Impact of nutritional status and body composition on postoperative outcomes after pelvic exenteration for locally advanced and locally recurrent rectal cancer

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Abstract

Background: Pelvic exenteration for locally advanced rectal cancer (LARC) and locally recurrent (LRRC) rectal cancer provides radical resection and local control, but is associated with considerable morbidity. The aim of this study was to determine risk factors, including nutritional status and body composition, for postoperative morbidity and survival after pelvic exenteration in patients with LARC or LRRC.

Methods: Patients with LARC or LRRC who underwent total or posterior pelvic exenteration in a tertiary referral centre from 2003 to 2018 were analysed retrospectively. Nutritional status was assessed using the Malnutrition Universal Screening Tool (MUST). Body composition was estimated using standard-of-care preoperative CT of the abdomen. Logistic regression analyses were performed to identify risk factors for complications with a Clavien–Dindo grade of III or higher. Risk factors for impaired overall survival were calculated using Cox proportional hazards analysis.

Results: In total, 227 patients who underwent total (111) or posterior (116) pelvic exenteration were analysed. Major complications (Clavien–Dindo grade at least III) occurred in 82 patients (36.1 per cent). High risk of malnutrition (MUST score 2 or higher) was the only risk factor for major complications (odds ratio 3.99, 95 per cent c.i. 1.76 to 9.02) in multivariable analysis. Mean follow-up was 44.6 months. LRRC (hazard ratio (HR) 1.61, 95 per cent c.i. 1.04 to 2.48) and lymphovascular invasion (HR 2.20, 1.38 to 3.51) were independent risk factors for impaired overall survival.

Conclusion: A high risk of malnutrition according to the MUST is a strong risk factor for major complications in patients with LARC or LRRC undergoing exenteration surgery.

Introduction

Worldwide, rectal cancer is one of the most commonly diagnosed cancers[1,2]. Approximately 10 per cent of patients with this disease present with locally advanced rectal cancer (LARC)[3,4]. Despite improvements in the multimodal treatment of primary rectal cancer, 4–8 per cent develop locally recurrent rectal cancer (LRRC) after total mesorectal excision (TME)[5–7]. Radical resection remains the cornerstone of curative treatment for primary and locally recurrent rectal cancer[8–10]. Most patients with LARC or LRRC are treated with neoadjuvant chemoradiotherapy (NACRT) followed by surgical resection. Achieving radical resection of LARC and LRCC is especially challenging when adjacent pelvic organs are involved. In some patients, partial resection of the adjacent organ is sufficient for a radical resection, but a multivisceral anatomical resection is often needed (total (PPE) or posterior (PPE) pelvic exenteration). TPE and PPE are major procedures, and are associated with significant morbidity and (in-hospital)

mortality. Previous studies[10–17] have shown that 30-day morbidity and hospital mortality rates are higher after exenteration surgery for rectal cancer than those after TME surgery (69 and 3 per cent *versus* 21 and 0.6 per cent respectively).

Malnutrition and altered body composition are known predictive factors for postoperative complications and impaired survival in patients with colorectal cancer[18–26]. Nutritional status and body composition as risk factors in patients with LARC or LRRC undergoing exenteration surgery have rarely been described. Taken into account the high proportion of patients who are exposed to severe surgery-related complications, risk factors for perioperative morbidity should be identified, and if possible corrected during the preoperative assessment of these patients. The aim of this study was to identify prognostic parameters for postoperative morbidity, mortality, and survival in patients with LARC or LRRC undergoing pelvic exenteration surgery.

Methods

Patients

For this retrospective cohort study, patients with LARC or LRCC, who underwent curative TPE or PPE between January 2003 and December 2018 at a tertiary referral centre in the Netherlands, were identified from a prospectively maintained database. Patient information was extracted retrospectively from medical records. Survival data were retrieved from the municipal register.

All patients with LARC or LRRC were discussed in a multidisciplinary tumour board meeting for advanced colorectal cancers comprising dedicated surgical, medical, and radiation oncologists and radiologists. LARC was defined as rectal adenocarcinoma diagnosed as cT4, with mesorectal fascia involvement, N2 disease and/or suspicious extramesorectal lymph nodes, based on MRI. LRRC was defined as recurrent rectal cancer within the pelvis, diagnosed either by MRI or histology. Patients were referred to a dietitian if suspected of having malnutrition, at the discretion of the treating physician. Neoadjuvant therapy usually consisted of long-course radiation therapy (either 25×2 Gy for LARC and LRRC, or 15×2 Gy for LRRC if previously irradiated) with concomitant capecitabine (1500 mg twice daily). Tumours were restaged by CT of the thorax and abdomen and MRI of the pelvis 2 months after the last treatment. Surgery was planned when curative treatment was still deemed feasible (resectable tumour and no extensive distant metastases). All patients included in this study were treated surgically and followed up in the Erasmus MC Cancer Institute. TPE was defined as complete resection of the rectum (with or without anal canal), bladder and (partial) posterior vaginal wall, uterus, and adnexa (in women) or the prostate and seminal vesicles (in men). PPE was defined as a resection of the rectum, posterior vaginal wall, uterus, and adnexa without removal of the bladder.

