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Abstract 250word

Objective: This study aimed to validate an MRI staging classification that preoperatively assessed the relationship between tumour and the low rectal cancer surgical resection plane (mrLRP).

Background: Low rectal cancer oncological outcomes remain a global challenge, evidenced by high pathological circumferential resection margin (pCRM) rates and unacceptable variations in permanent colostomies.

Methods: Between 2008-2012, a prospective, observational, multicentre study (MERCURY II) recruited 279 patients with adenocarcinoma ≤ 6 cm from anal verge. MRI assessed: mrLRP "safe or unsafe", venous invasion (mrEMVI), depth of spread, node status, tumour height and tumor quadrant. MRI based treatment recommendations were compared against final management and pCRM outcomes.

Results: 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 five-fold for an 'unsafe' compared with 'safe' preoperative mrLRP (OR5.5 [$^{95\%}$ CI 2.3-13.3]). Post-treatment MRI reassessment indicated a 'safe' ymrLRP in 33 of 113 (29.2%), none of whom had ypCRM involvement. In contrast, persistent "unsafe" ymrLRP post therapy resulted in 17.5% ypCRM involvement. Further independent MRI assessed risk factors were: EMVI (OR3.8 [$^{95\%}$ CI 1.5-9.6]), tumours < 4.0 cm from anal verge (OR3.4 [$^{95\%}$ CI 1.3-8.8]) and anterior tumors (OR2.8 [$^{95\%}$ CI 1.1-6.8]).

Conclusions: The study validated MRI low rectal plane assessment; reducing pCRM involvement and avoiding overtreatment through selective pre-operative therapy and rationalised use of permanent colostomy. It also highlights the importance of post-treatment re-staging.

1 Prospective Validation Of A Low Rectal Cancer MRI Staging System
 2 And Development Of A Local Recurrence Risk Stratification Model:
 3 The MERCURY II Study
 4

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46 **Running title:** MRI assessment of the low rectal plane

47

48 **Pages 15, Figures 3, Tables 6.**

49

1 Introduction

2 In rectal cancer management an incomplete cancer resection, identified by
3 histopathological circumferential resection margin (pCRM) involvement results in increased
4 local recurrence and poor oncological outcomes.^{1, 2} Low rectal cancer, defined as
5 adenocarcinoma less than six centimeters from the anal verge, accounts for one-third of all
6 rectal cancers. pCRM involvement occurs in 20-36% of low rectal cancer surgical
7 specimens, which is significantly worse than resection outcomes for mid and upper rectal
8 cancer.³⁻⁶ These poor outcomes are attributed to suboptimal traditional abdominoperineal
9 excision (APE) techniques that fail to achieve an adequate CRM at the distal mesorectum
10 and at the sphincter complex.^{4, 5} Additionally the surgical decision-making between
11 restorative-resection and an APE has been inconsistent.⁷ From the patient's perspective
12 this has led to unacceptable variations in permanent colostomy rates.⁷ Hence, low rectal
13 cancer management is a unique challenge due to poor oncological outcomes and high
14 permanent colostomy rates.

15 A curative low rectal cancer restorative-resection requires both the mesorectal fascia plane
16 and the intersphincteric plane to be clear of tumor (Figure 1). The MERCURY study
17 prospectively validated the ability of high-resolution MRI to pre-operatively assess the
18 'tumor-mesorectal fascia relationship'.^{3, 8} No pre-operative staging system to assess the
19 intersphincteric plane has been prospectively validated. If tumour invades the
20 intersphincteric plane, sphincter excision and a permanent stoma are needed to achieve a
21 clear pCRM. Therefore currently it is not possible to pre-operatively assess the feasibility of
22 a restorative resection or quantify the risk of pCRM involvement in low rectal cancer.

23 An MRI staging system to assess 'tumor-intersphincteric plane relationship' has been
24 developed, figure 2a&b.⁹ This staging system was retrospectively tested in low rectal
25 cancer patients from the MERCURY study; tumor extending into the intersphincteric plane
26 had a seventeen-fold increased risk of pCRM involvement.⁹ The MERCURYII study was

1 designed to prospectively validate this MRI low rectal cancer staging system. This MRI
2 assessment guided pre-operative decisions by identifying tumors at risk of pCRM
3 involvement. The primary aim was to reduce low rectal cancer pCRM involvement to less
4 than 15% by using MRI planning to determine the relationship of tumor to both the
5 mesorectal fascia and intersphincteric plane. This information allows a clear pCRM to be
6 achieved through appropriate selection for pre-operative therapy and choosing the correct
7 plane of surgery.

8 **Patients and Method**

9 **Eligibility for Enrolment**

10 The prospective, multicentre, observational MERCURY II low rectal cancer study
11 ([NCT02005965](#)) was approved by UK research and ethics committee (REC 07/Q1702/75)
12 and local review boards in Aarhus, Belgrade, Berlin and Dresden. Consecutive patient
13 enrolment occurred between January 2008 - March 2012. Eligibility criteria included
14 adenocarcinoma with distal margin at or below 6.0cm from anal verge on clinical
15 examination and MRI. Exclusion criteria were pregnancy, previous pelvic malignancy, pelvic
16 radiotherapy, pelvic floor surgery or contraindicated MRI.

17 **Radiological Assessment**

18 Pelvic high-resolution MRI was performed according to MERCURY protocol.¹⁰ Twenty one
19 designated radiologists (7-18 years experience) from 14 centres prospectively proforma
20 reported MRIs for: tumor height (determined by distance from inferior tumor edge to anal
21 verge on sagittal MRI view); tumor quadrant (defined by the site of maximal invasion on
22 axial MRI imaging); mrT stage (mrT1-submucosa invasion, T2-muscularis propria invasion,
23 T3a&b<5mm beyond muscularis propria, T3c&d≥5mm beyond muscularis propria, T4-
24 invasion into adjacent structure or perforating peritoneum¹¹); mrN status (morphologic
25 rather than size criteria determined whether a node was benign or malignant - malignant
26 nodes require irregular outlines or internal signal heterogeneity [mrN1 0-3 nodes, mrN2

1 ≥ 4 nodes¹¹); extramural venous invasion (tumor signal intensity expanding a vessel¹²).

