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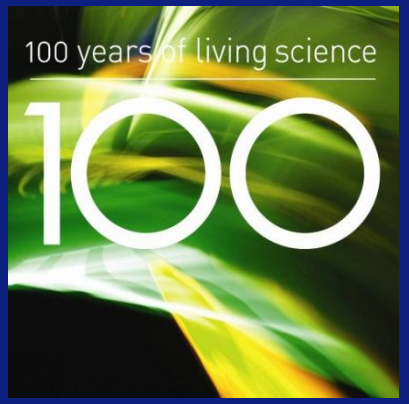

Multimodal management of colorectal cancer

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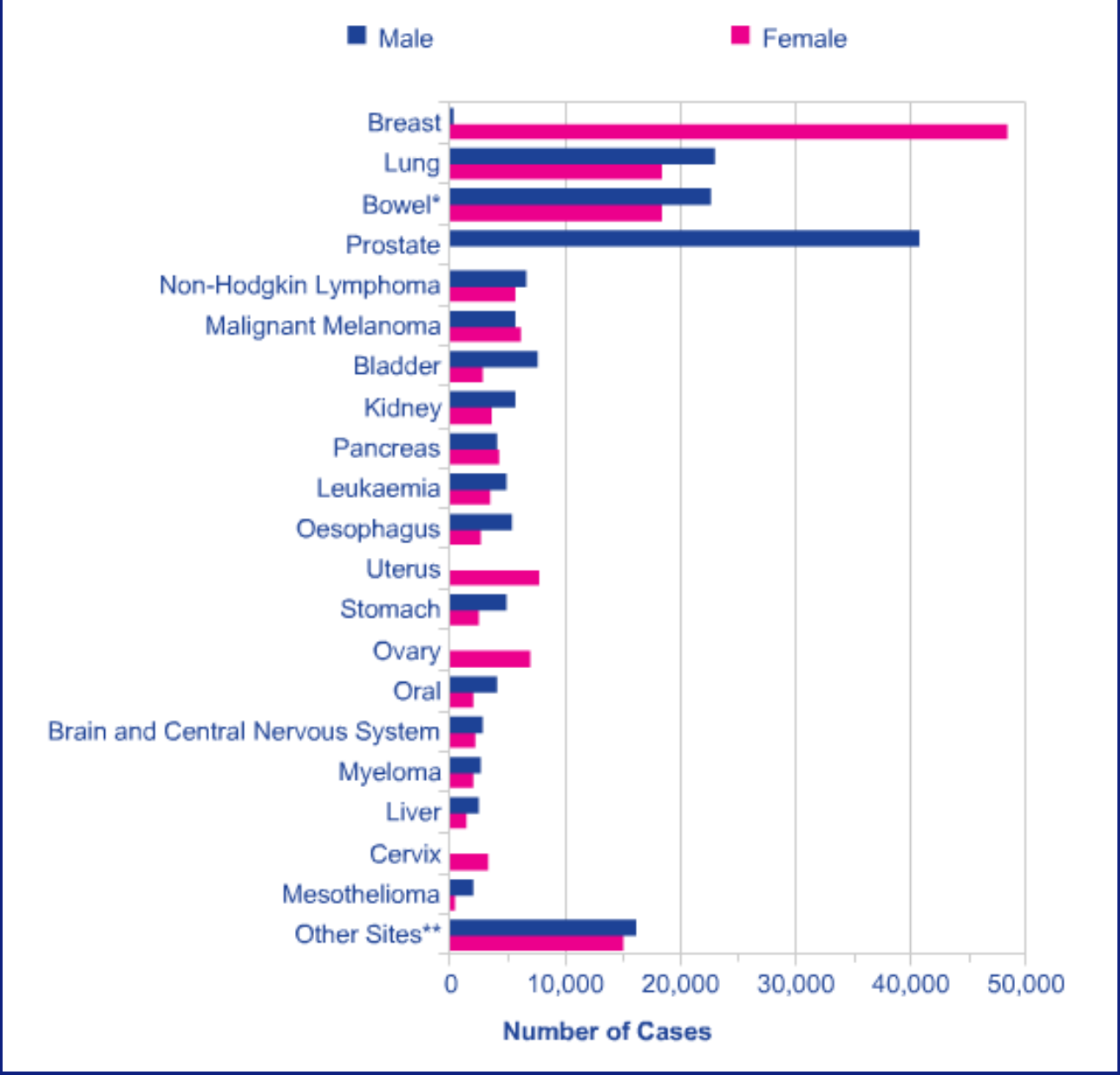
Learning Objectives

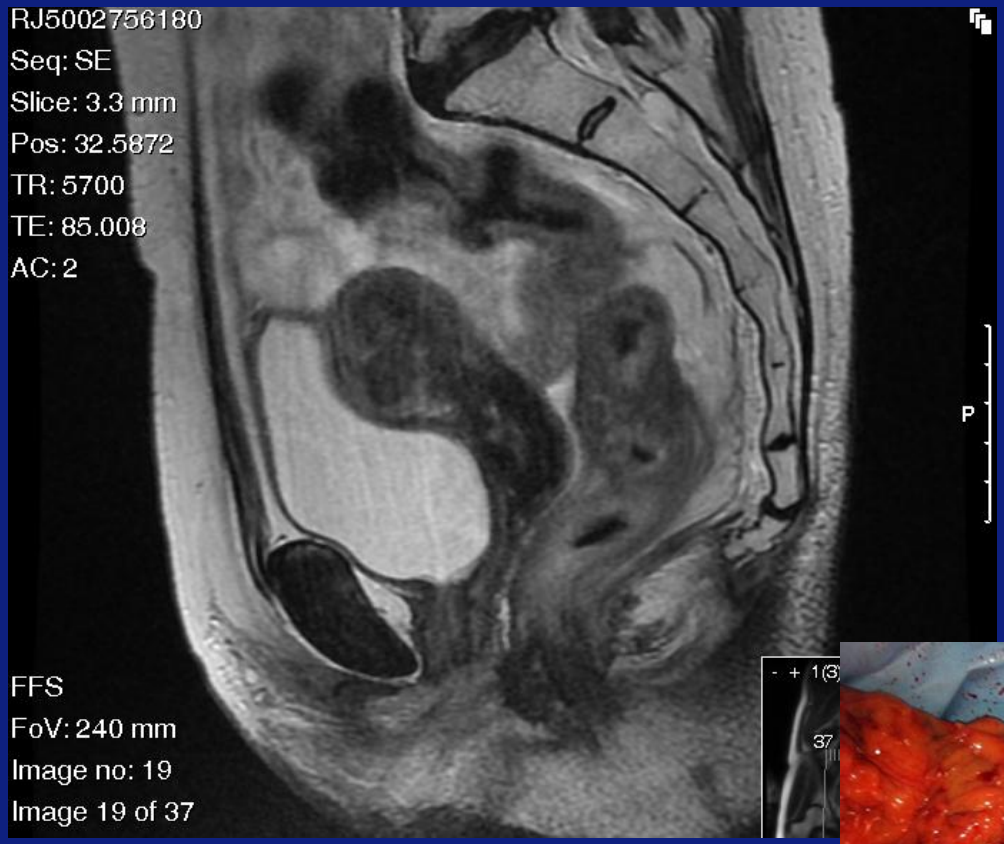
- Predictors of local recurrence in rectal cancer
- Neoadjuvant therapy for advanced rectal cancer
- Management of early rectal cancer
- Adjuvant for colon cancer
- Future
  - Predictors of response to chemotherapy
  - Neoadjuvant therapy for colon cancer

