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NHS Foundation Trust

Mandatory Staging in Rectal Carcinoma

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Cuthbert Dukes 1932: Nodes as a prognostic factor

- *A cases* - carcinoma is limited to the wall of the rectum, no extension into the extra-rectal tissues and no metastases in lymph nodes.
- *B cases* - carcinoma has spread by direct continuity to the extra-rectal tissues but has not yet invaded the regional nodes,
- *C cases* - metastases are present in the regional lymph nodes.
- system predicted **prognosis** and became a gold standard: Three-year survival after surgery was 80%, 73% and **7%** for A,B and C respectively.

There are big problems with the current TNM system and preoperative staging rectal cancer…..

The problems with TNM

- T3 category is enormous and survivals range from 90% (same as Dukes A) to 25%
- Stage III classification is too heterogeneous
- TNM does not take into account CRM status
- TNM does not take into account extramural vascular invasion
- TNM does not take into account low rectal cancer stage system
- Using T and N staging does not perform adequately in the assessment following neoadjuvant therapy

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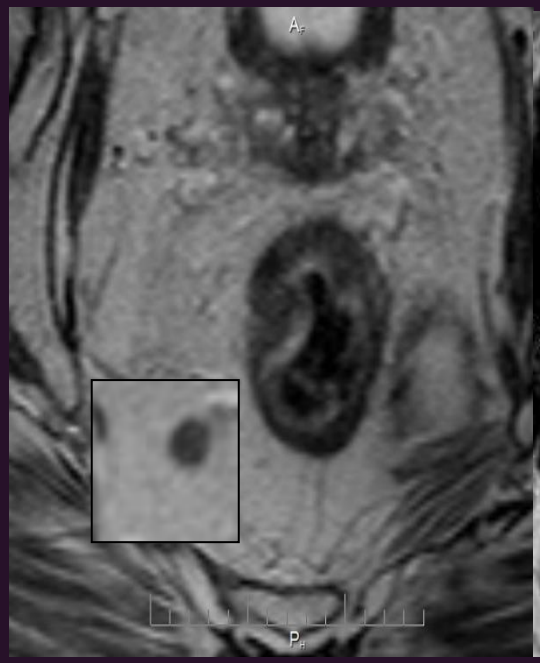
These tumours have entirely different prognostic outcomes

Stage II (T3N0)

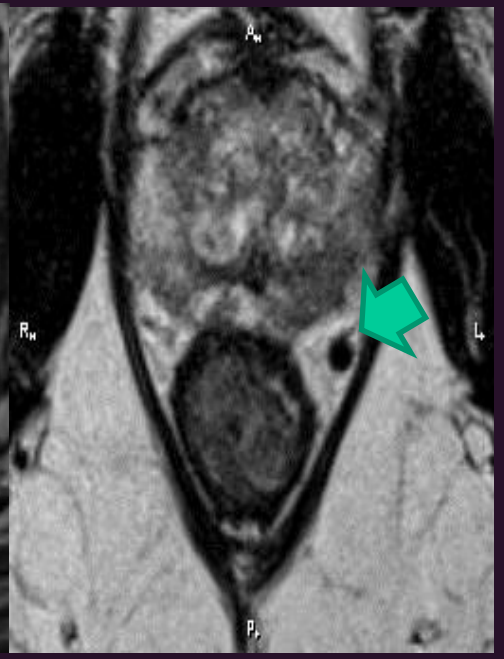
mrT3dN0EMVI pos
CRM+:CRT+chemo + beyond TME surgery

Stage III (T3N1)

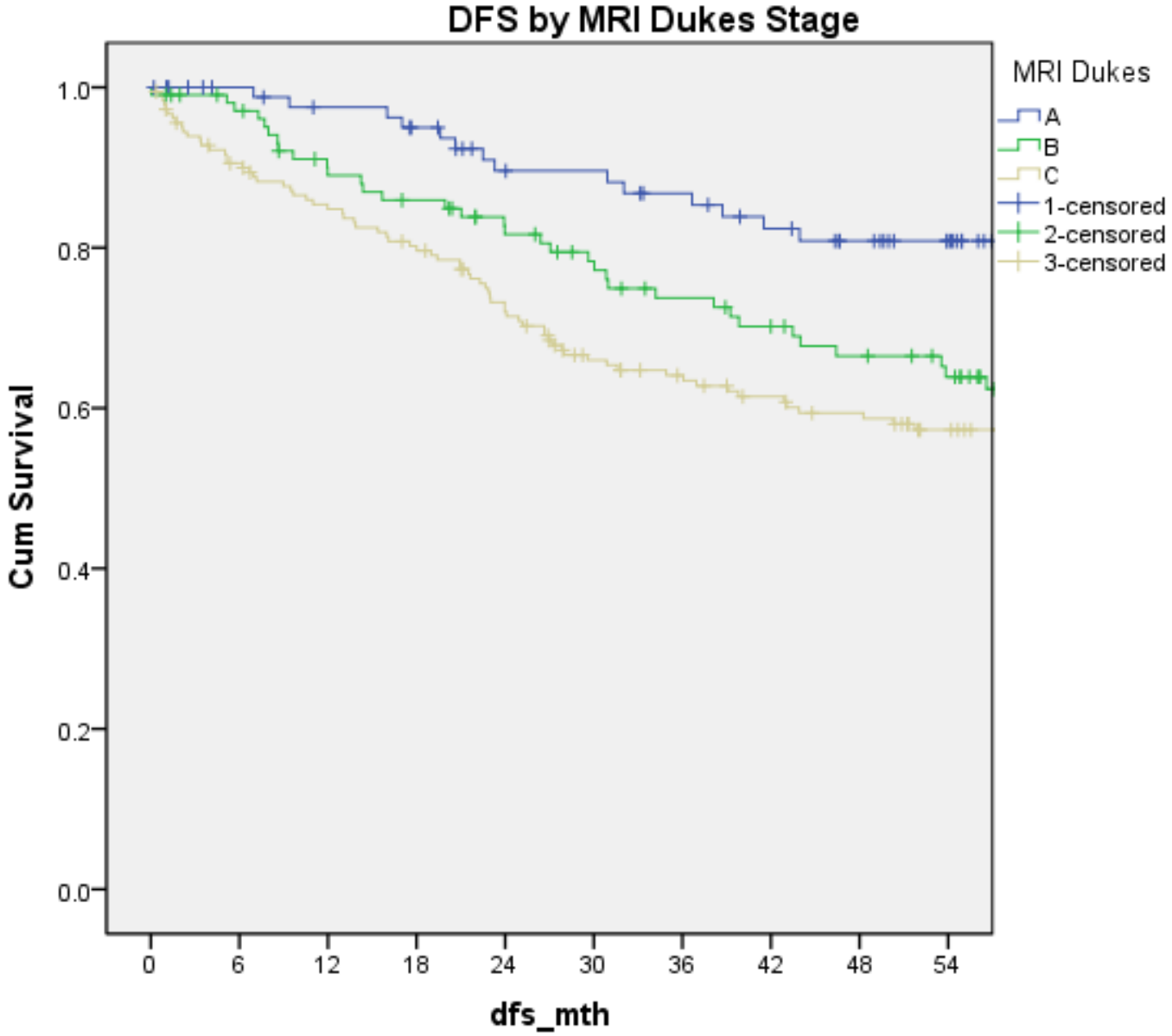


mrT3aN1CRM-ve
Primary TME surgery

Stage I (T1N0)



mrT1 EMVI deposit, CRM+ve, Preoperative CRT and ELAPE

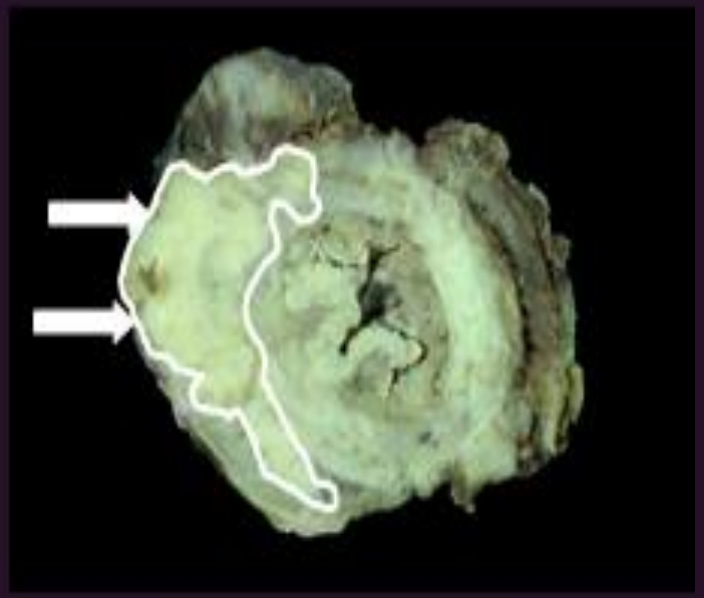

DFS by MRI Dukes Stage
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
6
12
18
24
30
36
42
48
54
dfs_mth
MRI Dukes
A
B
C
1-censored
2-censored
3-censored

Current evidence base for preoperative local staging assessment using MRI

#1. Identifying patients at risk of Local Recurrence

Cancer death in colorectal cancer

- Tumour present at the circumferential resection margins of the specimen
- Local recurrence
- Survival <40%



#1. Identifying patients at risk of Local Recurrence

First description of the mesorectal fascia using MRI. Brown G, Radiology 1999

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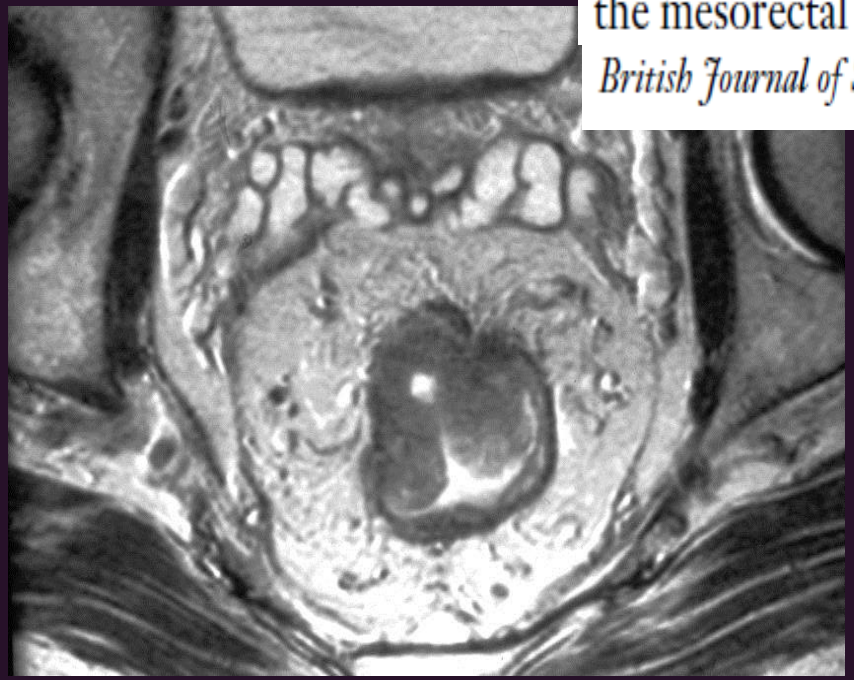
First description of the meso
MRI. Brown G, Radiology 199

The mesorectal fascia represents the potential CRM in patients undergoing TME. Clear demonstration of the mesorectal fascia by MRI enables prediction of final CRM status in patients having this operation. CRM involvement was predicted when tumour extended to within 1 mm of the mesorectal fascia on magnetic resonance images; while

British Journal of Surgery 2003; 90: 355–364



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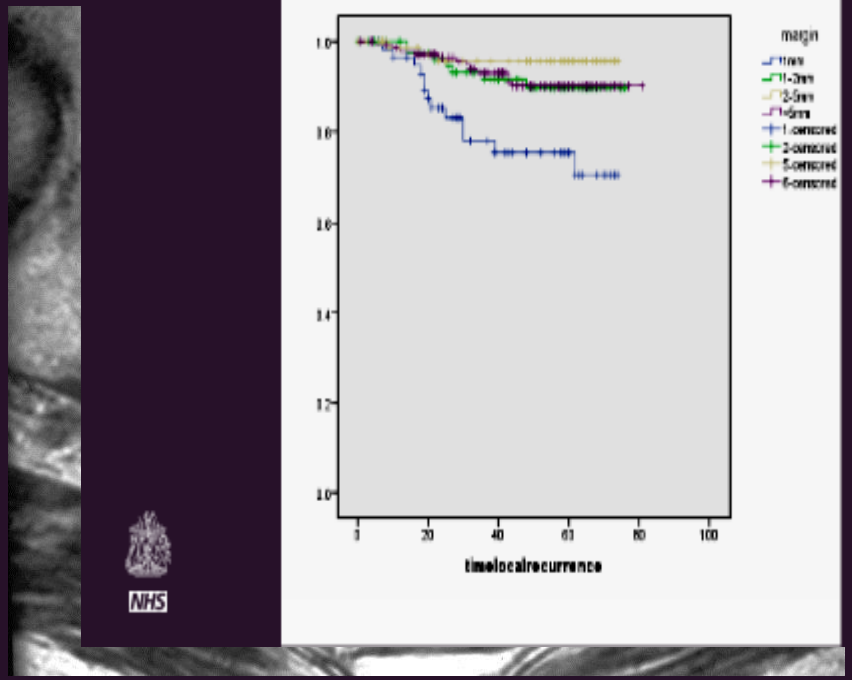
only 1mm cut-off on MRI predicts local recurrence



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#1. Identifying patients at risk of Local Recurrence

Firs
MR

Published Ahead of Print on November 25, 2013 as 10.1200/JCO.2012.45.3258
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2012.45.3258

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Preoperative Magnetic Resonance Imaging Assessment of Circumferential Resection Margin Predicts Disease-Free Survival and Local Recurrence: 5-Year Follow-Up Results of the MERCURY Study

Fiona G.M. Taylor, Philip Quirke, Richard J. Heald, Brendan J. Moran, Lennart Blomqvist, Ian R. Swift, David Sebag-Montefiore, Paris Tekkis, and Gina Brown

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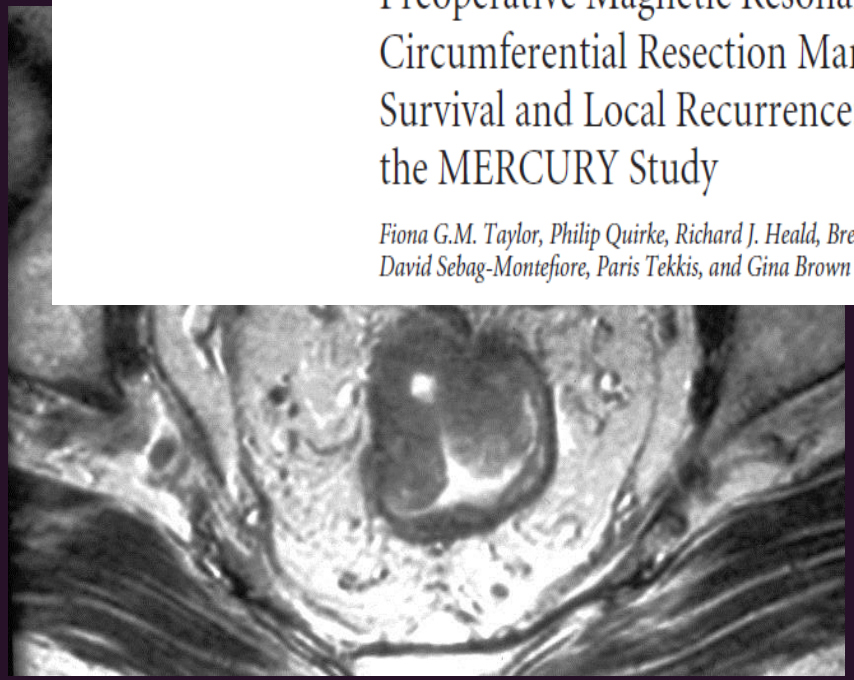

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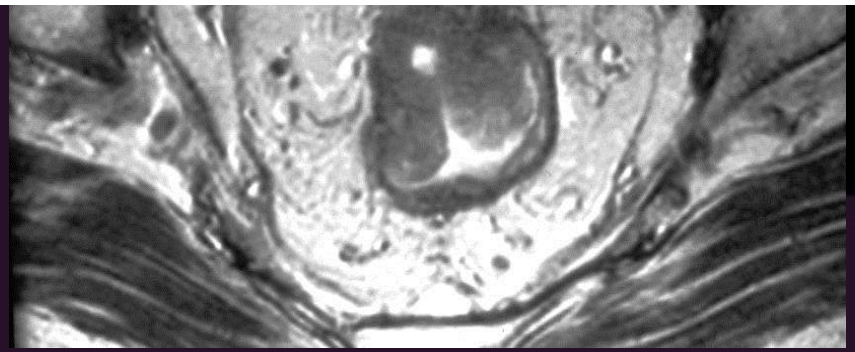
JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Firs… MR…

…ntial CRM in …tration of the … of final CRM

Conclusion

High-resolution MRI preoperative assessment of CRM status is superior to AJCC TNM–based criteria for assessing risk of LR, DFS, and OS. Furthermore, MRI CRM involvement is significantly associated with distant metastatic disease; therefore, colorectal cancer teams could intensify treatment and follow-up accordingly to improve survival outcomes.



