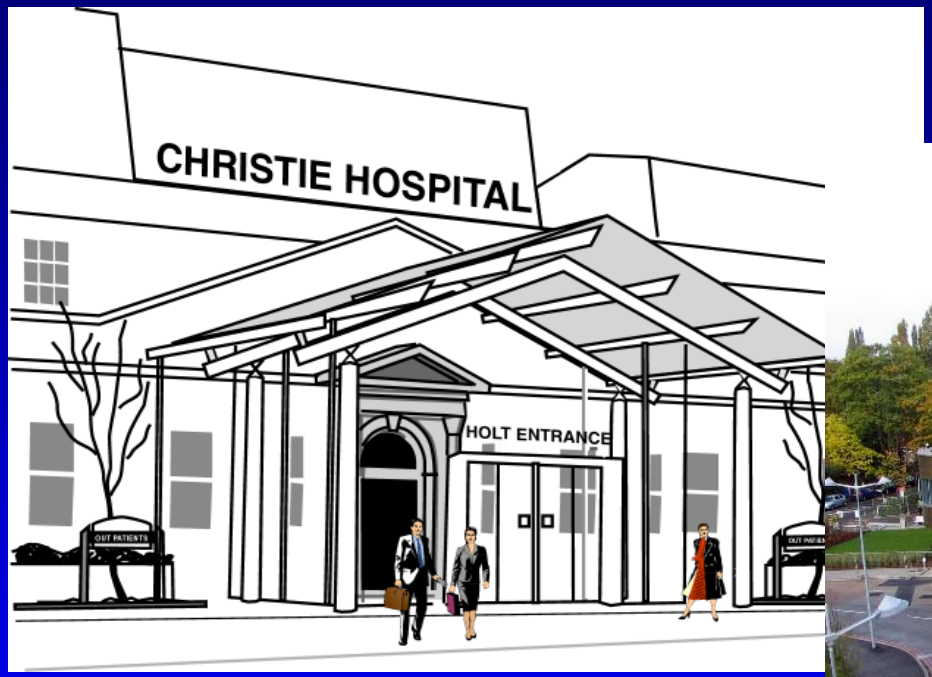
Dr Mark Saunders

Christie Hospital and Paterson Institute of Cancer Research

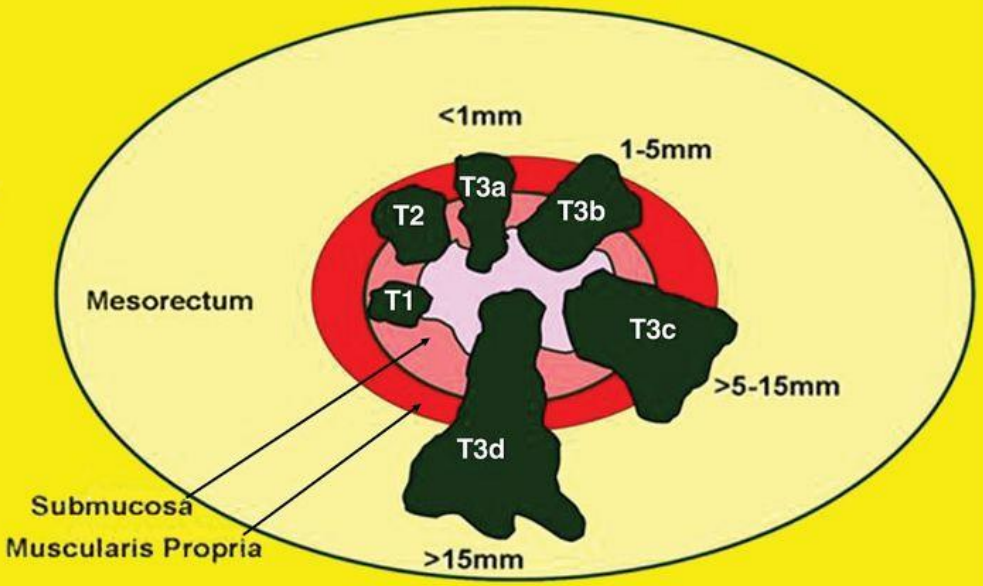


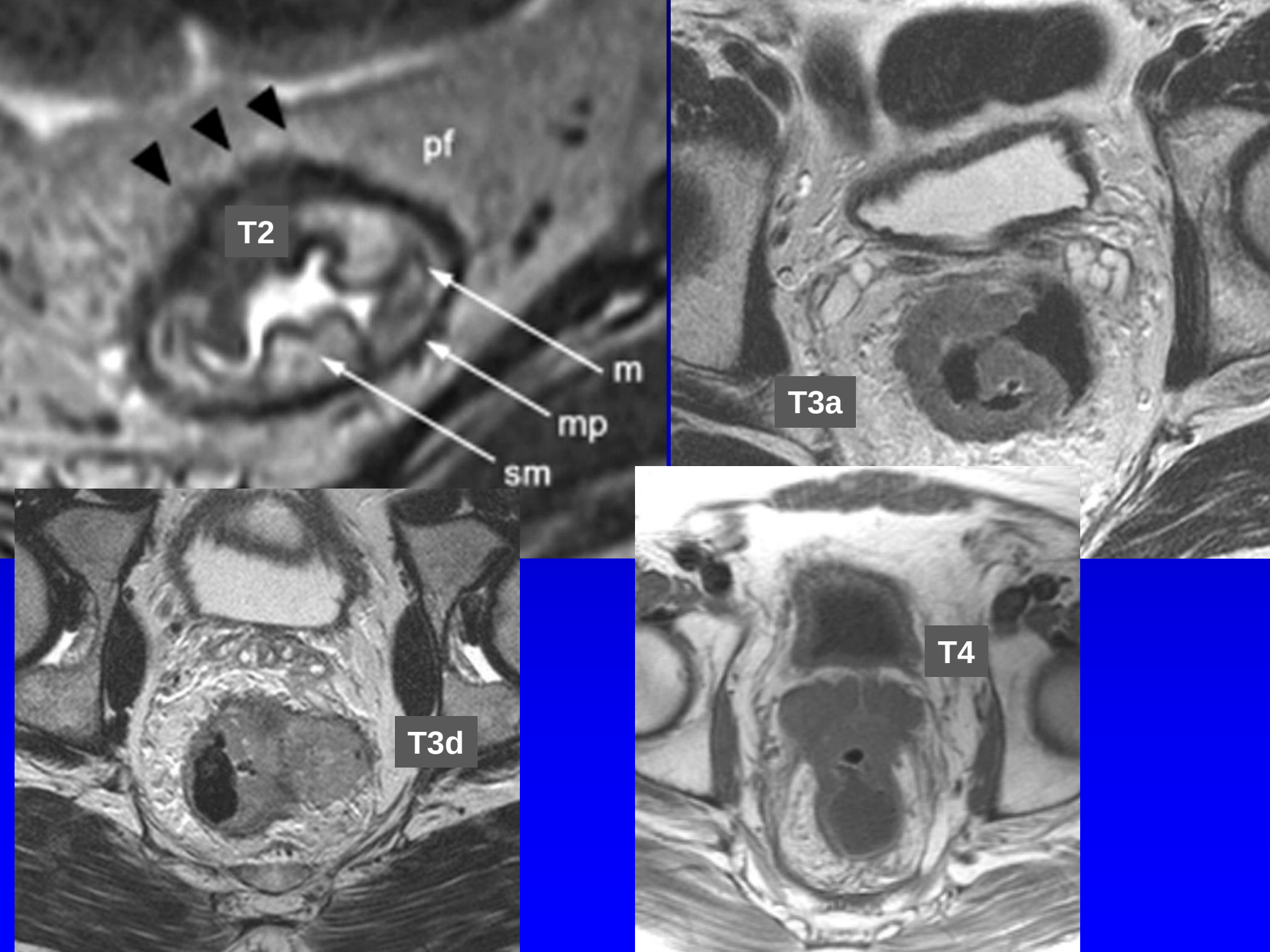
“Perioperative radio/chemoradiotherapy for rectal cancer”

T-staging for rectal cancer

T1: Invades submucosa (sm).
T2: Invades muscularis propria (mp).
T3: Through mp into subserosa or peri-rectal tissues.
T4: Invades other organs / structures and/or perforates visceral peritoneum.

