Nomogram to predict disease recurrence in patients with locally advanced rectal cancer undergoing rectal surgery after neoadjuvant therapy: retrospective cohort study

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Abstract

Introduction: Prognostic models can be used for predicting survival outcomes and guiding patient management. TNM staging alone is insufficient for predicting recurrence after chemoradiotherapy (CRT) and surgery for locally advanced rectal cancer. This study aimed to develop a nomogram to better predict cancer recurrence after CRT followed by total mesorectal excision (TME) and tailor postoperative management and follow-up.

Materials and Methods: Between 2002 and 2019, data were retrospectively collected on patients with rectal adenocarcinoma. Data on sex, age, carcinoembryonic antigen (CEA) level, tumour location, induction chemotherapy, adjuvant chemotherapy, tumour downsizing, perineural invasion, lymphovascular invasion, pathological stage, resection margins (R0 versus R1), and pelvic septic complications were analysed. The variables significantly associated with cancer recurrence were used to build a nomogram that was validated in both the training and validation cohorts. Model performance was evaluated by receiver operating characteristic curve and area under the curve (AUC) analyses.

Results: After applying exclusion criteria, 634 patients with rectal adenocarcinoma were included in this study. Eight factors (CEA level, adjuvant chemotherapy, tumour downsizing, perineural invasion, lymphovascular invasion, pathological stage, resection margins (R0 versus R1), and pelvic septic complications) were identified as nomogram variables. Our nomogram showed good performance with an AUC of 0.74 and 0.75 in the training and validation cohorts respectively.

Conclusion: Our nomogram is a simple tool for predicting cancer recurrence in patients with locally advanced rectal cancer after neoadjuvant CRT followed by TME. It provides an individual risk prediction of recurrence to tailor surveillance.

Introduction

Colorectal cancer ranks third in incidence and second in terms of cancer-related mortality worldwide. With the introduction of total mesorectal excision (TME) and neoadjuvant chemoradiotherapy (CRT), 5-year local recurrence (LR) rates have decreased from 25 per cent to 5–10 per cent. The primary cause of LR is the involvement of the circumferential resection margin (CRM). Other factors include anastomotic leakage (AL), abdominoperineal excision (APE), nodal positivity, advanced T category, lymphovascular invasion, perineural invasion, and poor differentiation; however, it is still difficult to predict LR, and its prognosis remains poor. The overall 5-year survival rate is 15 per cent, owing to difficulties in early diagnosis and surgical treatment. LR is most often diagnosed following patients experiencing worsening symptoms linked to advanced disease. Achieving R0 resection is the main independent prognostic factor, which can be challenging in this patient group.

Early detection of LR before symptom development increases the R0 resection rate and enhances prognosis which could be achieved by identifying high-risk patients earlier through enhanced surveillance.

With improvements in locoregional control, the leading cause of death in patients with locally advanced rectal cancer (LARC) is now distant metastasis (DM), raising the question of the importance of systemic therapy. Presently, adjuvant chemotherapy is recommended in node-positive (N+) patients after CRT and TME; however, its value remains debated as no benefit has been proven for disease-related outcomes in these patients, possibly because of low compliance in dedicated studies.

Recently, randomized clinical trials (RCTs) have reported significant improvement in distant metastases and survival rates in patients with LARC using a ‘total neoadjuvant therapy’ (TNT) approach, which consists of intensifying preoperative treatment with a combination of radiotherapy or chemoradiotherapy and systemic chemotherapy. This strategy has become the
standard treatment for LARC; however, the impact of postoperative chemotherapy remains unclear. Although systematically planned in the study protocol, compliance with postoperative chemotherapy is limited. Non-administration of this chemotherapy was linked to a medical decision in two-thirds of cases. This reflects current practices regarding the personalization of treatments according to the consensus of the multidisciplinary team and not only according to the TNM staging system, which does not consider certain radiological and pathological factors or the preoperative treatment response.

Given the importance of risk stratification and prognosis prediction, a stable and easily computable prediction model is needed for clinical applications to help clinicians make postoperative medical decisions as a step toward enhanced personalized treatment of rectal cancer. This study aimed to develop a nomogram that could accurately predict the probability of recurrence after CRT and TME for patients with LARC.

**Methods**

**Patient population**

Between January 2002 and June 2019, we evaluated all consecutive patients who underwent curative surgery for LARC after CRT at our department (Paoli-Calmettes Institute, Marseille, France). Exclusion criteria were as follows: the presence of concomitant cancer, previous pelvic irradiation, emergency surgery, local excision, or synchronous metastases.

