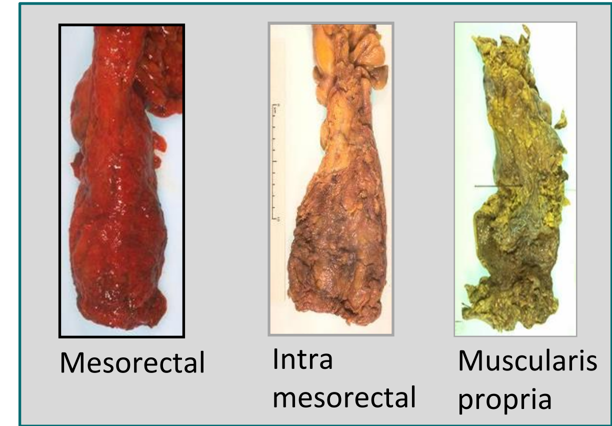
- Intact mesorectum with only minor irregularities of a smooth mesorectal surface; no defect deeper than 5 mm; no coning; and smooth circumferential resection margin on slicing

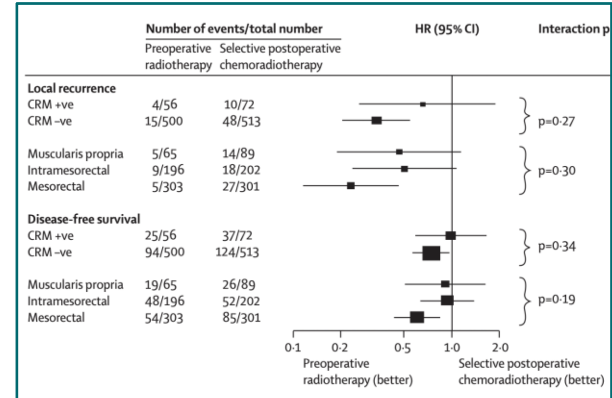
Intramesorectal plane (moderate plane of surgery achieved)

- Moderate bulk to mesorectum, with irregularities of the mesorectal surface; moderate distal coning; muscularis propria not visible with the exception of levator insertion; and moderate irregularities of circumferential resection margin

Muscularis propria plane (poor plane of surgery achieved)

- Little bulk to mesorectum with defects down onto muscularis propria; very irregular circumferential resection margin; or both

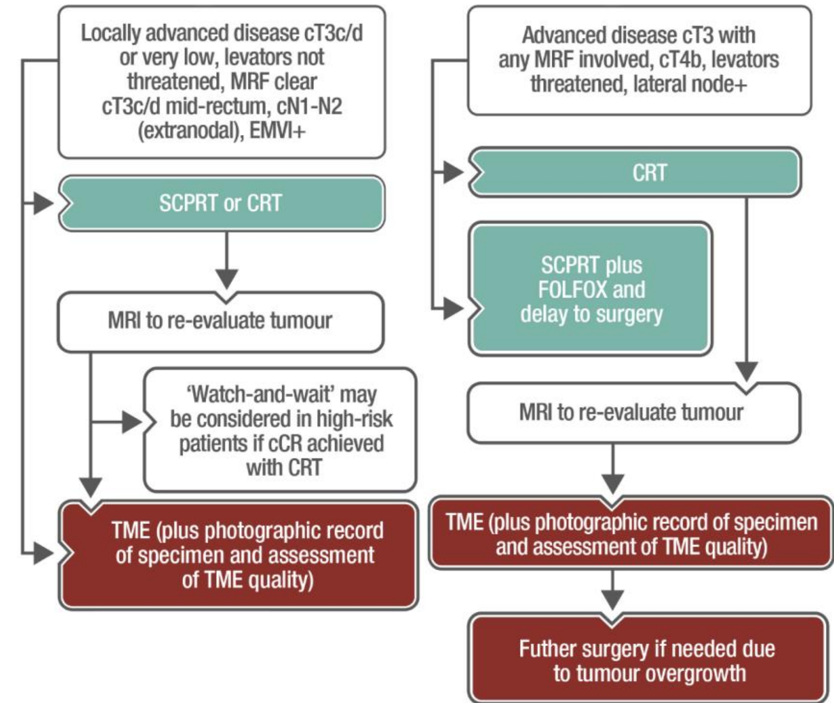




Quirke et al Lancet 2009

ESMO rectal cancer practice guidelines – locally advanced disease

- **Pre-operative (chemo) radiotherapy is mandated**
- Local recurrence rates high **without radiotherapy** in this patient group
- Increasing use of neoadjuvant chemotherapy **AND** (chemo) radiotherapy to address local and systemic risk
- Insufficient randomised evidence to change SoC
- **So, pre-operative (chemo) radiotherapy should not be omitted**