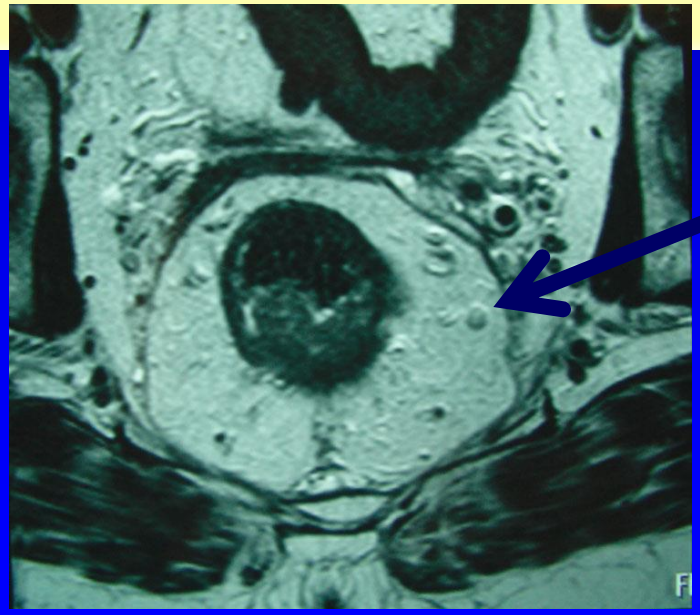
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor invades submucosa but does not extend into circular muscle layer
T2	Tumor invades but does not penetrate MP
T3	Tumor invades subserosa through MP
T3a	• Tumor extends <1mm beyond MP
T3b	• Tumor extends ≥1-5mm beyond MP
T3c	• Tumor extends >5-15mm beyond MP
T3d	• Tumor extends >15mm beyond MP
T4	Tumor invades:
T4a	• Peritoneal reflection
T4b	• Others organs

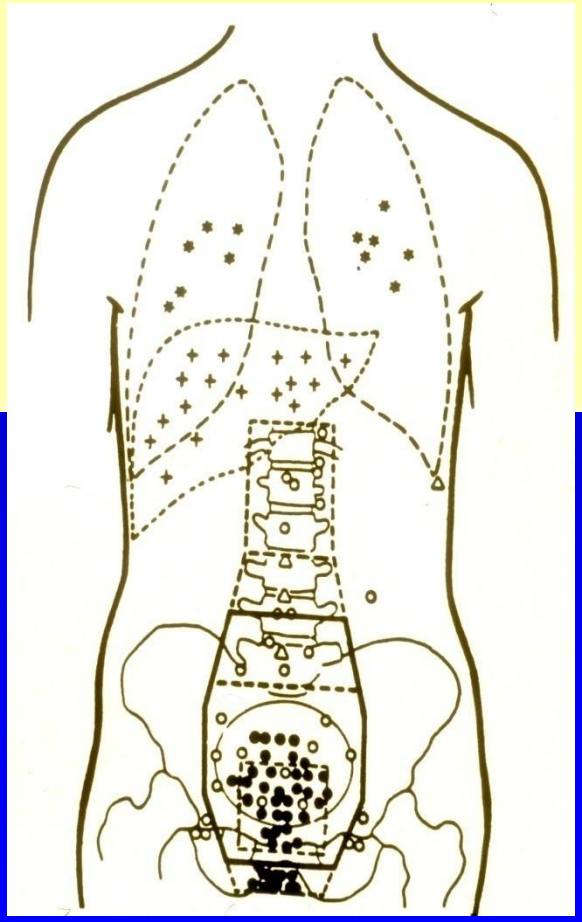



pf
T2
m
mp
sm
T3a
T3d
T4

Risk for N+

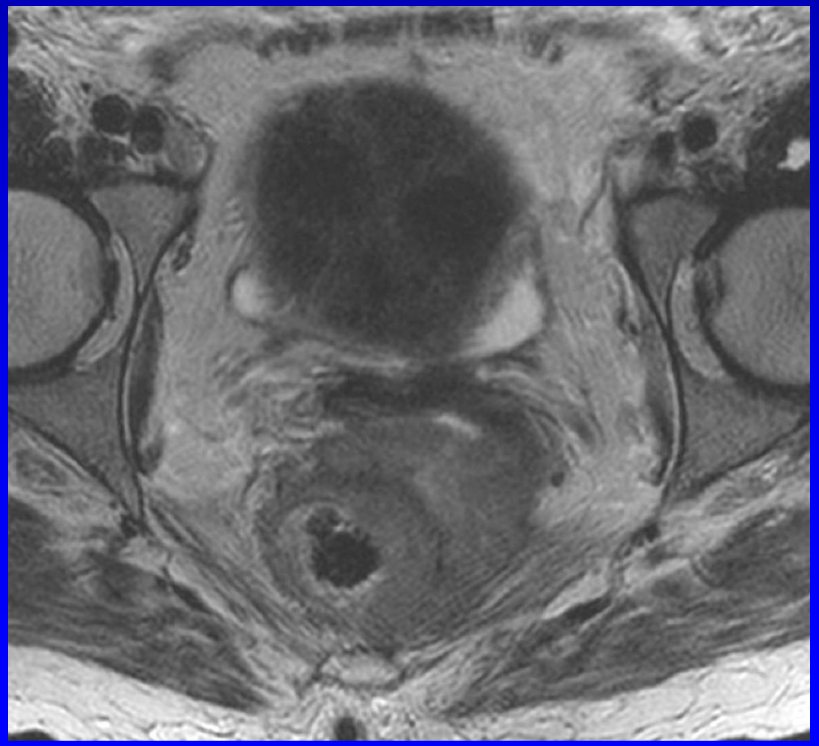
T1	5-10%
T2	15-20%
T3	> 30%
T4	> 50%





MRI high risk features

- Tumour within 1mm or beyond MR fascia
- T3 low lying tumour at/or below levators
- Tumour extending 5mm or more into peri-rectal fat (T3c)
- T4 tumours
- N2 tumours



Gina Brown

Treatment algorithm for localised rectal cancer

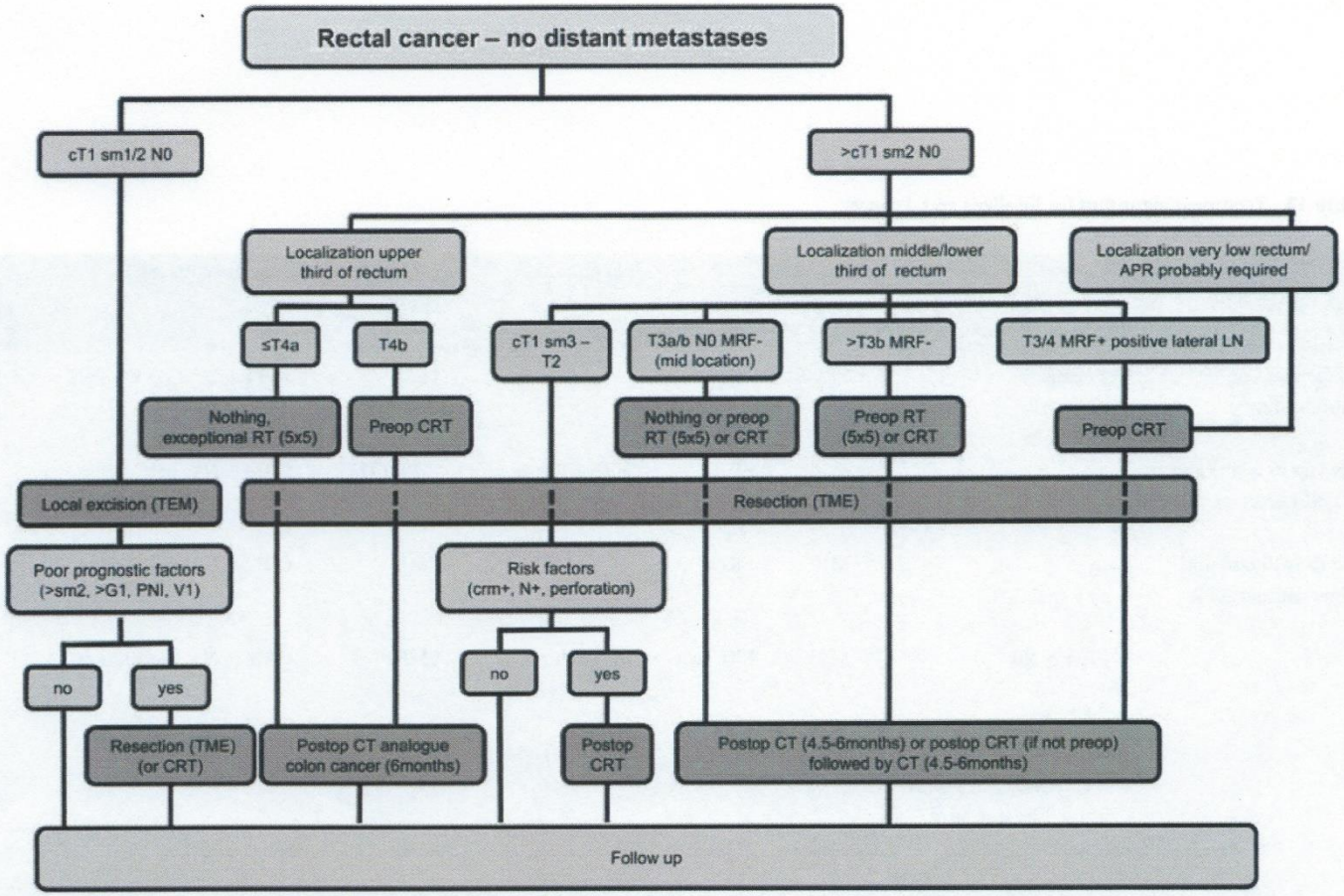


Figure 1. Treatment algorithm for localized rectal cancer. (Lateral LN: drainage of the a rectalis media (if present) or along the obturatorius or internal iliac vessels).

Simplified version !

Pre-operative RT – short or long course?