The study was approved by the Erasmus MC local medical ethics committee (MEC 2020–0104).

Variables and measurements

Data collected included: demographics (age, sex), treatment, and disease characteristics. BMI was divided into low (below 20 kg/m^2), normal (20–25 kg/m^2), and high BMI (over 25 kg/m^2). Weight loss was expressed as a percentage by calculating the difference between the patient's weight before NACRT and before surgery $(((\text{weight}_{NACRT} - \text{weight}_{surgery})/\text{weight}_{NACRT}) \times 100$ per cent) and was categorized into weight loss of at least 5 per cent, or less than 5 per cent weight loss (or muscle gain). Nutritional status before surgery was assessed using the Malnutrition Universal Screening Tool (MUST). This tool was used to identify adults who were malnourished or at risk of malnutrition based on three determinants from patients' records: unplanned weight loss, BMI, and absence of nutritional intake for more than 5 days[27]. Risk of malnutrition according to the MUST was categorized into three groups: score 0 (no risk), 1 (medium risk) and 2 or more (high risk). The Charlson Co-morbidity Index (CCI) score was calculated and categorized by using the 75th percentile as cut-off point. Albumin levels were determined after chemoradiation. Hypoalbuminaemia was defined by a serum albumin level below 35 g/l. The severity of complications was graded according to the Clavien–Dindo classification[28].

Body composition measurement

Body composition was estimated by three muscle-related variables: skeletal muscle mass, muscle wasting, and skeletal muscle density (SMD); these were obtained from routine abdominal CT before and after radiation therapy. Low skeletal muscle mass was defined as a low skeletal muscle index (SMI) using sex-specific cut-off points as described previously in a large population of patients with non-metastatic colorectal cancer[29].The SMI was estimated by measuring the total cross-sectional skeletal muscle area at the level of the third lumbar vertebra (L3) on CT images with a program developed in house (FatSeg) and was adjusted for body height[30]. Muscle loss was expressed by calculating the difference between the SMI before NACRT and the SMI before surgery $(((\text{SMI}_{NACRT} - \text{SMI}_{surgery})/\text{SMI}_{NACRT}) \times 100$ per cent). Muscle wasting was defined as that above the 75th percentile of muscle loss compared with the other patients in this study. SMD was expressed in terms of average Hounsfield units (HU) within the measured skeletal muscle mass. Low SMD was defined using HU cut-off points[22], as shown in *Fig. 1*.

Outcomes of interest

The primary outcome of interest was complications with a Clavien–Dindo grade of III or higher within 30 days after surgery. The secondary outcome was overall survival.

Statistical analysis

Continuous data are reported as median (i.q.r.) and categorical data as count (percentage). The Mann–Whitney U test was used
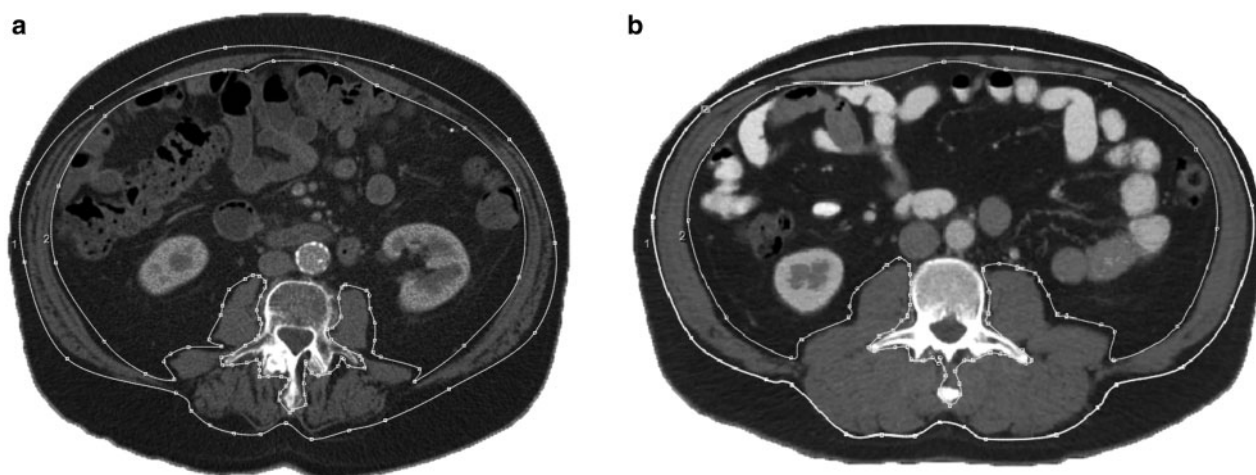