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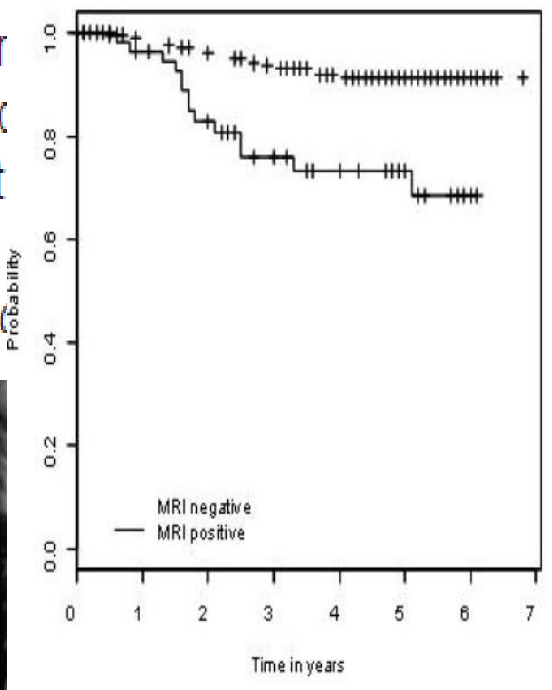
ORIGINAL REPORT

Kaplan – Meier plots for Time till Local Recurrence

by MRI CRM Positive & Negative Patients



Conclusion
High-resol
criteria for
associated
treatment

J Clin On

MRI directed multidisciplinary team preoperative treatment strategy: the way to eliminate positive circumferential margins?

- 26% rate of tumour involvement of margins when preoperative discussion of MRI scans compared with 8% when preoperative discussion takes place ($p<0.001$)
- Mandatory discussion of preoperative MRI scans introduced in 2003, positive CRM rate is now 2-3%

Burton S, Brown G, Daniels IR, Norman AR, Mason B, Cunningham D. Br J Cancer. 2006 Feb 13;94(3):351-7.

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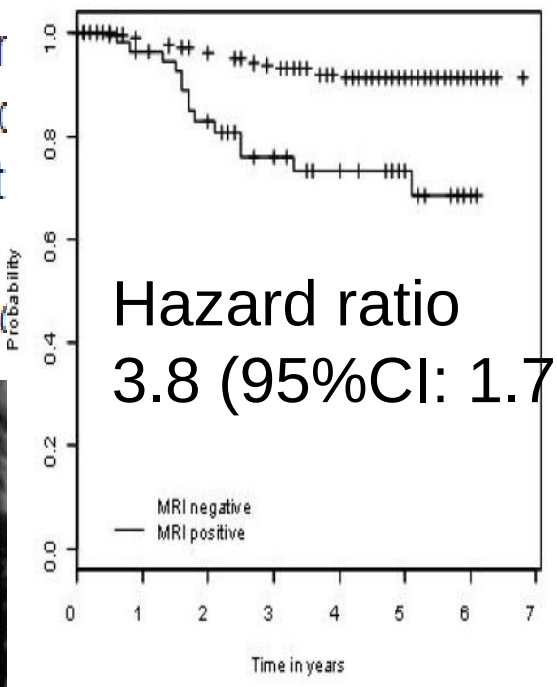

Hazard ratio
3.8 (95%CI: 1.7 -8.5)

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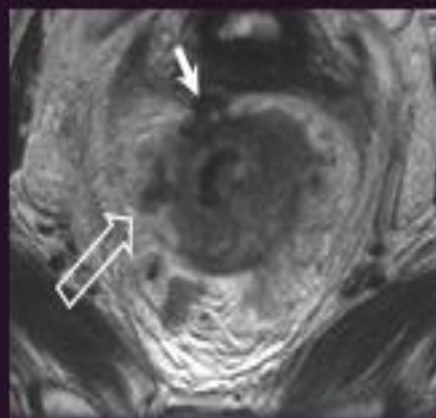
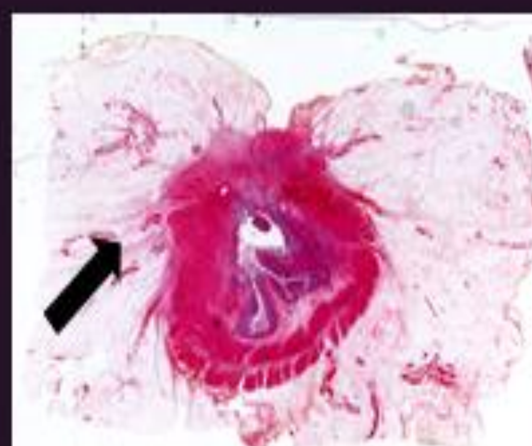
#2. Identifying patients who require surgery beyond TME

30% of patients present with tumour involving mesorectal margins
Preoperative CRT reduces this rate to 15% on post treatment MRI
Persistence of ymrCRM involvement associated with 4 fold risk of local recurrence compared with ymrCRM clear





#2. Identifying patients who require surgery beyond TME

Guidelines

Consensus statement on the multidisciplinary management of patients with recurrent and primary rectal cancer beyond total mesorectal excision planes

The Beyond TME Collaborative*

Correspondence to: Professor P. Tekkis, Department of Colorectal Surgery, Imperial College and the Royal Marsden Hospital, Fulham Road, London SW3 6JJ, UK (e-mail: p.tekkis@imperial.ac.uk)

Consensus abstract

Background: The management of primary rectal cancer beyond total mesorectal excision planes (PRC-bTME) and recurrent rectal cancer (RRC) is challenging. There is global variation in standards and no guidelines exist. To achieve cure most patients require extended, multivisceral, exenterative surgery, beyond conventional total mesorectal excision planes. The aim of the Beyond TME Group was to achieve consensus on the definitions and principles of management, and to identify areas of research priority.

Methods: Delphi methodology was used to achieve consensus. The Group consisted of invited experts from surgery, radiology, oncology and pathology. The process included two international dedicated discussion conferences, formal feedback, three rounds of editing and two rounds of anonymized web-based voting. Consensus was achieved with more than 80 per cent agreement; less than 80 per cent agreement indicated low consensus. During conferences held in September 2011 and March 2012, open

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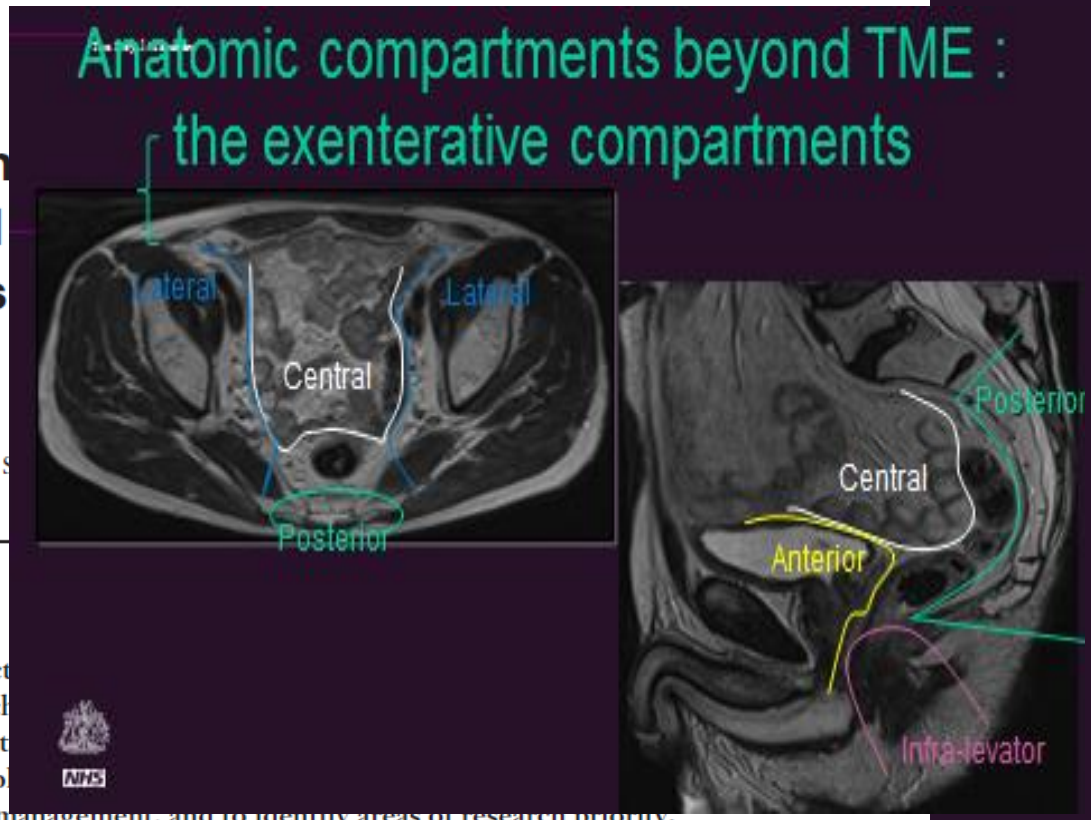

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#2. Identifying patients who require surgery beyond TME

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Disease affects central compartment
Above the peritoneal reflection within the pelvis
Disease is present/ absent
Ureters are free of disease

Below the Peritoneum anteriorly
Bladder /Uterus/Vagina/Ovaries Prostate/Seminal vesicles/Urethra are free of disease

Posteriorly
The bony cortex/periosteum from S1-S2 is / is not involved by disease
The bony cortex/periosteum from S3-S5 /coccyx is/ is not involved by disease
Presacral fascia (S1/S2/S3/S4/S5) is not involved by disease
Sciatic nerve/ S1/S2 nerve roots
No disease
Disease is present

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Laterally
Pelvic fascia are free of disease
Pelvic sidewall compartment are free of disease
Internal/external iliac arterial /venous branches are free of disease
Sacrotuberous/sacrospinous
Piriformis/Obturator

Infralevator compartment
Levator muscles are free of disease
Sphincter complex are free of disease

Anterior urogenital triangle/Perineum
Vaginal introitus/urethra : free of disease
Retropubic space: : free of disease

Summary:
MRI Overall stage: T N M , [EMVI positive] [EMVI negative],[PSW positive] [PSW negative], Total number of compartments, Closest potential surgical margins are located, Resection would require:

ents beyond TME :
compartments

priority.
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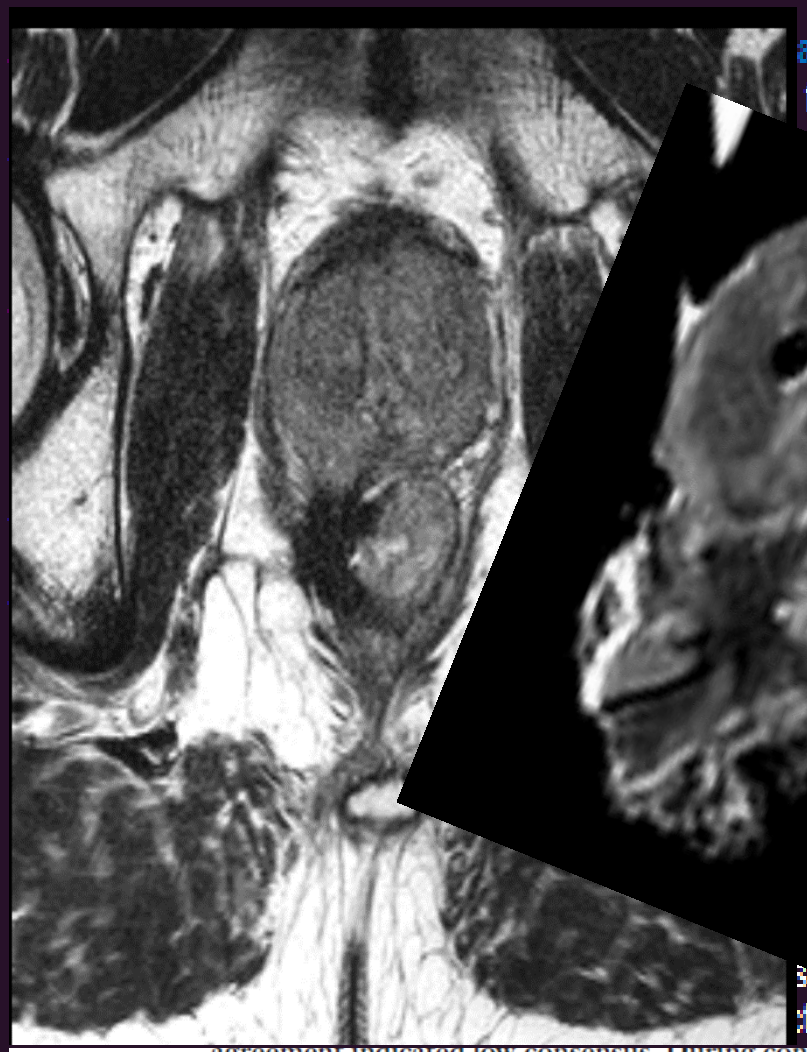