**Ethical statement**

This study was conducted in accordance with the most recent version of the Declaration of Helsinki, and the study protocol was approved by the Institutional Ethics Committee of the Paoli-Calmettes Institute (IPC 2021-084).

**Preoperative assessment**

The pre- and post-therapeutic evaluations included a digital rectal examination, thoracoabdominal and pelvic CT, serum carcinoembryonic antigen (CEA) measurement, pelvic MRI, and endoscopic ultrasound.

**Neoadjuvant therapy**

In our department, preoperative CRT is indicated for patients with T3 and/or N+ adenocarcinomas of the lower and middle rectum, as well as for those with ultra-low T2 tumours. Our standard CRT protocol consists of a total dose of 50 Gy, with a daily dose of 2 Gy combined with capecitabine 800 mg/m² administered twice daily on each day of radiotherapy.

Since 2010, patients with a predicted threatened CRM (1 mm or less) on MRI received induction chemotherapy (FOLFIRINOX: leucovorin calcium, fluorouracil, irinotecan hydrochloride, and oxaliplatin, four cycles) before CRT.

**Rectal surgery**

Rectal surgery consisted of TME with a minimum 1 cm distal margin and was performed 8–10 weeks at the end of CRT. A transanal approach with standardized endoanal dissection was used for low rectal tumours. For lesions more than 3 cm from the anorectal junction, mechanical trans-sutural anastomosis was performed. A colonic J pouch anal or side-to-end anastomosis was preferred over a straight anastomosis, with a covering defunctioning loop ileostomy.

Extra-levator APE was performed in cases of levator or external anal sphincter involvement after CRT.

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**Fig. 1 Flow chart**

CRT, chemoradiotherapy.
Histological analysis
The tumour stage was assessed using the eighth edition of the UICC/AJCC staging system. A negative margin was defined as clear circumferential and longitudinal margins (at least 1 mm).

Adjuvant therapy
The strategy was decided upon at a multidisciplinary team meeting. According to the reference, patients with positive lymph nodes (stage 3) were indicated for adjuvant chemotherapy (LV5FU2 or FOLFOX). Some patients with initial lymph node involvement and negative lymph nodes in the specimen also received postoperative chemotherapy.

Follow-up
Patients were followed up every 3 months for the first 2 years and every 6 months for the next 3 years through clinical examination and thoracoabdominal CT and evaluation of CEA levels. An annual follow-up was then proposed until the 10th year or until death.

Primary endpoint
Recurrence was defined as the presence of a radiologically and biopsy-proven tumour. LR was defined as a tumour within the pelvis (including the perineal wound) and the site of anastomosis, and DM was defined as the evidence of a tumour outside these areas.

Time to recurrence was defined by the interval between the surgery and the date of recurrence (local or metastatic).

Risk stratification
To improve the clinical impact of this study, we defined three levels of risk of recurrence. In the absence of a precise staging of the recurrence risk for patients with rectal cancer, we based the risk stratification by extrapolating from colonic cancer. As patients with stage 2 and 3 colonic cancer have an estimated 5-year recurrence risk of 30 per cent and 55 per cent respectively, we categorized patients into high-risk (estimated risk of 55 per cent or higher), intermediate (estimated risk between 30 per cent and 55 per cent) and low-risk groups (estimated risk of less than 30 per cent) based on nomogram scores.

Data collection
Data on patient and tumour characteristics, treatment details, and oncological outcomes were collected from a retrospective database.

Table 1 Clinical and surgical characteristics of locally advanced rectal cancer patients after chemoradiotherapy followed by surgery