Colorectal cancer: 3rd most common cancer



Rectal Cancer

- 25% colorectal cancers
- Radical surgery with Total Mesorectal Excision is only curative treatment
  - Anterior resection
  - APER
- Low local recurrence rates of 4-6%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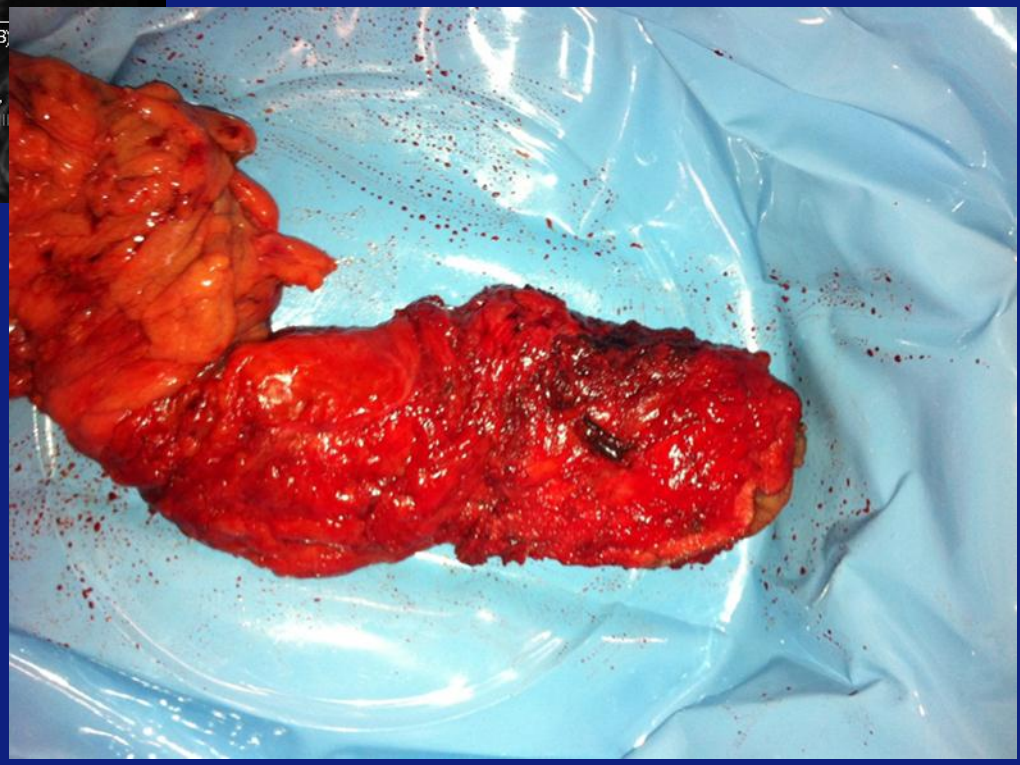


Rectal Cancer

- Prognosis can be predicted by stage of disease
- Dukes Stage
  - Dukes' A: Invasion into but not through the bowel wall(90% 5-yr survival)
  - Dukes' B: Invasion through the bowel wall but not involving lymph nodes(70% 5-yr)
  - Dukes' C: Involvement of lymph nodes(30% 5-yr)
  - Dukes' D: Widespread metastases (<10 5-yr)

Rectal Cancer

- TNM

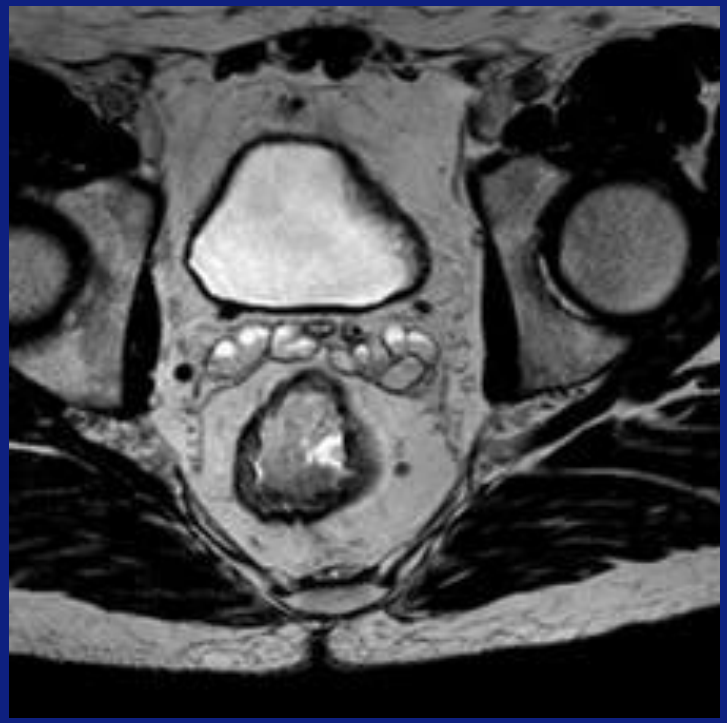
Stage	T	N	M	Dukes
0	Tis	N0	M0	--
I	T1	N0	M0	A
	T2	N0	M0	A
IIA	T3	N0	M0	B
IIB	T4a	N0	M0	B
IIC	T4b	N0	M0	B
IIIA	T1-T2	N1/N1c	M0	C
	T1	N2a	M0	C
IIIB	T3-T4a	N1/N1c	M0	C
	T2-T3	N2a	M0	C
	T1-T2	N2b	M0	C
IIIC	T4a	N2a	M0	C
	T3-T4a	N2b	M0	C
	T4b	N1-N2	M0	C
IVA	Any T	Any N	M1a	--
IVB	Any T	Any N	M1b	--

Rectal Cancer

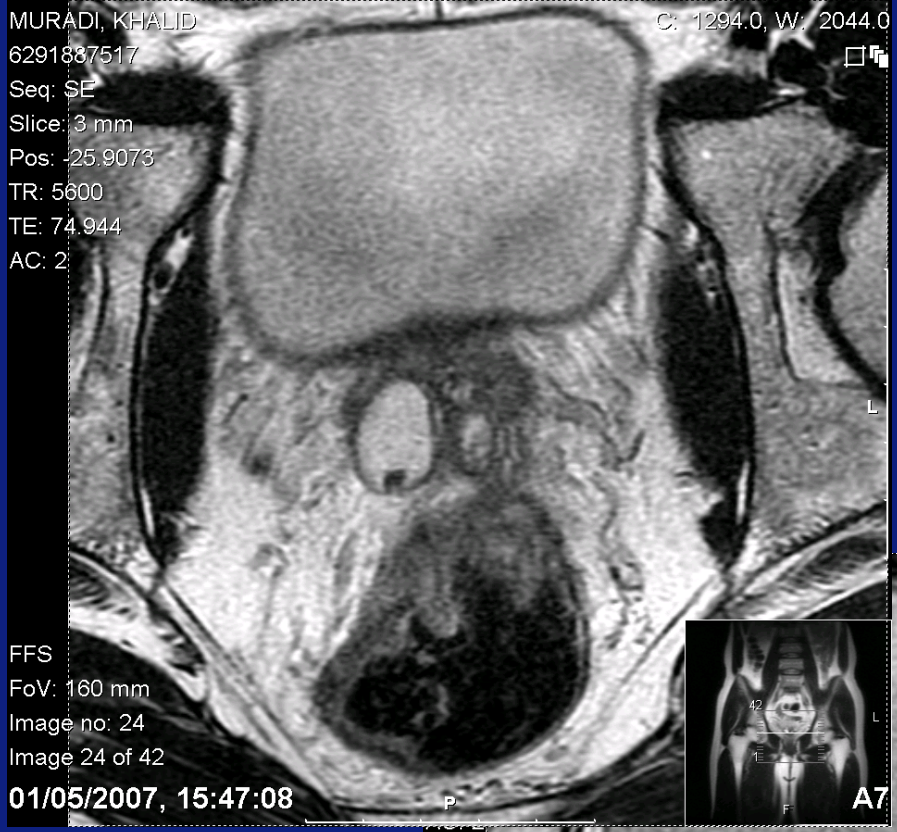
- Chemotherapy and radiotherapy
  - Neoadjuvant: preop treatment with curative intent
    - Radiotherapy
  - Adjuvant: postop treatment with curative intent
    - Chemotherapy

Rectal Cancer

- Predictors of local recurrence
  - Lymphovascular invasion
  - Perineural invasion
  - Circumferential margin involvement: 75% recurrence rate