Fig. 1 Examples of abdominal CT images at the level of the third lumbar vertebra from patients with different types of body composition.
a Low skeletal mass and density and **b** normal skeletal mass and density.

for comparison of continuous data, and the χ^2 test for categorical data. Logistic regression analyses were carried out to identify possible risk factors for major complications. Univariable analyses were performed of the individual variables. Age, sex, and variables with a significance level of $P < 0.100$ were included in multivariable analysis. BMI and weight loss were not included in the multivariable analysis because these variables were already determinants of the MUST. Overall survival was calculated from the date of surgery until the date of last follow-up or death. It was estimated using the Kaplan–Meier method and compared by means of the log rank test. Adjusted risk factors for overall survival were calculated using multivariable Cox proportional hazards analysis. Variables with $P < 0.100$ in univariable analysis were included in the multivariable analysis. The level of statistical significance was set at $P < 0.050$. Statistical analyses were carried out using SPSS® version 25.0.0.1 (IBM, Armonk, NY, USA) and R version 4.0.2 (R Project for Statistical Computing, Vienna, Austria).

Results

In total, 227 patients were included. Baseline characteristics are summarized in *Table 1*. Patients lost a median of 1.5 (i.q.r. −5 to 0.2) kg of total bodyweight, and a median of 0.48 (−5.82 to 3.88) per cent of skeletal muscle mass, during neoadjuvant treatment. Muscle wasting was present in 38 patients with more than 5.8 per cent skeletal muscle mass loss (above 75th percentile). A total of 58 patients were referred to a dietitian. The MUST was used in 208 patients, of whom 32 (15.4 per cent) had a MUST score of 2 or higher. Of the patients with a MUST score of at least 2, 15 (47 per cent) were referred to a dietitian. Major complications were more prevalent in patients with a MUST score of 2 or higher than in patients with a score below 2 (26 *versus* 9 per cent; $P = 0.004$).

Postoperative complications

In total, 171 patients (75.3 per cent) developed complications, of whom 89 (39.2 per cent) had minor complications (grade I–II). Eighty-

Table 1 Baseline characteristics of patients according to Clavien–Dindo grade of complications

	Total (*n* = 227)	Grade < III (*n* = 145)	Grade ≥ III (*n* = 82)	P†
Sex				0.180
M	92 (41)	54 (37)	38 (46)	
F	135 (60)	91 (63)	44 (54)	
Age (years)*	64 (55–71)	64 (56–71)	65 (55–70)	0.740
< 70	154 (68)	95 (66)	59 (72)	0.319
≥ 70	73 (32)	50 (35)	23 (28)	
ASA fitness grade				0.753
I	51 (25)	32 (24)	19 (26)	
II	124 (61)	78 (60)	46 (62)	
III	30 (15)	21 (16)	9 (12)	
BMI (kg/m^2)				0.059
Low (< 20)	31 (14)	16 (11)	15 (19)	
Normal (20–25)	91 (41)	60 (42)	31 (39)	
High (> 25)	100 (45)	66 (46)	34 (43)	
Weight loss (%)				0.065
< 5	149 (73)	101 (79)	48 (64)	
5–10	33 (16)	16 (13)	17 (23)	
> 10	21 (10)	11 (9)	10 (13)	
MUST score				0.004
Low risk (0)	139 (67)	96 (73)	43 (57)	
Medium risk (1)	37 (18)	24 (18)	13 (17)	
High risk (≥ 2)	32 (15)	12 (9)	20 (26)	
Charlson Co-morbidity Index score				0.397
< 5	168 (74)	110 (76)	58 (71)	
≥ 5	59 (26)	35 (24)	24 (29)	
Hypoalbuminaemia	31 (22)	18 (21)	13 (25)	0.621
Skeletal muscle mass				0.331
Normal	71 (36)	49 (39)	22 (32)	
Low	124 (64)	77 (61)	47 (68)	
Muscle wasting	38 (25)	25 (26)	13 (24)	0.845
Skeletal muscle density				0.286
Normal	83 (43)	58 (46)	26 (38)	
Low	111 (57)	68 (54)	43 (62)	
Neoadjuvant therapy				0.266
None	10 (4)	6 (4)	4 (5)	
Chemoradiation	171 (75)	109 (75)	62 (76)	
Radiotherapy alone	44 (19)	30 (21)	14 (17)	
Chemotherapy alone	2 (1)	0 (0)	2 (2)	
Tumour type				0.061
LARC	148 (65)	101 (70)	47 (57)	
LRRC	79 (35)	44 (30)	35 (43)	
Distant metastasis at presentation	35 (15)	23 (16)	12 (15)	0.806
Pelvic exenteration				0.103
Posterior	116 (51)	80 (55)	36 (44)	
Total	111 (49)	65 (45)	46 (56)	
(Lympho)vascular invasion	39 (19)	22 (25)	17 (14)	0.200
Radical resection (R0)	179 (79)	121 (83)	58 (71)	0.024