2

3 MRI low rectal cancer plane staging

4 As routine current practice, radiologists reported the relationship of the tumor to the
5 mesorectal fascia. All MERCURYII radiologists underwent workshop training in order to
6 implement a previously developed staging system⁹ assessing the intersphincteric plane
7 (figure 2a&b). MRI intersphincteric plane 'safe' tumors do not involve the intersphincteric
8 plane or levator muscle. MRI intersphincteric plane 'unsafe' tumors extend into the
9 intersphincteric plane, ≤ 1 mm of levator ani or involve adjacent structures such as the
10 external sphincter. By combining the previously validated assessment of the mesorectal
11 fascia with intersphincteric plane staging, for the first time, radiologists were able to assess
12 the entire low rectal cancer plane (figure 1). Combined staging of intersphincteric plane and
13 mesorectal fascia plane was termed MRI low rectal plane (mrLRP). Hence, low rectal
14 cancer threatening: mesorectal fascia or the intersphincteric plane was termed mrLRP
15 'unsafe'. Recommended surgical techniques were advocated according to MRI staging of
16 the operative plane (table 1).

17 When pre-operative therapy was utilised, post-treatment MRI reassessment of all tumor
18 characteristics occurred (post-treatment staging was denoted by 'y' pre-fix). Post-treatment
19 assessment included low rectal cancer plane (ymrLRP) restaging and evaluation of
20 treatment response using MRI tumor regression grade (mrTRG), as previously described.¹³
21 A 'good response' was defined as mrTRG1-2 and a tumour regressing from a mrLRP
22 'unsafe' plane to a ymrLRP 'safe' plane.

23 **Treatment and Surgery**

24 Treatment decisions were made by multidisciplinary cancer teams. Pre-operative therapy
25 was recommended for adverse radiological features: an 'unsafe' intersphincteric plane,
26 tumor < 1 mm from mesorectal fascia CRM, \geq mrT3c, mrN2 or mrEMVI. The policy for high-
27 risk stage II and all stage III rectal cancer was to offer adjuvant chemotherapy.

1 A standardised technique for high-quality mesorectal dissection was used.¹⁴ An extra-
2 levator APE (ELAPE) was recommended for tumors extending beyond the intersphincteric
3 plane; whereby a wider resection margin at the level of puborectalis was achieved by an
4 extended excision that included a cuff of levator muscle (figure 1c).¹⁵⁻¹⁷ Protocol pathway
5 deviations are recorded in figure 3.

6 **Histopathological Assessment**

7 Specialist colorectal histopathologists at each centre (26 in total with 5–25 years
8 experience) applied prospective proforma reporting by TNM5 classification and current UK
9 guidelines.¹⁸ To enable MRI comparison with histopathology additional detail relating to
10 planes of excision (mesorectum and sphincters), tumor orientation and relationship to
11 sphincter complex were recorded (appendix 1). Histopathologically involved circumferential
12 resection margin (pCRM) was defined as tumor ≤ 1 mm from the resection plane.¹⁹ An
13 ELAPE was distinguished from “standard” APE (sAPE) by operation record; confirmed by
14 the presence (ELAPE) or absence (sAPE) of a cuff of levator muscle on pathological
15 examination. For quality control, specimens were routinely photographed; auditing
16 mesorectal dissection quality,²⁰ and in APEs, tissue volume at puborectalis level.

17 **Statistical Analysis**

18 Demographic and outcome data were compared as proportions by χ^2 test, and ordered
19 categorical variables by Mann-Whitney U test. mrLRP status (‘safe’ and ‘unsafe’) was
20 assessed against the pCRM outcome (≤ 1 mm or > 1 mm) using χ^2 , a significant difference
21 was determined by p-value < 0.05 and by non-overlapping 95% confidence intervals.
22 Historically, with conventional staging, the low rectal cancer pCRM involvement rate has
23 been 30%.^{4, 5, 9} The primary end-point was to reduce pCRM involvement from 30% to 15%.
24 Sample size by single stage Simon design ($\alpha 0.05$, $\beta 0.9$),²¹ with 25% dropout, required 271
25 patients. The odds ratio and confidence limits for mrLRP resulting in pCRM involvement
26 were calculated by using Cox-Hinkley-Miettinen-Nurminen method.²²

1 Risk factors related to pCRM involvement were identified using univariate logistic
2 regression. Continuous variables were grouped into subcategories according to increasing
3 pCRM risk and univariate logistic regression used to compare these with a reference
4 category (table 5). Multivariate regression analysis to adjust for multiple risk factors and
5 their interactions was used, subsequently derived coefficients were used to weight the
6 predicted risk of an incomplete resection (pCRM involvement) (table 6).

7 Although no external validation was performed we internally validated the model by
8 bootstrapping method; deemed most suitable for this sample size.²³ Hosmer-Lemeshow
9 statistic²⁴ evaluated the model calibration or goodness of fit (model's ability to assign the
10 correct outcome probabilities to individual patients). Model discrimination (the ability to
11 assign higher probabilities of pCRM involvement to patients who actually develop an
12 involved margin) was measured by area under the receiver operator characteristic (ROC)
13 curve or c-index. Values exceeding 0.8 represent good discrimination.²⁵ Analyses were
14 performed using SPSS 21.0 (SPSS, Chicago,IL).

15 **Role Of The Funding Source**

16 The Pelican Cancer Foundation and NIHR Biomedical Research Centres had no role in
17 study design, data collection, analysis, interpretation, or writing of the report. The
18 corresponding author had full access to all study data and had final responsibility for the
19 decision to submit for publication.

20

21 **Results**

22 **Patients**

23 Fourteen units across Europe (Denmark, Germany, Serbia and UK) recruited 326 patients
24 with 38 exclusions and 9 additional dropouts, reported in figure 3. Thus, 279 patients were
25 eligible for primary endpoint analysis. Median age was 65 years (IQR 55-73), with 99
26 females (35%) and median BMI was 26 (IQR 23-28).

1 **MRI Assessment Of The Intersphincteric Plane**

2 Surgery confined to the intersphincteric plane was performed in 142 (83.0%,[95% CI 77.4-
3 88.7%]) of 176 MRI 'safe' intersphincteric plane patients compared with 39 (39.39%,[95%
4 CI 29.6-49.2%]) of 103 MRI 'unsafe' intersphincteric plane patients ($p<0.0001$). Pre-
5 operative therapy was also offered selectively, 87 (49.4%,[95% CI 42.0-56.9%]) of 176 MRI
6 intersphincteric plane 'safe' patients were treated compared with 83 (80.6%,[95% CI 72.8-
7 88.4%]) of 103 MRI 'unsafe' patients ($p<0.0001$). Hence, the baseline intersphincteric
8 plane assessment guided low rectal cancer management. Furthermore, pCRM involvement
9 occurred in 9 (5.1%,[95% CI 1.8-8.4%]) of 176 MRI intersphincteric plane 'safe' patients
10 compared with the significantly higher rate of 16 (15.5%,[95% CI 8.4-22.7%]) of 103 for the
11 MRI 'unsafe' cases ($p=0.003$).