- 74yo male referred with PRB and tenesmus
- Controlled hypertension; NIDDM
- PR - mass at 8cms; mobile
- Sigmoidoscopy and biopsy – adenocarcinoma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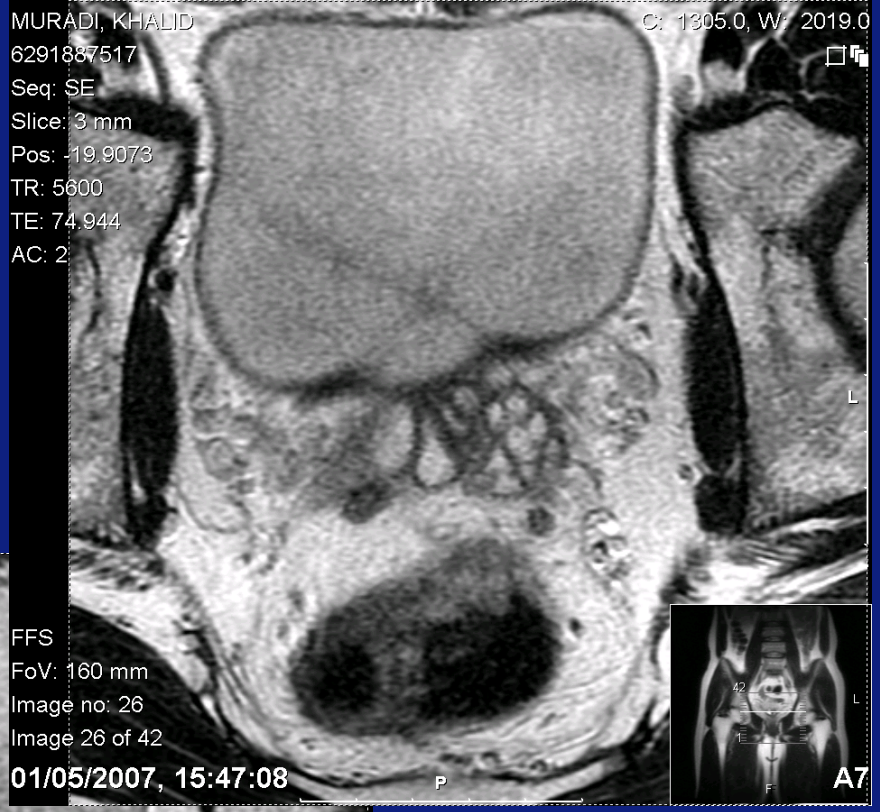
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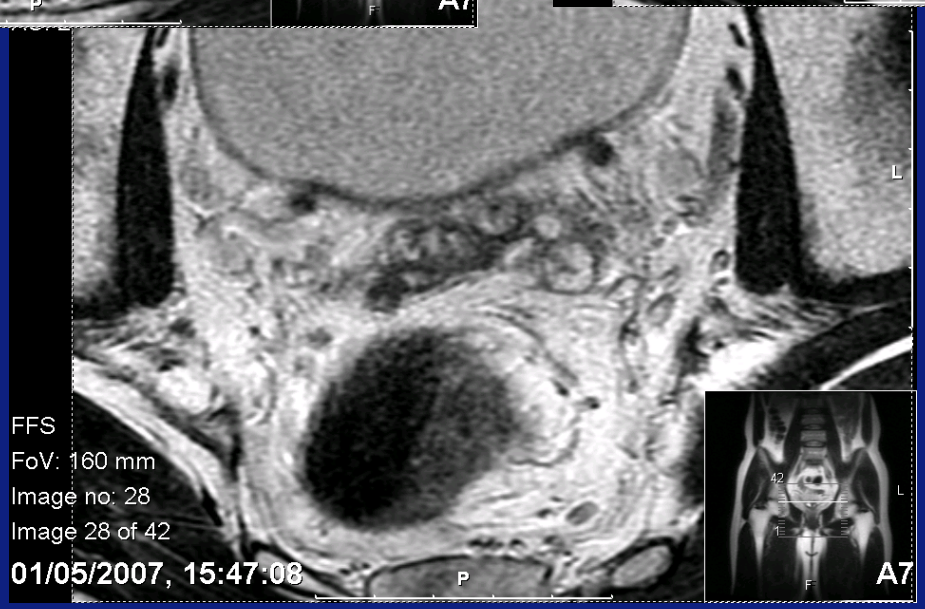
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Imperial College London

Neoadjuvant Therapy for Rectal Cancer

Treatment Choices

- Surgery alone
- Pre or postoperative radiotherapy
- Neoadjuvant chemoradiotherapy
- Postoperative chemoradiotherapy

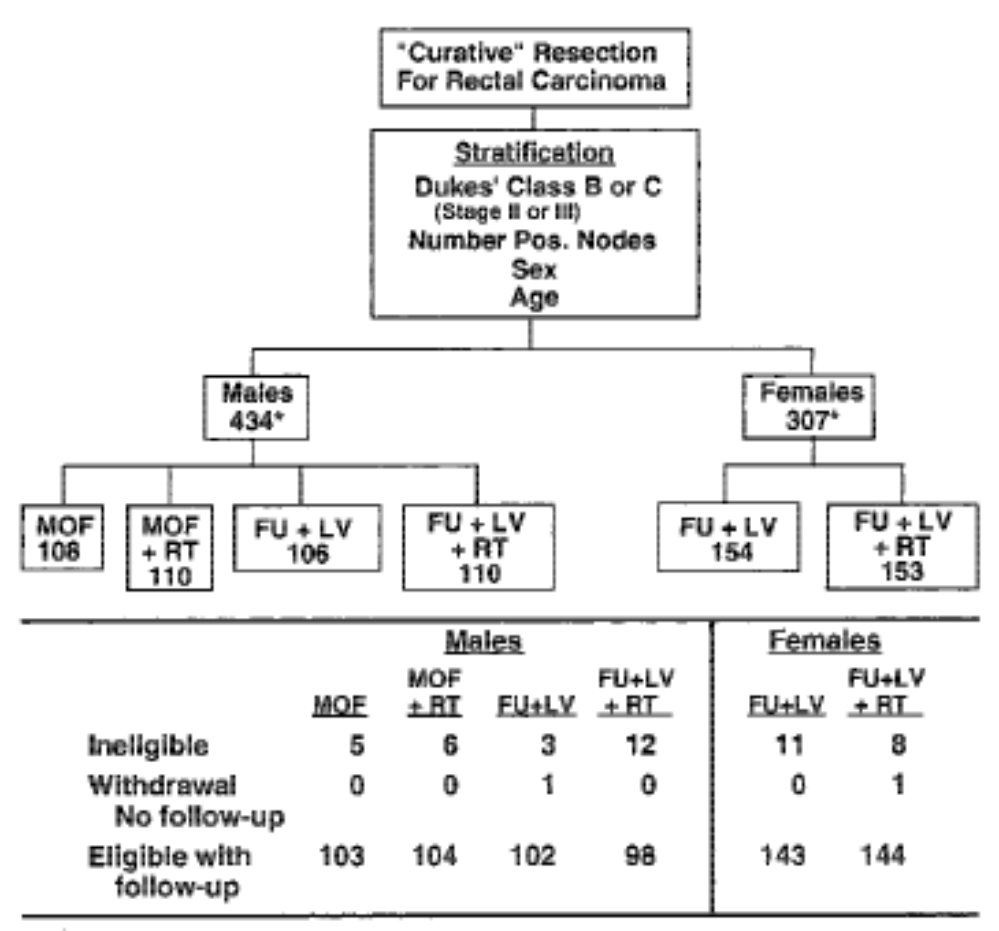
Fisher et al JNCI 1988

Postoperative chemotherapy vs postop DXT vs surgery alone: NSABP R01

- N = 555 with Dukes B and C
- Surgery vs Chemotherapy (5FU, semustine, vincristine [MOF])
  - Disease free survival: 29 vs 47%
  - Survival: 37% vs 60%
  - Survival advantage for B&C
  - Males > female
- DXT 45 Gy in 25 fractions
  - Reduced local recurrence: 25% vs 16%
  - No benefit in terms of survival