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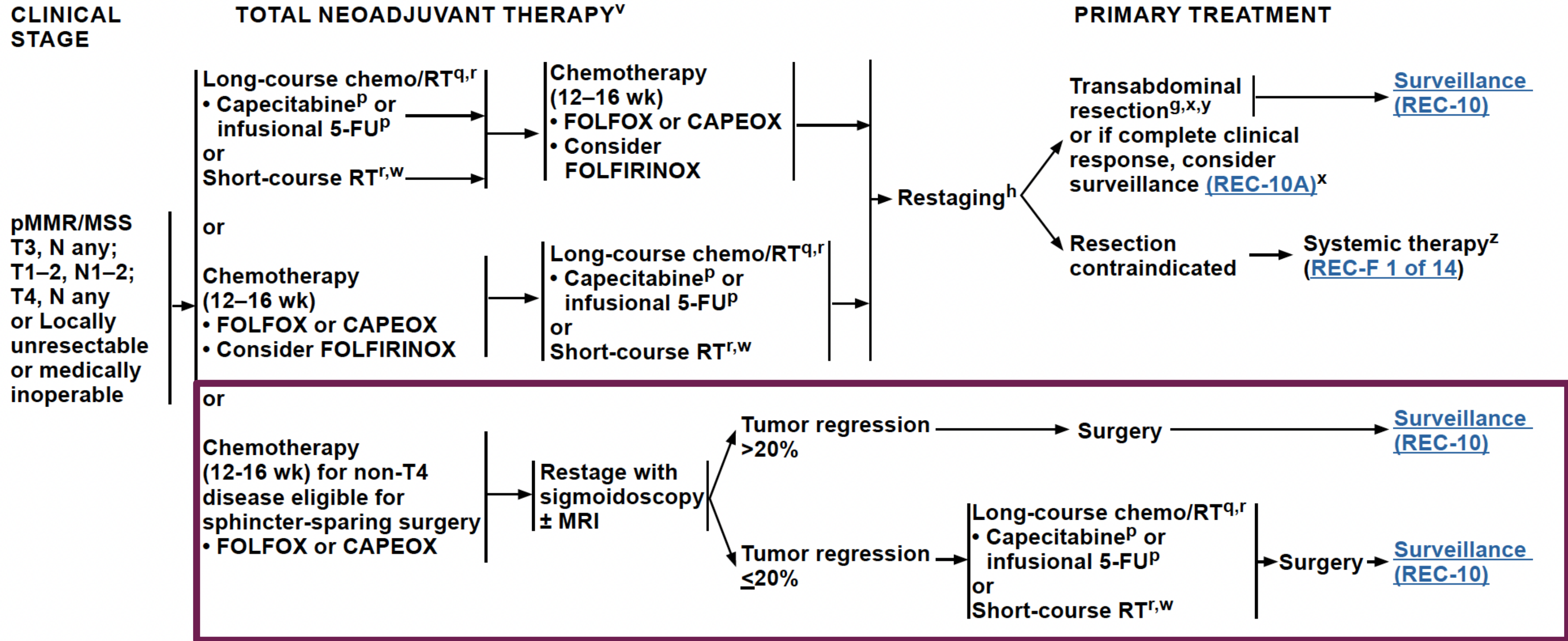
NCCN Rectal Cancer Guidelines v5.2023 – pMMR / MSS



This treatment option is not supported by high level clinical trial evidence for most of the defined subgroups of patients

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Can we avoid pre-operative (chemo) radiotherapy in locally advanced rectal cancer patients?

NO!