12 **MRI Assessment Of The Low Rectal Plane (mrLRP)**

13 This study has validated MRI staging system for evaluating the intersphincteric plane, which
14 complements the previous MRI mesorectal fascia validation.³ Hence, MRI assessment of
15 the entire low rectal plane (mrLRP) is valid (table 2). All cause pCRM involvement occurred
16 in 8 (4.2%,[95% CI 1.3-7.1%]) of 191 MRI 'safe' mrLRP patients, compared with 17
17 (19.3%,[95% CI 10.9-27.7%]) of 88 'unsafe' mrLRP patients ($p<0.0001$).

18 **Overall pCRM Involvement**

19 Overall, pCRM involvement occurred in 25 (9.0% [95%CI 5.6-12.3%]) of 279 patients,
20 therefore the primary end point of $\leq 15\%$ pCRM involvement was achieved. Table 3 provides
21 a comparison between recommended and actual treatment according to baseline mrLRP
22 and adverse MRI features, where CRT was given the re-assessed plane of surgery is
23 reported (ymrLRP). This shows that 62 of 124 (50%) the low-risk mrLRP safe group
24 followed MRI recommendations to proceed straight to surgery with a resulting 1.6% pCRM
25 involvement rate, overall the pCRM rate for this group was 4.0%. In contrast an unsafe
26 baseline mrLRP with adverse MRI features resulted in a 17.7% pCRM involvement risk,
27 which represented a five-fold increase in pCRM involvement (OR 5.1, [95%CI 1.8-

1 14-5], $p=0.0020$). Following CRT 41 patients underwent ELAPE/Exenteration for adverse
2 features and unsafe ymrLRP the resulting pCRM involvement rate was 20.41%.

3 **Preoperative MRI Predictors for pCRM Involvement**

4 The demographics and tumour characteristics are reported in table 4 according to pCRM
5 involvement rate, with univariate and multivariate regression analysis of key pCRM
6 involvement predictors reported in table 5. The mrT stage and mrNode status were
7 significant pCRM involvement predictors on univariate but not on multivariate regression
8 analysis. Four significant factors were evident on multivariate regression analysis: an
9 'unsafe' mrLRP, MRI anterior quadrant tumor invasion, an MRI tumor height <4.0cm from
10 anal verge and mrEMVI. The respective score weightings for these factors were: 1.23, 1.00,
11 1.20 and 1.30. The respective 95% confidence intervals, based on 5000 bootstrap samples,
12 were: 1.4-11.3; 1.1-8.0; 1.4-11.0; and, 1.3-10.8. The model fitted the data well, as evidence
13 by the Hosmer-Lemeshow statistic $\chi^2 = 6.23$, 6df, $p=0.398$.²⁴ The c-index or AUC on ROC
14 analysis was 0.82 (95% CI 0.74-0.90), which suggests the model is strongly predictive for
15 pCRM involvement.²⁵

16 Probabilities derived from multivariate regression analysis are reported as a percentage risk
17 of pCRM involvement in Table 6. Of the 279 patients, 176 (63%) had one risk factor or less
18 and were low risk (risk $\leq 5\%$) for pCRM involvement, 70 (25%) patients had two risk factors
19 and were intermediate risk (risk 6-14%) and 33 (12%) patients had three or all four risk
20 factors and were high risk (risk >15%). The results imply that tumors <4.0cm from anal
21 verge with an 'unsafe' mrLRP have a 12.6% pCRM involvement risk. If the tumor was also
22 anterior the pCRM risk increased to 28.6%, this high pCRM risk is despite 77% (13 of 17) of
23 patients receiving pre-operative therapy and 77% receiving an ELAPE (n=9) or exenteration
24 (n=4). These high pCRM involvement figures, along with the unsafe ymrLRP data in table 3,
25 suggests that high-risk patients may require treatment beyond CRT and an ELAPE.

1 **Discussion:**

2 In this prospective multicentre international study, the MRI low rectal cancer plane (mrLRP)
3 can reliably assess extent of tumor invasion and predict for pathological circumferential
4 resection margin (pCRM) involvement. Furthermore, in this multicentre setting, through
5 standardised and better preoperative staging, we have achieved our stated objective of
6 appropriately selecting the correct plane of surgery and guiding use of pre-operative
7 therapy. This enabled optimal clinical management, which led to reduced pCRM
8 involvement to 9.0%; a marked improvement on previously published low rectal cancer
9 results,³⁻⁵ and meets the primary objective of reducing pCRM involvement to $\leq 15\%$. Thus,
10 an improved approach to low rectal cancer treatment potentially eliminated a significant
11 proportion of preventable pelvic recurrences.

12 **A 'safe' low rectal plane on baseline MRI ('safe' mrLRP)**

13 Almost half (44.4%, 124/279) of study participants had a 'safe' mrLRP and no adverse MRI
14 features. The recommended management was to proceed straight to surgery with an
15 intersphincteric resection, encouragingly adhering to this guidance (50%) led to a clear
16 pCRM in 98% of cases. Added clinical concern may result in these low-risk patients being
17 offered CRT or an ELAPE, however this resulted in a higher pCRM involvement. Additional
18 treatment and more radical surgery did not result in a benefit to the patient and may
19 represent overtreatment. Therefore when the baseline mrLRP is 'safe', with no other risk
20 factors and optimal TME dissection is anticipated, it is feasible and safe to avoid the
21 morbidity of chemoradiotherapy or an extralevator resection by offering sphincter-
22 preserving surgery alone.

23 **Post-treatment MRI low rectal plane assessment (ymrLRP)**

24 The majority of patients with an MRI 'unsafe' surgical plane received CRT (81.4%) as
25 recommended. Favourable tumor-regression occurred in 29.2% (33/113) of patients. The
26 operative strategy varied from local excision to an exenteration but notably, amongst these
27 'good responders', there were no cases of pCRM involvement. The plane of surgery

1 became less radical in 8 (24.2%) of these 33 patients (local excision n=1, anterior resection
2 n=6, intersphincteric resection n=1) compared with the initial plan for an ELAPE.
3 Furthermore five patients who initially entered the study were excluded from analysis due to
4 deferral of surgery, all of whom had no evidence of regrowth at 1 year follow-up. Contrary to
5 current consensus,²⁶ this emphasises the importance of restaging the primary tumor with a
6 willingness to selectively change the initial plan.