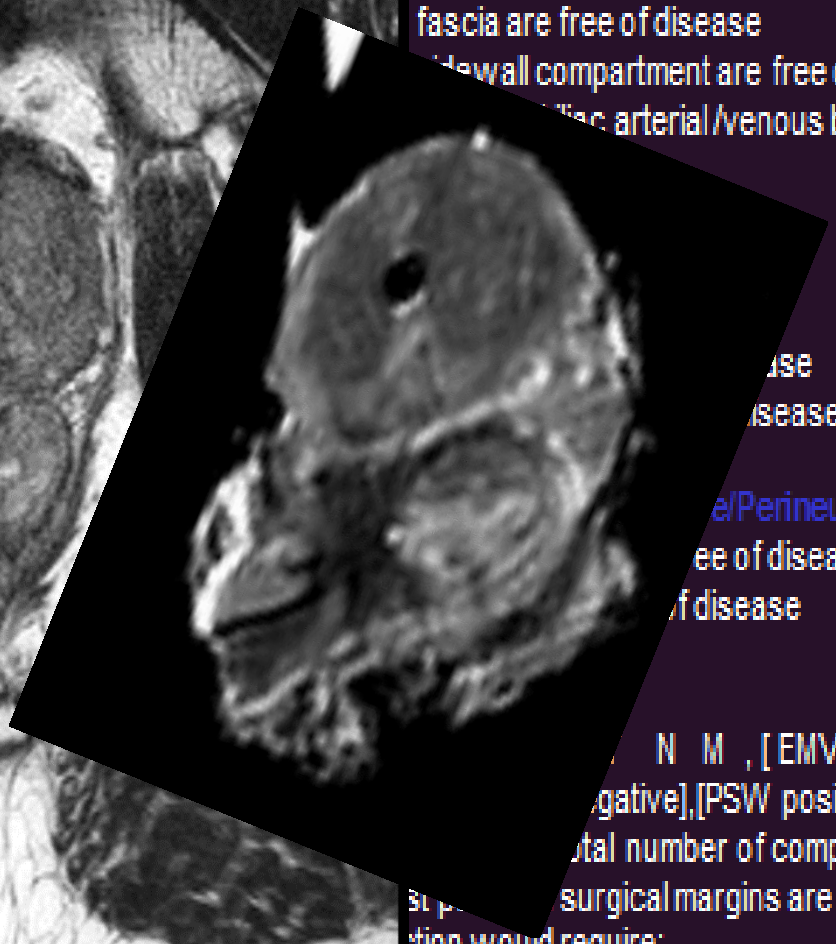

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dewall compartment are free of disease
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N M , [EMVI
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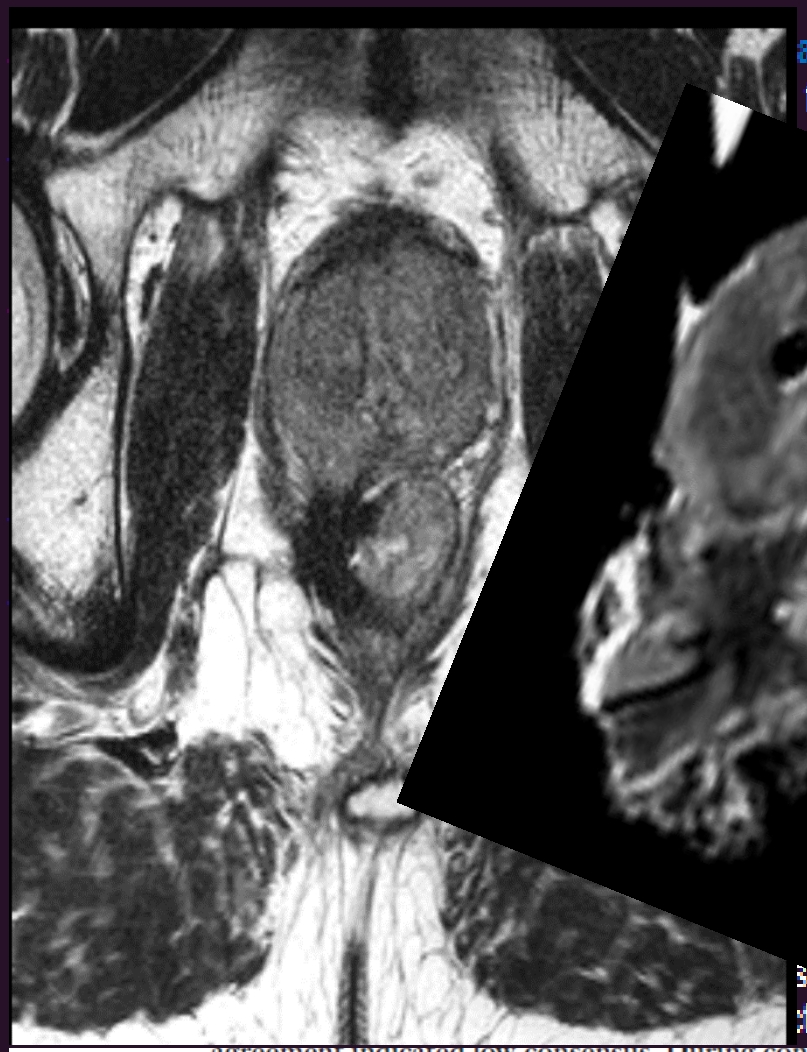

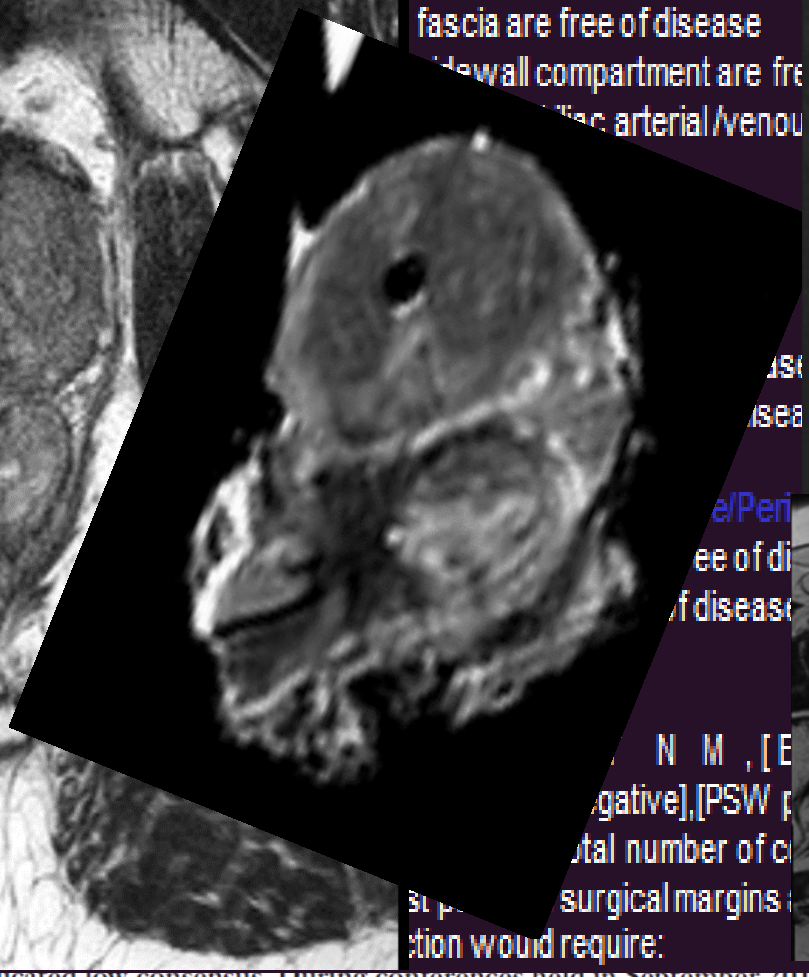

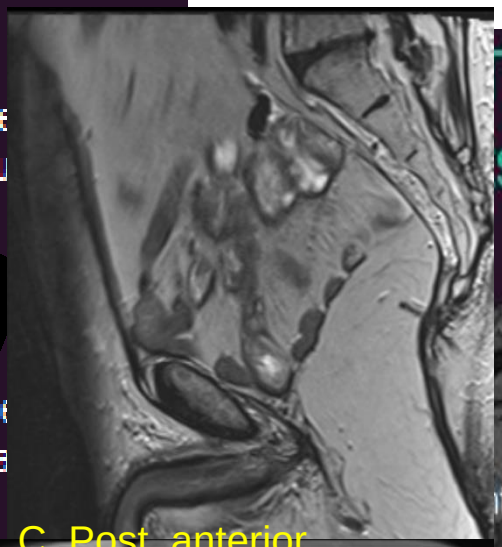

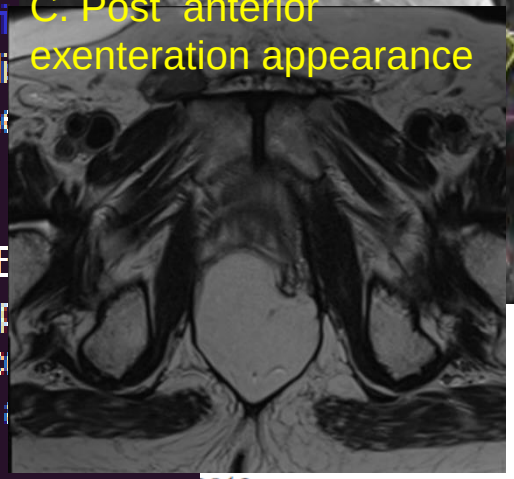

C. Post anterior exenteration appearance

fascia are free of disease

wall compartment are fre

arterial /venou

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surgical margins

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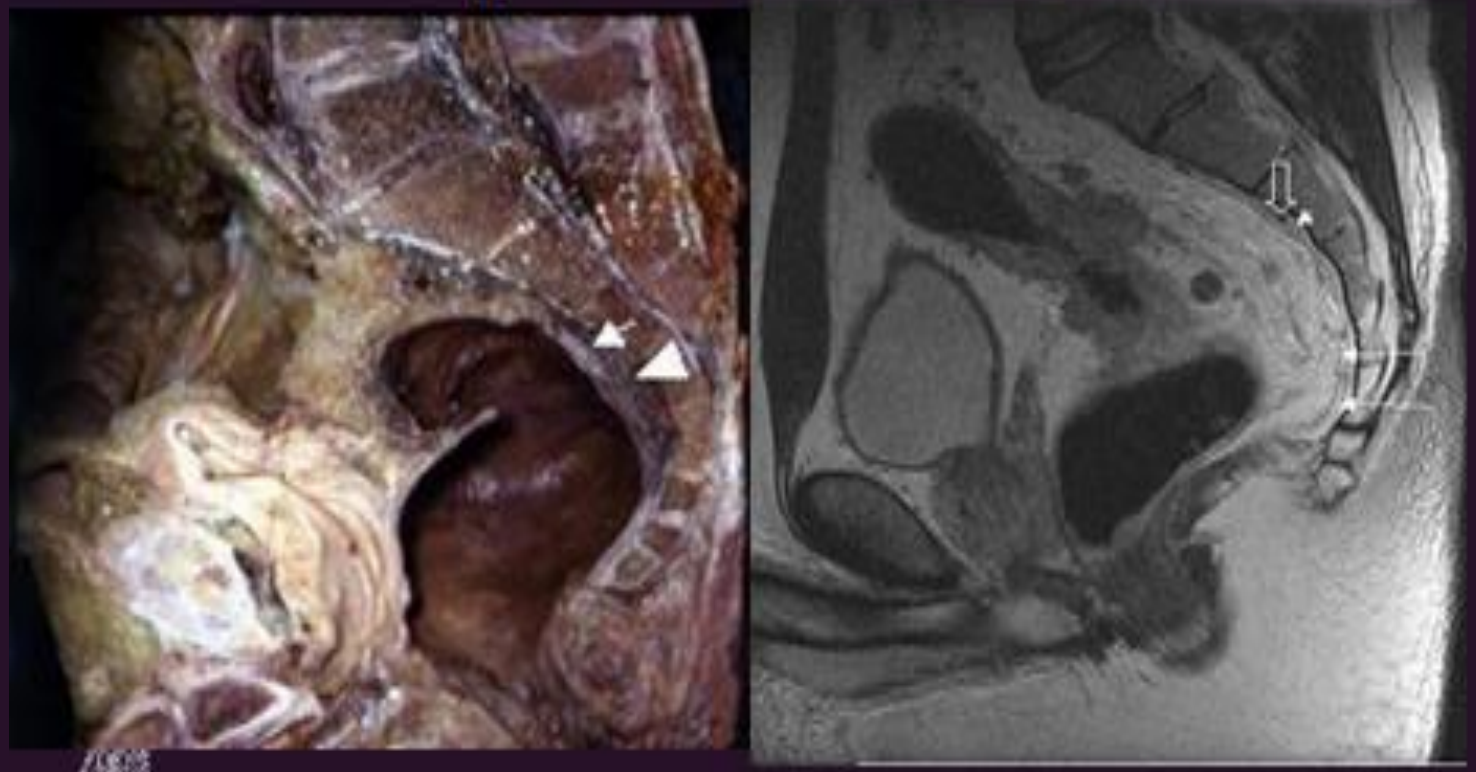
3. Anatomic Surgical and Therapeutic Road Map

3. Anatomic Surgical and

Mesorectal fascia and

presacral fascia



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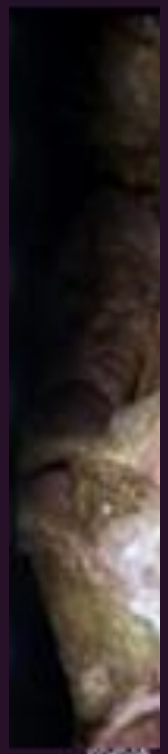
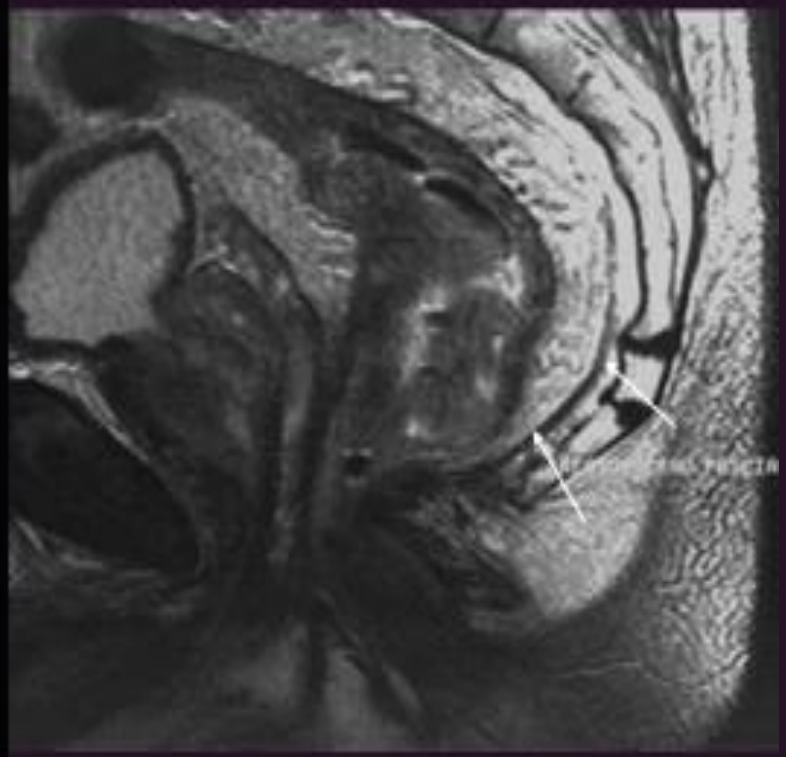
Rectosacral fascia