In **locally advanced** rectal cancer **we should NOT**:

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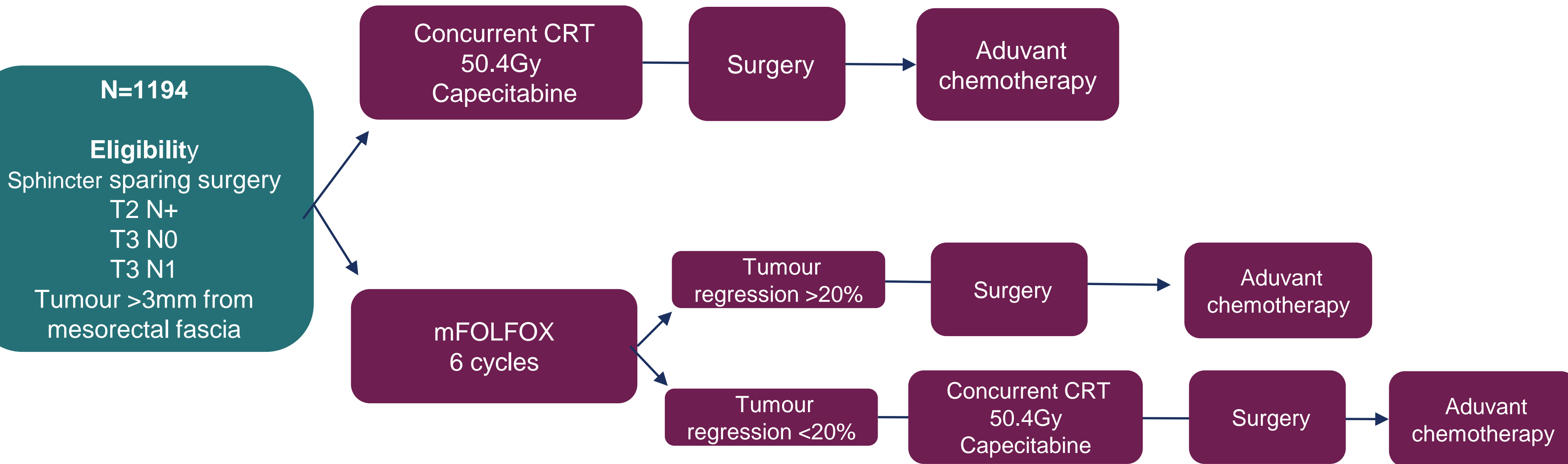
The PROSPECT trial – study design

An important and large phase III trial comparing FOLFOX and CRT



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N Engl J Med. 2023 Jul 27;389(4):322-334c

The PROSPECT trial - case mix

Included:

- Suitable for a sphincter-sparing treatment approach
- T2 N1
- T3 node negative
- T3 N1
- Tumour >3mm of the mesorectal fascia

Excluded

- T4 tumours
- Four or more pelvic lymph nodes with a short axis >10mm
- Tumour visible within **3mm** of the radial margin

	FOLFOX n=585	CRT n=543
T2 node +ve	10.8%	7.0%
T3 N0	39.7%	36.5%
T3 node +ve	49.5%	56.5%

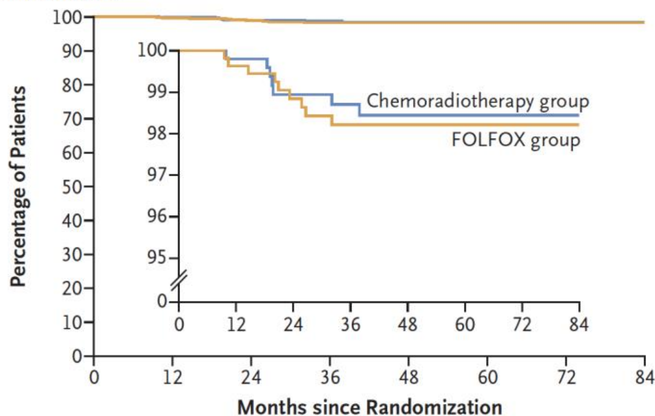
84% patients underwent staging MRI

- **38% T3 N0 with >=3mm from tumour to the mesorectal fascia**
- **Low tumours not included**
- **FOLFOX and CRT over-treatment for many patients**
- **<u>Not</u> locally advanced disease in many patients (ESMO guidelines)**