7 On the other hand, almost 25% of ymrLRP unsafe patients developed pCRM involvement
8 (table 3). Routinely offering CRT and an ELAPE to this high-risk group does not appear to
9 be sufficient. In order to improve pCRM involvement, efforts are required to preoperatively
10 determine specific factors that cause individuals to become high-risk and to offer patient
11 tailored management, such as carefully planned exenterative surgery and optimal pre-
12 operative therapy.

13

14 **Additional Risk Factors for pCRM involvement**

15 After validating the role of mrLRP in predicting pCRM involvement, additional MRI
16 predictors were investigated by multiple regression analysis. Three other key risk factors
17 were identified: anterior quadrant tumor invasion; mrEMVI; and, tumor height.

18

19 Tumors less than 4cm from the anal verge carry a 3.4 fold increased pCRM involvement
20 risk, however in the absence of additional risk factors the pCRM involvement risk is 4%.
21 Arguably these are precisely the patients who should avoid radiotherapy in order to achieve
22 optimal function,²⁷ equally with suitable CRT there is a reported 19.5% chance of an
23 excellent clinical and radiological response which may enable deferral of surgical.^{28, 29} Each
24 approach requires careful patient discussion and deferral should be performed in the
25 context of a clinical trial.³⁰

26

1 Overall pCRM involvement was 2·8 fold more likely in the 35% of tumors with anterior
2 quadrant invasion. This supports findings by West et al that even the wider excision
3 produced by ELAPE surgery still removes relatively less volume anteriorly compared with
4 other quadrants.^{15, 31, 32} In high-risk cases an ELAPE may fail to achieve a clear pCRM for
5 these anterior tumors and an anterior compartment exenteration should be considered.

6
7 The majority of high-risk patients received chemoradiotherapy, yet mrEMVI (19%, 54/279)
8 was associated with a 3·8 fold increased risk of pCRM involvement. Histological EMVI is
9 associated with a poor prognosis (30% five-year overall survival), high local recurrence and
10 distant failure rates.³³ In several independent series mrEMVI also carries a poor
11 prognosis.^{12, 34, 35} Perhaps the high pCRM involvement seen in this group relates to
12 inadequate downstaging in mrEMVI positive patients. Seemingly mrEMVI is associated with
13 relative chemoradiotherapy resistance.³⁵ Although, promising early work indicates that
14 following induction chemotherapy mrEMVI status is more likely to change from positive to
15 negative and better outcomes are observed.^{35, 36} Thus pre-operative chemotherapy may be
16 a useful treatment strategy for mrEMVI patients.

17
18 Compared with all the assessable low rectal cancer pCRM involvement risk factors outlined
19 above, we did not find mrT and mrN stage to be significant on multivariate regression
20 analysis. Therefore their importance regarding the surgical approach and use of pre-
21 operative therapy may be superseded in favour of plane 'safety' (mrLRP) and the risk
22 factors reported on multivariate regression analysis.

23
24 From the patient's perspective, the risk quantifying model has special relevance. This model
25 improves the information available to healthcare professionals and patients, which
26 enhances the consent process and increases the likelihood of concordant patient decision-
27 making. It may be hypothesised that 'predicted risk' information will hinder consent by

1 overwhelming the patient. However, a recent Canadian study by Kennedy et al used a
2 threshold decision-making tool to assess the local recurrence risk that patients' were willing
3 to take in order to avoid pre-operative therapy.³⁷ Most patients (84%) changed their choice
4 of treatment depending on the risks presented to them and many patients accepted
5 surprisingly high risks of recurrence in order to avoid pre-operative therapy.³⁷ It is therefore
6 feasible to expect the majority of patients to participate in the decision-making process.
7 Long-term outcomes and quality of life data are still awaited and this accumulating data will
8 also provide important information for this discussion and decision-making process.

9

10 **Limitations**

11 The study was designed to test MRI low rectal cancer plane assessment and the pre-stated
12 sample size criteria for this primary endpoint were met. However, the quantification model
13 will need validating in independent datasets and prospective implementation to test the
14 impact on oncological outcomes. Finally, although this multicentre study demonstrates the
15 reproducibility of mrLRP, the MERCURY group required exacting standards from highly
16 trained individuals from specialist centres, this implies that results may not be immediately
17 and universally applicable. However, units that recruited to MERCURY II did not wholly
18 represent teaching hospitals and the key to success has been optimal MDT functioning
19 which can be achieved by appropriate training.³⁸

20

21 **Conclusion**

22 This is the first study to prospectively validate MRI staging of the entire low rectal cancer
23 plane (mrLRP). The use of optimal staging in an MDT setting has aided the decision for pre-
24 operative therapy and improved surgical planning, resulting in a significant reduction in
25 pCRM involvement after low rectal cancer surgery. The study findings indicate mrLRP

1 reporting is required for all low rectal cancers and in those who have pre-operative therapy,
2 post-treatment restaging should be routine.

3 The commonly used strategy of managing low rectal cancer with chemoradiotherapy and an
4 ELAPE potentially overtreats low-risk patients and undertreats the high-risk group. The
5 pCRM risk stratification model will require further validation in independent datasets but it
6 has the potential to mark a step forwards in low rectal cancer management by providing
7 patient-tailored treatment according to the predicted likelihood of circumferential resection
8 margin involvement.

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1 **Legends**

2 Figure 1. *Figure 1a*. Diagrammatic coronal oblique view through long-axis of anal canal. Low rectal
 3 cancer is defined as adenocarcinoma with an inferior tumour edge less than six centimeters from the
 4 anal verge, anatomically represented by a line between the origins of the levator muscle (horizontal
 5 beige line).³⁸ The horizontal black line (1cm above puborectalis sling) represents the site between
 6 mesorectal fascia plane and intersphincteric plane. MRI evaluation of the mesorectal fascia (dashed
 7 green line) has been validated previously.³ This study aimed to validate a previously reported technique
 8 for MRI assessment of the intersphincteric plane (dashed red line).⁹

9 Low rectal cancer circumferential resection margin involvement may occur at the mesorectal fascia
 10 plane or at the intersphincteric plane (*figure 1b*). When tumour extends beyond muscularis propria/
 11 internal sphincter the intersphincteric plane is 'unsafe' (*figure 1c*) therefore pre-operative therapy and
 12 an extra-levator abdominoperineal excision (dashed blue line) is recommended. When the
 13 intersphincteric plane is 'safe' (*figure 1d*) an intersphincteric resection (dashed green line) +/-
 14 anastomosis is feasible.