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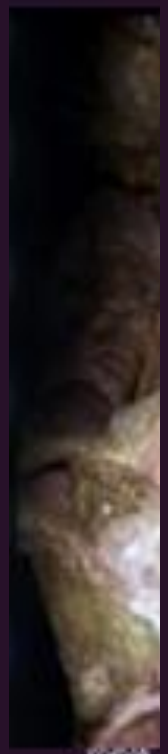
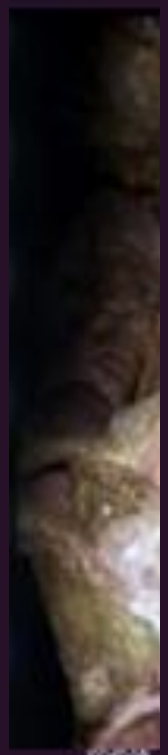
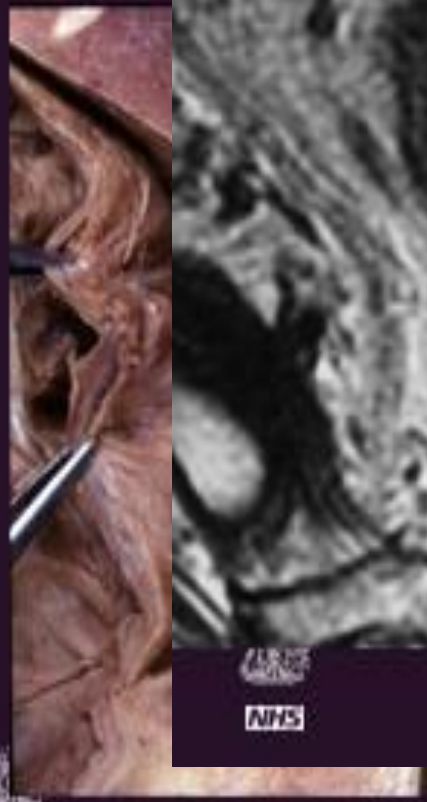
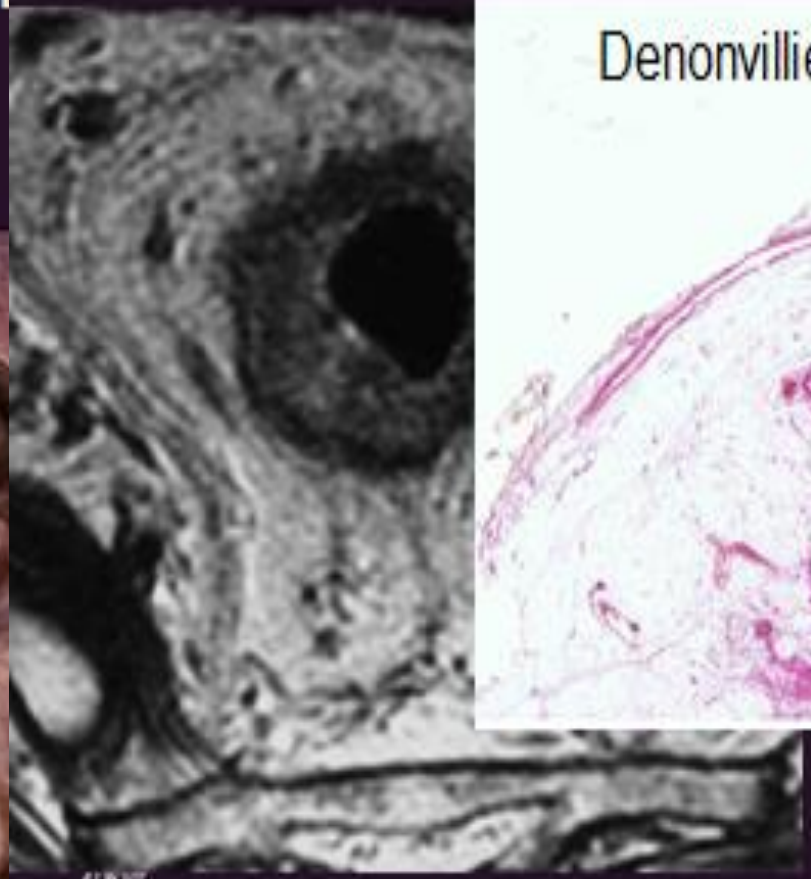


Peritoneal reflection

3. Anatomic Surgical and M







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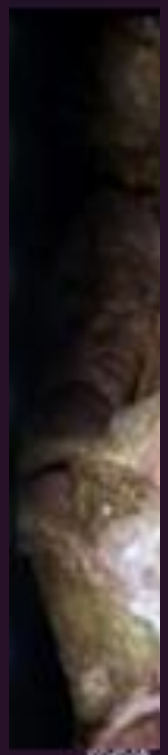
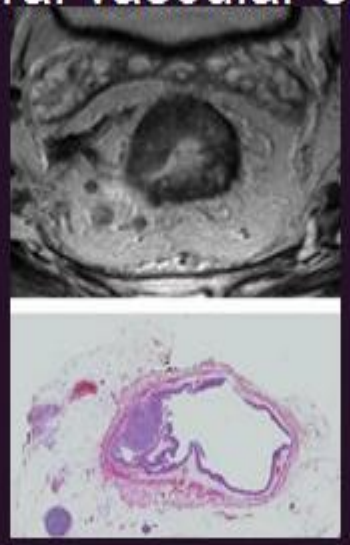


Lateral vascular spread



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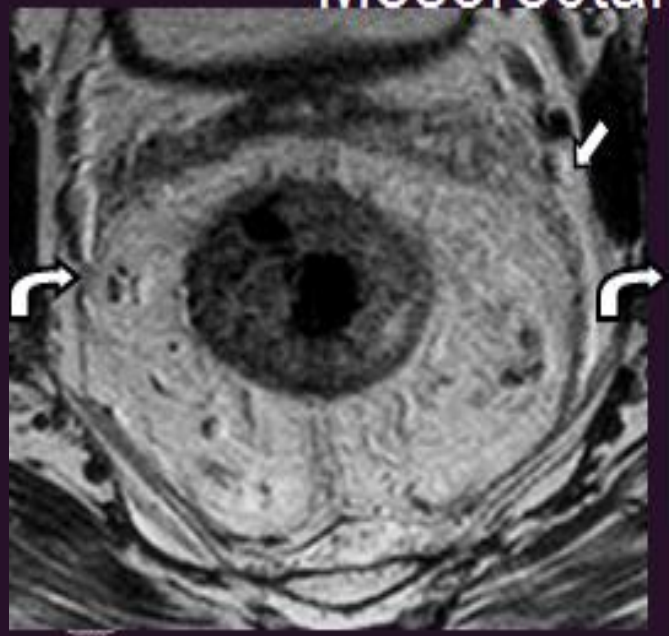
Mesorectal fascia



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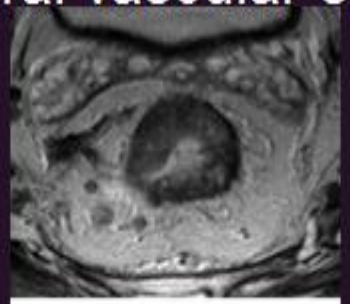

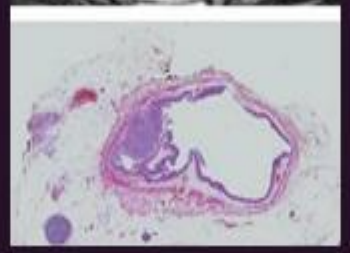

#3. Anatomic Surgical and Therapeutic Road Map

4. Staging and assessment of low rectal cancer

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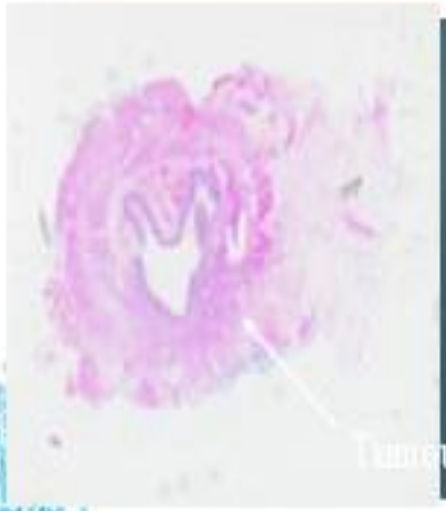
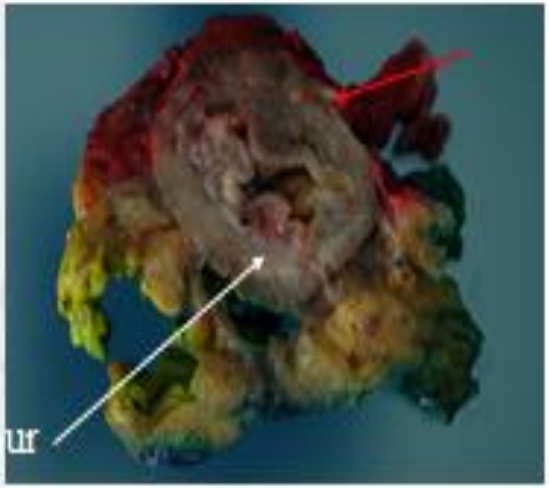
APE showing perforation just above level of levator insertion (red arrow)

Area of perforation lies in upper anal canal 42mm from anal verge
Salerno et al BJS 2008





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PELICAN cancer foundation

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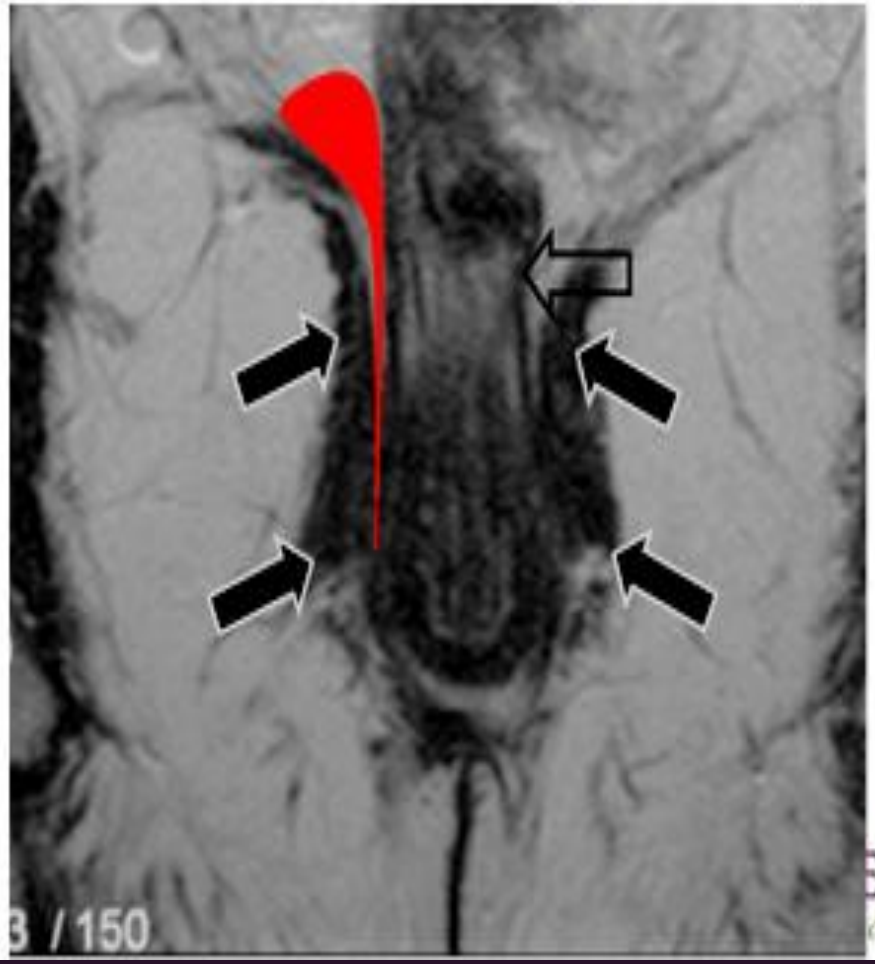
The triangle of "danger" – at or just above puborectalis sling

Tumour in this space results in TME plane CRM involvement

These tumours require ELAPE to avoid positive CRM

The outer 1mm of internal sphincter/muscularis (open arrow) must be free of tumour for plane to be safe –as the distal muscle tube forms the CRM in TME plane APE compared with ELAPE



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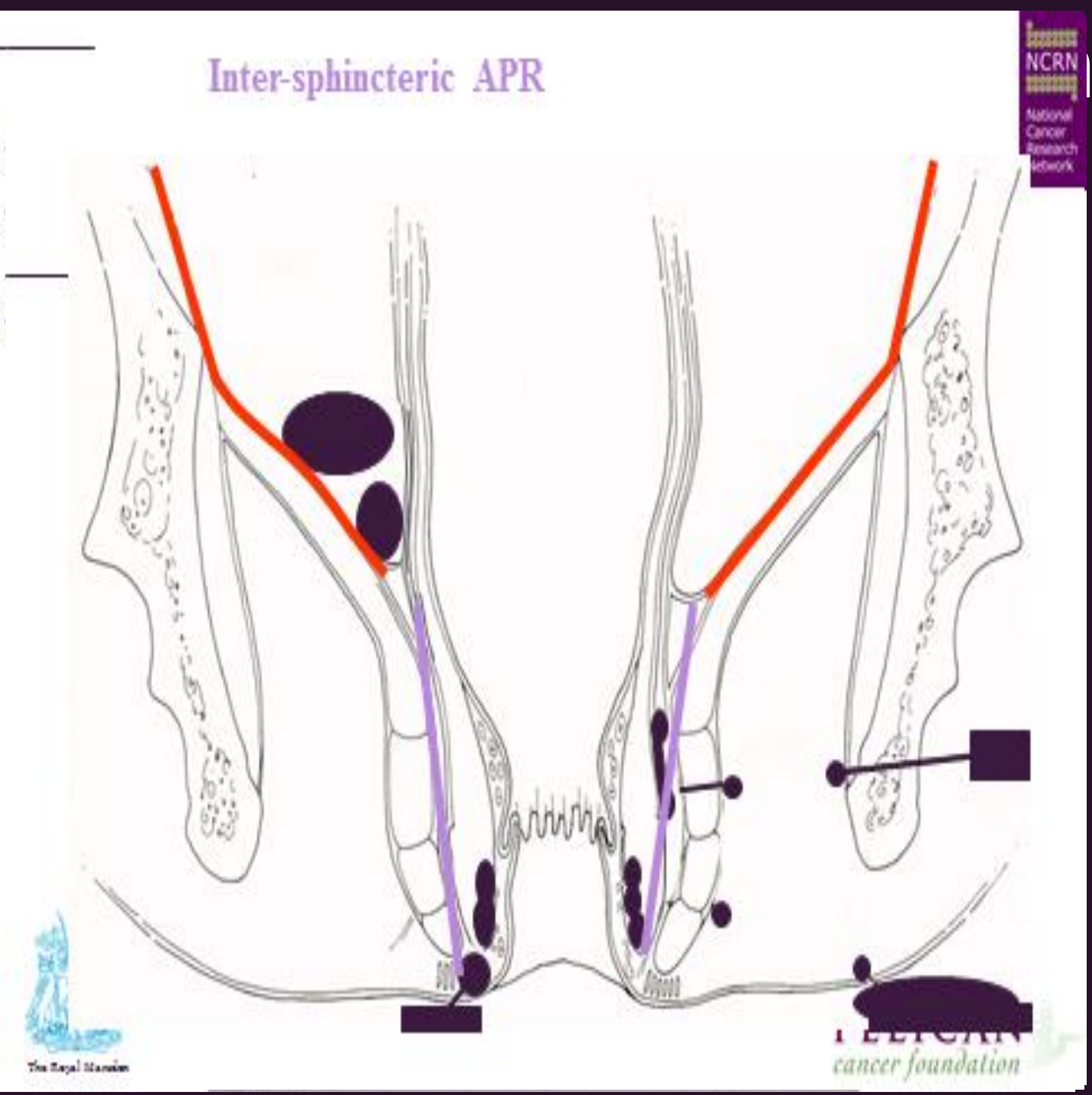
Inter-sphincteric APR
NCRN
National Cancer Research Network
cancer foundation