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). Percentages may not total 100 due to rounding. MUST, Malnutrition Universal Screening Tool; LARC, locally advanced rectal cancer; LRRC, locally recurrent rectal cancer. †χ^2 test, except Mann–Whitney *U* test.

two patients (36.1 per cent) had major complications (grade III or higher), of whom 11 (4.8 per cent) died within 30 days of surgery (grade V). Fifty-eight patients (25.6 per cent) were readmitted within 90 days and five (9 per cent) died during readmission . The results of logistic regression analyses are shown in *Table 2*. Low BMI (odds ratio (OR) 2.11, 95 per cent c.i. 0.96 to 4.64), weight loss of 5–10 per cent (OR 2.24, 1.04 to 4.80), MUST score at least 2 (OR 3.72, 1.67 to 8.29) and LRRC (*versus* LARC) (OR 1.71, 0.97 to 3.00) were associated with major complications in univariable analysis . In multivariable logistic regression analysis, only MUST score at least 2 was associated with major complications (OR 3.99, 1.76 to 9.02).

Overall survival

Mean follow-up was 44.6 months. Median overall survival after exenteration for all included patients was 51.3 (95 per cent c.i. 42.4 to 70.0) months. Patients with low SMD had impaired overall survival compared with those with normal SMD (5-year overall survival rates 37 and 53 per cent; P = 0.045). The outcomes of the Cox proportional hazards analysis are shown in *Table 3*. Independent risk factors for impaired overall survival were LRRC (*versus* LARC) (hazard ratio (HR) 1.61, 95 per cent c.i. 1.04 to 2.48) and lymphovascular invasion (HR 2.20, 1.38 to 3.51). Overall survival curves for patients with LARC *versus* those with LRRC, and among patients with or without lymphovascular invasion are depicted in *Fig. 2*. No significant association was found between age, low SMD or distant metastasis at presentation and survival in multivariable analysis.

Discussion

In this retrospective cohort study, 82 patients (36 per cent) with LARC or LRRC undergoing exenteration surgery developed major complications. Nutritional status by MUST was a strong predictor of major complications. Patients with a high preoperative risk of malnutrition (MUST score at least 2) had a fourfold increased risk of developing major complications compared with patients with a low or medium risk of malnutrition. LRRC and lymphovascular invasion are widely accepted as poor prognostic factors[31–33] and were the only two independent prognostic factors for impaired survival in this cohort.

The major complication rates after pelvic exenteration in this study are in line with those of previous studies[10–16], which reported 30-day major morbidity and mortality rates of 25–44 per cent and 0–25 per cent respectively, and are considerably higher than those of non-exenterative colorectal cancer surgery[17]. The MUST score has been established as a predictor of impaired outcome in colorectal cancer surgery[34], but has not been investigated in patients undergoing pelvic exenteration. Morbidity was more common in patients with higher MUST scores, but this did not seem to influence survival. The finding that BMI was not a predictor of major complications was consistent with previous results in colorectal cancer surgery[35]. Although TPE is technically a more extensive procedure than PPE, it was not associated with more major complications. Furthermore, major complications were not significantly more common in patients with LRRC, even though these patients had undergone oncological treatment previously. This finding appears to be in line with a larger series describing similar complication rates in patients with LARC or LRRC undergoing pelvic exenteration[36].

Of the body composition variables investigated, patients with low SMD had impaired overall survival compared with those with normal SMD; however, SMD was not independently associated with survival in the multivariable analysis. Muscle wasting,

Table 2 Univariable and multivariable logistic regression analyses for major complications (grade III or higher)

	Univariable analysis		Multivariable analysis*	
	Odds ratio	P	Odds ratio	P
Sex				
M	1.00 (reference)		1.00 (reference)	
F	0.69 (0.40, 1.19)	0.181	0.81 (0.44, 1.47)	0.481
Age (per year)	1.00 (0.98, 1.02)	0.889	1.00 (0.97, 1.02)	0.790
BMI (kg/m²)	2.11 (0.96, 4.64)	0.063	–†	
Normal (20–25)	1.00 (reference)			
Low (< 20)	1.81 (0.79, 4.17)	0.158		
High (> 25)	1.00 (0.55, 1.82)	0.992		
Weight loss (%)				
< 5	1.00 (reference)		–†	
5–10	2.24 (1.04, 4.80)	0.039		
> 10	1.91 (0.76, 4.81)	0.168		
MUST score				
Low risk (0)	1.00 (reference)		1.00 (reference)	
Medium risk (1)	1.21 (0.56, 2.60)	0.626	1.22 (0.56, 2.63)	0.618
High risk (≥ 2)	3.72 (1.67, 8.29)	0.001	3.99 (1.76, 9.02)	0.001
Charlson Co-morbidity Index score ≥ 5	1.30 (0.71, 2.39)	0.398		
Hypoalbuminaemia	1.23 (0.54, 2.77)	0.621		
Low skeletal muscle mass	1.36 (0.73, 2.53)	0.332		
Muscle wasting	0.93 (0.43, 2.00)	0.845		
Low skeletal muscle density	1.39 (0.76, 2.53)	0.287		
Tumour type				
LARC	1.00 (reference)		1.00 (reference)	
LRRC	1.71 (0.97, 3.00)	0.062	1.58 (0.85, 2.95)	0.148
Pelvic exenteration				
Posterior	1.00 (reference)			
Total	1.57 (0.91, 2.72)	0.104		

