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Predicting Difficult Laparoscopic Total Mesorectal Excision for Locally-advanced Mid-low Rectal Cancer: The *EuMaRCS* Score Validation

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Abstract. *Background/Aim: The European MRI and Rectal Cancer Surgery (EuMaRCS) score was proposed to identify preoperatively difficult laparoscopic total mesorectal excision (L-TME) for locally advanced rectal cancer (LARC). This study aimed to test EuMaRCS's validity. Patients and Methods: Data were retrieved from a European multicenter database, including patients with mid/low LARC, treated with neoadjuvant chemoradiation therapy and L-TME with primary anastomosis. The EuMaRCS score was calculated on: BMI>30 (3 points), interspinous distance<96.4 mm (2 points), ymrT stage≥T3b (4 points), and male sex (1 point). Results: The sample was composed of 141 patients, of whom 23 (16.3%) had a difficult L-TME. The EuMaRCS score demonstrated high accuracy in predicting difficult surgery (AROC: 0.806, 95%CI=0.72-0.88), with a cut-off >3 being associated with the best balance in sensitivity (82.6%) and specificity (66.1%). Conclusion: The EuMaRCS score represents a validated tool to predict preoperatively difficult L-TME in LARC patients.*

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A multimodal approach is recommended for the treatment of locally advanced rectal cancer (LARC) of the middle or low rectum (1). This approach includes neoadjuvant chemoradiation therapy (NCRT) and radical surgery, which represents the curative treatment that impacts patient prognosis the most (2-4). The gold standard procedure is a total mesorectal excision (TME) with clear resection margins (5), which is currently performed more frequently *via* a minimally invasive approach such as laparoscopy (L-TME) (2, 6-9). Several patient- and tumor-related factors can influence surgical difficulty and make surgical outcomes worse. Among these, anatomical constraints (*e.g.*, narrow pelvis), obesity, tumor volume and height have been shown to be associated with more difficult L-TME procedures, namely, longer operative times, blood loss, intraoperative complications, and conversion to open surgery (4, 10-15). Incomplete mesorectal excision or positive resection margins should be considered to indicate unsuccessful surgical treatment because they are associated with a significantly increased risk of both local and systemic recurrence (3, 11, 16-19). Thus, predicting surgical difficulties and adapting the surgical strategy (technique and approach) to the patient and tumor characteristics could impact the probability of achieving optimal surgical outcomes, consequently improving rectal cancer patient survival.

Recently, a morphometric score to predict surgical difficulty in LARC patients who are candidates for L-TME has been proposed (20). This score was developed based on a multicentric European database, namely, the *European MRI and Rectal Cancer Surgery* (*EuMaRCS*) database, composed of data from consecutive patients with LARC located at the middle or low rectum who were treated with NCRT and L-TME in four referral hospitals in Spain, France and Switzerland (20). The proposed *EuMaRCS* score is easy to assess by taking into account criteria related to the patient (*i.e.*, male sex, obesity, and the pelvimetric measure of the interspinous distance) and the tumor (*i.e.*, ymrT stage), which can all be assessed preoperatively. In the training population set on which the EuMaRCS score was developed, the score showed good accuracy with an area under the receiving operating characteristics (ROC) curve of 0.802 (20).

The aim of the present study was to test the external validity of the EuMaRCS score in an independent multicentric population and to evaluate the accuracy and usefulness of this score to predict L-TME surgical difficulty in LARC patients.