| Variable                                           | All patients (n = 634) | No recurrence (n = 462) | Recurrence (n = 172) | P     |
|----------------------------------------------------|-----------------------|------------------------|----------------------|-------|
| Sex ratio (M:F)                                     | 406 (64:228 (36)     | 296 (64:1):166 (35.9) | 110 (63.9):62 (36.1) | 0.999 |
| Age (years), median (range)                         | 64 (24–91)           | 64 (24–91)            | 63 (33–88)           | 0.720 |
| BMI (kg/m²), median (range)                         | 24.6 (14.8–45.0)     | 24.5 (14.8–40.6)      | 24.7 (15.1–45.0)     | 0.570 |
| Malnutrition                                       |                       |                        |                      |       |
| Yes                                                | 101 (15.9)           | 75 (16)                | 26 (15)              |       |
| No                                                 | 533 (84.1)           | 387 (84)              | 146 (85)             |       |
| Co-morbidities                                     |                       |                        |                      |       |
| Cardiovascular history                              | 82 (12.9)            | 64 (13.8)             | 18 (10.5)            | 0.260 |
| Diabetes mellitus                                  | 71 (11.1)            | 55 (12)               | 16 (9.3)             | 0.360 |
| Respiratory                                        | 59 (9.3)             | 47 (10)               | 12 (7)               | 0.220 |
| ASA score                                          |                       |                        |                      |       |
| 1–2                                                | 551 (86.9)           | 403 (87.2)            | 148 (86.1)           | 0.690 |
| 3                                                  | 83 (13.1)            | 59 (12.8)             | 24 (13.9)            |       |
| CEA level (mg/l)                                    |                       |                        |                      |       |
| <5                                                 | 460 (74.2)           | 360 (79.3)            | 100 (60.2)           | <0.001|
| ≥5                                                 | 160 (25.8)           | 94 (20.7)             | 66 (39.8)            |       |
| Missing data                                       | 14                    | 8                      | 6                    |       |
| Tumour location                                    |                       |                        |                      |       |
| Low                                                | 380 (59.9)           | 267 (57.8)            | 113 (65.7)           | 0.067 |
| Mid                                                | 254 (40.1)           | 195 (42.2)            | 59 (34.3)            |       |
| Distance from anal verge (mm), median (range)      | 50 (0–190)           | 55 (0–190)            | 50 (0–130)           | 0.004 |
| cT stage                                           |                       |                        |                      |       |
| 1–2                                                | 42 (6.6)             | 37 (8)                | 5 (2.9)              | 0.004 |
| 3–4                                                | 592 (93.4)           | 425 (92)              | 167 (97.1)           |       |
| Neoadjuvant chemotherapy                            | 71 (11.2)            | 51 (11)               | 20 (11.6)            | 0.830 |
| Interval between CRT and surgery (weeks), median (range) | 7 (1–46)         | 7 (1–25)              | 8 (1–46)             | 0.460 |
| Surgical approach                                  |                       |                        |                      |       |
| Open                                               | 95 (15)              | 61 (13.2)             | 34 (19.8)            | 0.198 |
| Laparoscopy                                        | 385 (60.7)           | 287 (62.1)            | 98 (57)              |       |
| Robotic                                            | 48 (7.6)             | 37 (8)                | 11 (6.4)             |       |
| TaTME                                              | 106 (16.7)           | 77 (16.7)             | 29 (16.8)            |       |
| Surgical procedure                                 |                       |                        |                      |       |
| LAR                                                | 508 (80.1)           | 387 (83.8)            | 121 (70.4)           | 0.003 |
| APE                                                | 126 (19.9)           | 75 (16.2)             | 51 (29.6)            |       |
| Pelvic infectious complication                      |                       |                        |                      | <0.001|
| No                                                 | 494 (77.9)           | 385 (83.3)            | 109 (63.4)           |       |
| Yes                                                | 140 (22.1)           | 77 (16.7)             | 63 (36.6)            |       |
| 90 days morbidity                                  |                       |                        |                      | 0.012 |
| Clavien 1–2                                       | 519 (81.9)           | 389 (84.2)            | 130 (75.6)           |       |
| Clavien 3–4                                       | 115 (18.1)           | 73 (15.8)             | 42 (24.4)            |       |

Values are n (%) unless otherwise indicated. CRT, chemoradiotherapy; TaTME, transanal total mesorectal excision; AR, anterior resection; APE, abdominoperineal excision, LAR, low anterior resection.
Malnutrition was defined as patients with a low bodyweight (BMI of less than 18.5 kg/m² in patients aged under 70 years and less than 21 kg/m² in patients aged more than 70 years and/or unintentional weight loss of 5 per cent or higher in 1 month or 10 per cent or higher in 6 months).

Postoperative complications were analysed and classified using the Clavien–Dindo classification. Postoperative pelvic infectious complications (PICs) were defined as AL, purulent drainage from the pelvic drain or surgical site, and/or pelvic abscess on imaging.

The present study complies with STROBE guidelines (Fig. S1).