Values in parentheses are 95 per cent confidence intervals. *Nineteen patients with missing values were not included in multivariable analyses. †Already included in the Malnutrition Universal Screening Tool (MUST). LARC, locally advanced rectal cancer; LRRC, locally recurrent rectal cancer.

Table 3 Univariable and multivariable Cox proportional hazard analysis for overall survival

	Univariable analysis		Multivariable analysis	
	Hazard ratio	P	Hazard ratio	P
Female sex	0.82 (0.58, 1.18)	0.285		
Age per year	1.02 (1.00, 1.04)	0.022	1.02 (1.00, 1.04)	0.142
MUST score ≥ 2	1.30 (0.81, 2.08)	0.277		
Low skeletal muscle mass	1.29 (0.86, 1.94)	0.217		
Muscle wasting	1.40 (0.87, 2.24)	0.169		
Low skeletal muscle density	1.49 (1.00, 2.20)	0.050	1.36 (0.88, 2.12)	0.172
LRRC (*versus* LARC)	1.70 (1.18, 2.45)	0.004	1.61 (1.04, 2.48)	0.032
Distant metastasis at presentation	2.00 (1.26, 3.17)	0.003	1.43 (0.81, 2.52)	0.213
Lymphovascular invasion	2.47 (1.61, 3.79)	< 0.001	2.20 (1.38, 3.51)	0.001
Radical resection	0.80 (0.53, 1.21)	0.289		

Values in parentheses are 95 per cent confidence intervals. *Fifty-two patients with missing values were not included in multivariable analyses. MUST, Malnutrition Universal Screening Tool; LARC, locally advanced rectal cancer; LRRC, locally recurrent rectal cancer.
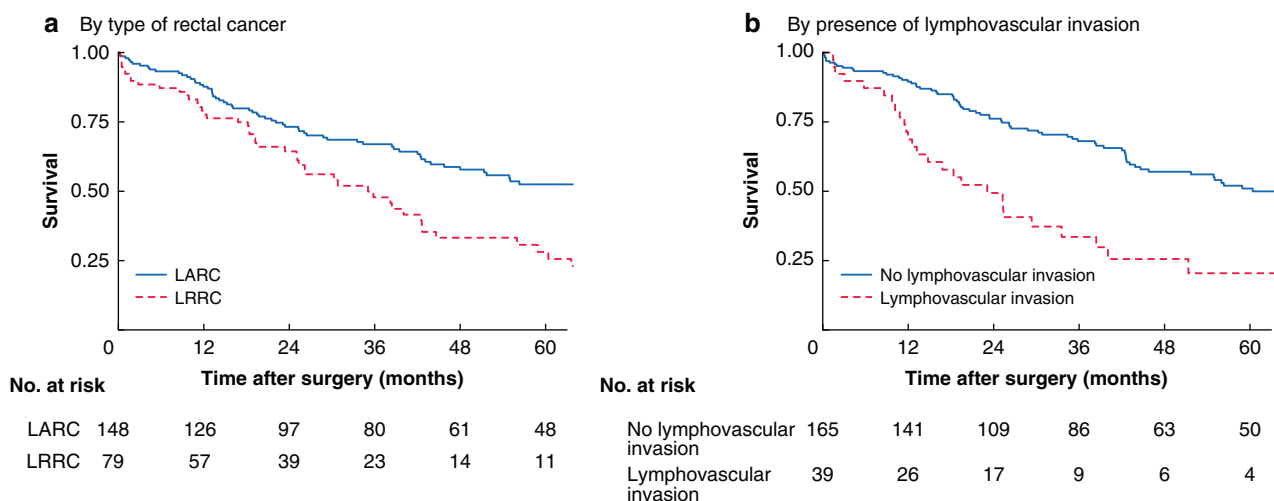

Fig. 2 Overall survival according to type of rectal cancer and presence of lymphovascular invasion

a Patients with locally advanced rectal cancer (LARC) *versus* locally recurrent (LRRC) rectal cancer and **b** patients with or without lymphovascular invasion. **a** P = 0.003, **b** P < 0.001 (log rank test).

which has been associated with disease-free survival but not with overall survival in patients with LARC undergoing neoadjuvant treatment[37], was neither associated with major complications nor overall survival in the present study. Sex, age, weight loss, CCI score, hypoalbuminaemia, distant metastasis at presentation, and radical resection were not predictive factors for morbidity and survival, but have been described in larger studies including patients with colorectal disease[10,11,14,21,24,38,39].