Patients and Methods

Study design and study population. To validate the *EuMaRCS* score (20) in an independent population (validation set), we build a new European multicentric database of consecutive patients with locally advanced mid- or low-rectal cancer treated between February 2016 and June 2019 in 5 colorectal referral centers: Henri Mondor University Hospital of Créteil, France; Doctor Peset University Hospital of Valencia, Spain; Geneva University Hospital of Geneva, Switzerland; University Hospital of Padova, Italy; and Vall d'Hebron University Hospital of Barcelona, Spain. All included patients signed an informed consent form allowing their data to be used for retrospective analyses and research. Thus, the study was conducted exclusively with anonymous patient records that were treated in conformity to the principles declared by the National Commission for Data Protection and Liberties and in accordance with the ethical principles described in the Declaration of Helsinki. The inclusion criteria were the same as those of the EuMaRCS original population (11, 20, 21) and consisted of patients diagnosed with histologically proven, locally advanced [American Joint Committee on Cancer (AJCC) stages II to IIIc] (22) mid- or low-rectal cancer (within 12 cm from the anal verge), who received NCRT and were operated on by elective laparoscopic anterior resection (LAR) with total mesorectal excision (L-TME) (23, 24) and who had undergone an MRI before (pretreatment MRI) and after (restaging MRI) NCRT (11, 25). Records of patients who had received laparoscopic abdominoperineal resections (L-APR) and low Hartmann's procedures with TME, open surgery, transanal TME (Ta-TME), and robotic procedures were not considered.

Pretreatment MRI was used for primary tumor staging and pelvimetry (12, 26-31), as previously described (11). Restaging MRI, performed 8-10 weeks after the completion of NCRT, was used for tumor restaging and tumor response evaluation by applying the magnetic resonance tumor regression grade (mrTRG) (1 to 5) (32, 33), with an mrTRG of 4 or 5 identifying poor responders (34).

Table I. *The EuMaRCS predictive score for surgical difficulty.*

Item	Score weight
BMI (kg/m^2)	
<30	0
≥30	3
Interspinous distance (mm)	
≥96.4	0
<96.4	2
ymrT stage	
<T3b	0
≥T3b	4
Gender	
Female	0
Male	1

All MRIs were performed following standard protocols (2-dimensional T2-weighted fast spin-echo sequences in 3 orthogonal directions and an additional diffusion-weighted sequence in the axial plane) (25).

Treatment protocols and definition of surgical difficulty. All patients completed long-course NCRT with a total radiation dose of 45-50.4 Gy delivered in daily fractions of 1.8-2 Gy over a 5- to 6-week period, combined with 5-fluorouracil or capecitabine (Xeloda) (2, 35).

All procedures were L-TMEs with low colorectal or coloanal anastomosis and were carried out according to the standard protocols by senior colorectal surgeons highly experienced in minimally invasive surgery (2, 11, 20). Conversion was defined as the premature interruption of the laparoscopic approach followed by the need for a conventional laparotomy to complete the procedure.

The predictable endpoint of surgical difficulty was defined using the grading system proposed by Escal *et al*. (12) and was previously applied for the development of the EuMaRCS score (20). Difficult surgeries were identified based on a composite variable including the following operative and postoperative parameters: operative time (>300 min), blood loss (>200 ml), conversion to laparotomy, use of transanal dissection, occurrence of postoperative Dindo-Clavien complications grades II and III (36), and duration of hospital stay (>15 days). The surgical difficulty grade ranges from 0 to 12; a score of 6 or more is considered to indicate high surgical difficulty (12).

Estimating the EuMaRCS score. The EuMaRCS score was originally proposed in two versions: the 3-criteria score and the 4-criteria score. However, the 4-criteria score showed a better accuracy than the 3-criteria one and it was then chosen to be externally validated (20). Thus, the EuMaRCS score was calculated based on the following 4 variables: BMI (≥30 kg/m^2), interspinus distance (<96.4 mm), ymrT stage (≥T3b) measured on restaging MRI, and male sex. Each variable contributes to the score with a specific weight, as displayed in Table I. The obtained total score can range from 0 to 10 (20).

Statistical analysis. Based on the surgical difficulty grade (12), the sample was divided into two groups: the low and high surgical difficulty groups. Patient demographics, clinical characteristics, and operative and postoperative variables were evaluated by descriptive statistics and compared between groups by the chi-squared test,