N Engl J Med. 2023 Jul 27;389(4):322-334c

The PROSPECT trial - cancer outcomes

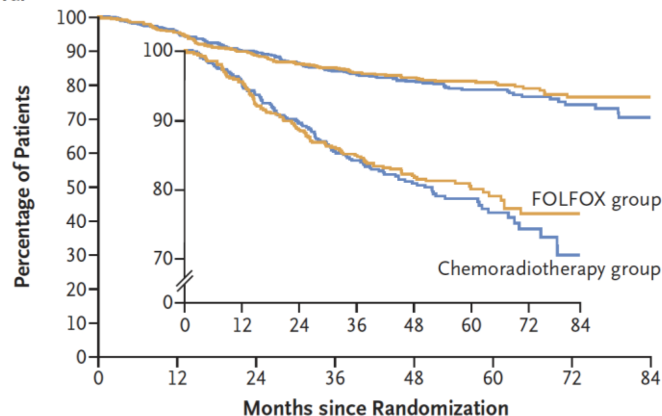
Freedom from Local Recurrence



No. at Risk	0	12	24	36	48	60	72	84
FOLFOX group	585	542	483	438	339	195	95	39
Chemoradiotherapy group	543	499	455	389	289	175	78	36

Group	No. of Events/ Total No.	Hazard Ratio (95% CI)	5-Year Estimate
			percent
FOLFOX group	9/585	1.18 (0.44–3.16)	98.2 (97.1–99.4)
Chemoradiotherapy group	7/543	Reference	98.4 (97.3–99.6)

Disease-free Survival



No. at Risk	0	12	24	36	48	60	72	84
FOLFOX group	585	543	489	443	342	200	97	42
Chemoradiotherapy group	543	500	456	395	295	181	80	37

Group	No. of Events/ Total No.	Hazard Ratio (90.2% CI)	5-Year Estimate	Stratified P Value for NI
			percent	
FOLFOX group	114/585	0.92 (0.74–1.14)	80.8 (77.9–83.7)	0.005
Chemoradiotherapy group	113/543	Reference	78.6 (75.4–81.8)	—

<2% local recurrence and >78% disease free survival indirect evidence of a very good prognosis group of patients (i.e. not locally advanced)

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The PROSPECT trial - acute toxicity during neo-adjuvant treatment

	FOLFOX	CRT	p value
Acute >= Grade 3 toxicity			
Overall	**41%**	**23%**	p<0.001
PRO-CTCAE SAE (Composite Score 3)			
Fatigue	**42%**	20%	p<0.001
Constipation	**27%**	11%	p<0.001
Pain	22%	18%	0.13
Appetite loss	**22%**	9%	p<0.001
Nausea	**21%**	7%	p<0.001
Neuropathy	19%	5%	p<0.001
Mucositis	**11%**	2%	p<0.001
Diarrhoea	6%	**20%**	p<0.001

N Engl J Med. 2023 Jul 27;389(4):322-334

The PROSPECT trial - acute toxicity 12 months post surgery

	FOLFOX	CRT	p value
PRO-CTCAE SAE (Composite Score 3)			
Fatigue	3%	7%	NS
Constipation	3%	4%	NS
Pain	5%	4%	NS
Appetite loss	1%	1%	NS
Nausea	1%	0%	NS
Neuropathy	3%	**8%**	p=0.01
Mucositis	0%	0%	NS
Diarrhoea	2%	4%	NS

N Engl J Med. 2023 Jul 27;389(4):322-334

The PROSPECT trial - media coverage

We must strive for objective public engagement

UK NEWS WEBSITE OF THE YEAR

The Telegraph

News Sport Money Business Opinion Ukraine Royals Life Style Travel Culture Puzzle

UK news Politics World Health Defence Science Education Environment Investigations Global Health

Thousands of bowel cancer patients can be spared brutal radiotherapy, study finds

The Guardian
Newspaper of the year

"Radiotherapy has been used to treat bowel cancer patients for decades, but **the side effects can be brutal**. It can cause problems that negatively effect quality of life, including infertility, the need for a temporary colostomy, diarrheoa, cramping and bladder problems…"