This study has several limitations. First, it was a retrospective analysis with a selected group of patients from a single centre. Its retrospective nature meant that there was information missing in some patient records (such as CT, serum level of albumin, and weight loss). Serum albumin was not determined routinely at a single fixed time before surgery, which resulted in a wide time variation. Some potential confounders could not be corrected for, including preoperative dietitian involvement and nutritional support. Low skeletal muscle mass was estimated based on radiological muscle quality and quantity only, and was not confirmed or further investigated by, for example, determination of muscle strength or physical performance[40]. It should be noted that selection bias by eligibility screening for major pelvic surgery might have influenced the outcomes in this study. For example, elderly patients were treated only when considered exceptionally fit for their age, whereas younger patients with unfavourable tumour

characteristics might have been more readily considered as a candidate for exenteration surgery.

This study has provided important and useful insights for predicting complications and survival in patients with LARC and LRRC, and the future potential for preoperative optimization strategies, such as prehabilitation[41–46]. The present findings may contribute to a more accurate preoperative risk assessment in the future for patients with LARC or LRRC undergoing pelvic exenteration surgery. Further research is needed to determine whether preoperative intervention by a dietitian and nutritional support in patients with a high MUST score will diminish major complication rates in patients undergoing pelvic exenteration. Not even half of the patients in the present cohort with a high risk of malnutrition (47 per cent) had been referred to a dietitian for preoperative nutritional support. This may leave room for improvement taken that a high MUST score proved such a strong independent predictor of major complications this study. The MUST score is very easily applicable and repeatable in daily clinical practice, which is an advantage over measures such as body composition. A more accurate risk assessment may help optimize patients' physical status before surgery to improve postoperative outcomes by identifying potential targets for prehabilitation[34,38,47].

Prehabilitation is a process to enhance and optimize a patient's functional capacity before surgery. The programme

consists of a combination of optimizing nutrition, exercising, and restricting risk factors, usually in the setting of a multidisciplinary team of medical specialists, dietitians, and physiotherapists. There is growing evidence for improvement in postoperative outcomes in patients with colorectal cancer after administering a prehabilitation programme during neoadjuvant treatment[41–46]. A meta-analysis[46] found that even prehabilitation based on nutrition alone decreased the length of hospital stay by 2 days. The first international multicentre study[48] investigating multimodal prehabilitation for patients undergoing colorectal cancer surgery is ongoing.

This study has demonstrated that a high risk of malnutrition (MUST score 2 or higher) is a strong risk factor for major morbidity and mortality within 30 days after exenteration surgery in patients with LARC or LRRC. Prehabilitation with nutritional support for patients at high risk of malnutrition might improve perioperative outcomes, and identification of other prehabilitation targets merits further research.

Disclosure. The authors declare no conflict of interest.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;**68**:394–424.

2. Fitzmaurice C, Abate D, Abbasi N, Abbastabar H, Abd-Allah F, Abdel-Rahman O *et al.*; Global Burden of Disease Cancer Collaboration. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: a systematic analysis for the Global Burden of Disease Study. *JAMA Oncol* 2019;**5**:1749–1768.

3. de Neree Tot Babberich MPM, Vermeer NCA, Wouters M, van Grevenstein WMU, Peeters K, Dekker E *et al.*; Dutch ColoRectal Audit. Postoperative outcomes of screen-detected *vs* non-screen-detected colorectal cancer in the Netherlands. *JAMA Surg* 2018;**153**:e183567.

4. PelvEx Collaborative. Surgical and survival outcomes following pelvic exenteration for locally advanced primary rectal cancer: results from an international collaboration. *Ann Surg* 2019;**269**: 315–321.

5. Ikoma N, You YN, Bednarski BK, Rodriguez-Bigas MA, Eng C, Das P *et al.* Impact of recurrence and salvage surgery on survival after multidisciplinary treatment of rectal cancer. *J Clin Oncol* 2017;**35**:2631–2638.

6. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T *et al.* Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001;**345**:638–646.

7. Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S *et al.* Preoperative radiotherapy *versus* selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *Lancet* 2009;**373**:811–820.

8. Gosens MJ, Klaassen RA, Tan-Go I, Rutten HJ, Martijn H, van den Brule AJ *et al.* Circumferential margin involvement is the crucial prognostic factor after multimodality treatment in patients with locally advanced rectal carcinoma. *Clin Cancer Res* 2007;**13**: 6617–6623.

9. Adam IJ, Mohamdee MO, Martin IG, Scott N, Finan PJ, Johnston D *et al.* Role of circumferential margin involvement in the local recurrence of rectal cancer. *Lancet* 1994;**344**:707–711.

10. Ferenschild FT, Vermaas M, Verhoef C, Ansink AC, Kirkels WJ, Eggermont AM *et al.* Total pelvic exenteration for primary and recurrent malignancies. *World J Surg* 2009;**33**:1502–1508.