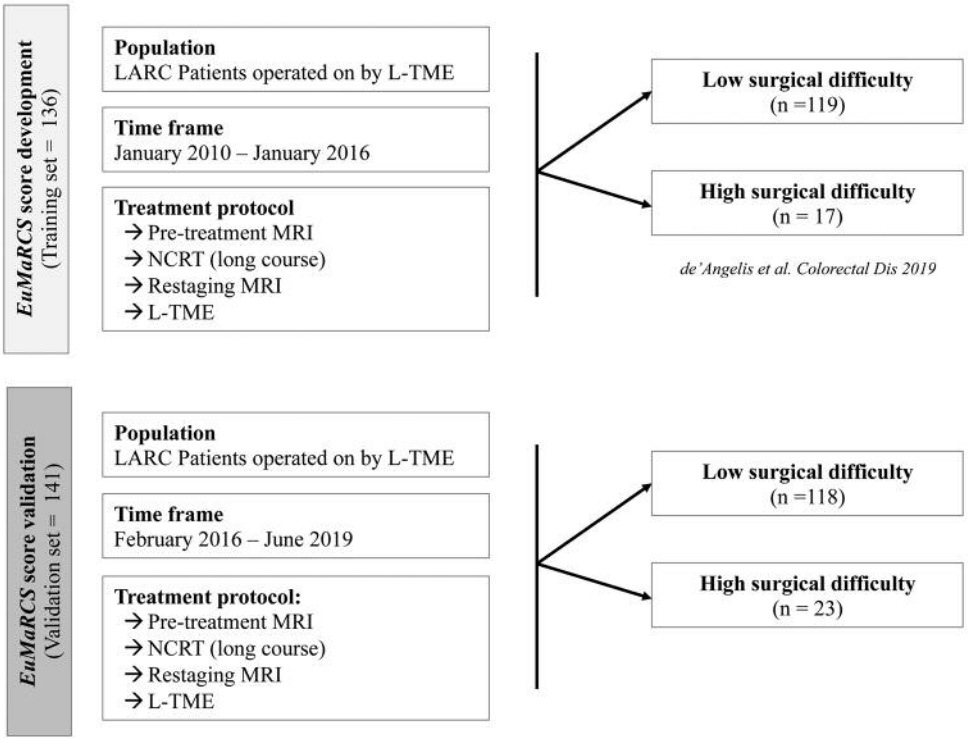

Figure 1. *Characteristics of the study populations in which the EuMaRCS score was originally developed (training set) (20) and validated (validation set, present study). LARC: Locally advanced rectal cancer; L-TME: laparoscopic total mesorectal excision; MRI: magnetic resonance imaging; NCRT: neoadjuvant chemoradiation therapy.*

Fisher's exact test, and Mann-Whitney *U*-test. The validity and accuracy of the EuMaRCS score were assessed by calculating sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the area under the receiver operating characteristics (ROC) curve (AROC). Sensitivity and specificity were considered low for values <60%, moderate for values between 60% and 79%, and high for values ≥80%. The accuracy determined by the AROC curve was interpreted as poor if the value was between 0.51 and 0.69; useful if the value was between 0.70 and 0.79; and good if the value was ≥0.80 (37-40). Sensitivity, specificity, and AROC were scrutinized to find the cut-off point that provides the best predictive value to identify patients at risk of difficult surgery. The product of sensitivity*specificity and a weighted Youden index were used to determine the best cut-off to predict a difficult surgery (41). Statistical analyses were performed using Statistical Package for Social Sciences software (Statistical Package for Social Science, IBM SPSS Statistics, Version 23 for Macintosh; IBM Corp., Armonk, NY, USA). *p*-Values <0.05 were considered to indicate statistical significance.

Results

The study population (validation set) was comparable to the population in which the EuMaRCS score was originally developed (training set) (20) (Figure 1). The study population consisted of 141 LARC patients undergoing L-TME with primary anastomosis. Based on the surgical difficulty grade, 118 (83.7%) patients were classified as having low surgical difficulty, and 23 (16.3%) were classified as having high surgical difficulty. Demographic, clinical, and histopathological variables were similar between the groups. As expected, group differences were observed for operative and postoperative outcomes that contributed to defining surgical difficulty (Table II).

Compared to patients with low surgical difficulty, patients in the high surgical difficulty group had a significantly higher proportion of cancers staged as ymrT3 or more (69.6% *vs*. 28.8%; p=0.001) and a significantly smaller mean interspinous distance (99.23±13.63 mm *vs*. 103.01±13.06 mm; p=0.033). Differences concerning obesity (26.1% *vs*. 16.9%; p=0.376) and male sex (78.3% *vs*. 61.9%; p=0.158) were not significantly different between the high and low surgical difficulty groups.