Statistical analysis
Statistical analyses were performed using SAS® software version 9.4 (SAS Institute, Cary, NC, USA) and R version 4.2.0, at a significance level of \( \alpha = 0.05 \). Categorical variables are expressed as numbers and percentages, whereas continuous variables are expressed as median (minimum–maximum). In this study, each patient was randomly assigned to the training and validation cohorts at a 2:1 ratio. Patient characteristics were compared using the Fisher’s exact, chi-squared (categorical variables), or Wilcoxon’s test (quantitative endpoints), depending on the training/validation cohort and sample size. The training cohort was used to identify prognostic factors for rectal cancer recurrence using univariable logistic models. Significant variables in the univariable analysis were then included as independent covariates in a multivariable logistic regression model. ORs, with their two-sided Wald’s confidence intervals and tests for significance, were provided. An associated nomogram was built, and the validation cohort was used to assess the performance of the model. Calibration plots and Pearson’s goodness-of-fit tests were used to demonstrate the reliability of the multivariable model in the training and validation cohorts. Diagnostic performances were evaluated both in the training and validation cohorts using receiver operating characteristic (ROC) curves and area under the curve (AUC) (with their bilateral confidence intervals). The maximum value of AUC was 1.0, indicating a perfect classifier, whereas 0.5 indicated a random chance to correctly discriminate recurrence with the model. To determine correlations, Pearson’s simple correlation coefficient was used.

Results
Clinicopathological characteristics
Among the 779 patients with rectal adenocarcinoma who underwent surgery after CRT, 145 were excluded based on the exclusion criteria or due to missing data (Fig. 1).

Table 2 Oncological characteristics of locally advanced rectal cancer patients after chemoradiotherapy followed by surgery

| Variable                              | All patients (n = 634) | No recurrence (n = 462) | Recurrence (n = 172) | P     |
|---------------------------------------|------------------------|-------------------------|----------------------|-------|
| Tumour size (mm), median (range)      | 25 (0–170)             | 20 (0–120)              | 30 (0–170)           | <0.001|
| Missing data                          | 3                      | 1                       | 2                    |       |
| Downsizing                           |                         |                         |                      |       |
| <50%                                  | 345 (54.4)             | 234 (50.7)              | 111 (64.5)           | 0.003 |
| >50%                                  | 289 (45.6)             | 228 (49.3)              | 61 (35.5)            |       |
| CRM (mm), median (range)              | 6 (0–50)               | 8 (0–34)                | 4 (0–50)             | <0.001|
| Missing data                          | 35                     | 32                      | 3                    |       |
| Distal margin (mm), median (range)    | 50 (0–190)             | 55 (0–190)              | 50 (0–130)           | 0.003 |
| Differentiation                       |                         |                         |                      |       |
| Poor                                  | 34 (5.4)               | 19 (4.1)                | 15 (8.7)             | 0.014 |
| Moderate                              | 246 (38.8)             | 170 (36.8)              | 76 (44.2)            |       |
| Well                                  | 341 (53.8)             | 264 (57.1)              | 77 (44.8)            |       |
| Mucinous                              | 13 (2)                 | 9 (2)                   | 4 (2.3)              |       |
| Perineural invasion                   |                         |                         |                      | <0.001|
| No                                    | 550 (86.7)             | 418 (90.5)              | 132 (76.7)           |       |
| Yes                                   | 84 (13.3)              | 44 (9.5)                | 40 (23.3)            |       |
| Lymphovascular invasion               |                         |                         |                      | <0.001|
| No                                    | 543 (85.7)             | 416 (90)                | 127 (73.8)           |       |
| Yes                                   | 91 (14.3)              | 46 (10)                 | 45 (26.2)            |       |
| Pathological T category               |                         |                         |                      | <0.001|
| 0                                     | 95 (15)                | 86 (18.6)               | 9 (5.2)              |       |
| 1                                     | 61 (9.6)               | 52 (11.3)               | 9 (5.2)              |       |
| 2                                     | 185 (29.2)             | 147 (31.8)              | 38 (22.1)            |       |
| 3                                     | 266 (41.9)             | 167 (36.1)              | 99 (57.6)            |       |
| 4                                     | 27 (4.3)               | 10 (2.2)                | 17 (9.9)             |       |
| Pathological N category               |                         |                         |                      | <0.001|
| Negative                              | 429 (67.7)             | 352 (76.2)              | 77 (44.8)            |       |
| Positive                              | 205 (32.4)             | 110 (23.8)              | 95 (55.2)            |       |
| Stage                                 |                         |                         |                      | <0.001|
| 0–I–II                                | 429 (67.7)             | 352 (76.2)              | 77 (44.8)            |       |
| III                                   | 205 (32.3)             | 110 (23.8)              | 95 (55.2)            |       |
| Resection margin                      |                         |                         |                      | <0.001|
| R0                                    | 567 (89.4)             | 428 (92.6)              | 139 (80.8)           |       |
| R1                                    | 67 (10.6)              | 34 (7.4)                | 33 (19.2)            |       |
| Adjuvant chemotherapy                 | 224 (35.3)             | 125 (27.1)              | 99 (57.6)            | <0.001|
| Follow-up (months), median (range)    | 70.4 (2.1–233)         | 75 (2.1–233)            | 57.1 (4.8–224)       | <0.001|
| Loss of follow-up                     | 78 (12)                | 56 (12)                 | 22 (15)              | 0.822 |
| Death                                 |                         |                         |                      | <0.001|
| CRC-related                           | 106 (57)               | 1 (1)                   | 105 (98)             |       |
| Non-CRC-related                       | 80 (43)                | 78 (99)                 | 2 (2)                |       |