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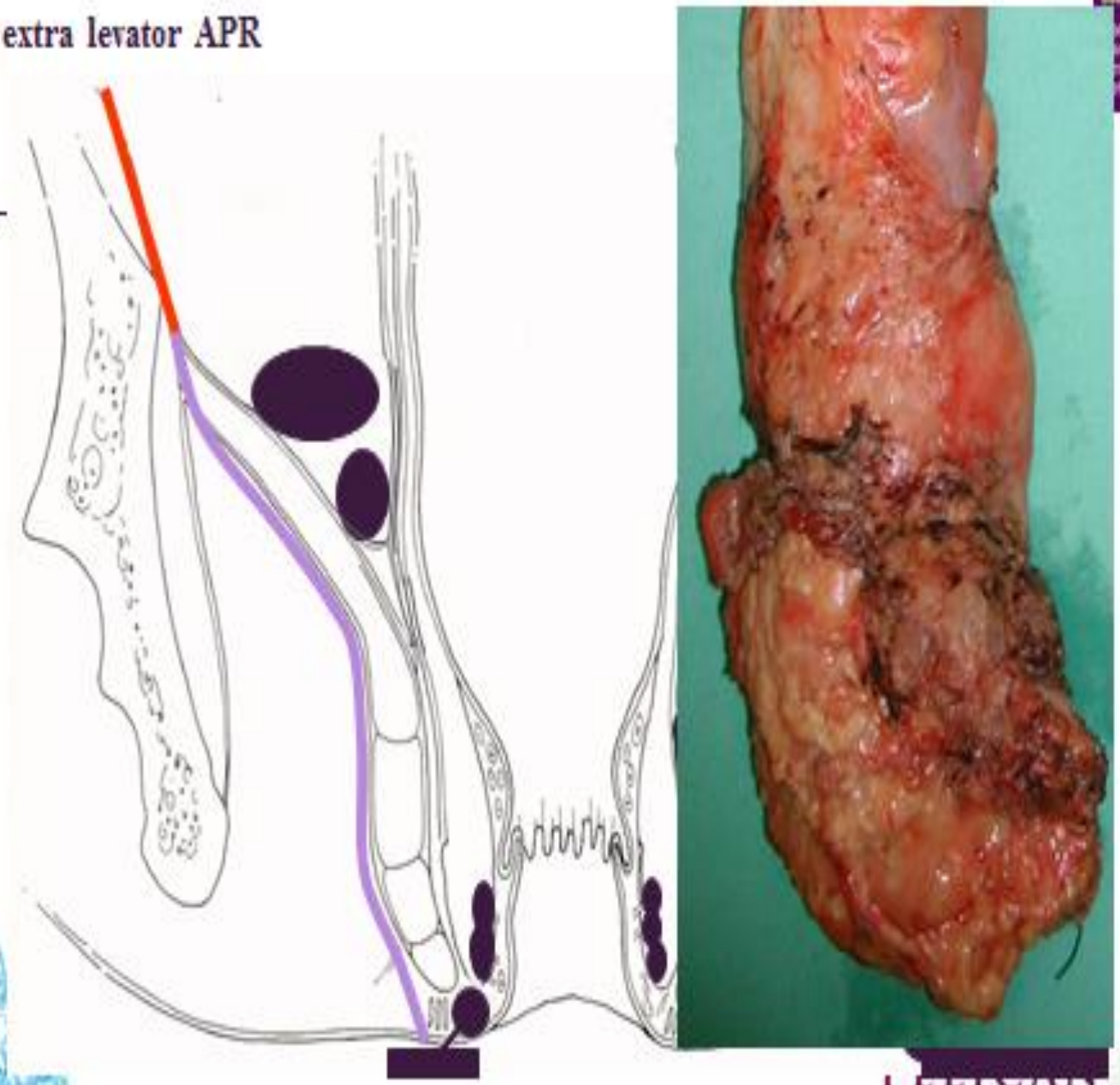

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Staging nomenclature

- MRI Stage 1, tumor on MRI images appears confined to bowel wall but not through full thickness (with intact outer muscle coat).
- 2. MRI Stage 2, tumor on MRI replaces the muscle coat but does not extend into the intersphincteric plane.
- 3. MRI Stage 3, tumor on MRI invading into the intersphincteric plane or lying within 1mm of levator muscle.
- 4. MRI Stage 4, tumor invading into the external anal sphincter and infiltrating/extending beyond the levators +/- invading adjacent organ.

NCRN National Cancer Research Network

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PELICAN cancer foundation

MRI prediction of outcome for low rectal cancer

TABLE 2. Resection margin status

Patient characteristics	N	Positive margins	Negative margins	Odds ratio (95% CI)	P value (univariate)
All patients	101	27 (26.7%)	74 (73.3%)		
MRI stage					<0.001
1-2	54	3 (5.6%)	51 (94.4%)	1	
3-4	47	24 (51.1%)	23 (48.9)	17.7 (4.8-64.9)	
Quadrant					0.026
Anterior	49	18 (36.7%)	31 (63.3%)	2.8 (1.1-7)	
Posterior	52	9 (17.3%)	43 (82.7%)	1	
Operation					0.109
APE	70	22 (31.4%)	48 (68.6%)	2.4 (0.8-7)	
LAR	31	5 (16.1%)	26 (83.9%)	1	
TRG					0.001
3-5	15	11 (73.3%)	4 (26.7%)	17.9 (2.7-116.9)	
1-2	15	2 (13.3%)	13 (86.7%)	1	
Preoperative treatment					0.557
Yes	55	16 (29.1%)	39 (70.9%)	1.305 (0.5-3.2)	
No	46	11 (23.9%)	35 (76.1%)	1	

Diseases Of The Colon & Rectum Volume 52: 4 (2009)

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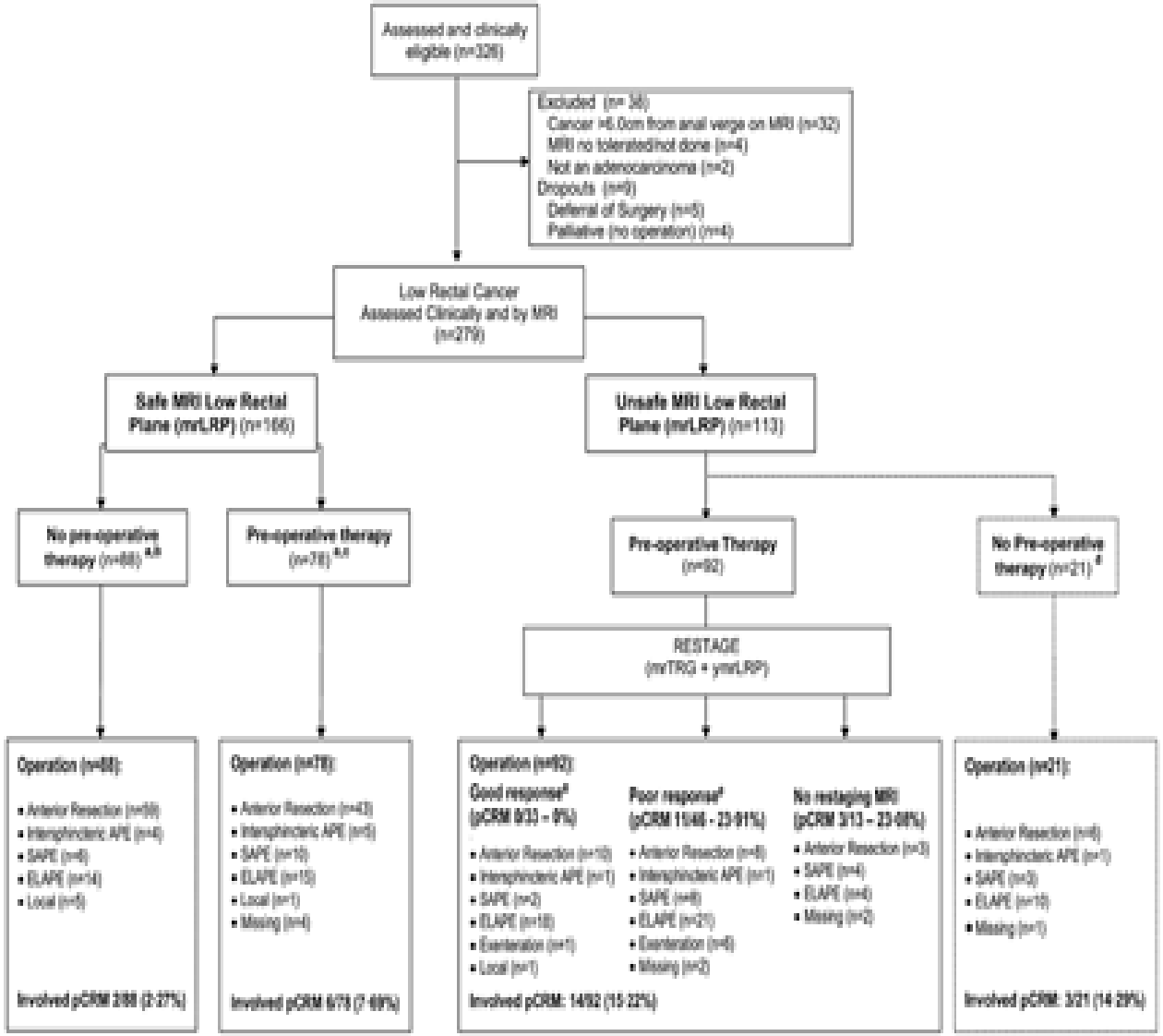

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Findings

- Overall pCRM involvement was 9.0% [95% CI : 5.9–12.3], significantly lower than previously reported rates of 30%.
- Patients with no adverse MRI features and a "safe" mrLRP underwent sphincter preserving surgery without preoperative radiotherapy, resulting in a 1.6% pCRM rate.
- The pCRM rate increased 5-fold for an "unsafe" compared with "safe" preoperative mrLRP [odds ratio (OR)=5.5; 95% CI, 2.3–13.3)].

#4. Staging and assessment of low rectal cancer

rates of 30%.

- Patients with no adverse MRI features and a "safe" mrLRP underwent sphincter preserving surgery without preoperative radiotherapy, resulting in a 1.6% pCRM rate.
- The pCRM rate increased 5-fold for an "unsafe"

Battersby, N. J., How, P., Moran, B., Stelzner, S., West, N. P., Branagan, G. et al. MERCURY II Study Group. (2015).
Prospective Validation of a Low Rectal Cancer Magnetic Resonance Imaging Staging System and
Development of a Local Recurrence Risk Stratification Model: The MERCURY II Study. *Ann Surg*. 2015

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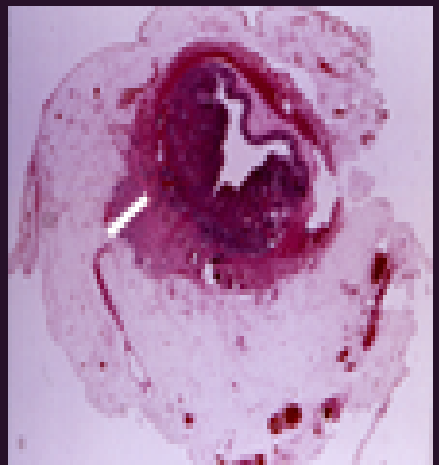
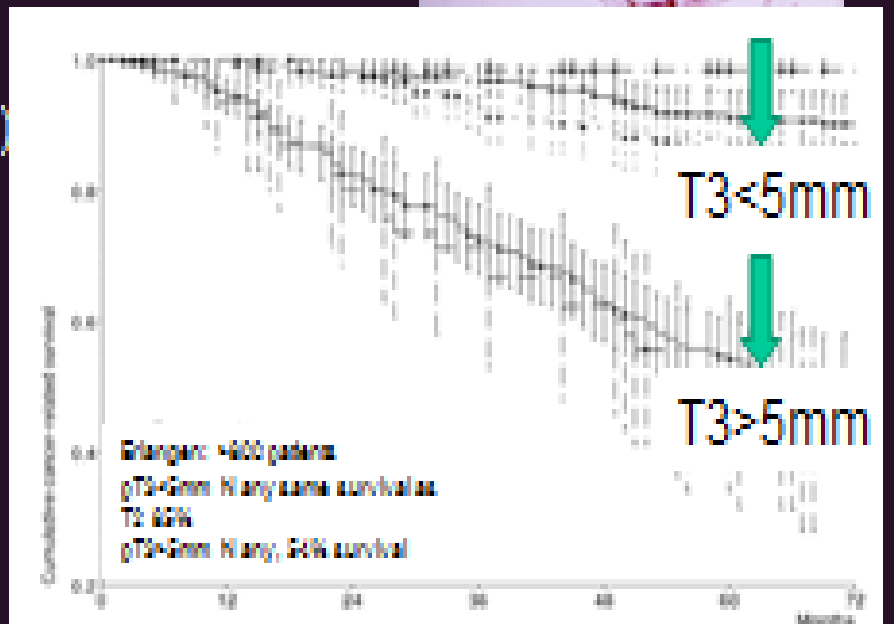
#5. MRI assessment of depth of tumour spread gives the most accurate prognostic information

Limitations of the TNM – T3 category forms 80% of rectal cancers

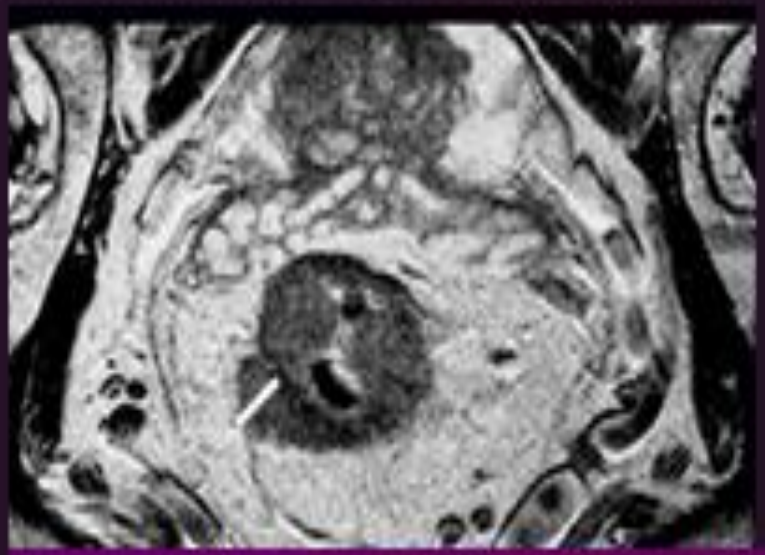
- Jass (St Marks, UK) : – independent prognostic significance
- Harrison (Tennessee, USA): prognostic score depth of spread in mm
- Cawthorne (Guildford, UK): depth of spread significance
- Merkel and Hermanek (Erlangen, Germany)
  - T3 subclassification
    - T3a <1mm
    - T3b>1-5mm,
    - T3c>5-15mm
    - T3d>15mm (TNM staging system 1993 supplement)

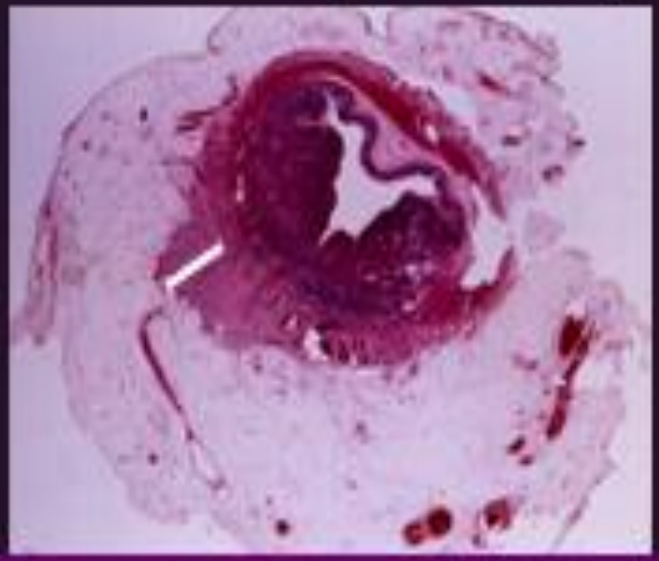




#5. MRI assessment of depth of tumour spread gives the most accurate prognostic information

"measuring extramural depth is the least subjective and most reliable of all the observations by radiologists"