EuMaRCS score validity. The accuracy of the EuMaRCS score is displayed by the ROC curve (Figure 2). The score was associated with good accuracy (AROC: 0.806). Once plotted the score values to determine the cut-off with the best balance between sensitivity and specificity and the higher weighted Youden score (Table III), a total score >3 appeared

Table II. *Demographic, operative and histopathological variables of LARC patients undergoing L-TME after NCRT. The sample was divided into two groups based on the assessed surgical difficulty.*

Variables	Whole sample (n=141)	Low surgical difficulty (n=118)	High surgical difficulty (n=23)	*p*-Value
Demographic and clinical variables				
Age (yr) [mean (SD)]	64.53 (10.45)	64.19 (10.23)	66.26 (11.58)	0.388
Male sex [n (%)]	91 (64.5)	73 (61.9)	18 (78.3)	0.158
BMI (kg/m2) [median SD]	26.05 (4.32)	25.79 (4.19)	27.16 (4.89)	0.164
ASA score I/II/III [n]	15/94/32	15/78/25	0/16/7	0.218
Albumin serum level (g/l) [mean (SD)]	41.32 (3.78)	41.25 (3.88)	41.65 (3.28)	0.978
Preoperative serum CEA (U/ml) [mean (SD)]	4.57 (7.07)	4.29 (6.74)	6.01 (8.60)	0.334
CR POSSUM score [mean (SD)]	12.32 (3.27)	12.20 (3.19)	12.91 (3.66)	0.478
Patients with comorbidity [n (%)]	99 (70.2)	80 (67.8)	18 (82.6)	0.214
Patients with multiple comorbidities (>1) [n (%)]	54 (38.3)	42 (35.6)	12 (52.2)	0.162
L-TME procedures [n (%)]				0.079
Low colorectal anastomosis	123 (87.2)	106 (89.8)	17 (73.9)	
Coloanal anastomosis	18 (12.8)	12 (10.2)	6 (26.1)	
Operative and postoperative variables				
Operative time (min) [median (range)]	286 (145-640)	277.5 (145-534)	336 (210-640)	**<0.0001**
Conversion to laparotomy [n (%)]	10 (7.1)	3 (2.5)	7 (30.4)	**<0.0001**
Use of transanal dissection [n (%)]	39 (27.7)	29 (24.6)	10 (43.5)	0.077
Operative blood loss (ml) [median (range)]	75 (0-1005)	65 (0-700)	130 (0-1500)	**0.034**
Transfused patients [n (%)]	9 (6.4)	3 (2.5)	6 (26.1)	**0.001**
Time to flatus (days) [mean (SD)]	2.14 (1.71)	1.92 (1.48)	3.20 (2.30)	**0.004**
Return to regular diet (days) [mean (SD)]	3.28 (3.46)	3.90 (3.26)	6.10 (3.85)	**0.001**
ISGRC anastomotic leakage [n (%)]				**<0.0001**
A	3 (2.1)	1 (0.8)	2 (8.7)	
B	8 (5.7)	6 (5.1)	2 (8.7)	
C	5 (3.5)	1 (0.8)	4 (17.4)	
Postoperative complications (Dindo-Clavien) [n (%)]				**<0.0001**
I/II	28 (19.9)	19 (16.1)	9 (39.1)	
III/IV	22 (15.2)	12 (10.2)	10 (43.5)	
V	0	0	0	
Hospital stay (days) [median (range)]	9 (4-156)	8 (4-156)	20 (8-55)	**<0.0001**
Mortality at 90 days [n (%)]	0	0	0	NA
Readmission within 60 days [n (%)]	19 (13.5)	17 (14.4)	2 (8.7)	0.739
Adjuvant chemotherapy [n (%)]	80 (57.1)	68 (58.1)	12 (52.1)	0.649
Histopathological (yp) variables				
(yp) T category [n (%)]				0.678
ypT0	29 (20.6)	26 (22)	3 (13)	
ypT1	10 (7.1)	8 (6.8)	2 (8.7)	
ypT2	34 (24.1)	26 (22)	8 (34.8)	
ypT3	60 (42.6)	51 (43.2)	9 (39.1)	
ypT4	8 (5.7)	7 (5.9)	1 (4.3)	
Tumor regression grade (MANDARD) [n (%)]				0.787
I	29 (20.4)	26 (22)	3 (13)	
II	35 (24.8)	29 (24.6)	6 (26.1)	
III	64 (45.4)	52 (44.1)	12 (52.2)	
IV	13 (9.2)	11 (9.3)	2 (8.7)	
V	0	0	0	
R1 resection margin [n (%)]	14 (9.9)	9 (7.6)	5 (21.7)	0.054
ypCRM (mm) [mean (SD)]	9.53 (7.96)	9.22 (7.62)	11.01 (9.55)	0.499
Positive ypCRM [n (%)]	12 (8.5)	8 (6.8)	4 (17.4)	0.108
ypDRM (mm) [mean (SD)]	26.24 (15.22)	25.49 (14.91)	29.62 (16.50)	0.330
Positive ypDRM [n (%)]	4 (2.8)	3 (2.5)	1 (4.3)	0.514
Harvested lymph nodes [mean (SD)]	13.55 (7.46)	13.6 (7.6)	13.3 (6.87)	0.890
Lymphovascular invasion [n (%)]	27 (19.1)	22 (18.6)	5 (21.7)	0.773
Perineural invasion [n (%)]	23 (16.3)	17 (14.4)	6 (26.1)	0.214
Tumor deposit [n (%)]	29 (30.5)	23 (28.4)	6 (42.9)	0.348