Wolmark et al JNCI 2000

NSABP R02



	Males				Females	
	MOF	MOF + RT	FU+LV	FU+LV + RT	FU+LV	FU+LV + RT
Ineligible	5	6	3	12	11	8
Withdrawal No follow-up	0	0	1	0	0	1
Eligible with follow-up	103	104	102	98	143	144

- No differences in DFS and survival at five years with or without DXT
- Lower local recurrence rates with DXT - 13 vs 8%
- Improved DFS for 5FU/folinic acid, but not overall survival

Marks et al Int J Rad Onc Biol Phys 1993

Preoperative radiotherapy: 45-60Gy over 4.5 to 6 weeks for advanced tumours

- Improvement in sphincter sparing surgery due to downstaging (20%)
- 14% local recurrence rates overall
- High distal failure rates

Neoadjuvant Chemoradiotherapy

Luna-Perez et al J Surg Oncol 2003:
32 patients with low rectal cancer (3-6 cms from anal verge):
T3 and T4
Radiotherapy plus 5FU
3/32 CR and 18/32 PR
At median 25 months:
3% local recurrence rates
10% distal failure rate

Advantages:

- treat micrometastatic disease
- increased response to multimodal therapy
- reduce positive CRM rates

Disadvantages:

- over treatment of patients due to overstaging

Neoadjuvant Chemoradiotherapy

Sauer et al NEJM 2004

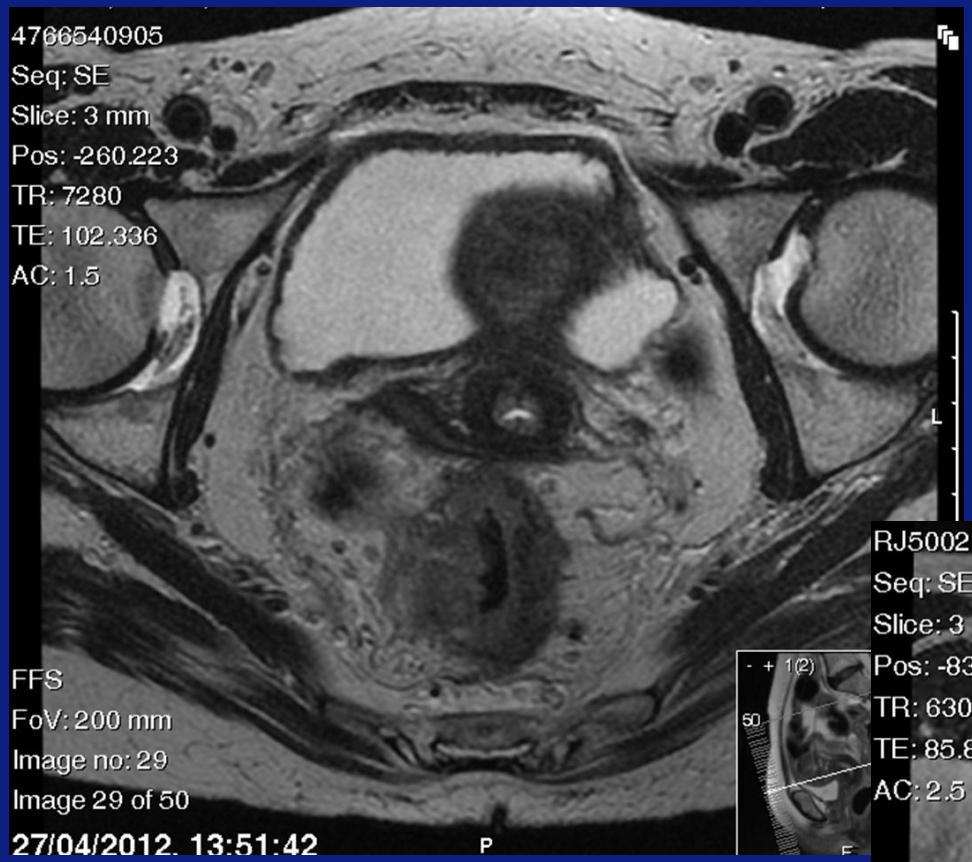
- Preop vs postop chemoradiotherapy
- T3 and T4 cancers

  - Survival similar (76 vs 74%)
  - Local recurrence improved by preop chemoradiotherapy:
    - 6% vs 13%

  - Increased toxicity in postop group

Neoadjuvant Chemoradiotherapy

- Inoperable or CRM threatened rectal cancers
  - Long course chemoradiotherapy
  - 5 week course
  - Restage at 8-10 weeks
  - Surgery at 12 weeks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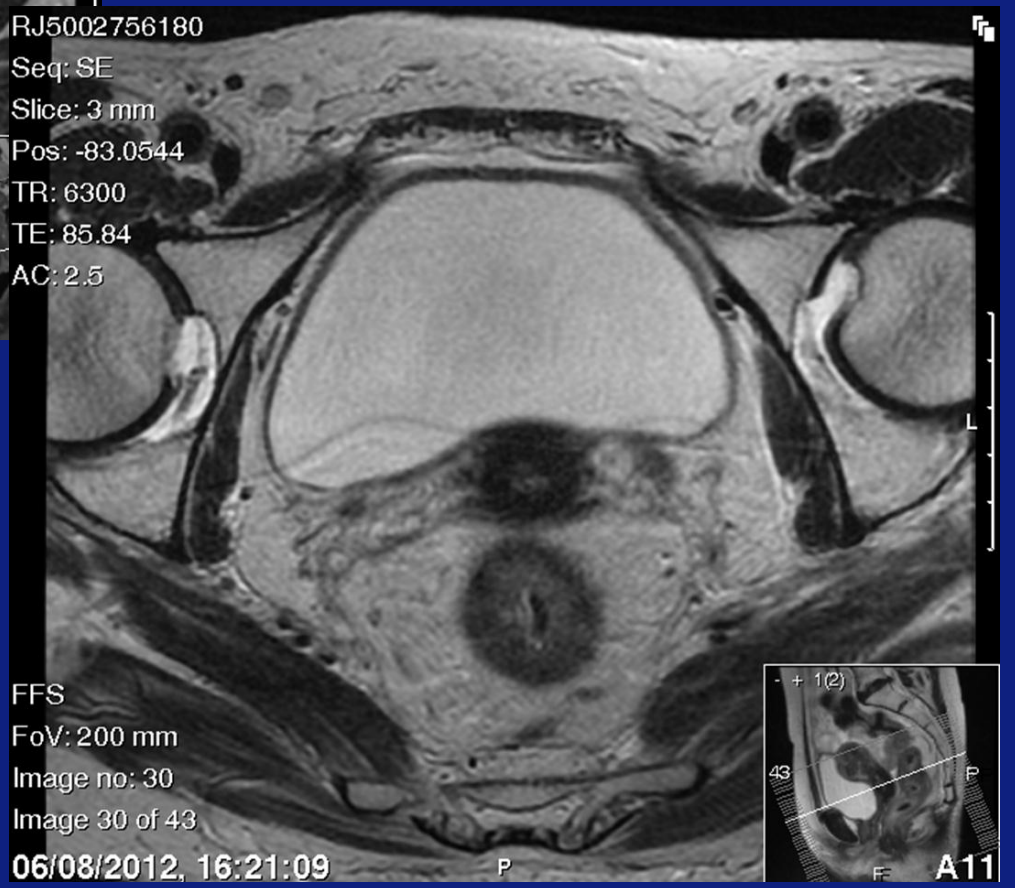
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Blomqvist 2003 BJS

Involved CRM identified by MRI had a significantly higher risk of recurrence and cancer-related death

Mercury Study Group BJC 2006

- positive CRM in 16/62 cases (26%) as compared to 1 out of 116 (1%) in those patients with MDT discussion of MRI.