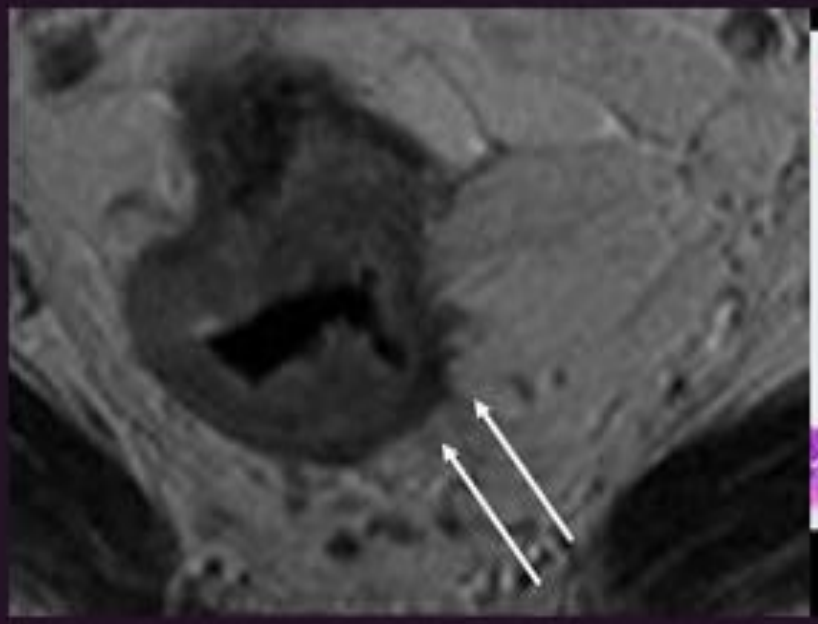
295/311 (95 %) patients who underwent primary surgery.
The mean difference between MRI and histopathology assessment of tumor EMD was -0.046 mm, SD = 3.85 mm, the 95 % CI was -0.487 to 0.395 mm.
MRI and histopathology assessment of tumor spread are considered equivalent to within 0.5 mm (6R). ***Radiology 2007***

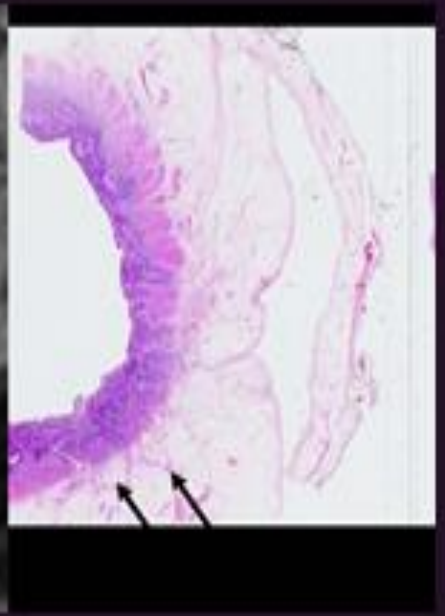
#5. MRI assessment of depth of tumour spread gives the most accurate prognostic information

"measuring extramural depth is the least subjective and

diologists"

mrT3<5mm has same outcomes as pT2 tumours
if mrCRM and mrEMVI negative
Irrespective of N stage





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mrT3<5mm h

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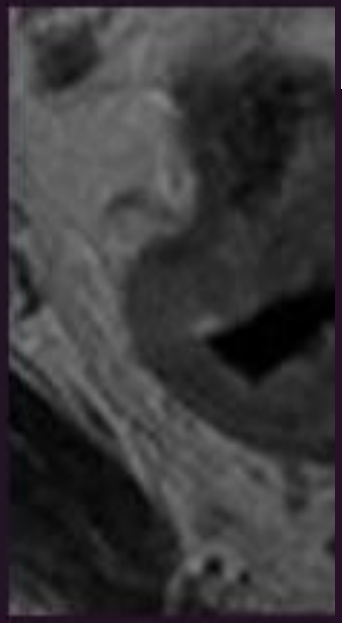
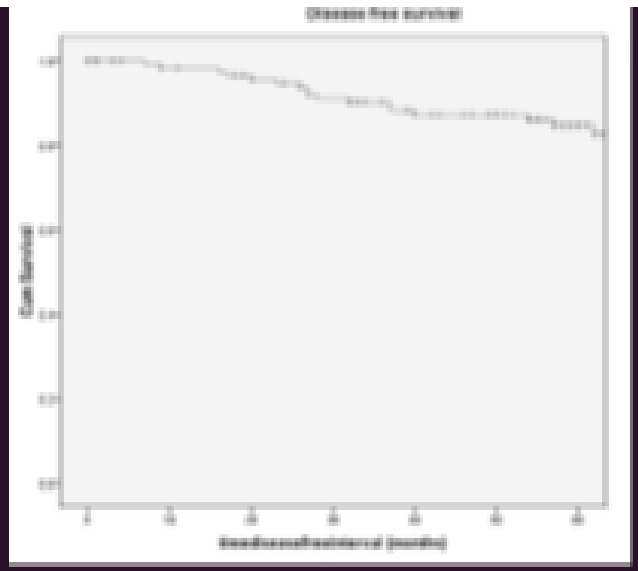


Outcomes for MRI good prognosis rectal cancers: regardless of N stage

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%) .



Taylor et al, MERCURY
Annals of Surgery 2011

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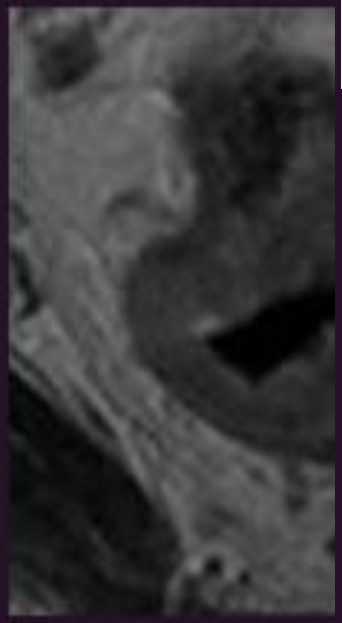

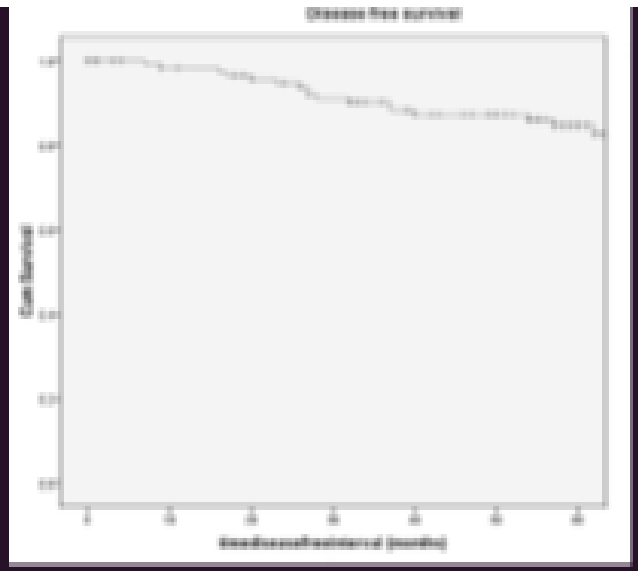

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#6 An opportunity to identify Early Rectal Lesions suitable for local excision approach

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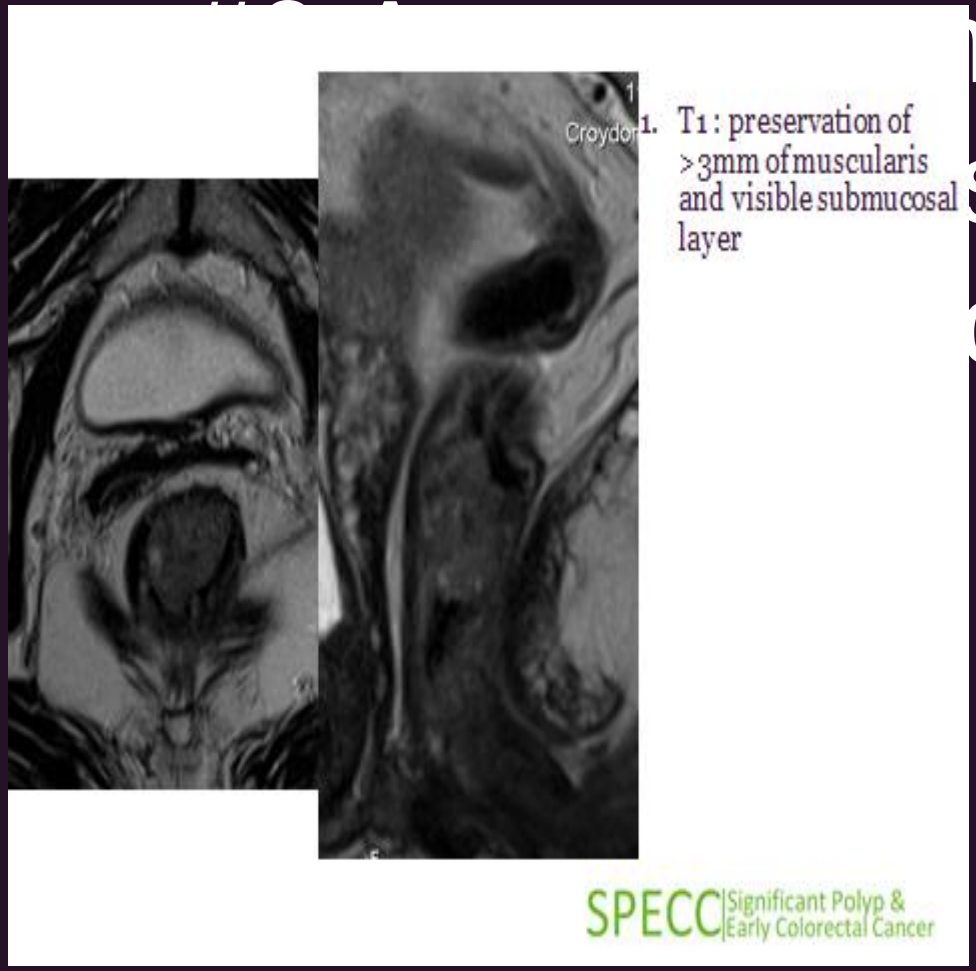

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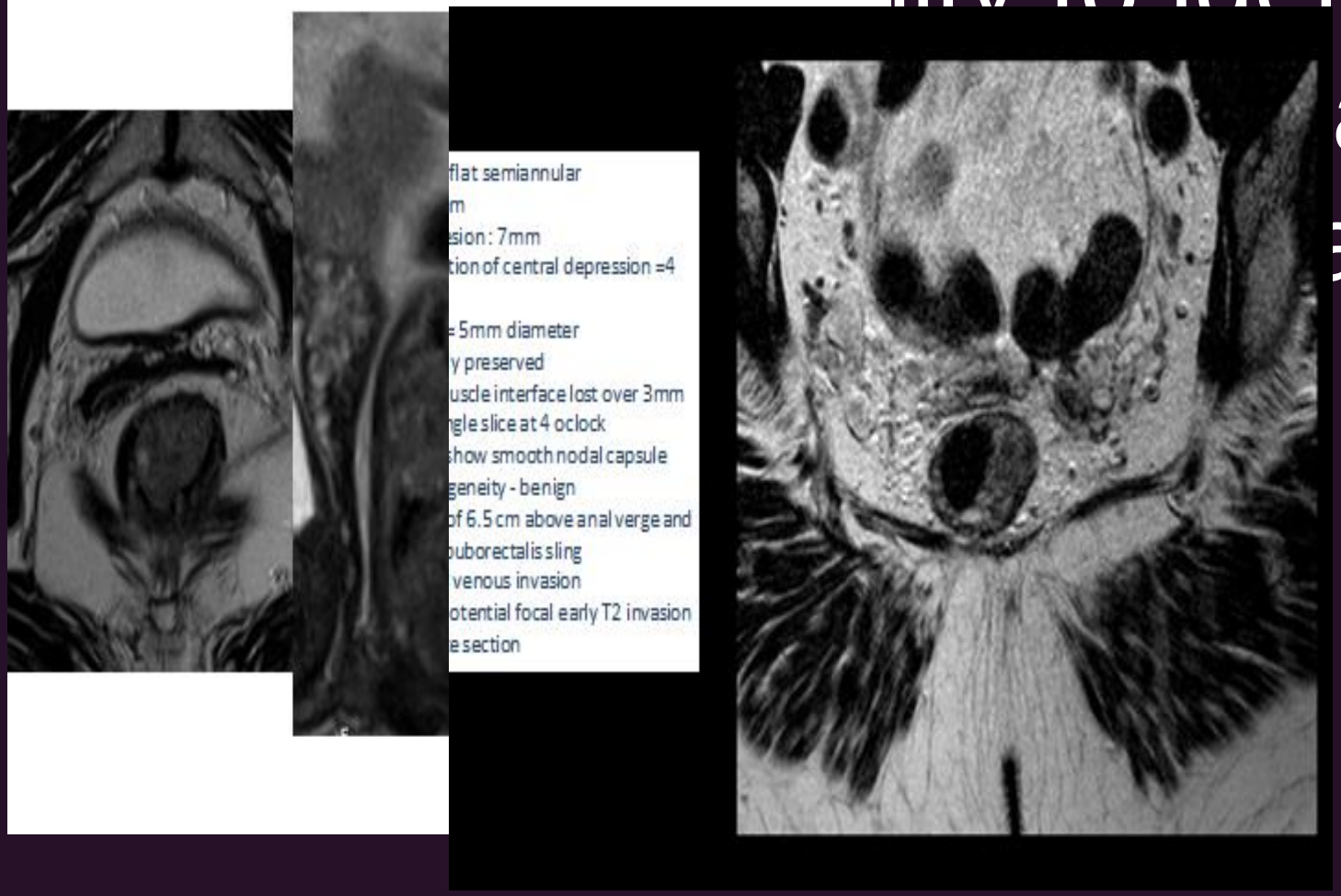