15 Figure 2a & b. A coronal oblique high-resolution MRI image through long-axis of anal canal for two
 16 different low rectal cancers. Figure 2a shows a tumor confined to the muscularis propria (+). The MRI
 17 assessed low rectal cancer resection plane (mrLRP) appears 'safe' suggesting an intersphincteric
 18 resection is feasible. In figure 2b the tumor (¥) appears to breach the muscularis propria and is invading
 19 the distal mesorectum and intersphincteric plane. This tumor is mrLRP 'unsafe' and an intersphincteric
 20 resection would be high-risk for pCRM involvement, therefore an extralevator APE was suggested.

21 Figure 3. The Mercury II study profile.

22

23 Table 1 outlines the recommended operation according to the MRI staging.

24 Table 2. The relationship between the MRI assessed low rectal cancer plane and pathological
 25 circumferential resection margin (pCRM) involvement.

26 Table 3 provides a comparison between recommended and actual treatment according to baseline
 27 mrLRP and adverse MRI features, where CRT was given the re-assessed plane of surgery is reported
 28 (ymrLRP).

29 Table 4. The proportion of low rectal cancer cases with pCRM involvement according to demographics
 30 and MRI assessed tumor characteristics.

31 Table 5. A unifactorial and multifactorial logistic regression analysis evaluating pre-operative factors that
 32 predict pathological circumferential resection margin (pCRM) involvement in low rectal cancer.

33 Table 6. The MRI predicted risk (%) of pCRM involvement according to the four risk factors identified on
 34 multivariate regression analysis of 279 low rectal cancer patients.

35 Appendix 1. The MRI and Pathology low rectal cancer study proformas.

Table1

Recommended low rectal cancer surgery according to MRI assessment of the low rectal cancer plane (mrLRP)			
MRI intersphincteric plane (mrIP) status	MRI mesorectal fascia (mrMF) status	Distance from Puborectalis	Recommended Surgery
'Safe': tumor above intersphincteric plane	tumor >1mm from MF	>10mm	Intersphincteric Resection +/- colo-anal anastomosis
'Safe': tumor confined to submucosa with full thickness of muscularis propria preserved	tumor >1mm from MF	≤10mm	Local excision
'Safe': tumor involving part of muscularis propria	tumor >1mm from MF	≤10mm	Intersphincteric Resection +/- colo-anal anastomosis
'Unsafe' (one of): <ul style="list-style-type: none"> • full thickness of the muscularis propria/ internal sphincter • extends into the intersphincteric plane • tumor extends into the external sphincter or <1mm from levator ani 	tumor >1mm from MF	≤10mm	Extralevator APE
'Safe' or 'Unsafe'	tumor extends beyond MF into adjacent structures (prostate/vagina/bladder/sacrum/pelvic fascia)	-	Exenteration

Table2

	Total	clear pCRM	Involved pCRM	pCRM rate (%)	p-value
	279 [170]	254 (91.04%)	25 (8.96%)	(95% CI)	
MRI intersphincteric plane (mrIP)					
'Safe' (at baseline)	176	167	9	5.11 (1.83-8.40)	0.0032
'Unsafe' (at baseline)	103	81	16	15.53 (8.42-22.65)	
'Safe'* [ymr] (pre-operative)	203 [108]	194 [101]	9 [7]	4.43 (1.58-7.29)	0.00002
'Unsafe'*[ymr] (pre-operative)	76 [46]	60 [36]	16 [10]	21.05 (11.67-30.43)	
Missing	0 [16]	0 [13]	0 [3]		
MRI mesorectal fascia plane (mrMF)*					
'Safe' [ymr]	237 [120]	222 [112]	15 [8]	6.32 (3.18-9.37)	0.0001
'Unsafe' [ymr]	42 [34]	32 [25]	10 [9]	23.81 (10.98-39.02)	
Missing	0 [16]	0 [13]	0 [3]		
MRI Low Rectal Plane (mrLRP)					
'Safe' (at baseline)	166	158	8	4.82 (1.53-8.11)	0.0033
'Unsafe' (at baseline)	113	96	17	15.04 (8.35-21.74)	
'Safe'* [ymr]	191 [96]	183 [91]	8 [5]	4.19 (1.32-7.06)	0.00004
'Unsafe'* [ymr]	88 [58]	71 [46]	17 [12]	19.32 (10.91-27.73)	
Missing	0 [16]	0 [13]	0 [3]		

*The preoperative MRI is used; this would be the post treatment MRI [reported in brackets] for patients who received preoperative therapy. The mrLRP is the combined assessment of the mesorectal fascia and the intersphincteric plane.

Table3 Baseline MRI staging Recommended Management	Preoperative MRI assessment of low rectal plane (mrLRP) [post-treatment (ymrLRP)]						Surgery performed [Surgery performed post-treatment]							Overall pCRM Involvement		
	Clear TME/intersphincteric plane [post-CRT]			Involved TME/intersphincteric plane [post-CRT]			TME/ intersphincteric plane*			ELAPE/ Exenteration				Total (n)	pCRM (n)	pCRM rate (95% CI)
	Involved	pCRM rate	Total (n)	Involved	pCRM rate	Total (n)	Involved	pCRM rate	Total (n)	Involved	pCRM rate	missing				
	pCRM (n)	(%)		pCRM (n)	(%)		pCRM (n)	(%)		pCRM (n)	(%)					
Safe plane with no adverse MRI features†(n=124) TME plane surgery	76 [46 ¹]	2 [3]	2.63 [6.52]	0 [2]	[0]	0 [0]	62 [35]	1 [2]	1.61 [5.71]	14 [10]	1 [1]	7.14 [10]	3	124	5	4.03% (0.52-7.54)
Safe Plane with adverse MRI features (n=42) TME plane surgery with pre-op treatment	12 [24 ¹]	0 [3]	0 [12.5]	0 [6]	[0]	0 [0]	12 [24]	0 [2]	0 [8.33]	0 [5]	0 [1]	0 [20]	1	42	3	7.00% (0.98-15.27)
Unsafe Plane with no other MRI adverse features (n=17) ELAPE/Exent with pre-op treatment	0 [16]	[0]	0 [0]	0 [1]	0	0 [0]	0 [8]	0	0 [0]	0 [9]	0 [0]	0 [0]	0	17	0	0
Unsafe Plane with adverse MRI features (n=96) ELAPE/Exent with pre-op treatment	0 [17]	[0]	0 [0]	21 [58 ⁶]	3 [14 ¹]	14.29 [24.14]	10 [30]	2 [4]	20 [11.11]	10 [41]	1 [10]	10 [20.41]	5	96	17	17.71% (9.93 – 25.48)
Total														279	25	8.96% (5.59-12.33)

The straight to surgery data is adjacent to post-treatment data, with post-treatment values reported in [brackets]. †MRI adverse features were ≥mrT3c,mrN2 or mrEMVI. ELAPE – extralevator abdominoperineal excision (APE) *The operations performed are reported in figure 3. The ‘y’ value denotes post-treatment report. Pre-operative short course radiotherapy was used in 8 cases with 1 involved pCRM, these are denoted by [superscript].