Operable tumours

Surgery or SCRT

"potentially" operable tumours

LCRT

Less simplified version !

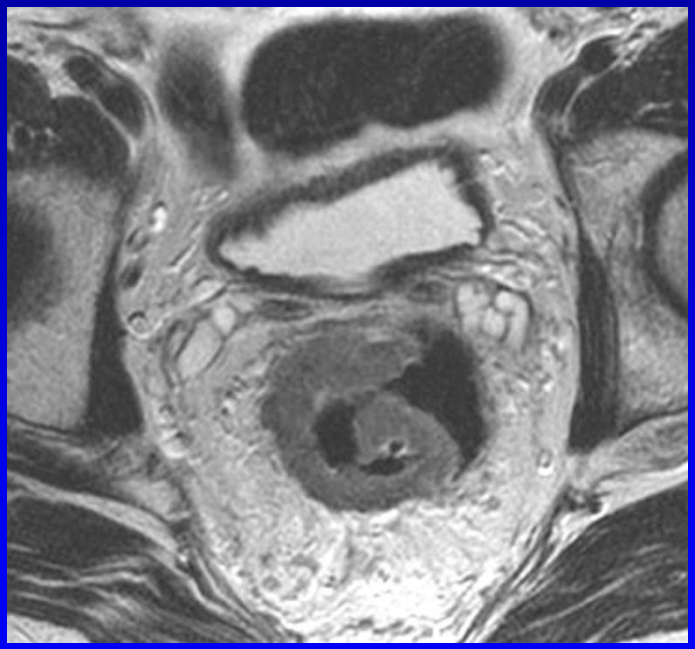
T-stage and Rectal Pre-op RT

	T1	T2	T3 >1mm*	T3 <1mm*	T4
			* Distance from tumour to CRM		
Upper	-	-	- /S(T3c)	L **	L **
Mid	-	-	S	L	L
Low	-	-	L	L	L

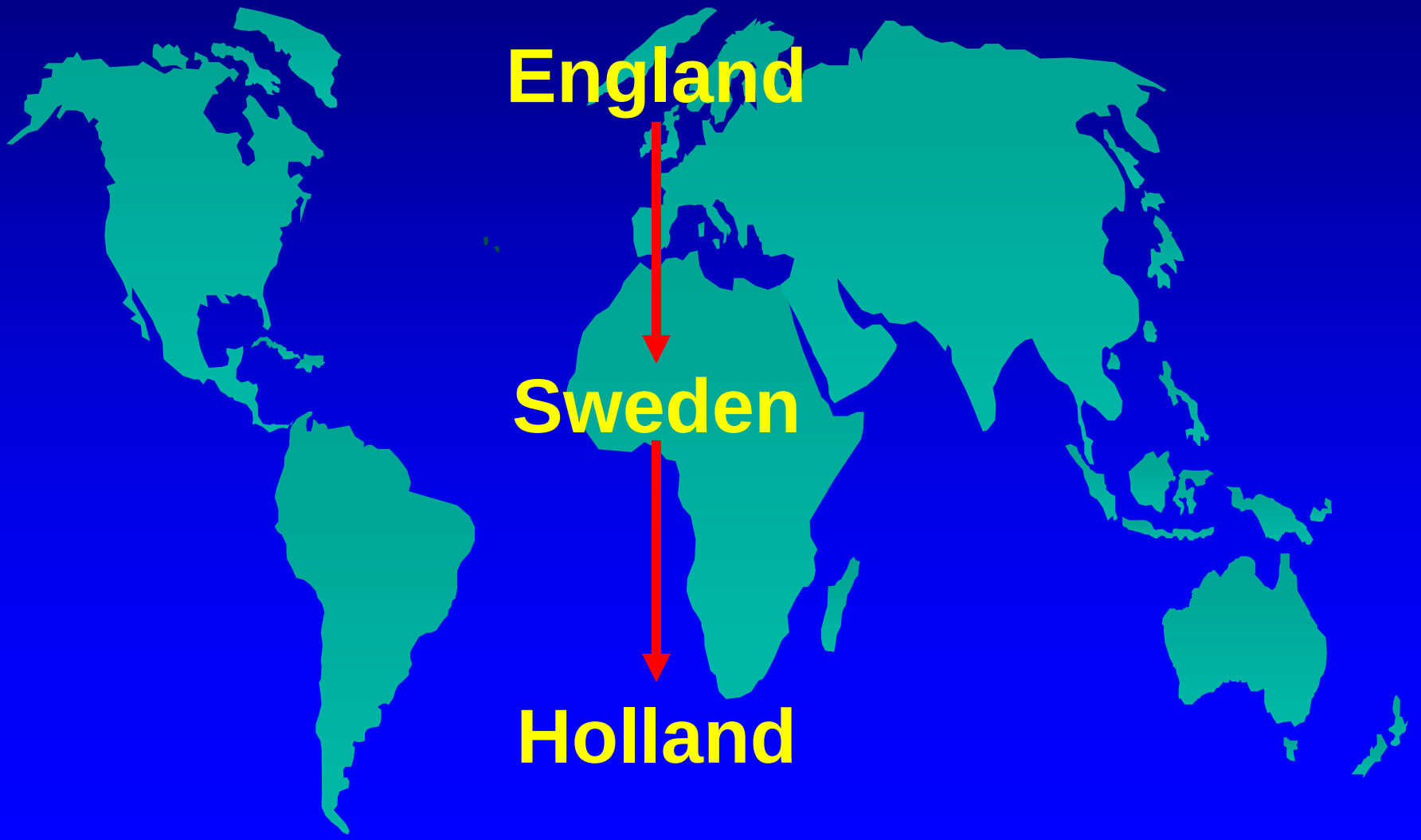
S: Short; L: Long course of RT

** ESMO: "Intensive chemotherapy might be an option, which however has not yet systematically been proved"

SCRT



European History of short course pre-op RT!



The "Swedish" study (1997, updated 2002)

13 years follow-up
1168 patients
Surgery v Surgery after pre-op RT (25Gy / 5 fractions)

	S + RT	S	
Local recurrence	9%	26%	p<0.001
Cancer specific survival	72%	62%	p=0.03
Overall survival	38%	30%	p=0.008

Benefits to all Dukes stages

(Folkesson et al, JCO 23, 24: 5644 - 5650)

The “Dutch” study (2001)

1861 patients

Operable rectal cancer

TME ± RT (25 Gy in 5 fractions)

Local recurrence at 5 years

TME: 11.4%

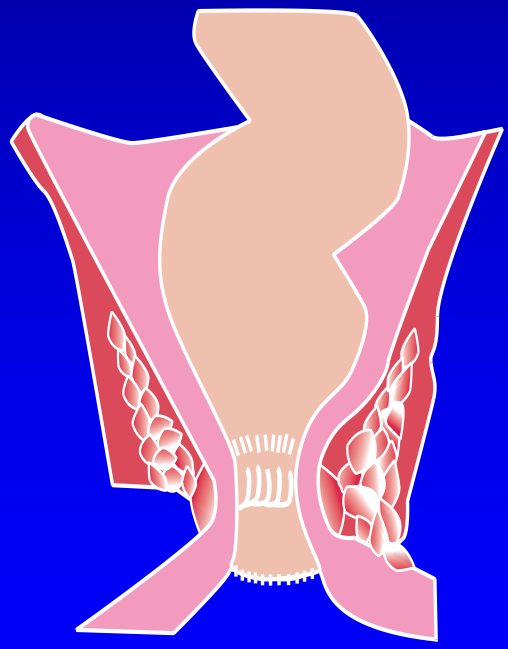
TME + RT: 5.8% (p<0.001)

No survival benefit

(Kapiteijn *et al*, NEJM, 345 (9), 638-646, 2001)

Recurrence and distance from anal verge

(At 2 years)	TME	RT/TME
• 10 - 15cm	3.8%	1.3%
• 5 - 10cm	10.1%	1.0%
• < 5cm	10.0%	5.8%



(Kapiteijn *et al*, NEJM, 345 (9), 638-646, 2001)

Trial	Date	Local recurrence Surgery alone	Local recurrence Surgery + DXT	p value	Length of follow up
CR02	1996	46%	36%	=0.04	5 years
CR03	1996	34%	21%	=0.001	5 years
North West	1994	36.5%	12.8%	=0.0001	8 years
Swedish	1997 2002	27% 26%	11% 9%	<0.001 <0.001	5 years 13 years
Dutch	2001	8.2% 11.4%	2.4% 5.8%	<0.01	2 years 5 years

Do we need to give RT?

Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial.

David Sebag-Montefiore *et al*.....

Lancet. 2009 Mar 7;373(9666):811-20.

CRO7

Pre-op 25Gy in 5 fractions

V

Selected* post-op CRT (45Gy in 25#)

(* If tumour within 1mm of CRM)

CRO7

1350 pts

80 centre (UK, Canada, S.Africa, NZ)

Operable rectal cancer

674 / 676 in each arm

Local recurrence (LR)

	Pre	Post	
3yrs	5%	11%	
5yrs	5%	17%	p<0.0001

LR less in the pre-op group

LR less at all stages in pre-op group

DFS better in the pre-op group

Conclusions from CRO7

"……short-course preoperative radiotherapy is an effective treatment for patients with operable rectal cancer."