ESTRO

"Unfortunately, several newspapers reported the PROPSECT trial using provocative and misleading headlines, describing the effects of radiation as brutal. **Such inflammatory language not only goes beyond the evidence of PROSPECT but also risks unnecessarily alarming a large group of rectal cancer patients for whom radiation therapy will form part of their cancer treatment with proven beneficial benefits in survival and quality of life"**

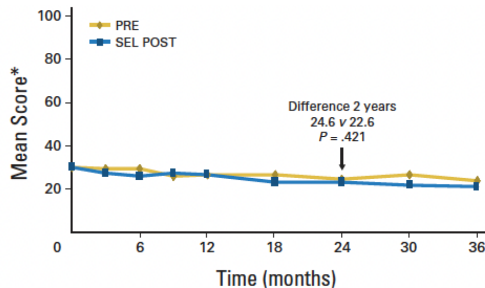
https://www.telegraph.co.uk/news/2023/06/04/bowel-cancer-patients-avoid-radiotherapy-without-risk/
https://www.theguardian.com/science/2022/jun/08/rectal-cancer-research-breakthrough-experimental-treatment-remission
https://www.estro.org/About/Newsroom/News/PROSPECT-trial-adds-another-treatment-possibility

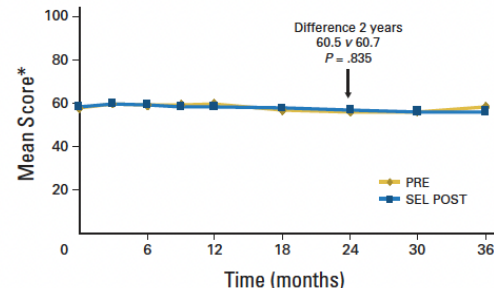
Impact of treatment modalities on patient quality of life

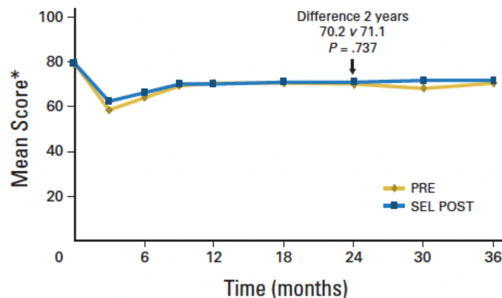
MRC CR07 NCIC C016 trial

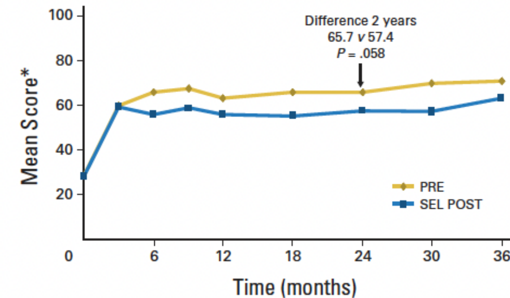
- Randomised trial testing +/- neoadjuvant short course RT
- Demonstrates the substantial detrimental impact of surgery
- Quantifies the additional detrimental impact of radiotherapy
- Greatest detrimental impact of radiotherapy is on sexual function
- Increasing use of advanced radiotherapy techniques

Stephens et al JCO 2010









Can pre-operative chemotherapy replace (chemo) radiotherapy in locally advanced rectal cancer?

- PROSPECT is a well conducted large scale multi-centre phase III trial that **provides valuable data to inform the benefits of using FOLFOX** as an alternative to CRT

- However, it defines FOLFOX as a treatment option for a **defined "intermediate risk" sub-group** of patients

- Many patients in PROSPECT are unlikely to have required either FOLFOX or CRT

- **FOLFOX should not replace receive (chemo) radiotherapy for patients with ESMO defined locally advanced / advanced disease**

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(Chemo) radiotherapy is the essential component of organ preservation +/- chemotherapy strategies

- **International Watch and Wait Database** - 880 (87%) patients with a cCR after pre-operative CRT. Median follow-up time 3·3 years (95% CI 3·1–3·6). The 2-year cumulative incidence of local regrowth was 25·2% (95% CI 22·2–28·5%)
- We **lack any high-level evidence to support the effectiveness of chemotherapy alone** in pMMR/MSS to achieve organ preservation
- **Chemoradiotherapy remains the standard of care** in locally advanced rectal cancer

Lancet 391 p2537 2545 2018

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