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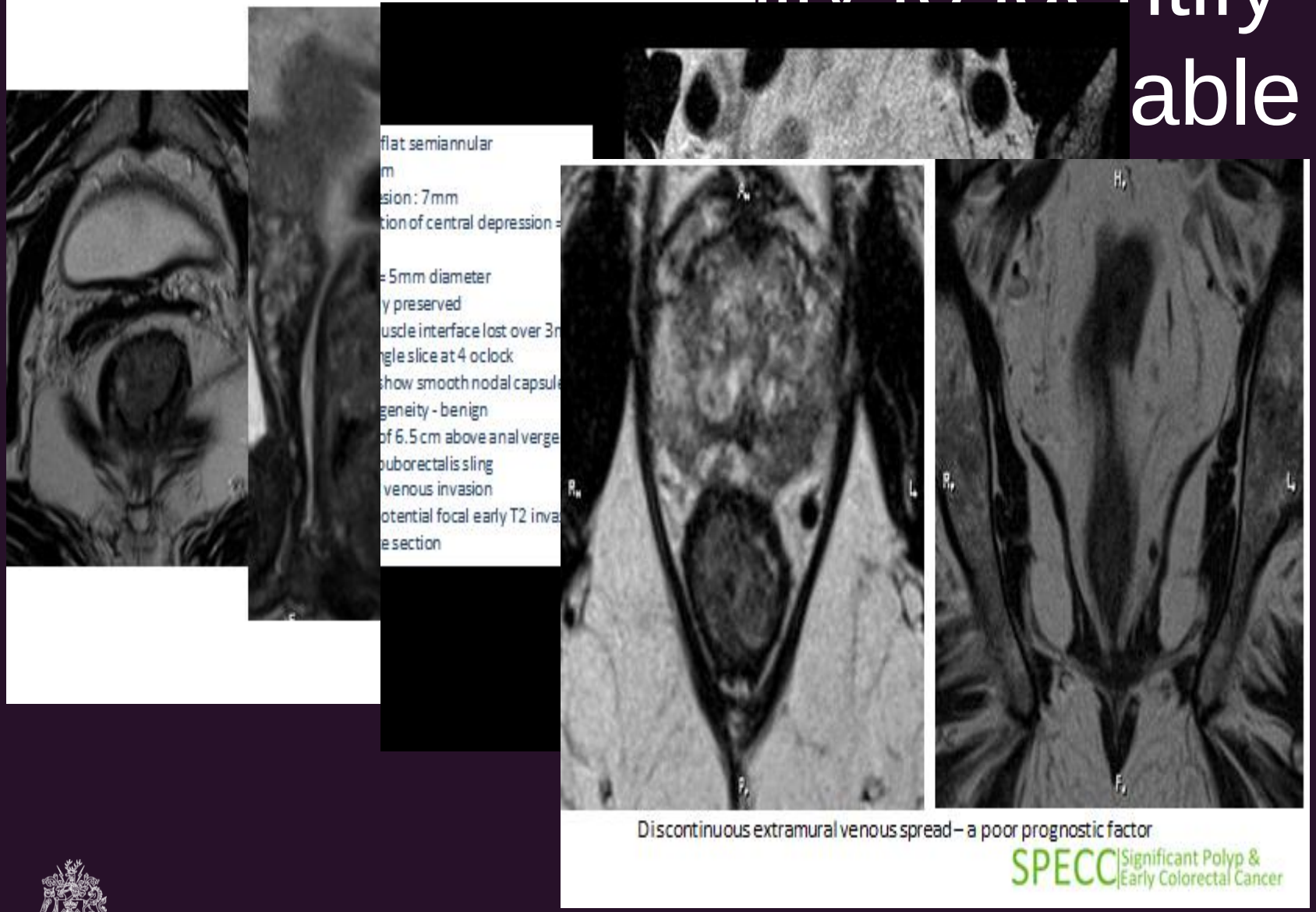

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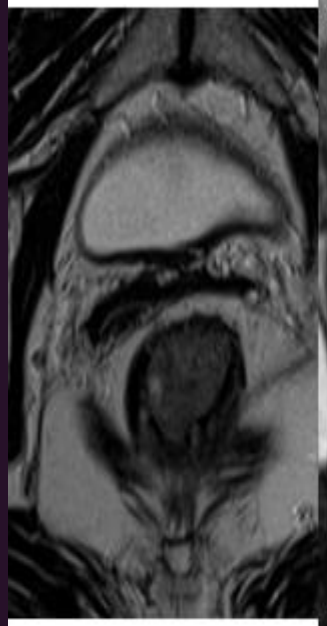

MRI indications in ERC

- To assess bulky polyps >5mm thick
- Initial assessment of disease remote from the lumen within entire mesorectum
- Identification of pelvic sidewall disease
- Road-mapping for surgical planning – identify site location of stalk or invasive borde... sling, peritoneal reflecti... border
- Identification of high risk... invasion
- Ongoing surveillance of ... for conservative approac...

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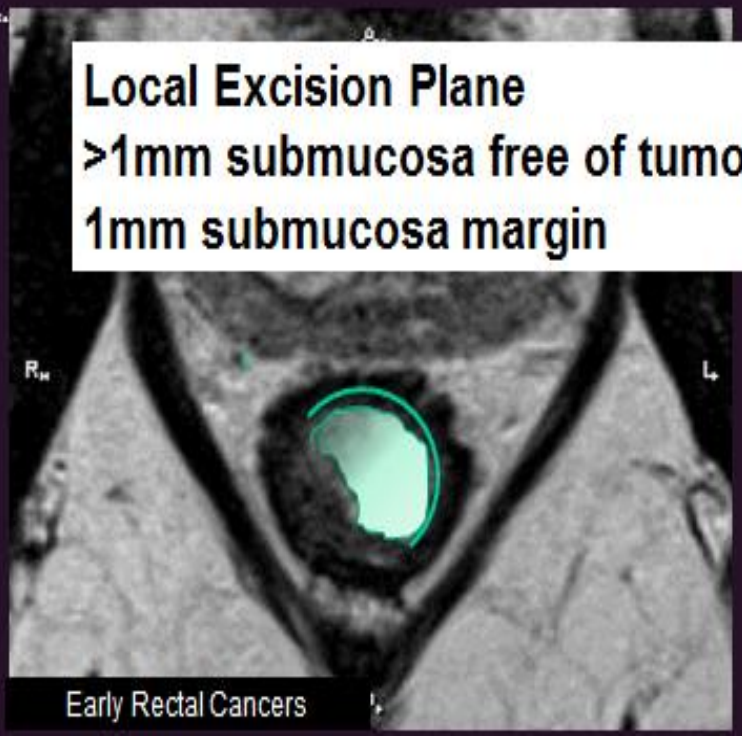

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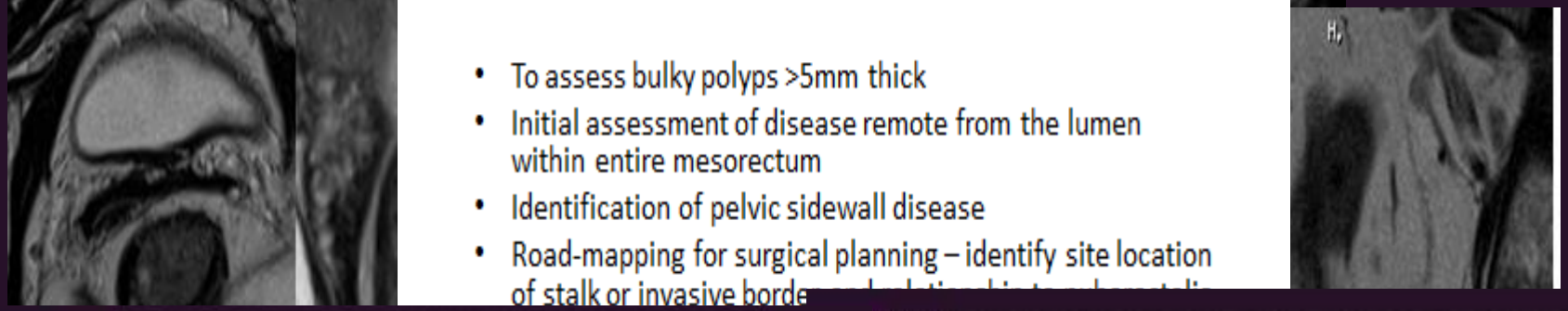

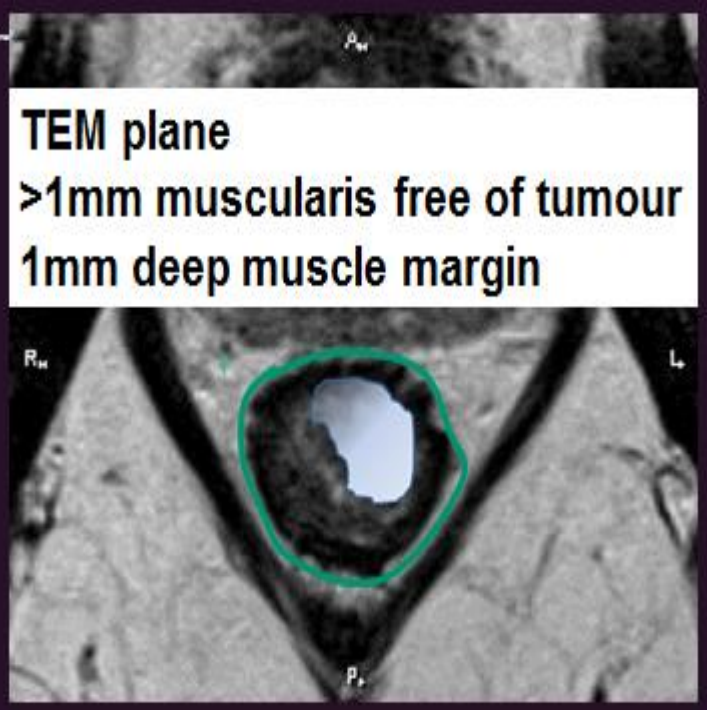

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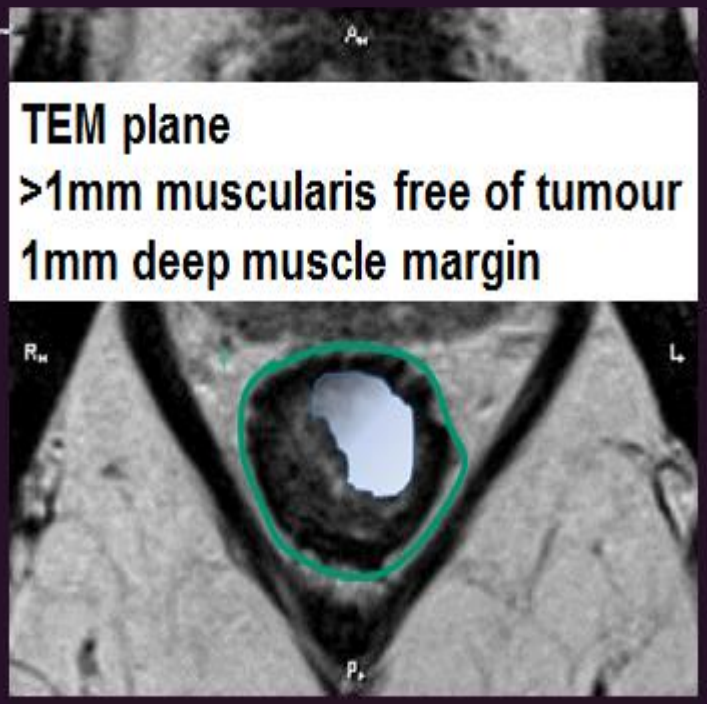

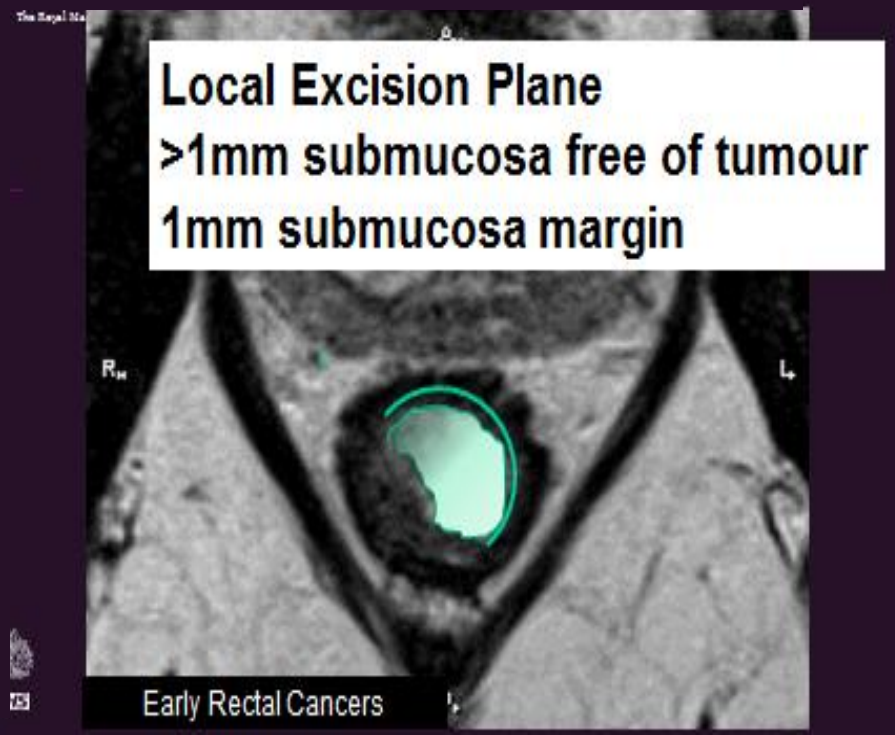

#7 MRI identification of EMVI

Original article

Preoperative assessment of prognostic factors in rectal cancer using high-resolution magnetic resonance imaging

G. Brown, A. G. Radcliffe, R. G. Newcombe, N. S. Dallimore, M. W. Bourne and G. T. Williams

Cardiff and the Vale NHS Trust, University of Wales College of Medicine, Correspondence to: Dr G. Brown, Department of Radiology, The Royal Marsden (e-mail: gina.brown@rmh.mdx.nhs.uk)

British Journal of Surgery 2003; 90: 355–364

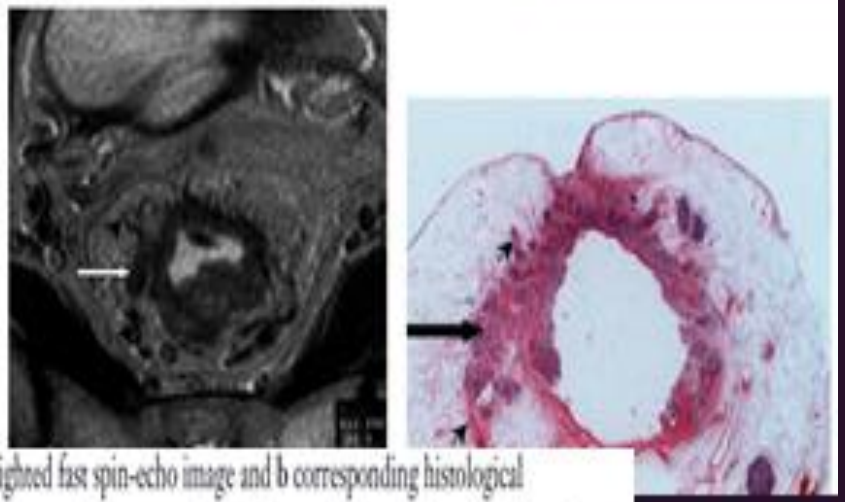

Fig. 1 Extramural vascular invasion. a High-resolution T2-weighted fast spin-echo image and b corresponding histological (haematoxylin and eosin stained) whole-mount section. Tubular or serpiginous extension of tumour of intermediate signal intensity into perirectal fat corresponded to extramural venous invasion on histological examination. In this example, a tubular tongue of tumour extends into perirectal fat (arrow); foci of signal void indicate associated vessel (arrowheads). This appearance was confirmed as representing extramural venous spread on histological examination

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#7 MRI identification of EMVI


Original article

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British Journa

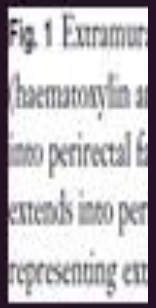
Fig. 1 Extramur
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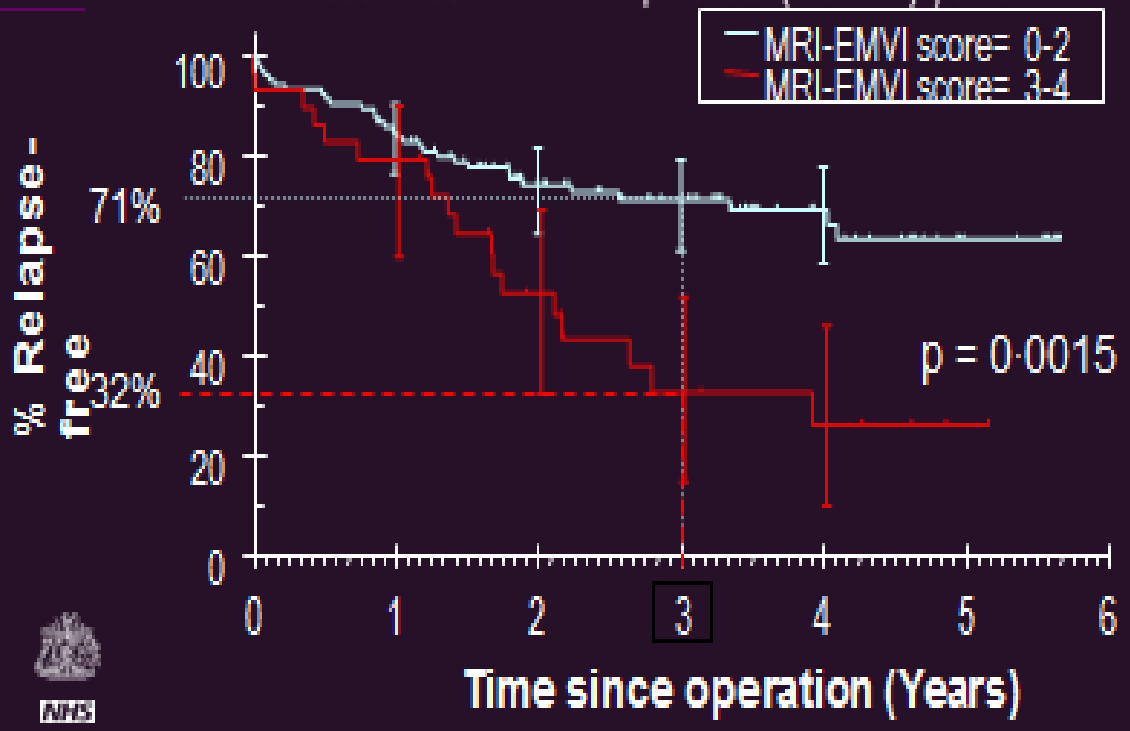
Smith et al: "Prognostic significance of MRI-detected Extramural Vascular Invasion."
BJS. 2008

MRI-EMVI score & Outcome

n=135. Median follow-up=3·12 (0·9-5·7) years.