ASA: American Society of Anesthesiology; BMI: body mass index; CEA: carcinoembryonic antigen; CR: colorectal; CRM: circumferential resection margin; DRM, distal resection margin; ISGRC: International Study Group for Rectal Cancer; LARC: locally advanced rectal cancer; L-TME: laparoscopic total mesorectal excision; NCRT: neoadjuvant chemoradiation therapy; T: tumor stage. Bold values indicate significance.

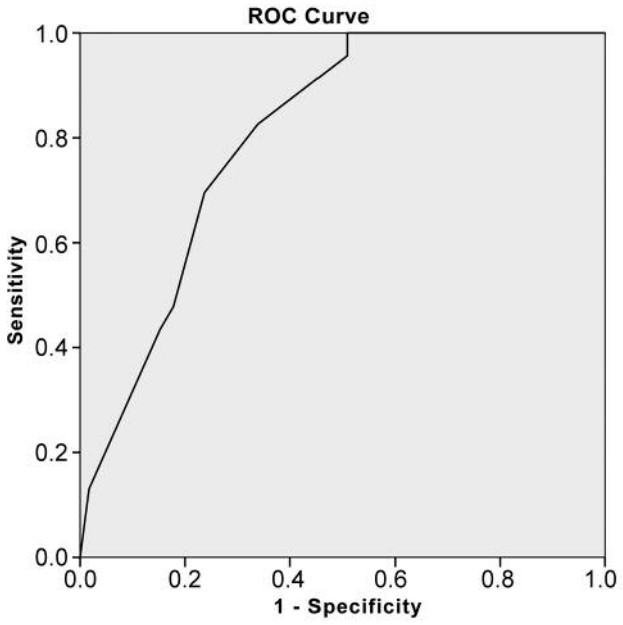

Figure 2. *Receiver operating characteristics (ROC) curves of the EuMaRCS predictive score for surgical difficulty. The area under the curve, AROC, is 0.806 (95%CI=0.728-0.884; p<0.0001).*

Table III. *Detailed report of sensitivity (Sn) and specificity (Sp) for the EuMaRCS predictive score for surgical difficulty.*

Score value	Sensitivity (Sn) (%)	Specificity (Sp) (%)	Sn * Sp	Weighted youden index
0	100	0	0	0.1
>1	100	32.9	0.329	0.3961
>2	95.7	49.2	0.470844	0.4955
>3	82.6	66.1	0.545986	0.5035
>4	69.6	76.3	0.531048	0.4523
>5	47.8	82.2	0.392916	0.2656
>6	43.5	84.7	0.368445	0.2408
>8	13	98.3	0.12779	0.0277
10	0	100	0	–0.1

to best differentiate patients with low and high surgical difficulty. Using this cut-off value, the EuMaRCS score was associated with a sensitivity of 82.6%, a specificity of 66.1%, a PPV of 32.2% and an NPV of 95.1%.