Table4

	Total	Clear pCRM	pCRM Involvement	p-value
	279	254 (91.0%)	25 (9.0%)	
Age [median (IQR)]	279	65 (56-73)	62 (54-74)	0.466
Gender				
Female	99	92	7	
Male	180	162	18	0.412
BMI [median (IQR)]	195	26 (23-28)	26 (25-29)	0.336
MRI Tumour height [median (IQR)]	279	4.25 (3.3-5.0)	3.4 (2.4-4.3)	0.003
Quadrant of tumour invasion				
Anterior	99	85	14	
Other	180	169	11	0.025
Pre-operative treatment				
No	109	104	5	
Yes	170	150	20	0.041
Time interval between pre-operative MRI and surgery [median(IQR)] (days)				
Surgery alone	100	29 (18-41)	46 (32-49)	0.100
Pre-operative therapy	155	26 (7-46)	29 (6-81)	0.311
missing	24			
mrT stage (baseline)				
mrT0&1	15	15	0	0.016
mrT2	72	70	2	
mrT3a&b	104	96	8	
mrT3c&d	49	41	8	
mrT4	39	32	7	
mrT stage* (pre-operative)				
mrT0&1 [ymrT0&1]	34	32 [20]	2 [2]	0.003
mrT2 [ymrT2]	87	85 [35]	2 [1]	
mrT3a&b [ymrT3a&b]	95	87 [45]	8 [6]	
mrT3c&d [ymrT3c&d]	33	27 [19]	6 [2]	
mrT4 [ymrT4]	30	23 [18]	7 [6]	
[missing]		0 [13]	0 [3]	
mrN stage*				
Negative [ymrN]	174	164 [106]	10 [12]	
Positive [ymrN]	101	86 [31]	15 [5]	0.011
Missing	4	4 [13]	[3]	
mrEMVI staging*				
Negative [ymrEMVI]	225	212[112]	13 [10]	
Positive [ymrEMVI]	54	42 [25]	12 [7]	<0.001
Missing		[13]	[3]	

*The preoperative MRI is used; this would be the post treatment MRI [reported in brackets] for patients who received preoperative therapy.

Table 5	Univariable Analysis		Multivariable Analysis	
	Odd ratio (95% CI)	p value	Odd ratio (95% CI)	p value
All Cause pCRM in all patients (Surgery with or without pre-operative therapy, n=279)				
All cause mrLRP†¹				
'Safe'	1		1	
'Unsafe'	5.48 (2.7 – 13.2)	0.0002	3.49 (1.3 – 9.0)	0.010
Quadrant of tumour invasion²				
Other	1		1	
Anterior	2.53 (1.1 – 5.8)	0.029	2.80 (1.1-6.8)	0.027
Height (from the anal verge)³				
≥ 4cm	1		1	
< 4cm	4.00 (1.7-9.7)	0.002	3.39 (1.3-8.8)	0.012
mrT stage				
≤mrT3b	1			
>mrT3b	4.42 (1.9 – 10.3)	0.0006		
mr Node status				
Negative	1			
Positive	2.86 (1.2 – 6.6)	0.014		
mr EMVI status⁴				
Negative	1		1	
Positive	4.66 (2.0 – 10.9)	0.0004	3.76 (1.5 – 9.6)	0.006
†The mrLRP is a combined binary score, 'unsafe' included either at risk mesorectal fascia margin or intersphincteric plane. C-index 0.82 (95% CI 0.74-0.90). Internal validation based on 5000 bootstrap samples 95% CI ¹ .(1.4-11.3), ² .(1.1-8.0), ³ .(1.4-11.0), ⁴ .(1.3-10.8).				

MRI predicted percentage (%) risk of pCRM involvement for all low rectal cancer patients‡.					
Table 6.		MRI Predicted Involved CRM (mrLRP†)			
		'SAFE'		'UNSAFE'	
mrEMVI Status	Tumour Site*	Tumour Height (Distance from Anal Verge)			
		≥ 4cm	<4cm	≥ 4cm	< 4cm
EMVI -ve	Not Anterior	1	4	4	13
	Anterior	3	10	11	29
EMVI +ve	Not Anterior	4	13	14	35
	Anterior	11	30	31	60

The risk of pCRM involvement: green, low risk ≤ 5%; amber, intermediate risk 14-6%; red, high risk ≥15%. The probabilities are calculated from the multivariate model (table 5), all values are reported as a predicted percentage (%) risk of pCRM involvement (n=279). †mrLRP, MRI assessment of low rectal cancer plane (a 'safe' mrLRP implies that the mesorectal fascia and intersphincteric planes are clear of tumour). *the quadrant of tumour invasion ‡the data is based on the preoperative MRI this would be the post treatment MRI for patients who received preoperative therapy.