Chemotherapy for rectal cancer?

We can reduce LR but can we improve survival?

ESMO: “adjuvant chemotherapy.....limited by small numbers and conflicting results”

Does adjuvant fluoropyrimidine-based chemotherapy provide a benefit for patients with resected rectal cancer who have already received neoadjuvant radiochemotherapy? A systematic review of randomised trials.

Bujko K, Glynne-Jones R, Bujko M

Poland

NO

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.

Valentini V, van Stiphout RG, Lammering G, Gambacorta MA, Barba MC, Bebenek M, Bonnetain F, Bosset JF, Bujko K, Cionini L, Gerard JP, Rödel C, Sainato A, Sauer R, Minsky BD, Collette L, Lambin P.

Italy

YES

ESMO

“The majority of consensus participants recommended adjuvant 5FU/Cap with or without oxaliplatin based on data from colon cancer”

.....Lancet Oncology April/MAY 2014 articles including and reply to Bossett et al Paper on EORTC 22921 trial (10.4 years FU – negative)

Short or Long course CRT for operable rectal cancer

Initial results of a randomized controlled trial comparing clinical and pathological downstaging of rectal cancer after preoperative short-course radiotherapy or long-term chemoradiotherapy, both with delayed surgery.

Latkauskas T, Pauzas H, Gineikiene I, Janciauskiene R, Juozaityte E, Saladzinskas Z, Tamelis A, Pavalkis D.

AIM:
RCT: long-course chemoradiotherapy (chRT) v short-course radiotherapy (sRT) followed by delayed surgery.

METHOD:
83 patients
Resectable stage II and III rectal adenocarcinoma
Surgery was performed 6 weeks after preoperative treatment in both groups.

RESULTS:
- There were more patients with early pT stage [pT0 (complete pathological response) pT1] in the chRT group [21.8%vs 2.7% (P=0.03)] and more patients with pT3 disease in the sRT group [75.7%vs 52.2% (P=0.036)].

- The R0 resection rate was 91.3% in the chRT and 86.5% in the sRT group (P=0.734).

- Similar postoperative morbidity was observed in each group.

CONCLUSION:
Long-course preoperative chemoradiation resulted in greater statistically significant tumour downsizing and downstaging compared with short-term radiation, but there was no difference in the R0 resection rates.

Colorectal Dis. 2012 Mar;14(3):294-8.

A Polish randomised study (n = 312) and an Australian randomised study (n = 326) compared these 2 schedules.

- **Both trials showed a lower rate of early adverse effects using a short-course radiation regimen and no differences in long-term oncologic outcomes and late toxicity rates between groups.**

- **The small number of fractions makes short-course radiation less expensive and more convenient than chemoradiation therapy.**

Timing of surgery after SCRT?

ESMO: “2-3 days after END of SCRT”

Patients > 75 years

Dutch data van den Broek et al (EJC 2013)

TME trial - 600 pts (median age 67 years)

Patients > 75 years old operated 4-7 days post last # RT had a higher chance of dying compared to surgery 0-3 days post last # RT (4.7 v 2.1%).

Stockholm III (Petterson BJS 2010) also showed an increase in post-op complications for those treated 11-17days post starting RT.

Hartley *et al*, BJS 2002 – reduced risk of complications if overall treatment time < 10 days.

.....operate early after SCRT especially in elderly

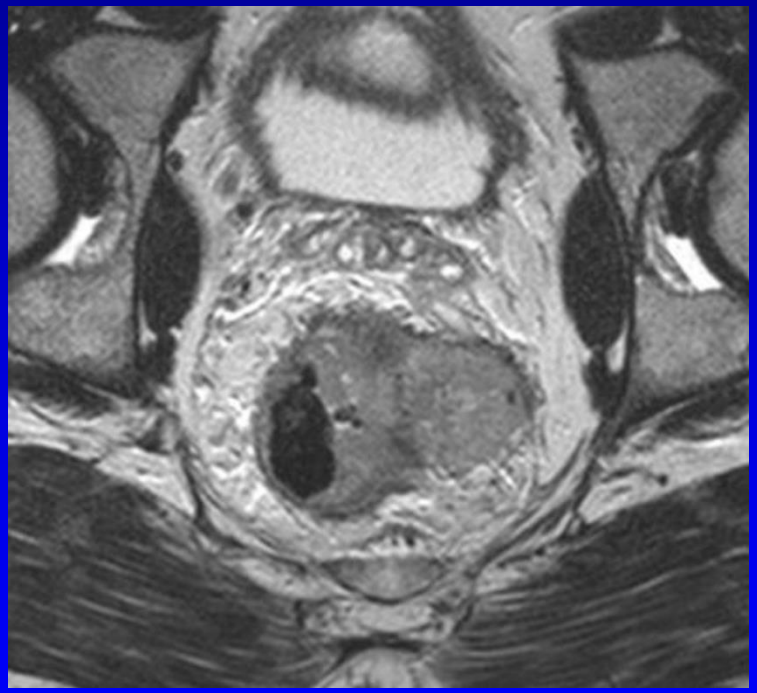
.....or ? Delayed surgery

Short course and delayed surgery?

SCRT and delayed op - 4 studies

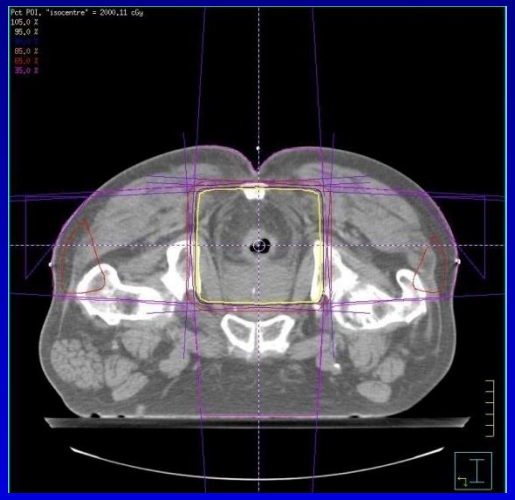
UK (Hatfield)	2009	43 pts	61% op RO: 85%
Sweden (Radu)	2008	46 pts	80% op pCR 11%
Pettersson (Sweden)	2012	112 pts	pCR 8%
Canada (Faria)	2014	52 pts	100% op RO: 100% pCR: 10%

LCRT



Conventional European CRT

- 3 or 4 field CT planned volume (MLC)



Capecitabine 825mg/m^2 bd for 7/7 per week

Radiotherapy 45 GY in 25# *

(* to 5040Gy/28#)

Chemoradiotherapy

- 4732 pts
- 77 phase II and III trials
- pCR 13.5%
- Adding 2nd drug to 5FU and total radiation dose were associated with higher pCR (small studies 20-30%)

Hartley - Br J Rad 2005; Sangera - Clin Onc update 2008

Timing of surgery after LCRT?

ESMO: “4-8 weeks after END of LCRT”

Regression of Rectal Cancer with Radiotherapy with or without Concurrent Capecitabine d Optimising the Timing of Surgical Resection

A. S. Dhadda*, A. M. Zaitouny, E. M. Bessell

Aims: To determine tumour regression (volume-halving time) obtained after chemo/radiotherapy, and thereby the ideal interval between the start of treatment and surgery in order to obtain a high rate of complete response.

Materials and methods: In total, 106 patients with cT3,4 rectal cancer who received preoperative radiotherapy alone or concurrently with capecitabine chemotherapy at Nottingham City Hospital, UK were studied. The rectal tumour volume visible on the computed tomography planning scan was compared with the residual pathological volume and the tumour volume-halving time calculated. The radiotherapy response was graded according to the Mandard system.

Results: Fifty-three patients had radiotherapy alone, with 53 patients having concurrent chemoradiotherapy. The median tumour volume-halving time was found to be 14 days and not influenced by the addition of chemotherapy. The Mandard score, the interval from the start of treatment to surgery and the tumour volume-halving time were statistically associated with tumour regression. The median tumour volume in our series of 54 cm3 would require an interval of 20 weeks after the start of treatment to surgery to regress to 0.1 cm3 (10 volume-halving times; 140 days).

Conclusions: The initial tumour volume and median volume-halving time provide the best estimates for determining the optimum length of interval between the completion of preoperative chemo/

Probably need to wait longer than the standard 8 weeks.....maybe even longer for larger tumours

Optimal time interval between neoadjuvant chemoradiotherapy and surgery for rectal cancer.

Sloothaak DA, Geijsen DE, van Leersum NJ, Punt CJ, Buskens CJ, Bemelman WA, Tanis PJ; Dutch Surgical Colorectal Audit.
Source: The Netherlands.

All evaluable patients who underwent preoperative CRT for rectal cancer between 2009 and 2011 were selected from the Dutch Surgical Colorectal Audit.
The interval between radiotherapy and surgery was calculated from the start of radiotherapy.
The primary endpoint was pathological complete response (pCR).