Discussion

The present study validated the EuMaRCS score in an independent population of LARC patients undergoing L-TME. This score is calculated preoperatively, and can help to predict the difficulty of L-TME with 82.6% sensitivity and 66.1% specificity, which indicate a good accuracy. However, when looking at the positive and negative predictive values, a LARC patient scoring 3 or less has a 95.1% chance of having a low difficult surgery (NPV), whereas a patient scoring >3 has a 32.3% chance of having a highly difficult surgery (PPV). It must be considered that the PPV is influenced by the sensitivity of the test and the prevalence of the outcome in the analyzed population. In this case, only 23/141 patients (16.3%) were classified as having highly difficult surgeries, thus limiting the observed PPV to approximately one-third of the population. Nevertheless, the EuMaRCS score performed similarly or even better than other predictive scores for postoperative complications widely used in rectal cancer patients, such as the Colorectal Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (CR-POSSUM), the Onodera's Prognostic Nutritional Index (PNI), and the Estimation of Physiologic Ability and Surgical Stress Comprehensive Risk Score (E-PASS CRS) (42). Thus, taking these findings together and considering the AROC of 0.806, the present study suggests that the EuMaRCS score is a valuable tool to preoperatively identify LARC patients at risk of having a difficult L-TME.

In the era of personalized medicine, there is an urgent need to develop scores and algorithms to predict treatment outcomes and prognoses. In the context of rectal cancer surgery, several studies have investigated the role of pelvic dimensions in predicting surgical difficulty or poor-quality surgery. Most often, male sex was associated with an increased risk of conversion from laparoscopy to laparotomy (14, 27, 30, 43), and this risk was mainly related to the narrow pelvic space that can cause insufficient counter traction and lead to an unfeasible L-TME. A previous EuMaRCS study that analyzed pelvimetry on pretreatment MRI of LARC patients found that the interspinous distance and the intertuberous distance were significantly associated with the need for conversion and postoperative complications, respectively (11). More recently, Chau and coworkers have investigated the predictive value of pelvic dimension in identifying poor quality resection as defined by incomplete mesorectal excision and positive resection margins (10). The authors have shown that only the S1-S5-bottom of a symphysis angle >74/3° was an independent predictor of poor-quality resection after adjustment for BMI, tumor height and pathologic T stage. Their results, however, support the use of pretreatment MRI to identify patients at risk and guide surgical planning, in accordance with several other studies assessing the role of pelvimetry in rectal cancer patients (11, 13, 26, 27, 29-31, 44-47). Conversely, Curtis and coworkers have reported that patient, tumor, and bony pelvic anatomical characteristics seemed to not influence the surgical difficulty of L-TME except for the mesorectal area, which was

associated with major intraoperative adverse events and postoperative morbidity (48). However, the studied population included 71 rectal cancer patients at different stages, as deemed by the fact that only 24% of the cases received NCRT; the heterogeneity of the tumor characteristics (*e.g.*, tumor location, stage, and treatment protocols) may significantly impact the surgical difficulty and bias the observed associations between the bony structures assessed by pelvimetry and the surgical outcomes (11).

Instead of using a single clinical or pelvimetric parameter, a comprehensive score that combines anatomical, morphological and clinical factors that appear to affect the technical difficulty of L-TME may be more useful and precise to identify patients at risk (12, 20). The use of a predictive score has several advantages, as it is objective, easy to assess, and may represent an optimal tool to assist the decision-making process and facilitate communication between colleagues, as well as between surgeons and patients. However, the score must be valid, accurate and associated with good sensitivity and specificity to be widely accepted.