11. Hagemans JAW, Rothbarth J, Kirkels WJ, Boormans JL, van Meerten E, Nuyttens J *et al.* Total pelvic exenteration for locally advanced and locally recurrent rectal cancer in the elderly. *Eur J Surg Oncol* 2018;**44**:1548–1554.

12. Nielsen MB, Rasmussen PC, Lindegaard JC, Laurberg S. A 10-year experience of total pelvic exenteration for primary advanced and locally recurrent rectal cancer based on a prospective database. *Colorectal Dis* 2012;**14**:1076–1083.

13. Platt E, Dovell G, Smolarek S. Systematic review of outcomes following pelvic exenteration for the treatment of primary and recurrent locally advanced rectal cancer. *Tech Coloproctol* 2018;**22**: 835–845.

14. Vermaas M, Ferenschild FT, Verhoef C, Nuyttens JJ, Marinelli AW, Wiggers T *et al.* Total pelvic exenteration for primary locally advanced and locally recurrent rectal cancer. *Eur J Surg Oncol* 2007;**33**:452–458.

15. Yamada K, Ishizawa T, Niwa K, Chuman Y, Aikou T. Pelvic exenteration and sacral resection for locally advanced primary and recurrent rectal cancer. *Dis Colon Rectum* 2002;**45**:1078–1084.

16. Yang TX, Morris DL, Chua TC. Pelvic exenteration for rectal cancer: a systematic review. *Dis Colon Rectum* 2013;**56**:519–531.

17. Staib L, Link KH, Blatz A, Beger HG. Surgery of colorectal cancer: surgical morbidity and five- and ten-year results in 2400 patients—monoinstitutional experience. *World J Surg* 2002;**26**: 59–66.

18. van Vugt JL, Braam HJ, van Oudheusden TR, Vestering A, Bollen TL, Wiezer MJ *et al.* Skeletal muscle depletion is associated with severe postoperative complications in patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis of colorectal cancer. *Ann Surg Oncol* 2015;**22**:3625–3631.

19. Levolger S, van Vugt JL, de Bruin RW, Ij JN. Systematic review of sarcopenia in patients operated on for gastrointestinal and hepatopancreatobiliary malignancies. *Br J Surg* 2015;**102**:1448–1458.

20. Miyamoto Y, Baba Y, Sakamoto Y, Ohuchi M, Tokunaga R, Kurashige J *et al.* Sarcopenia is a negative prognostic factor after curative resection of colorectal cancer. *Ann Surg Oncol* 2015;**22**: 2663–2668.

21. Reisinger KW, van Vugt JL, Tegels JJ, Snijders C, Hulsewé KW, Hoofwijk AG *et al.* Functional compromise reflected by sarcopenia, frailty, and nutritional depletion predicts adverse postoperative outcome after colorectal cancer surgery. *Ann Surg* 2015; **261**:345–352.

22. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ *et al.* Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol* 2013;**31**:1539–1547.

23. Dolan DR, Knight KA, Maguire S, Moug SJ. The relationship between sarcopenia and survival at 1 year in patients having elective colorectal cancer surgery. *Tech Coloproctol* 2019;**23**:877–885.

24. Lai CC, You JF, Yeh CY, Chen JS, Tang R, Wang JY *et al.* Low preoperative serum albumin in colon cancer: a risk factor for poor outcome. *Int J Colorectal Dis* 2011;**26**:473–481.

25. Sasaki M, Miyoshi N, Fujino S, Ogino T, Takahashi H, Uemura M *et al.* The Geriatric Nutritional Risk Index predicts postoperative complications and prognosis in elderly patients with colorectal cancer after curative surgery. *Sci Rep* 2020;**10**:10744.

26. Takagi K, Buettner S, Ijzermans JNM. Prognostic significance of the controlling nutritional status (CONUT) score in patients

with colorectal cancer: a systematic review and meta-analysis. *Int J Surg* 2020;**78**:91–96.

27. Elia M; British Association for Parenteral and Enteral Nutrition. *The 'MUST' Report: Nutritional Screening of Adults: a Multidisciplinary Responsibility: development and Use of the 'Malnutrition Universal Screening Tool' ('MUST') for Adults*. Redditch: BAPEN, 2003.

28. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;**240**: 205–213.

29. Caan BJ, Meyerhardt JA, Kroenke CH, Alexeeff S, Xiao J, Weltzien E *et al.* Explaining the obesity paradox: the association between body composition and colorectal cancer survival (C-SCANS Study). *Cancer Epidemiol Biomarkers Prev* 2017;**26**:1008–1015.

30. van Vugt JL, Levolger S, Gharbharan A, Koek M, Niessen WJ, Burger JW *et al.* A comparative study of software programmes for cross-sectional skeletal muscle and adipose tissue measurements on abdominal computed tomography scans of rectal cancer patients. *J Cachexia Sarcopenia Muscle* 2017;**8**:285–297.