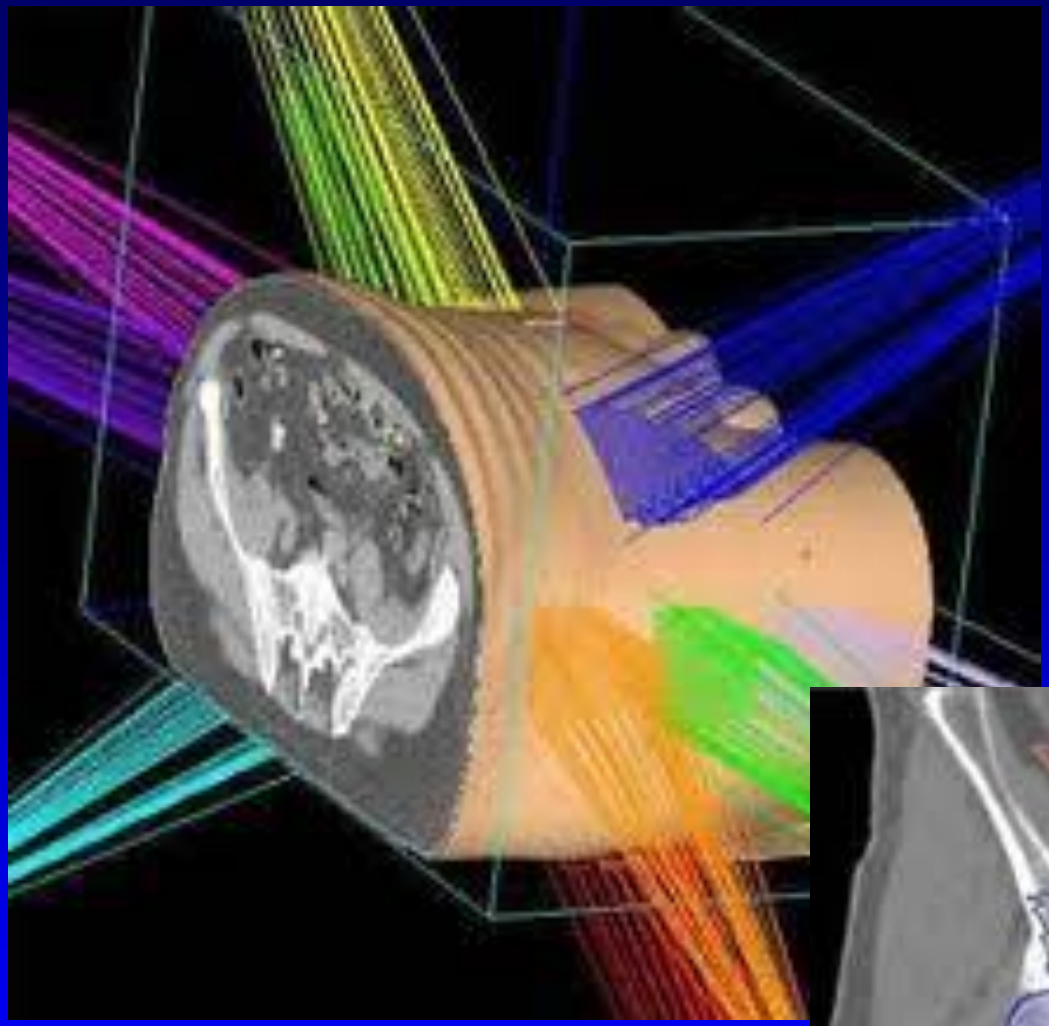
1593 patients.
The median interval between radiotherapy and surgery was 14 (range 6-85, interquartile range 12-16) weeks.

Outcome measures were calculated for intervals of less than 13 weeks (312 patients), 13-14 weeks (511 patients), 15-16 weeks (406 patients) and more than 16 weeks (364 patients).
Age, tumour location and R0 resection rate were distributed equally between the four groups.
Significant differences were found for clinical tumour category (cT4: 17·3, 18·4, 24·5 and 26·6 per cent respectively; P = 0·010) and clinical metastasis category (cM1: 4·4, 4·8, 8·9 and 14·9 per cent respectively; P < 0·001).

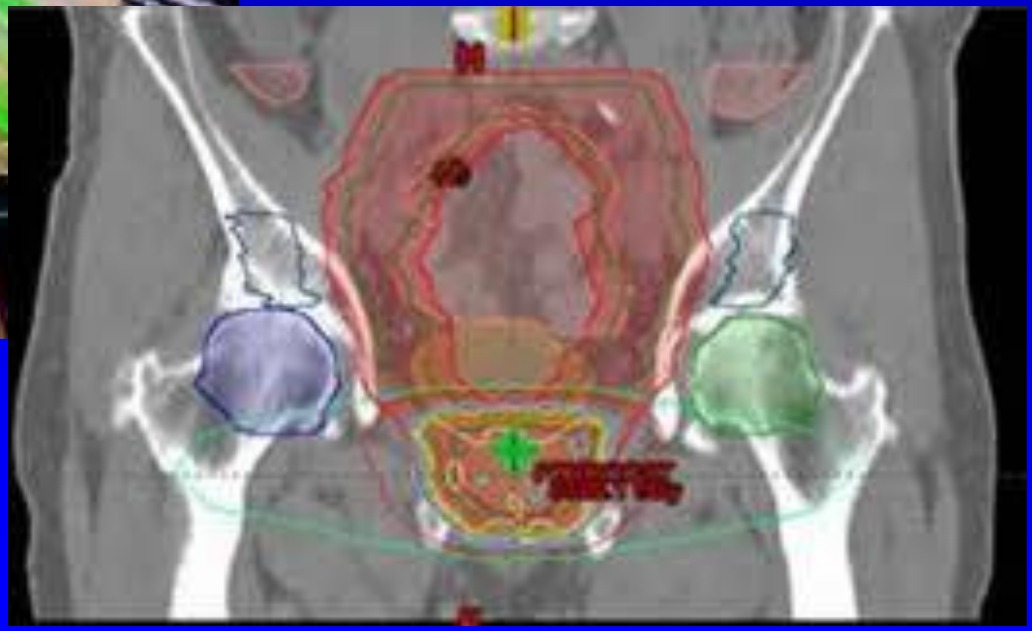
Resection 15-16 weeks after the start of CRT resulted in the highest pCR rate (18·0%; P = 0·013), with an independent association (hazard ratio 1·63, 95 per cent confidence interval 1·20 to 2·23).

CONCLUSION:
Delaying surgery until the 15th or 16th week after the start of CRT (10-11 weeks from the end of CRT) seemed to result in the highest chance of a pCR.

BJS: 2013 Jun;100(7):933-9.



IMRT for rectal cancer?



Four-week neoadjuvant intensity-modulated radiation therapy with concurrent capecitabine and oxaliplatin in locally advanced rectal cancer patients: a validation phase II trial.

Arbea L, Martínez-Monge R, Díaz-González JA, Moreno M, Rodríguez J, Hernández JL, Sola JJ, Ramos LI, Subtil JC, Nuñez J, Chopitea A, Cambeiro M,Gaztañaga M, García-Foncillas J, Aristu J.
Source: Spain

PURPOSE:
To validate tolerance and pathological complete response rate (pCR) of a 4-week preoperative course of intensity-modulated radiation therapy (IMRT) with concurrent capecitabine and oxaliplatin (CAPOX) in patients with locally advanced rectal cancer.

METHODS AND MATERIALS:
Patients with T3 to T4 and/or N+ rectal cancer received preoperative IMRT (47.5 Gy in 19 fractions) with concurrent capecitabine (825 mg/m(2) b.i.d., Monday to Friday) and oxaliplatin (60 mg/m(2) on Days 1, 8, and 15).
Surgery was scheduled 4 to 6 weeks after the completion of chemoradiation.

RESULTS:
A total of 100 patients were evaluated.
Grade 1 to 2 proctitis was observed in 73 patients (73%). Grade 3 diarrhea occurred in 9% of the patients. Grade 3 proctitis in 18% of the first 50 patients led to reduction of the dose per fraction to 47.5 Gy in 20 treatments. The rate of Grade 3 proctitis decreased to 4% thereafter (odds ratio, 0.27).
A total of 99 patients underwent surgery.
A pCR was observed in 13% of the patients, major response (96-100% of histological response) in 48%.
An R0 resection was performed in 97% of the patients.
After a median follow-up of 55 months, the LC, DFS, and OS rates were 100%, 84%, and 87%, respectively.

CONCLUSIONS:
Preoperative CAPOX-IMRT therapy (47.5 Gy in 20 fractions) is feasible and safe, and produces major pathological responses in approximately 50% of patients.