Short Course Radiotherapy

- 5gy each day for 5days
- Operate within 7 days

- No time to downstage the tumour
- ? Sterilises operative field

Swedish Rectal Cancer Group 1997

- Short course preop DXT
  - Reduced local recurrence rates
  - Improved survival

  - BUT very high local recurrence rates of 27%

Kapiteijin 2001 NEJM

- TME +/- Short course preop DXT
- Resectable rectal cancers
  - Reduced local recurrence rates 2.4 vs 8.2%
  - No effect on tumours above 10cms

  - Low rectal cancers increased risk of local recurrence
    - DXT – 5%
    - Surgery alone – 10%

  - No effect on survival at 2 years
  - +CRM: DXT – 10/897 surgery – 21/900

CRO7

- **Preop short course radiotherapy vs selective post op chemoradiotherapy**
- **All stage III – chemotherapy**

- 674 vs 676

- LR: 23 vs 61

- 3 yr LR rate of 4.7 vs 11.1% (HR 2.47 CI 1.61-3.79)

- DFS: 79.5 vs 74.9% (HR 1.31, CI 1.02-1.67)

- OS: 80.8 vs 78.7% (HR 1.25, CI 0.98-1.59)

- For all rectal tumour heights: 0-5, 5-10, >10cms

- Degree of tumour invasion into mesorectal fat: >5mm

- LVI +ve

Local Recurrences with TME

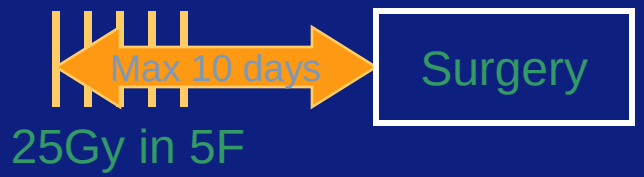
- Heald et al 4%
- ICHT 5.6%
- Short course radiotherapy will not downstage tumour
- If tumour resectable i.e R0, primary surgery indicated (or CR07)
- Increased toxicity being reported

Summary

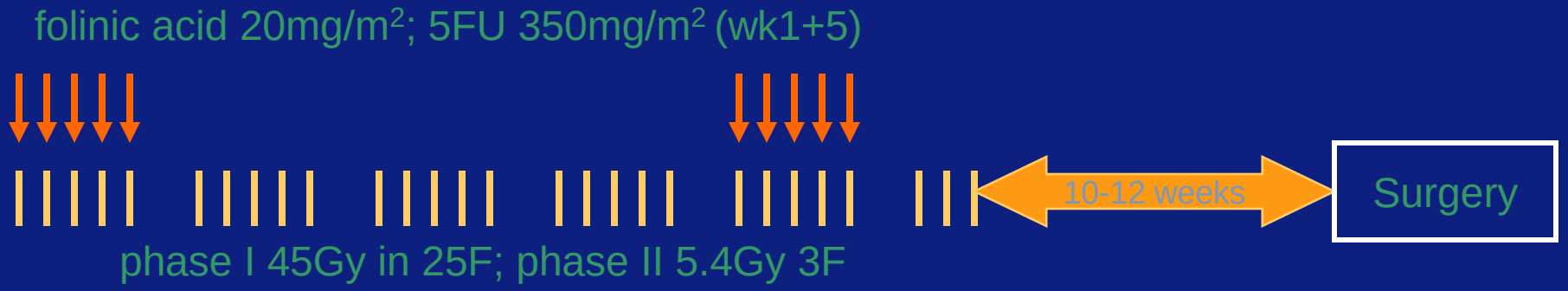
- **High and mid rectal tumours**
  - surgery (+/-CR07)
  - CRM-ve predicted
  - Include T3
  - Lymph node positivity ?contraindicated
- **Advanced high and mid rectal tumours**
  - neoadjuvant chemoradiotherapy
  - CRM +
  - Lymph node positive
- Low rectal cancers
  - Lower threshold for neoadjuvant treatment
  - Increased +CRM rates
  - Higher local recurrence rates
  - consider neoadjuvant chemoradiotherapy even in resectable tumours

Neoadjuvant radiotherapy schedules

SHORT COURSE PREOPERATIVE RADIOTHERAPY (SCPRT)



LONG COURSE PREOPERATIVE CRT

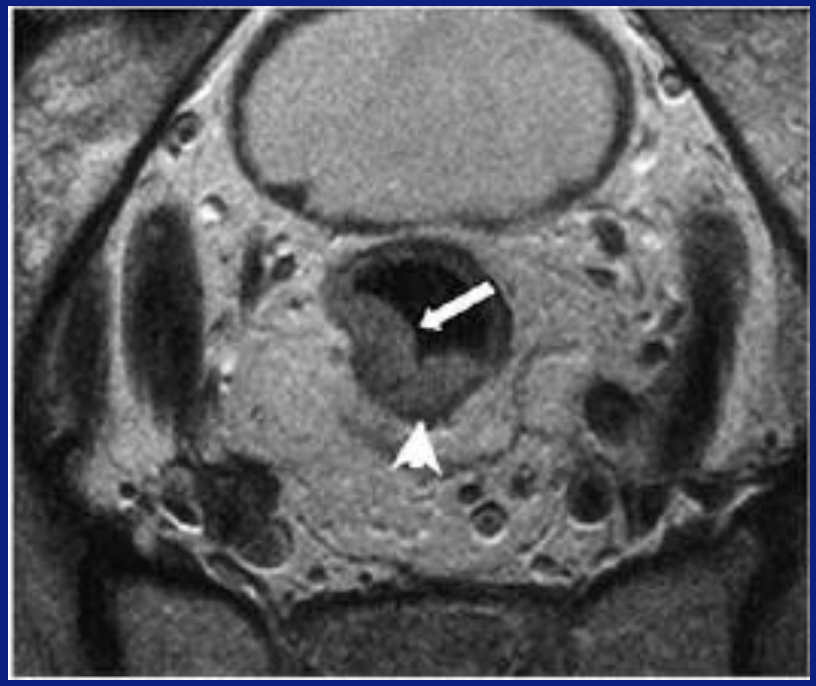


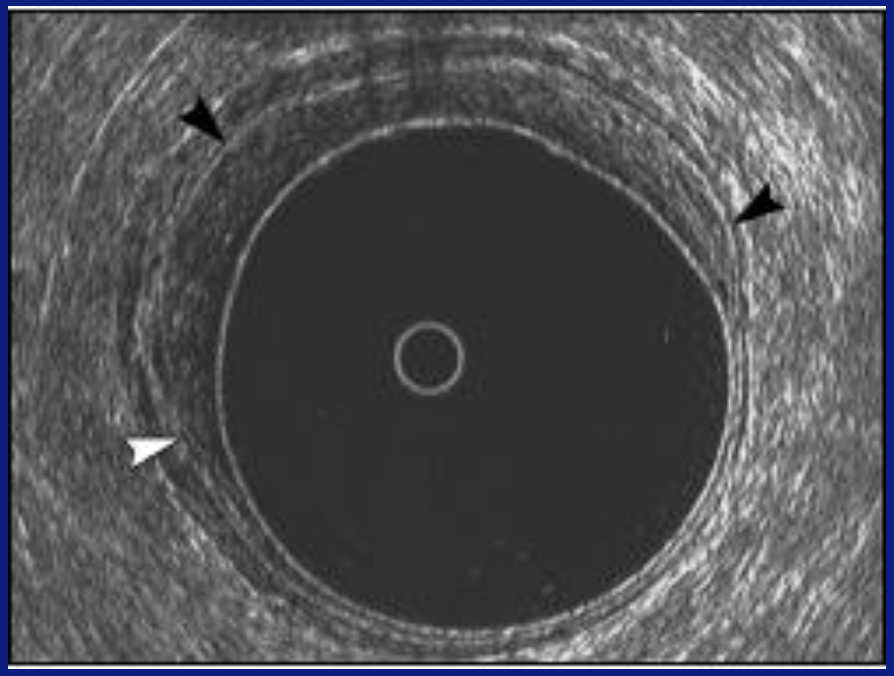
72yo male

Change of bowel habit and PRB

IHD, Coronary stenting 3 yrs ago

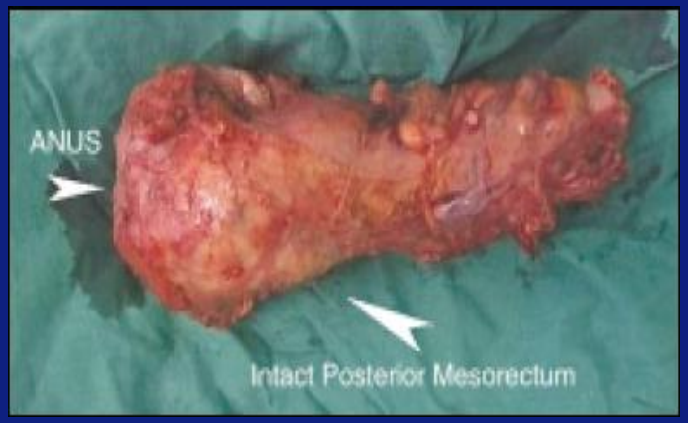
PR – posterior polypoidal lesion at 9cms