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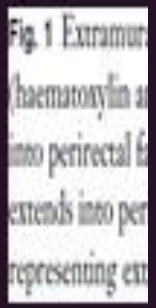
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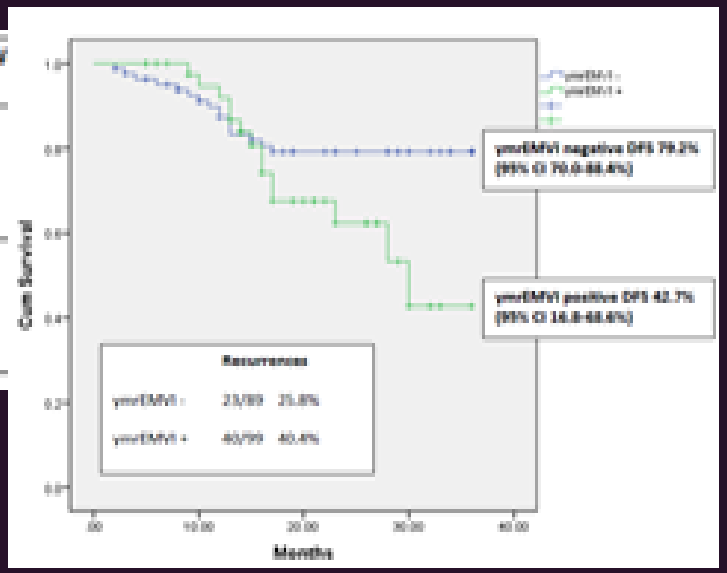
MRI detected more persistent EMVI post CRT than pathology

Group	Local/distant Recurrence		p-v
ypEMVI -	34/142	23.9%	
ypEMVI +	20/46	43.5%	<0.05
ymrEMVI -	23/89	25.8%	
ymrEMVI +	40/99	40.4%	<0.05

% Relapse-free

71

32



Chand M, Evans J, Swift RI, et al. Prognostic Significance of Postchemoradiotherapy High-Resolution MRI and Histopathology Detected Extramural Venous Invasion in Rectal Cancer. Ann Surg. 2014.

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#7 MRI identification of EMVI

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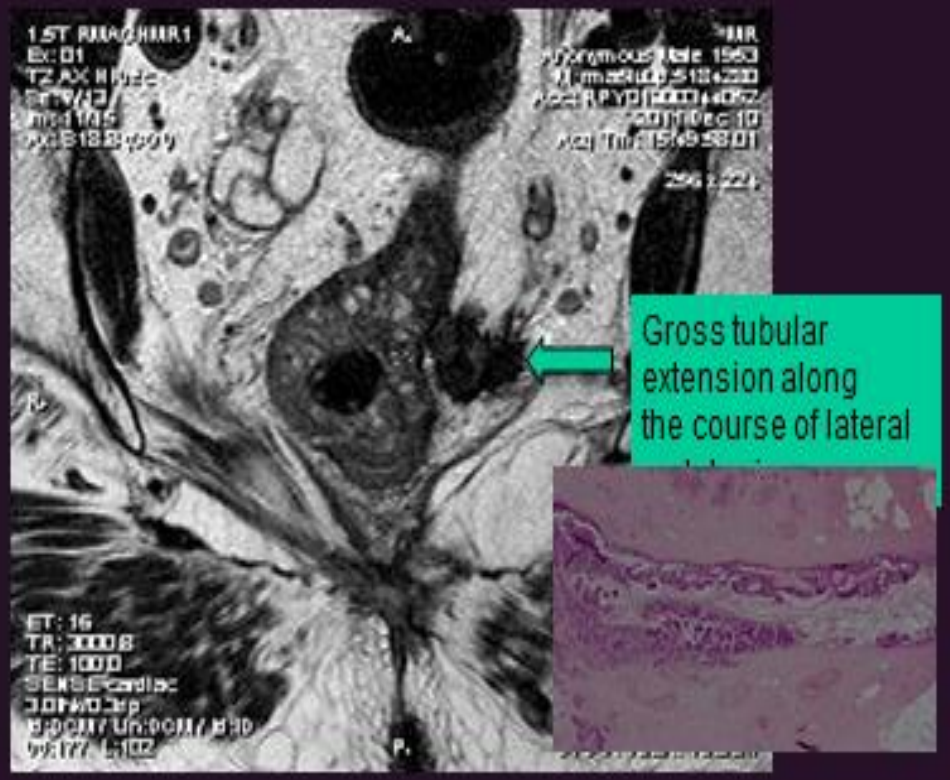
TABLE 4. Univariate and Multivariate Analysis (Cox Proportional Hazards for DFS) by Clinical, Preoperative MRI and Postoperative Histopathology Characteristics

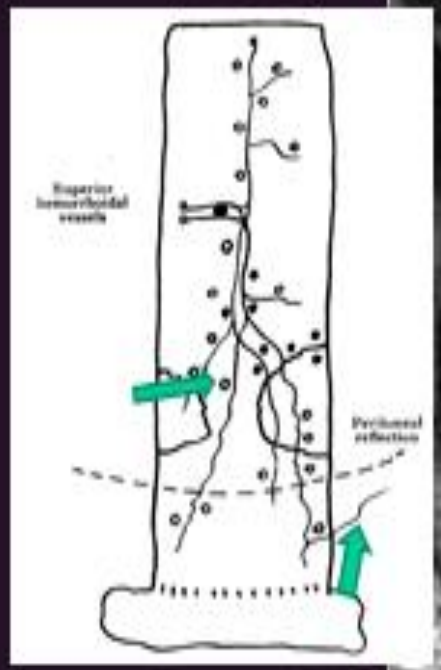
Variables		Group	Patient Numbers	Univariate Analysis HR	95% CI	P	Multivariate Analysis HR	95% CI	P
Patient characteristics	Sex	Female	67	Ref			Ref		
		Male	121	1.093	0.625–1.912	0.756	0.93	0.53–1.68	0.832
	Height	Upper/mid	119	Ref			Ref		
		Low	69	1.369	0.815–2.298	0.235	1.46	0.80–2.68	0.223
Baseline MR staging	mrT stage	Good	51	Ref			Ref		
		Poor	137	1.187	0.638–2.206	0.588	1.12	0.51–2.43	0.782
	mrN stage	Negative	65	Ref			Ref		
		Positive	123	1.196	0.691–2.071	0.523	1.72	0.90–3.28	0.199
	mrEMVI	Negative	0	Ref			Ref		
		Positive	188	0.902	0.527–1.544	0.706	0.89	0.42–1.89	0.078
	mrCRM	Negative	107	Ref			Ref		
		Positive	81	0.846	0.497–1.441	0.539	0.85	0.44–1.62	0.617
Post-CRT preoperative MR staging	ymrT stage	Good	116	Ref			Ref		
		Poor	72	1.218	0.723–2.052	0.459	1.01	0.54–1.89	0.984
	ymrN stage	Negative	104	Ref			Ref		
		Positive	84	1.179	0.701–1.982	0.534	0.431	0.21–0.91	0.206
	ymrEMVI	Negative	89	Ref			Ref		
		Positive	99	1.987	1.237–4.323	0.004	1.97	1.01–3.90	0.044
	ymrCRM	Clear	148	Ref			Ref		
		Involved/threatened	40	1.26	0.674–2.354	0.469	1.16	0.50–2.67	0.729
Final pathology staging	ypT	Good	64	Ref			Ref		
		Poor	124	1.125	0.695–1.279	0.534	0.99	0.11–8.62	0.994
	ypN	Negative	118	Ref			Ref		
		Positive	70	2.912	1.724–4.878	<0.001	3.41	0.91–12.82	0.069
	ypEMVI	Negative	142	Ref			Ref		
		Positive	46	3.889	2.088–6.281	<0.001	2.39	1.11–5.14	0.026
	ypCRM	Negative	178	Ref			Ref		
		Positive	10	3.352	1.421–7.907	0.006	1.32	1.24–2.38	0.032

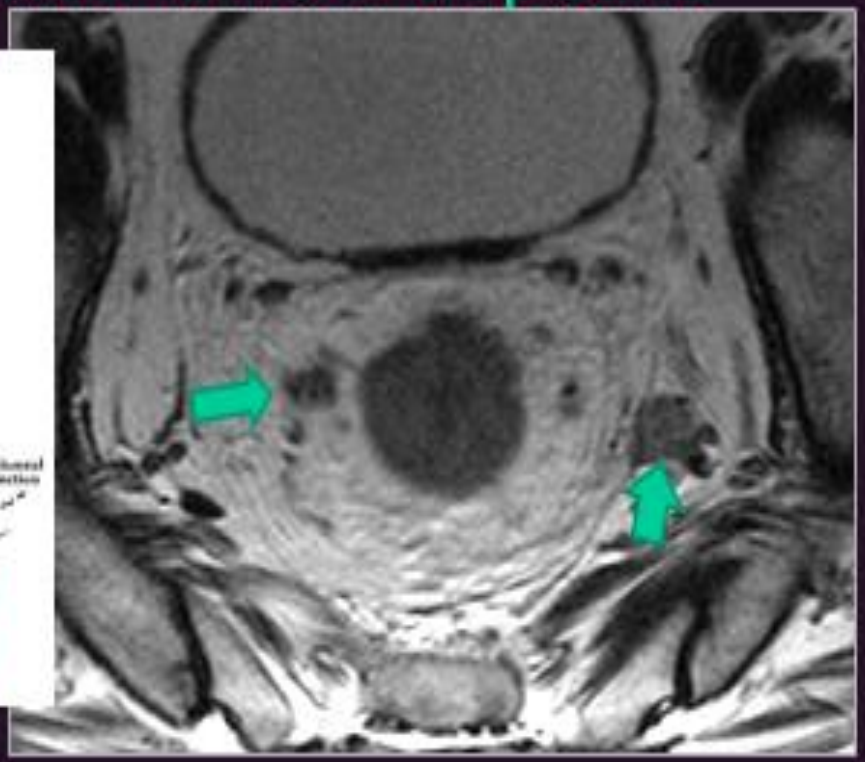
#8.Lateral Pelvic Tumour Spread



#8.Lateral Pelvic Tumour Spread

mrEMVI is associated with pelvic sidewall tumour deposits





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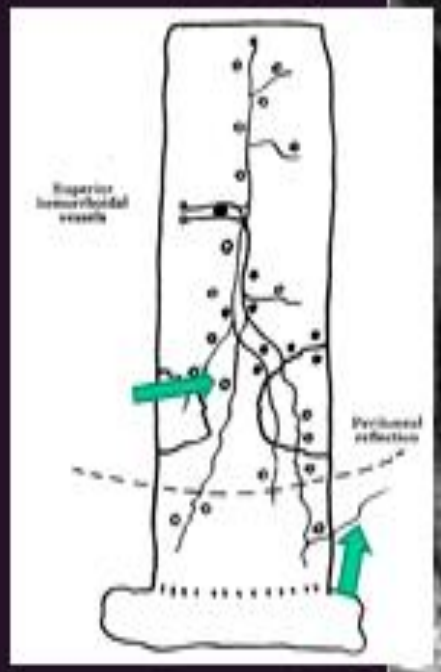
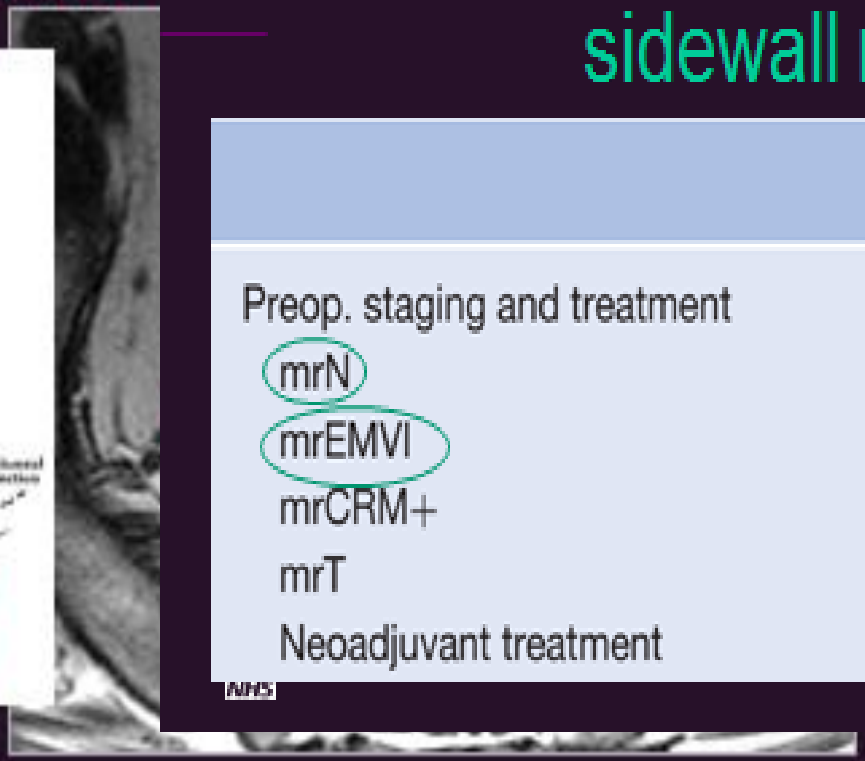
mrEMVI is as
sidewall





Preoperative risk factors associated with MRI pelvic sidewall nodes

	Odds ratio	*P*
Preop. staging and treatment		
mrN	3·64 (1·67, 7·94)	0·032
mrEMVI	2·48 (1·08, 5·69)	0·001
mrCRM+	0·85 (0·33, 2·17)	0·738
mrT	1·14 (0·64, 2·01)	0·663
Neoadjuvant treatment	1·72 (0·77, 3·86)	0·190

How do we find tumours that require neoadjuvant therapy?

- Definition of mrCRM at risk
- Importance of mrT substage rather than stage
- The importance of MRI detected EMVI as a gold standard
- Prognostic importance of assessment of height and MRI low rectal stage
- Prognostic relevance of mrTRG
- Prognostic relevance of mucinous tumours
- examples of how MRI is being used for treatment stratification in clinical surgical and oncological trials