In 2018, Escal and coworkers (12) proposed an MRI morphometric score based on 4 equally weighted criteria, including BMI ≥30, intertuberous distance <10.1 cm, mesorectal fat area ≥20.7 cm2, and the need for a coloanal anastomosis to predict surgical difficulty as defined in the present study. The score proposed by Escal and coworkers is easy to assess, but it includes a variable, *i.e.*, the need for coloanal or colorectal anastomosis, which is not always possible to determine preoperatively. Moreover, the diagnostic performance and accuracy of the score remain uncertain, although they were found to be poor when tested in an independent population (20).

The EuMaRCS score was found to have good accuracy in both the training set population (20) and the present validation set population, composed of homogeneous samples of LARC patients, all of which had received NCRT and L-TME. This demonstrated true replication in a similar but independent sample and supports the generalizability of the findings to the specific target population of patients with LARC (39, 49). Consistency was also shown because the outcome, *i.e.*, surgical difficulty, was defined by applying the same surgical grading system, which included meaningful operative and postoperative parameters. While proving to be a valuable tool, the EuMaRCS score has the specificity to be, in our knowledge, the only score in the literature to consider a post-NCRT item such as the ymrT stage, which allows for the prediction of the impact of tumor characteristics on surgical difficulty, taking into account the tumor response to NCRT (11, 20). Growing evidence supports a strong relationship between the response to NCRT, restaging MRI findings and histopathological outcomes (*e.g.*, depth of tumor invasion and involvement of CRM) (11, 34, 50-52). However, a restaging MRI is not yet systematically prescribed for all LARC patients, although an increased use in referral centers has been reported (53).

By using the EuMaRCS score, colorectal surgeons may be able to more easily and more precisely identify difficult cases that may deserve further evaluation, complementary treatments (*e.g.*, prolonged NCRT), extended resections, alternative approaches (*e.g.*, TaTME, robotic surgery) or surgical intervention performed by highly experienced surgeons rather than novice ones. Indeed, the assessment of risk and the identification of those factors that contribute most to the patient's risk can substantially assist in tailoring the surgical treatment. For instance, the presence of an ymrT3b or more should be considered to indicate a poor response to NCRT and a lower chance of achieving a complete mesorectal resection (25, 54, 55). The combination of male sex, narrow pelvis and BMI highlights the presence of anatomical factors that may particularly influence surgical difficulty during L-TME (26, 27, 30). Conversely, these parameters were recently found to have no influence on surgical quality outcomes if operating by TaTME (56), which may be seen as a valuable alternative in these cases.

The EuMaRCS score may also be useful for research applications. The score could be convenient in both retrospective and prospective studies to stratify patient populations by surgical difficulty risk and to compare the outcomes of different techniques or approaches, taking into account the predicted difficulty related to the patient and the rectal cancer characteristics. Moreover, future studies may evaluate the predictive role of the EuMaRCS score on oncological outcomes, such as recurrence rate and survival, which are strictly dependent on the possibility of achieving successful surgical resection.

In conclusion, the EuMaRCS score is a valid tool to identify patients susceptible to highly difficult L-TME, and it could be useful to choose the optimal treatment strategy for LARC.

Conflicts of Interest

All Authors have no conflicts of interest to disclose regarding this study.

Authors' Contributions

Study conception and design: Nicola de'Angelis, Aleix Martínez-Pérez, Alain Luciani, Francesco Brunetti, Eloy Espin, Frederic Ris, Salvatore Pucciarelli; Data collection: Giulio Cesare Vitali, Nicola de'Angelis, Aleix Martínez-Pérez, Giulio Cesare Vitali, Francesco Brunetti, Miquel Kraft, Eva Martí-Martínez, Paolo Moroni; Data analyses and interpretation: Nicola de'Angelis, Aleix Martínez-Pérez, Frederic Pigneur; Manuscript drafting: Nicola de'Angelis, Aleix Martínez-Pérez; Critical revisions and approval of the final version: Nicola de'Angelis, Aleix Martínez-Pérez, Giulio Cesare Vitali, Frederic Pigneur, Alain Luciani, Francesco Brunetti, Miquel Kraft, Eva Martí-Martínez, Paolo Moroni, Eloy Espin, Frederic Ris, Salvatore Pucciarelli.

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