Surgery for Rectal Carcinoma

- Total Mesorectal Excision
  - gold standard
  - Mid and lower rectal tumours
  - Low local recurrence rates: 4-7.3%[1-3]
  - short course radiotherapy
  - long course chemoradiotherapy



1. MacFarlane JK, Ryall RD, Heald RJ. *Lancet* 1993
2. Zaheer S,Pemberton JH, Farouk R, et al. *Ann Surg* 1998
3. Enker WE,Thaler HT, Cranor ML, et al. *J Am Coll Surg*. 1995

Radical vs Local Excision

Anterior Resection/APR with TME

- Mortality[1-2] 0.6-8%
- Morbidity[3]:
  - Overall: 6.1-37.6%
  - Anastomotic leak: 0.5-17%

1. Mella J, Biffin A, Radcliffe AG, et al. Br J Surg 1997
2. Tekkis PP, **Smith JJ,** Thompson MR, Stamatakis J: The ACPGBI Bowel Cancer Report 2004
3. S Breukink, J Pierie, T Wiggers *Cochrane Database of Systematic Reviews* 2007

Radical vs Local Excision for Rectal Cancer

Local Resection

- Mortality: 0-2%
- Morbidity[1]:
  - Overall: 0-22%
  - Minor

- BUT…
  - Positive resection margins 12–60%
  - local recurrence rates of 9–38%

1. Sengupta S, Tjandra JJ. Dis Colon Rectum. 2001

- Transanal Endoscopic Microsurgery
  - Increased precision
  - Stereoscopic
  - 20+ cms
  - Low morbidity

- Buess 1984 – rectal adenoma
  - Negative margins 92%
  - Recurrence rate 3.5%
  - Morbidity 5%

Mortality and Morbidity

- Mortality was 0%
- Overall morbidity was 18.4% (14 patients)

  - Minor complications
    - urinary retention (n=6)
    - minor bleeding (n=5)
    - pyrexia (n=2)
    - temporary incontinence to flatus and faeces (n=2)

  - Major complications (n=4)
    - Perforation of intraperitoneal rectum not amenable to primary closure (n=3).
      - » Anterior Resection (n=2)
      - » Transverse Loop Colostomy (n=1)
    - Faecal Peritonitis (n=1)
      - » Laparotomy with Transverse Loop Colostomy

Recurrence Rates

- T1 = 7.1%
- T2 = 45.5%
- T3 = 66.6%

TEM vs Radical Surgery

- Lee W, Lee D, Choi S, Chun H. Surg Endosc. 2003
  - 5-year local recurrence rates:

	TEM	Radical Surgery	P value
T1	4.1	0	0.95
T2	19.5	9.4	0.04*

TEM vs Radical Surgery

- The Colon/Rectal Cancer Study Group. Arch Surg 2007

	TAE & TEM Groups (n = 105)	**RR Group (n = 312)**	***p* value**
Actuarial 5-y local recurrence rate, %	6.0	2.0	.049
Actuarial 5-y tumor-free survival rate, %	91.4	92.3	.39
Actuarial 5-year overall survival rate, %	83.6	91.5	.16

Lymph Node Prediction Score
Tekkis et al ASCRS 2004

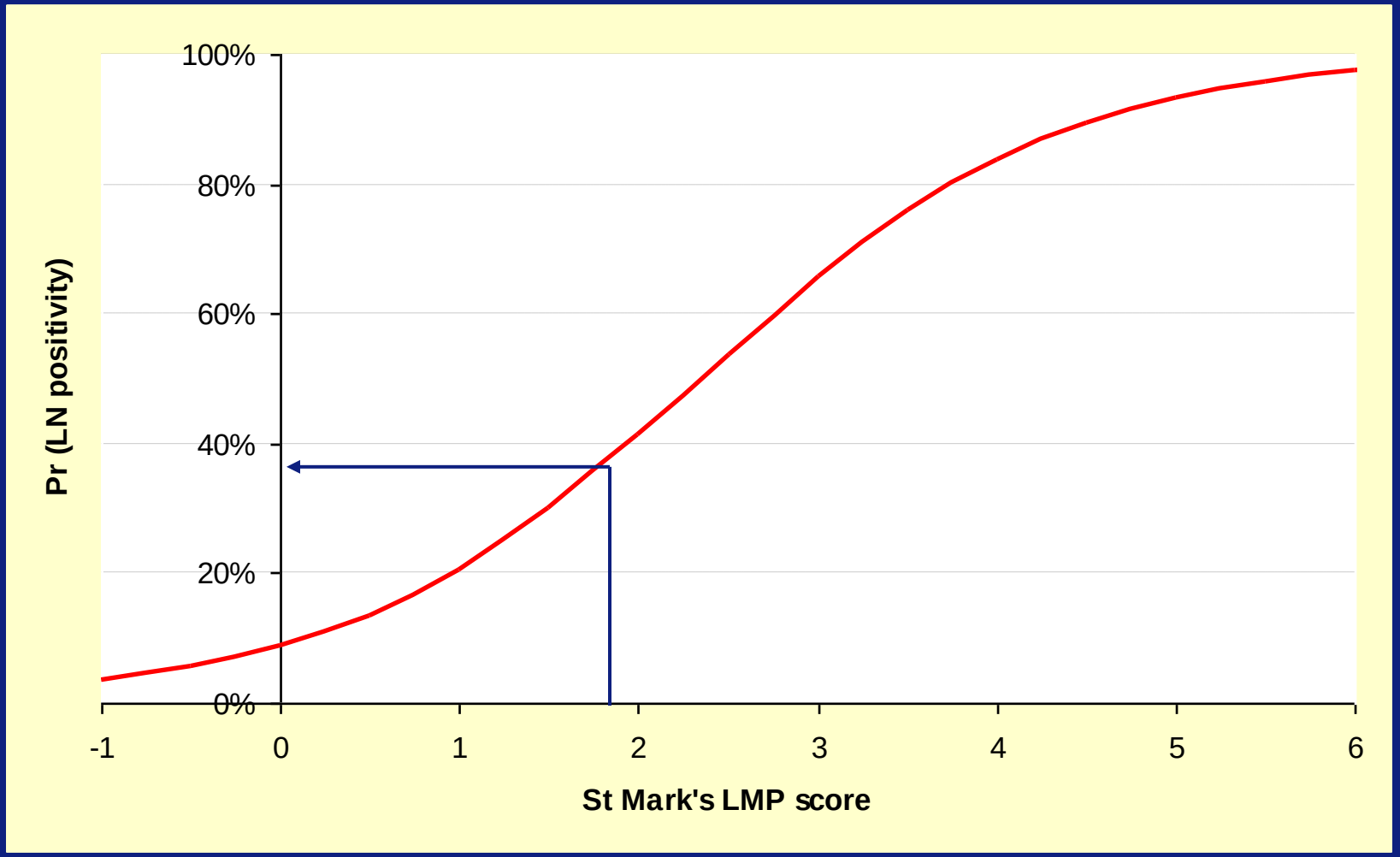
- age
  - <55 0
  - 55 - 65 - 0.2
  - 66 - 75 - 0.4
  - > 75 - 0.5
- depth of invasion
  - T1 0
  - T2 0.2
  - T3 or T4 1.2
- histological type
  - adenocarcinoma 0
  - signet cell/anaplastic 1.6
- lymphocytic infiltration
  - no 0
  - yes - 0.4
- differentiation
  - well 0
  - moderate 0.7
  - Poor 2.1
- vascular invasion
  - no 0
  - intra-mural 0.5
  - extra-mural 1.3
- perineural invasion
  - no 0
  - yes 0.6