31. Weiser MR. AJCC 8th edition: colorectal cancer. *Ann Surg Oncol* 2018;**25**:1454–1455.

32. Sun Q, Liu T, Liu P, Luo J, Zhang N, Lu K *et al.* Perineural and lymphovascular invasion predicts for poor prognosis in locally advanced rectal cancer after neoadjuvant chemoradiotherapy and surgery. *J Cancer* 2019;**10**:2243–2249.

33. Hogan J, Chang KH, Duff G, Samaha G, Kelly N, Burton M *et al.* Lymphovascular invasion: a comprehensive appraisal in colon and rectal adenocarcinoma. *Dis Colon Rectum* 2015;**58**:547–555.

34. Almasaudi AS, McSorley ST, Dolan RD, Edwards CA, McMillan DC. The relation between Malnutrition Universal Screening Tool (MUST), computed tomography-derived body composition, systemic inflammation, and clinical outcomes in patients undergoing surgery for colorectal cancer. *Am J Clin Nutr* 2019;**110**: 1327–1334.

35. van Vugt JL, Cakir H, Kornmann VN, Doodeman HJ, Stoot JH, Boerma D *et al.* The new body mass index as a predictor of postoperative complications in elective colorectal cancer surgery. *Clin Nutr* 2015;**34**:700–704.

36. PelvEx Collaborative. Changing outcomes following pelvic exenteration for locally advanced and recurrent rectal cancer. *BJS Open* 2019;**3**:516–520.

37. Levolger S, van Vledder MG, Alberda WJ, Verhoef C, de Bruin RWF, Ij JNM *et al.* Muscle wasting and survival following preoperative chemoradiotherapy for locally advanced rectal carcinoma. *Clin Nutr* 2018;**37**:1728–1735.

38. Ouellette JR, Small DG, Termuhlen PM. Evaluation of Charlson–Age Comorbidity Index as predictor of morbidity and mortality in patients with colorectal carcinoma. *J Gastrointest Surg* 2004;**8**: 1061–1067.

39. Alves A, Panis Y, Mathieu P, Mantion G, Kwiatkowski F, Slim K; Association Française de Chirurgie. Postoperative mortality and morbidity in French patients undergoing colorectal surgery: results of a prospective multicenter study. *Arch Surg* 2005;**140**: 278–283.

40. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T *et al.*; Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2019;**48**:16–31.

41. Mayo NE, Feldman L, Scott S, Zavorsky G, Kim DJ, Charlebois P *et al.* Impact of preoperative change in physical function on post-operative recovery: argument supporting prehabilitation for colorectal surgery. *Surgery* 2011;**150**:505–514.

42. Berkel AEM, Bongers BC, Kotte H, Weltevreden P, de Jongh FHC, Eijsvogel MMM *et al.* Effects of community-based exercise prehabilitation for patients scheduled for colorectal surgery with high risk for postoperative complications: results of a randomized clinical trial. *Ann Surg* 2021;Online ahead of print.

43. Heldens AF, Bongers BC, de Vos-Geelen J, van Meeteren NL, Lenssen AF. Feasibility and preliminary effectiveness of a physical exercise training program during neoadjuvant chemoradiotherapy in individual patients with rectal cancer prior to major elective surgery. *Eur J Surg Oncol* 2016;**42**:1322–1330.

44. Loughney L, West MA, Kemp GJ, Rossiter HB, Burke SM, Cox T *et al.* The effects of neoadjuvant chemoradiotherapy and an in-hospital exercise training programme on physical fitness and quality of life in locally advanced rectal cancer patients (the EMPOWER Trial): study protocol for a randomised controlled trial. *Trials* 2016;**17**:24.

45. Moug SJ, Barry SJE, Maguire S, Johns N, Dolan D, Steele RJC *et al.* Does prehabilitation modify muscle mass in patients with rectal cancer undergoing neoadjuvant therapy? A subanalysis from the REx randomised controlled trial. *Tech Coloproctol* 2020;**24**: 959–964.

46. Gillis C, Buhler K, Bresee L, Carli F, Gramlich L, Culos-Reed N *et al.* Effects of nutritional prehabilitation, with and without exercise, on outcomes of patients who undergo colorectal surgery: a systematic review and meta-analysis. *Gastroenterology* 2018;**155**: 391.e4–410.e4.

47. Margadant CC, Bruns ER, Sloothaak DA, van Duijvendijk P, van Raamt AF, van der Zaag HJ *et al.* Lower muscle density is associated with major postoperative complications in older patients after surgery for colorectal cancer. *Eur J Surg Oncol* 2016;**42**: 1654–1659.

48. van Rooijen S, Carli F, Dalton S, Thomas G, Bojesen R, Le Guen M *et al.* Multimodal prehabilitation in colorectal cancer patients to improve functional capacity and reduce postoperative complications: the first international randomized controlled trial for multimodal prehabilitation. *BMC Cancer* 2019;**19**:98.