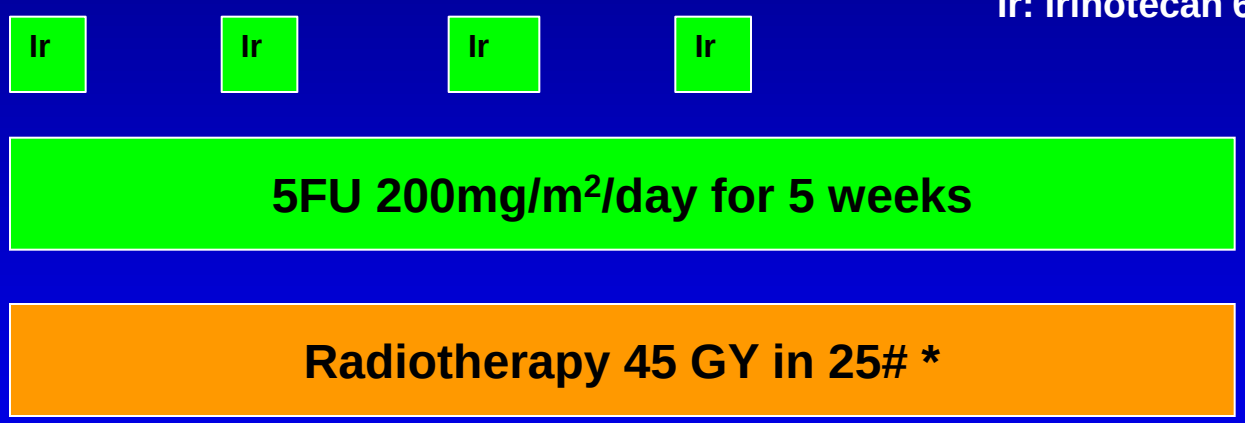
Int J Radiat Oncol Biol Phys. 2012 Jun 1;83(2):587-93.

CRT with Irinotecan

NWCOG - 1

Irinotecan+5-fluorouracil with concomitant pre-operative radiotherapy in locally advanced non-resectable rectal cancer: a phase I/II study.

Iles S, Gollins S, Susnerwala S, Haylock B, Myint S, Biswas A, Swindell R, Levine E.



31 patients

MRI: 19/24 (79%) reduction in T-stage, 7pts cCR

OP: 28pts – 81% clear CRM

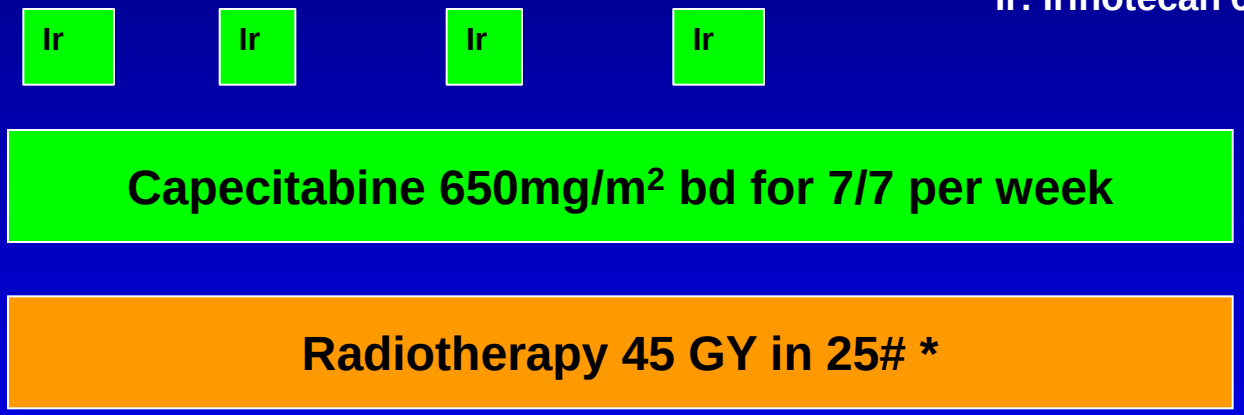
BJC 2008: 98(7):1210-6.

NWCOG - 2

Preoperative chemoradiotherapy using concurrent capecitabine and irinotecan in magnetic resonance imaging-defined locally advanced rectal cancer: impact on long-term clinical outcomes.

Gollins S, Sun Myint A, Haylock B, Wise M, Saunders M, Neupane R, Essapen S, Samuel L, Dougal M, Lloyd A, Morris J, Topham C, Susnerwala S.

Ir: Irinotecan 60mg/m^2 wk1-4



110 patients (MRI demonstration of tumour threatening (≤ 2 mm) or involving mesorectal fascia)

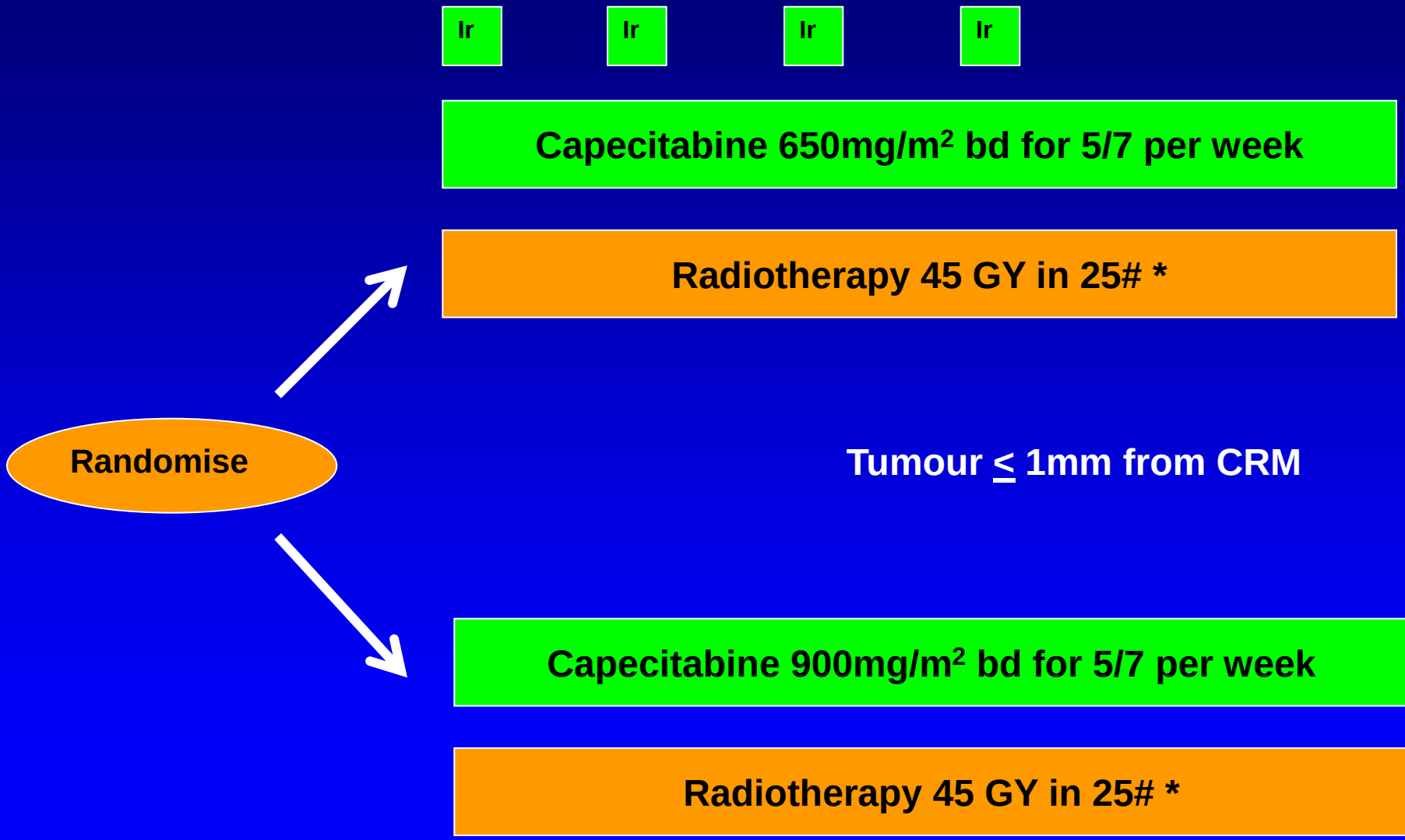
MRI: 72pts (67%) reduction in T-stage

OP: 107pts – 95 (89%) clear CRM (>2mm)

pCR: 22%

J Clin Oncol. 2011;29(8):1042-9.

ARISTOTLE NCRN (David Sebag-Montefiore) Ir: Irinotecan 60mg/m^2 wk1-4



CRT with Irinotecan....?