Lymph Node Prediction Score
Tekkis et al ASCRS 2004

- age
  - <55 — 0
  - 55 - 65 — - 0.2
  - 66 - 75 — - 0.4
  - > 75 — - 0.5
- **depth of invasion**
  - T1 — 0
  - T2 — 0.2
  - T3 or T4 — 1.2
- **histological type**
  - adenocarcinoma — 0
  - signet cell/anaplastic — 1.6
- lymphocytic infiltration
  - no — 0
  - yes — - 0.4
- differentiation
  - well — 0
  - moderate — 0.7
  - Poor — 2.1
- vascular invasion
  - no — 0
  - intra-mural — 0.5
  - extra-mural — 1.3
- perineural invasion
  - no — 0
  - yes — 0.6

LNP score = 1.8

Probability of LNP by LNP score



Accuracy of Radiological Staging

- MRI
  - Brown et al:
    - 94% agreement between MRI and pathologic T stage
    - Accuracy of nodal status was 85%[1]
  - T-stage: 65-91%[2]
  - Nodal Stage: 39% and 95%[2]

- Endoanal Ultrasound
  - T-staging accuracy: 62% to 92 %
  - Nodal status 64% to 88%[2,3]

1. G. Brown, et al Br J Surg 2003
2. Beets-Tan and Beets Radiology 2004
3. Schaffzin DM, Wong WD. Clin Colorectal Cancer 2004
4. Kim HJ, Wong WD. Semin Surg Oncol 2000

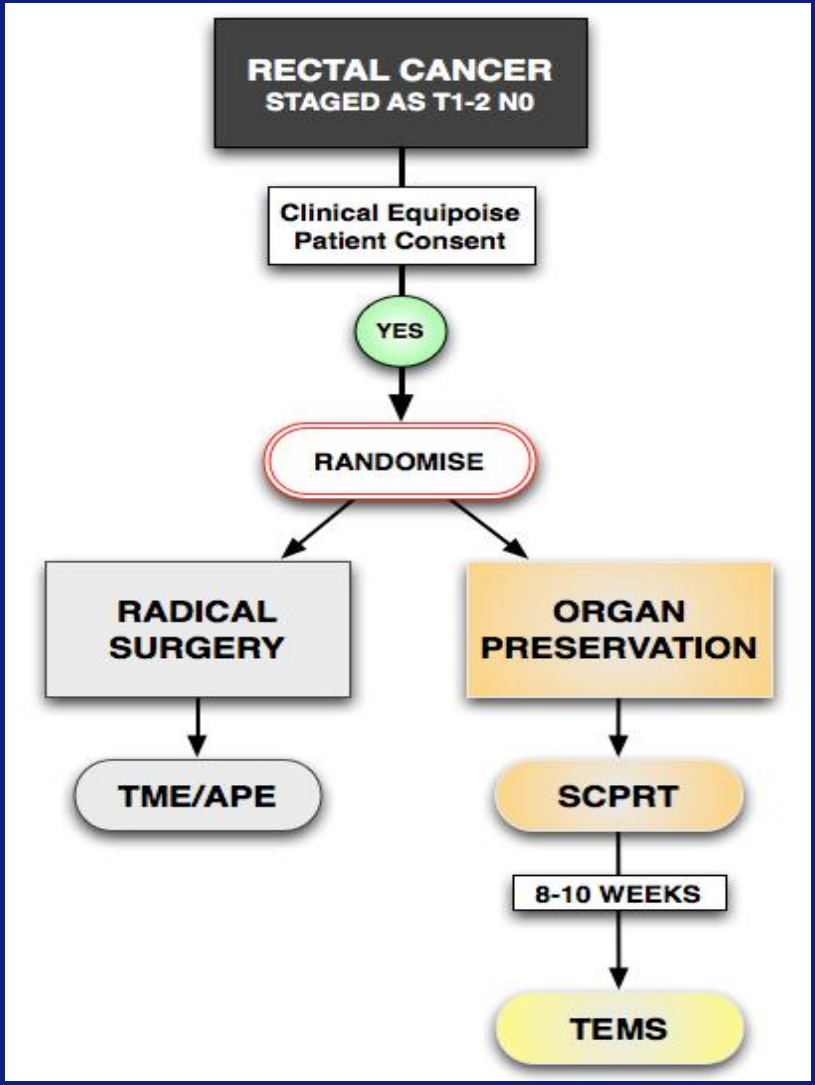
Neoadjuvant or Adjuvant Chemoradiotherapy

Study	No. of Patients	Stage	Local Recurrence Rate %	
			Surgery Alone	Surgery + ChemoDXT
Chakravarti A et al	99	T1+ T2	28	10
Guerrieri M et al	137	T1, T2, T3	N/A	5
Bonnem et al	26	T3	N/A	6
Lezoche	20	T2	N/A	5

Options

- Low risk T1: surgery alone
- High risk T1 and T2:
  - Neoadjuvant chemoradiotherapy followed by surgery
  - Surgery followed by true pathological T staging, then
    - Chemoradiotherapy
    - or Salvage surgery