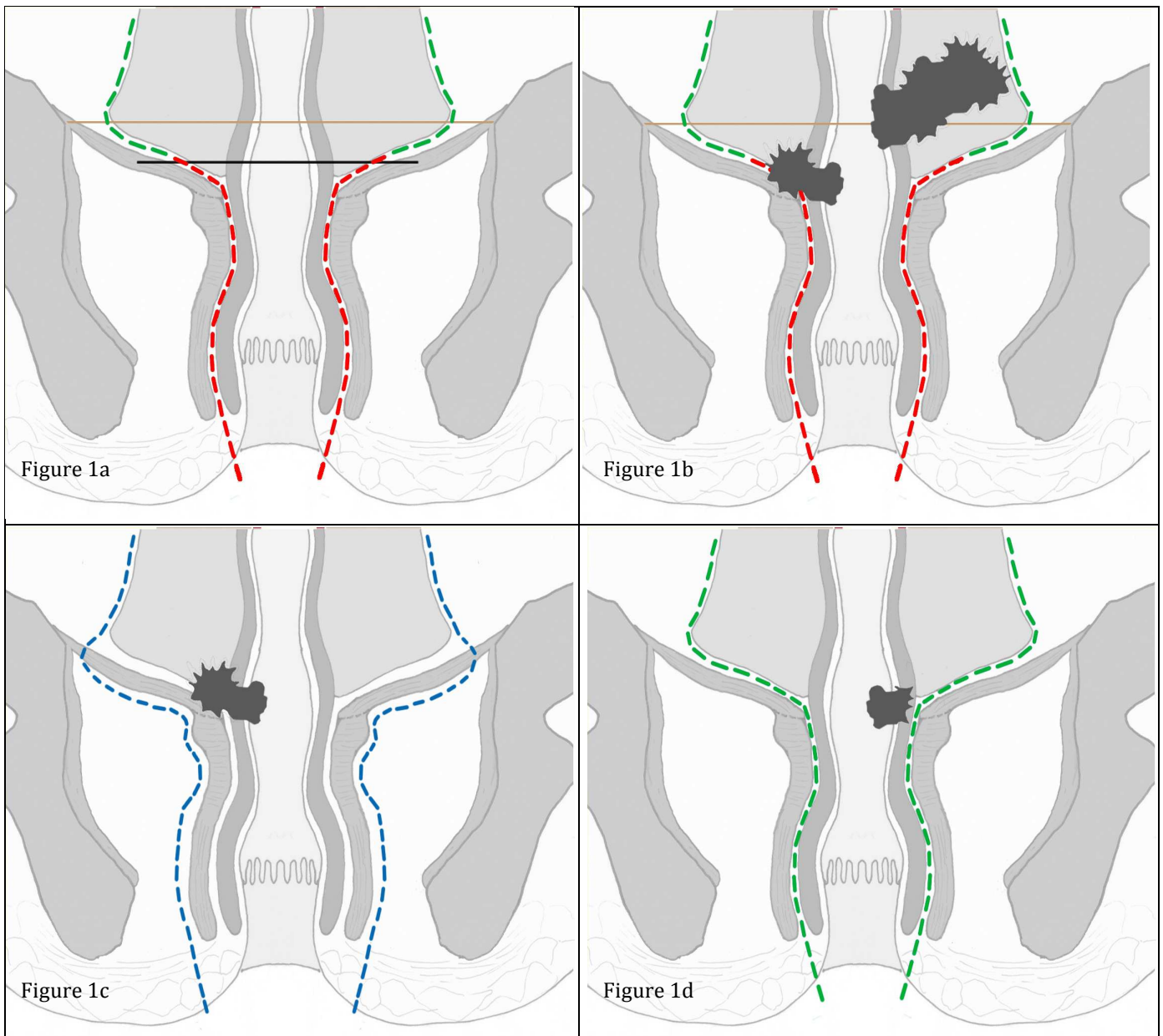
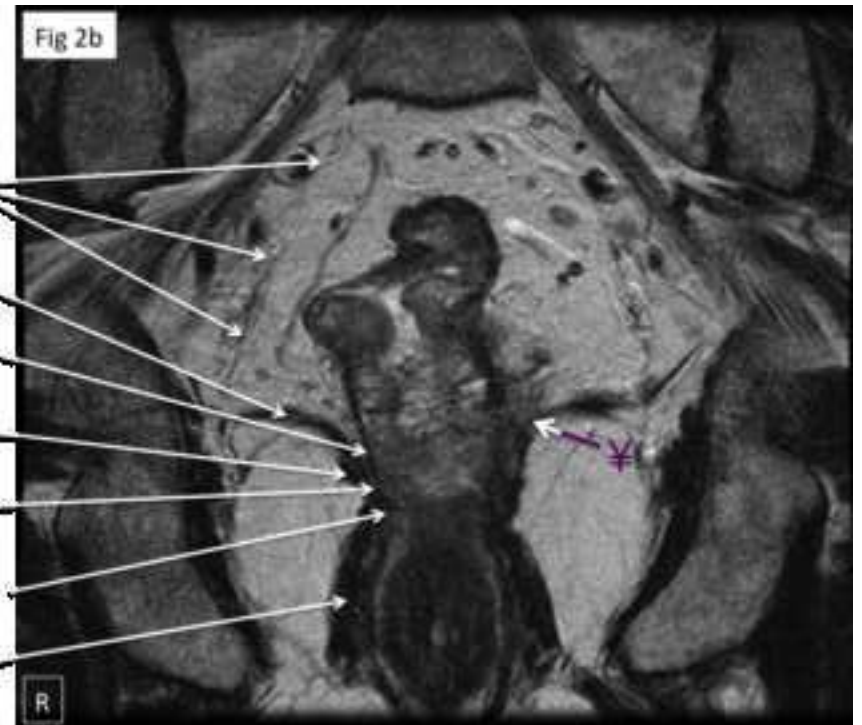
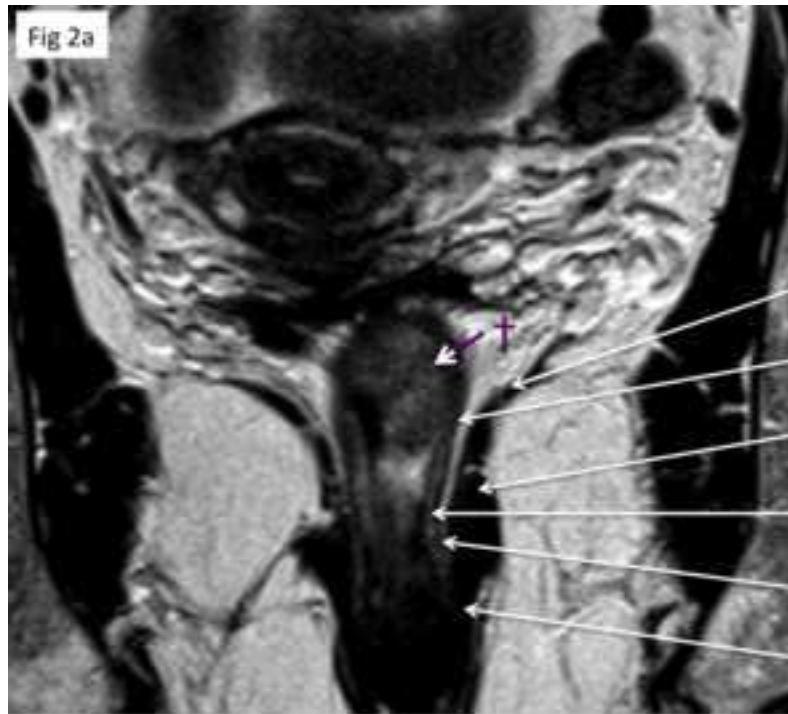