.....under investigation

CRT with Oxaliplatin

CRT with Oxaliplatin

CAO/ARO/AIO-04 (1)
Ox5FU
1265pts, pCR 17 v 13% p=0.038
Increased toxicity with oxaliplatin arm

ACCORD 12/0405-Prodige 2 (2)
OxCap
598pts, pCR 19.2 v 13.9% NS
Increased toxicity with oxaliplatin arm

STAR-01 (3)
Ox5FU
747pts, pCR 16 v 16% NS
Increased toxicity with oxaliplatin arm

(NSABP) R-04 (4)
OxCap
1608pts
No sig diff in pCR
Increased toxicity with oxaliplatin arm

PETACC6 (5)
RCT Cap v OxCap RT + adj
1094pts
Worse treatment compliance
Increased toxicity

No

1: Rodel: Lancet Oncol. 2012 Jul;13(7):679-87
2: Gerard: JCO 28(10) 1638-44, 2010
3: Aschelle: JCO 2011 Jul 10;29(20):2773-80.
4: O'Connell: JCO May 2014
5: Schmoll: ASCO 2013

CRT with VEGF inhibitors

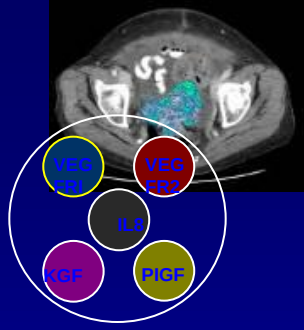
AVASTIN studies	Treatment	Number pts	pCR	
Gasparini 2012	RT + C + BVZ	43	14% (51% few cells)	CD34 Ki67 VEGFR-2
Volenik 2011		61	13%	62% developed peri-operative complications
Resch 2012	RT + C + BVZ	8	25%	Intestinal bleed Diarrhoea STOPPED
Crane 2010	RT + C + BVZ	25	32%	3 wound complications requiring surgical intervention
Spigel 2012	RT + 5FU + BVZ	3		
Willett 2009	RT + 5FU + BVZ	32	Regression in all pts (mean 5.0 – 2.4cm)	VEGF, IL-6 sVEGFR1 PIGF, CECs (post-op complications)
Kennecke 2012	RT + C + BVZ + Ox	42	16%	

Efficacious

Tolerance???

DREAMtherapy

NCRN (Mark Saunders)



Dual REctal Angiogenesis or MEK inhibition radioTHERAPY

Diagnostic biopsy

Bx

Resection specimen

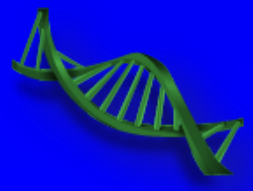
Capecitabine 825mg/m^2 bd for 7/7 per week

Radiotherapy 45 GY in 25#

-10 0 35 100 days

AZD 2171 or AZD6244

DCE-MRI:	√√	√				√
FLT-PET:	√	√				√
Blood:	√	√	√	√	√	√



Kalena Marti
Caroline Dive
Gordon Jayson
Andrew Renehan
Mark Saunders

Clinical / Pathological response

9 out of 17 patients have had an ECPR* (1: exc – NET)

cCR:	**4**	
pCR:	**2**	**(TRG 1)**
Microfoci:	**2**	**(TRG 2)**
cCR relapse:	**1**	**(10 months after RT completed)**

53%

41% cCR/pCR

ECPR: Excellent Clinical or Pathological Response

Assessing response to treatment

- pCR (cCR/ECPR)
- Tumour regression
- MRI response
  - Tumour regression grade (TRG)
  - DWI-MRI
  - Tumour thickness
  - Tumour length / volume

pCR

Complete pathologic response after combined modality treatment for rectal cancer and long-term survival: a meta-analysis.

Zorcolo L, Rosman AS, Restivo A, Pisano M, Nigri GR, Fancellu A, Melis M.
Source: Italy.

A systematic literature review was conducted to detect studies comparing long-term results of patients with CPR and NPR (partial or no response) after CMT for rectal cancer.

RESULTS:

Twelve studies (1,913 patients) with rectal cancer treated with CMT were included.

CPR was observed in 300 patients (15.6%).

CPR and NPR patient groups were similar with respect to age, sex, tumor size, distance of tumor from the anus, and stage of disease before treatment.

Median follow-up ranged from 23 to 46 months.

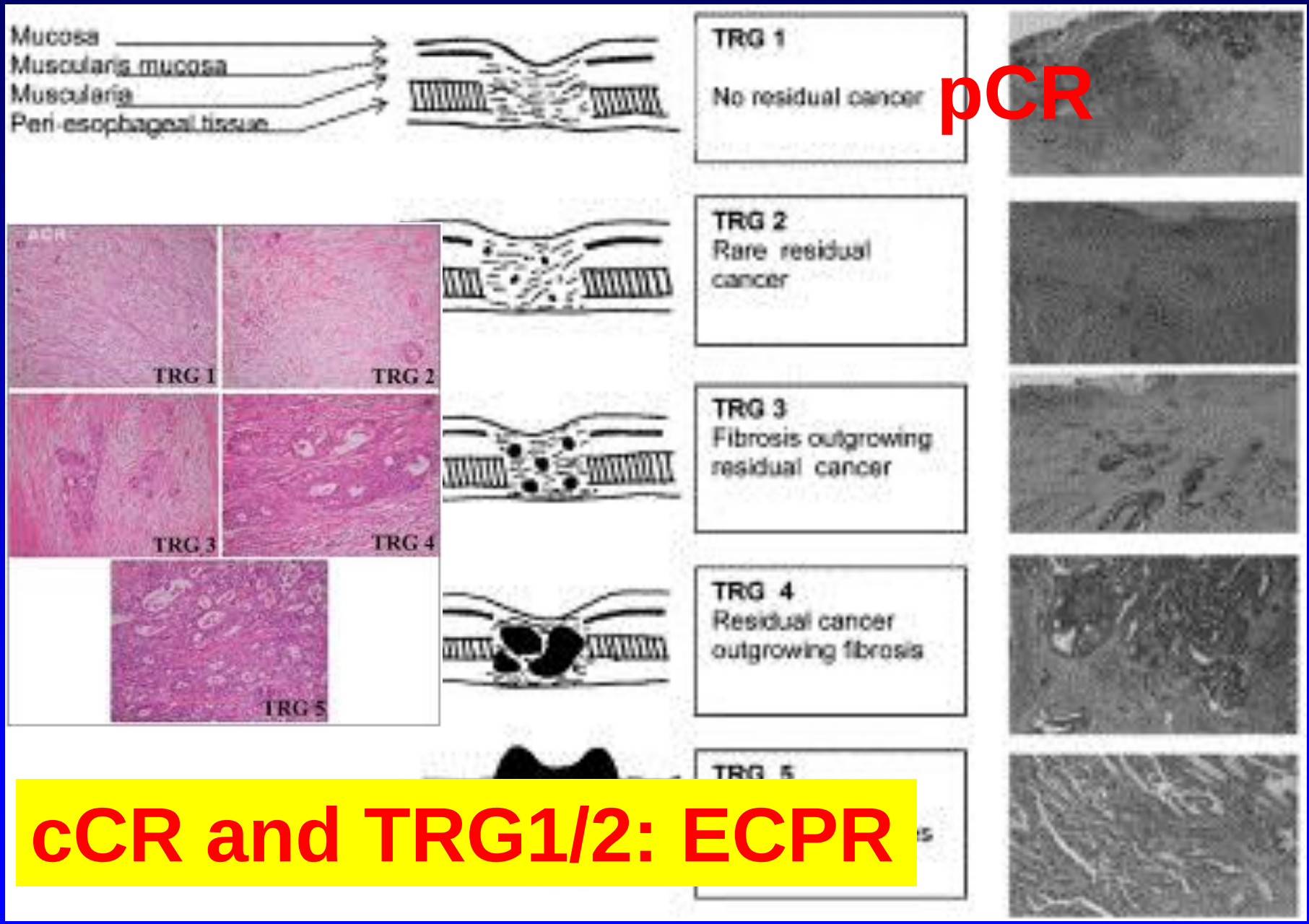
CPR patients had lower rates of LR [0.7% vs. 2.6%; odds ratio (OR) 0.45, 95% confidence interval (CI) 0.22-0.90, P = 0.03], DR (5.3% vs. 24.1%; OR 0.15, 95% CI 0.07-0.31, P = 0.0001), and simultaneous LR + DR (0.7% vs. 4.8%; OR 0.32, 95% CI 0.13-0.79, P = 0.01).
OS was 92.9% for CPR versus 73.4% for NPR (OR 3.6, 95% CI 1.84-7.22, P = 0.002), and DFS was 86.9% versus 63.9% (OR 3.53, 95% CI 1.62-7.72, P = 0.002).

CONCLUSIONS:

CPR after CMT for rectal cancer is associated with improved local and distal control as well as better OS and DFS.