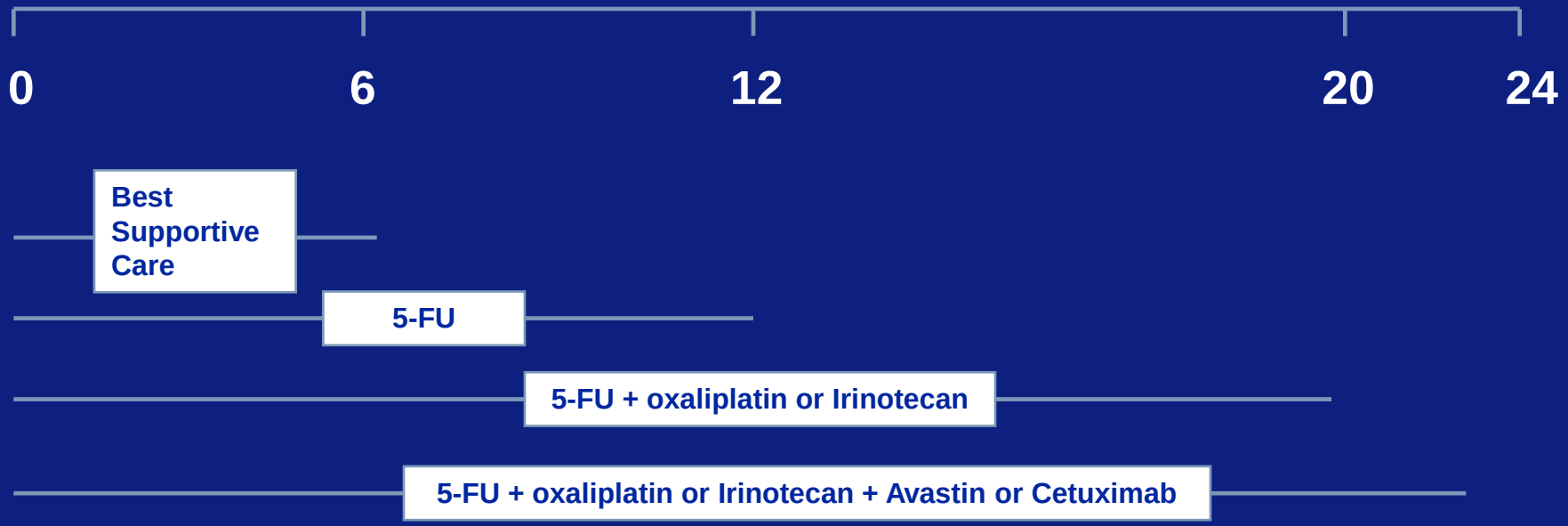
TREC Trial Design



Adjuvant chemotherapy for colon cancer

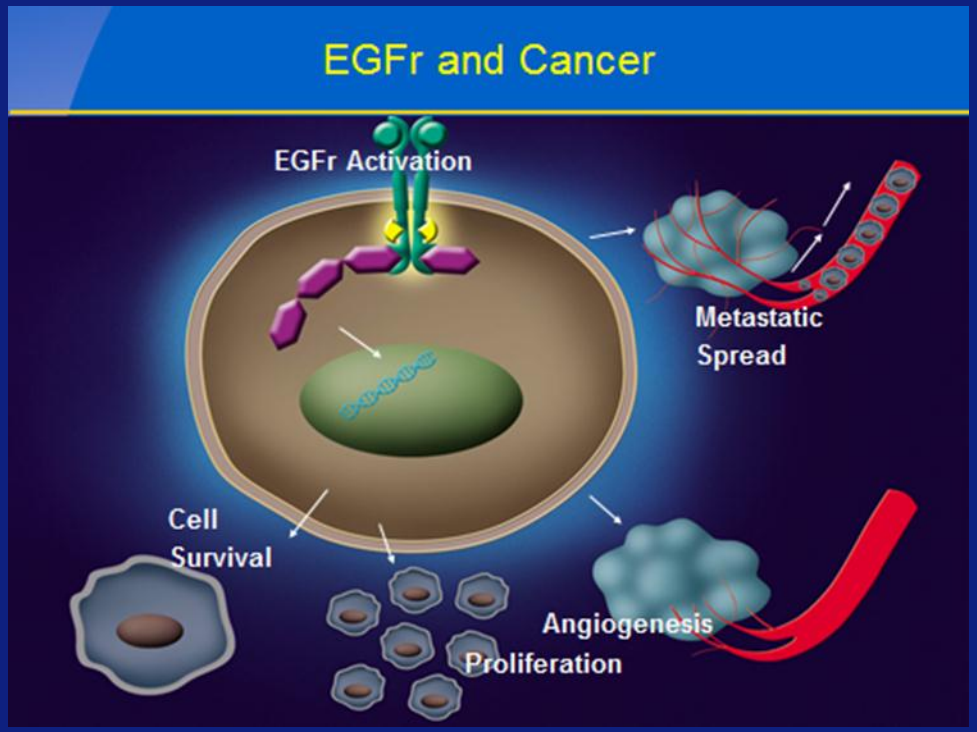
- Chemotherapy in Dukes C
  - 5FU and folinic acid
  - 30-40% improved survival
  - Plus Oxaliplatin
- QUASAR
  - 3.6% benefit in Dukes B

Approximate Survival with Metastatic CRC (months)



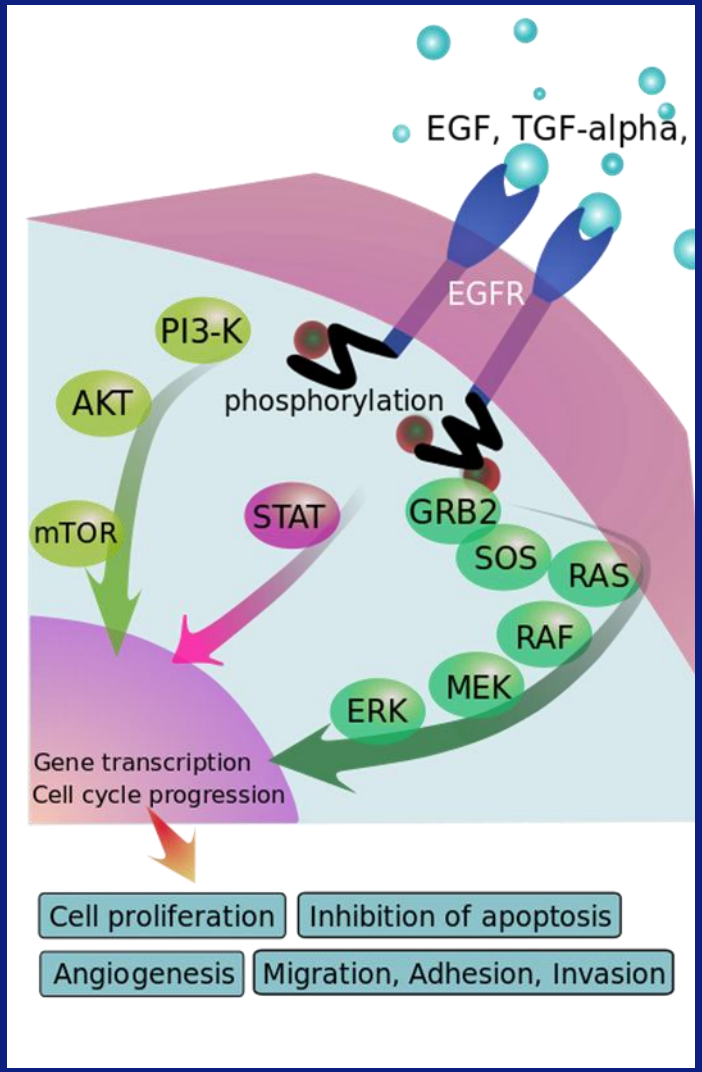
Predictors of response

- Cetuximab / Panitumumab
  - monoclonal antibody to epidermal growth factor receptor
  - EGFR inhibitor



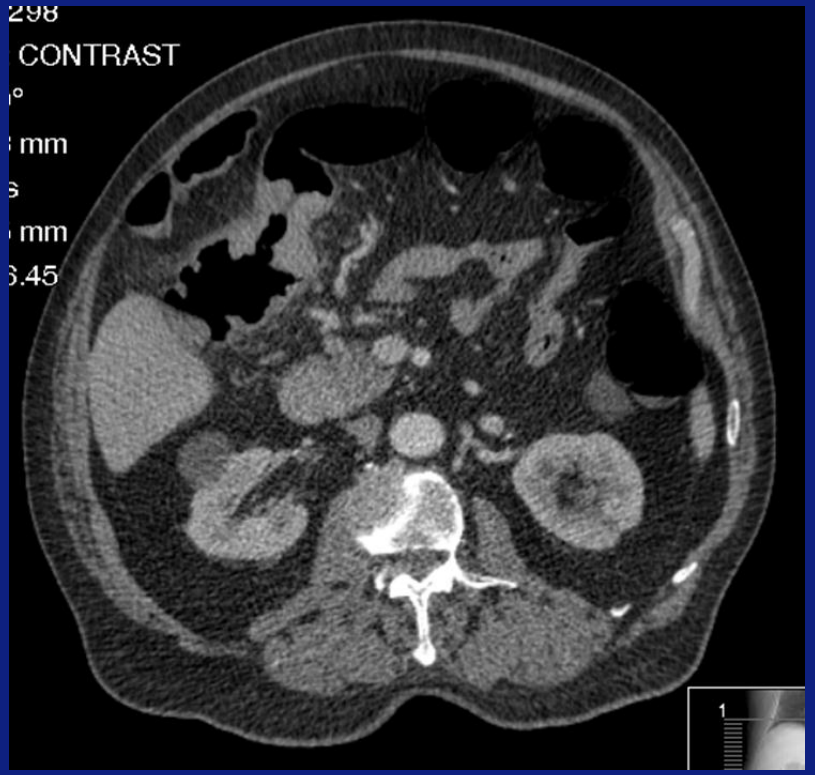
Predictors of response

- Cetuximab / Panitumumab
  - Poor response in patients with KRAS mutation
  - (Also BRAF mutations 10%)
  - All patients tested for KRAS and treatment given in wild-type



Colon Cancer

- Standard treatment is surgery
- Will neoadjuvant chemotherapy benefit outcomes?



FOxTROT

- Multi-centre RCT
- T3/T4 tunours

- **Primary objectives:**
  - To determine if neoadjuvant chemotherapy ± panitumumab followed by deferred surgery and completion of chemotherapy post-operatively can reduce 2-year recurrence as compared to surgery and postoperative chemotherapy ± panitumumab

  - To determine if adding panitumumab in the neoadjuvant treatment produces a measurable increase in anti-tumour efficacy as measured by tumour shrinkage.

  - Quality scoring of surgical resection

FOxTROT design

- colon cancer
- no mets
- fit for surgery
- operable but high risk on CT