Figure 1a. Diagrammatic coronal oblique view through long-axis of anal canal. Low rectal cancer is defined as adenocarcinoma with an inferior tumour edge less than six centimeters from the anal verge, anatomically represented by a line between the origins of the levator muscle (horizontal beige line).³⁸ The horizontal black line (1cm above puborectalis sling) represents the site between mesorectal fascia plane and intersphincteric plane. MRI evaluation of the mesorectal fascia (dashed green line) has been validated previously.³ This study aimed to validate a previously reported technique for MRI assessment of the intersphincteric plane (dashed red line).⁹

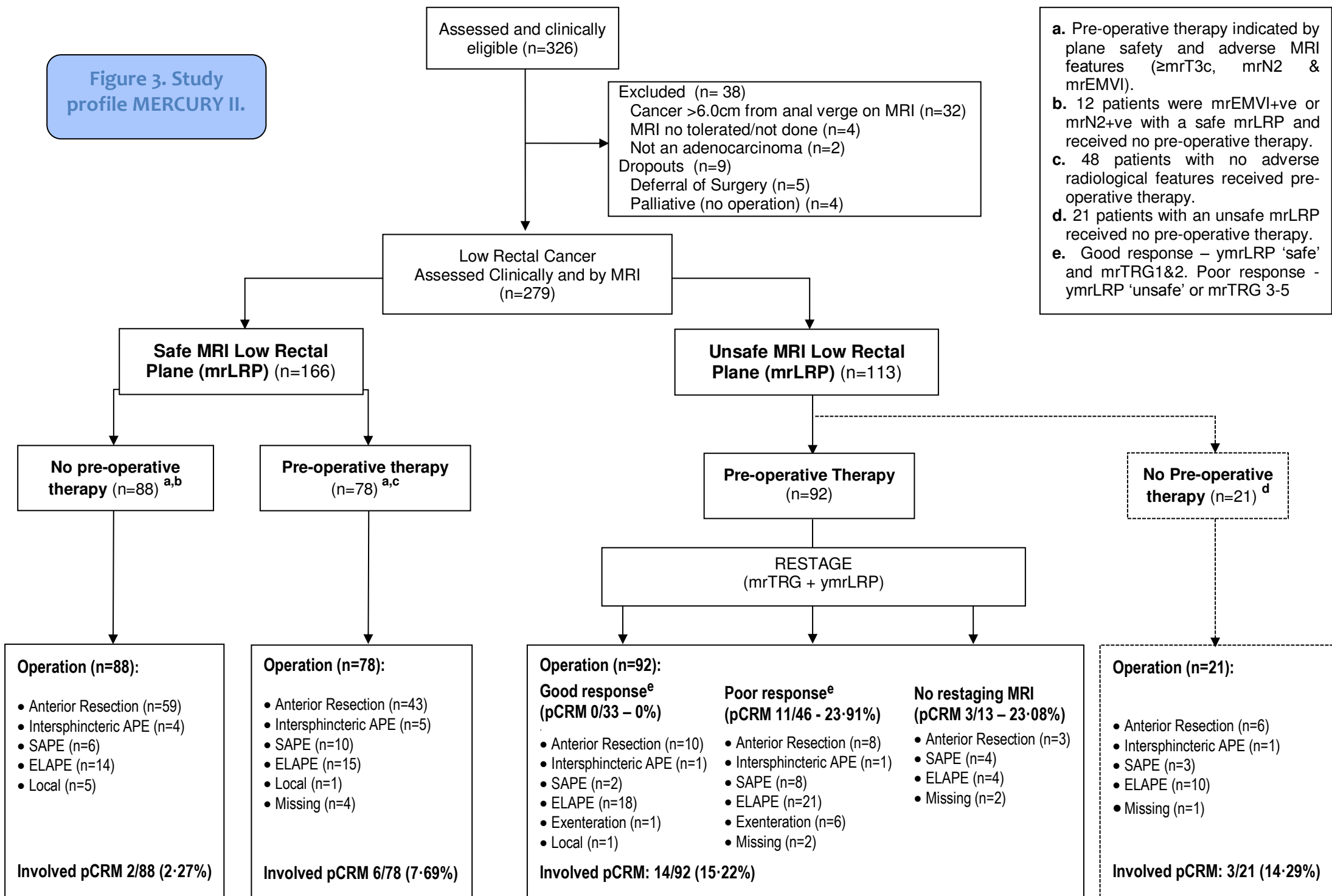
Low rectal cancer circumferential resection margin involvement may occur at the mesorectal fascia plane or at the intersphincteric plane (*figure 1b*). When tumour extends beyond muscularis propria/internal sphincter the intersphincteric plane is 'unsafe' (*figure 1c*) therefore pre-operative therapy and an extra-levator abdominoperineal excision (dashed blue line) is recommended. When the intersphincteric plane is 'safe' (*figure 1d*) an intersphincteric resection (dashed green line) +/- anastomosis is feasible.



- Mesorectum
- Levator ani
- Muscularis propria
- Puborectalis
- Intersphincteric space
- Internal sphincter
- External sphincter

Figure3

Figure 3. Study profile MERCURY II.



a. Pre-operative therapy indicated by plane safety and adverse MRI features (\geq mrT3c, mrN2 & mrEMVI).

b. 12 patients were mrEMVI+ve or mrN2+ve with a safe mrLRP and received no pre-operative therapy.

c. 48 patients with no adverse radiological features received pre-operative therapy.

d. 21 patients with an unsafe mrLRP received no pre-operative therapy.

e. Good response – ymrLRP ‘safe’ and mrTRG1&2. Poor response - ymrLRP ‘unsafe’ or mrTRG 3-5

Authorship

We appreciate that there are a large number of named co-authors but this is an international multicentre multidisciplinary study that required expertise in a number of specialties.

The thirteen authors listed below meet all of the following conditions: 1) substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data; 2) participated in drafting the article or revising it critically for important intellectual content; and 3) Authors give final approval of the version to be published.

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