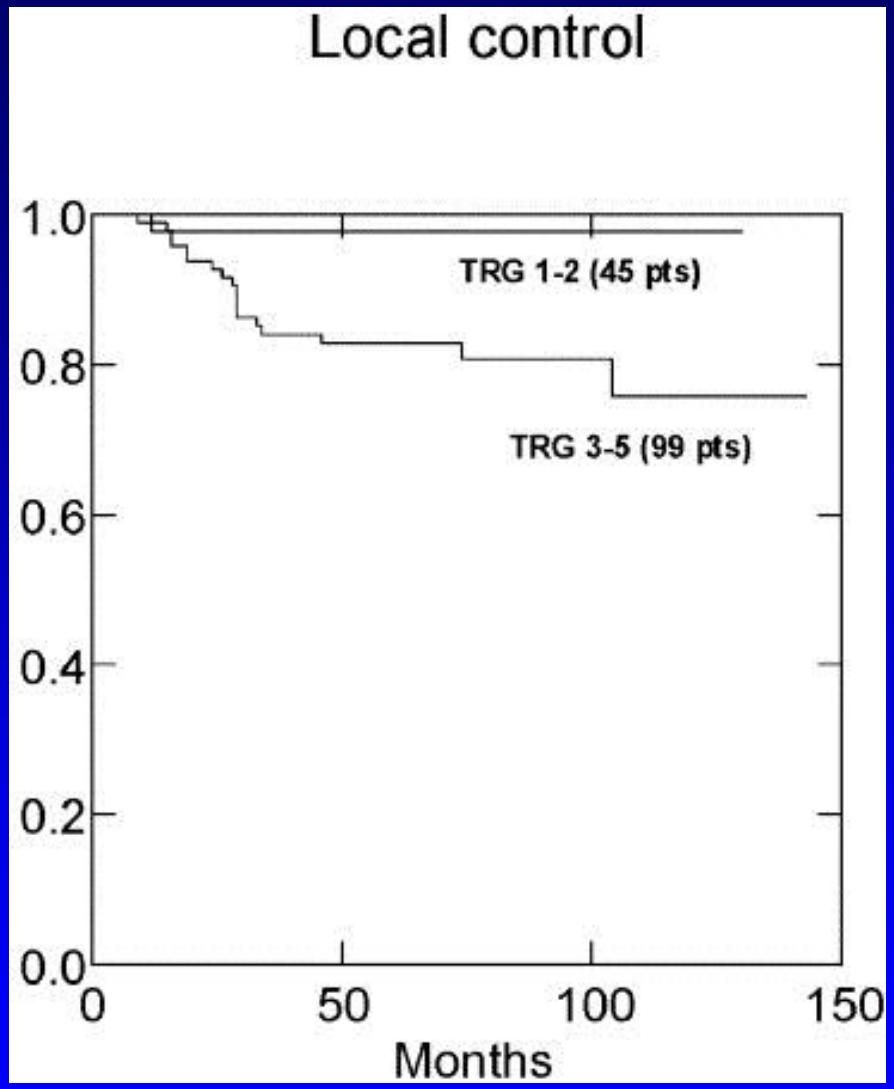
Ann Surg Oncol: 2012 Sep;19(9):2822-32.

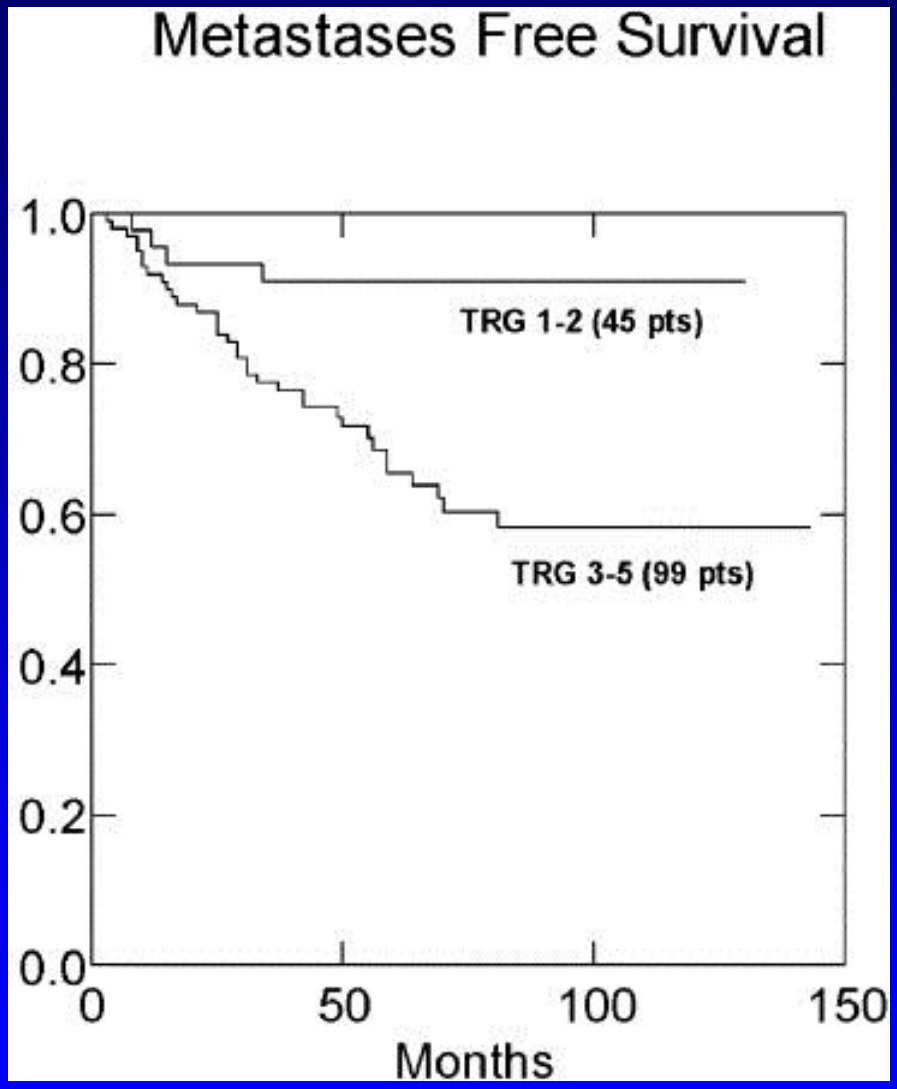
Tumour regression



cCR and TRG1/2: ECPR

Tumour regression





MRI

Magnetic resonance imaging-detected tumor response for locally advanced rectal cancer predicts survival outcomes: MERCURY experience.

Patel UB, Taylor F, Blomqvist L, George C, Evans H, Tekkis P, Quirke P, Sebag-Montefiore D, Moran B, Heald R, Guthrie A, Bees N, Swift I, Pennert K, Brown G.

PURPOSE:
To assess magnetic resonance imaging (MRI) and pathologic staging after neoadjuvant therapy for rectal cancer in a prospectively enrolled, multicenter study.

METHODS:
In a prospective cohort study, 111 patients who had rectal cancer treated by neoadjuvant therapy were assessed for response by MRI and pathology staging by T, N and circumferential resection margin (CRM) status.

Tumour regression grade (TRG) was also assessed by MRI.

RESULTS:
On multivariate analysis, the MRI-assessed TRG (mrTRG) hazard ratios (HRs) were independently significant for survival (HR, 4.40; 95% CI, 1.65 to 11.7) and disease-free survival (DFS; HR, 3.28; 95% CI, 1.22 to 8.80).

Preoperative MRI-predicted CRM independently predicted local recurrence (LR; HR, 4.25; 95% CI, 1.45 to 12.51).

CONCLUSION:
MRI assessment of TRG and CRM are imaging markers that predict survival outcomes for good and poor responders and provide an opportunity for the multidisciplinary team to offer additional treatment options before planning definitive surgery.

TRG: 1 rCR, 2 Good, 3 moderate, 4 slight, 5 No response

JCO: 2011 Oct 1;29(28):3753-60.

MRI-volumetric

MR volumetric measurement of low rectal cancer helps predict tumour response and outcome after combined chemotherapy and radiation therapy.

Nougaret S, Rouanet P, Molinari N, Pierredon MA, Bibeau F, Azria D, Lemanski C, Assenat E, Duffour J, Ychou M, Reinhold C, Gallix B.
Source: France.

PURPOSE:
To retrospectively determine whether magnetic resonance (MR) volumetry of rectal cancer is a reproducible method for predicting disease-free survival (DFS) in patients with locally advanced low or mid-rectal tumors who undergo combined chemotherapy and radiation therapy (CRT) before total mesorectal excision.

MATERIALS AND METHODS:
Fifty-eight patients were included in the study.
The tumour volume reduction ratio, circumferential resection margin, T stage, and occurrence of downstaging were compared with the histopathologic response and DFS.

RESULTS:
The interobserver correlation coefficient between the two radiologists was 0.87 (95% confidence interval [CI]: 0.76, 0.93) for pre-CRT volumetry and 0.81 (95% CI: 0.74, 0.90) for post-CRT volumetry.

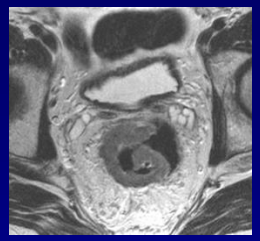
A tumour volume reduction of at least 70% was significantly associated with good histologic regression (tumour regression grade [TRG], 3 or 4) (P <.0001) compared with a volume reduction rate of less than 70%.

The mean follow-up of survivors at the time of analysis was 52 months ± 20 (standard deviation).

Patients with a volume reduction ratio of at least 70% had a higher DFS (P <.0001). Tumour volume reduction was an independent prognostic parameter in multivariate analysis for DFS (P = .003; 95% CI: 0.01, 0.4).

Radiology: 2012 May;263(2):409-18.

SUMMARY



Rectal Cancer

Thank you

Follow ESMO guide-lines for SCRT and LCRT !!

Adjuvant chemo for rectal cancer.....yes?

If operable disease and need RT.....SCRT and not LCRT

Timing after SCRT.....2-3 days (ASAP in elderly)

Timing after LCRT.....4-8 wks (? longer)

SCRT and delayed op.....interesting

LCRT and fluorpyrimidine is standard

- **+ oxaliplatin.....no**
- **+ irinotecan.....under investigation**
- **+ VEGFi.....under investigation**

Assessment of response.....path and MRI