Values are n (%) unless otherwise indicated. CRM, circumferential resection margin; TNM, tumour node metastasis.
With a median [min-max] follow-up of 70.4 (range 2.1–233) months, 172 of 634 patients (27.1 per cent) developed recurrence, of whom 116 (18.3 per cent) had distant metastases, 21 (3.3 per cent) developed LR, and 35 (5.5 per cent) developed both local and distant recurrences. For these patients, the median time to recurrence was 16.5 (range 1–100) months. The demographic and clinicopathological characteristics of all studied patients are summarized in Tables 1 and 2. Adjuvant therapy modalities are described in Table S1.

Nomogram variable screening

After reviewing the literature, we selected the following 12 variables impacting the prognosis of patients undergoing rectal cancer surgery and those available in our database for analysis: age (more than 70 years), sex, CEA level (more than 5 mg/l), neoadjuvant chemotherapy, tumour location (low versus medium), tumour downsizing (less than 50 per cent), lymphovascular invasion, perineural invasion, resection margin, AJCC staging (stages 1–2 versus stage 3), postoperative PIC, and adjuvant therapy (Table 3). Significant variables identified in the univariable analysis were then included in the multivariable logistic regression model.

Nomogram construction and validation

All 634 patients were randomly assigned to the training cohort (423 patients) and a validation cohort (211 patients) in a 2:1 ratio. There were no significant differences in the clinicopathological characteristics between the two cohorts (Table S2). Univariable analysis showed that CEA levels more than 5 mg/l, postoperative PIC, tumour downsizing, lymphovascular invasion, perineural invasion, resection margin, AJCC staging, and adjuvant therapy were significant predictors of recurrence (Table 3).

These variables were used to build a nomogram that can predict the probability of disease recurrence. For each patient, a score of 450 points was obtained to evaluate the risk of cancer recurrence (Fig. 2). We did not develop a nomogram that predicts LR or DM separately because of the insufficient number of events; however, preliminary analysis showed similar risk factors, regardless of the type of recurrence (Table S3).

Validation of the model

With an AUC value of 0.74 (95 per cent c.i. 0.69 to 0.8), the model had a good discrimination capability in the training cohort. The AUC value of the nomogram for prediction was approximately 0.75 (95 per cent c.i. 0.67 to 0.83) in the validation cohort. These data showed that the nomogram was sufficiently predictive in the validation group. The ROC curves are shown in Fig. 3. Calibration plot for the prediction model in the training and validation cohorts both demonstrated satisfactory consistency (Fig. S2). The likelihood ratio test for the nested models on training data showed that the nomogram provided highly significant supplementary information compared with the univariable model with only TNM staging (LR 33.1; d.f. 7; Table 3 Univariable and multivariable analysis of risk factors of recurrence in training cohort.

| Variables                              | Patients | Events | Univariate analysis | Multivariable analysis |
|----------------------------------------|----------|--------|---------------------|------------------------|
|                                        |          |        | OR (95% c.i.)       | P                      | OR (95% c.i.)       | P                      |
| Sex ratio (M:F)                        | 145:266  | 41 (28.3):9 (25.9) | 0.9 (0.6; 1.4) | 0.609                  | –                     | –                     |
| Age (years)                            |          |        |                     |                        |                       |                       |
| <70                                    | 285      | 78 (27.4) | 0.9 (0.6; 1.5) | 0.677                  | –                     | –                     |
| ≥70                                    | 126      | 32 (25.4) |                     |                        |                       |                       |
| CEA level (mg/l)                       |          |        |                     |                        |                       |                       |
| <5                                     | 306      | 68 (22.2) | 2.3 (1.5; 3.8) | <0.001                 | 1.7 (1.1; 2.9) | 0.035 |
| ≥5                                     | 105      | 42 (40)  |                       |                        |                       |                       |
| Tumour location                        |          |        |                     |                        |                       |                       |
| Low                                    | 249      | 73 (29.3) | 0.7 (0.5; 1.1) | 0.147                  | –                     | –                     |
| Mid                                    | 162      | 37 (22.8) |                     |                        |                       |                       |
| Neoadjuvant chemotherapy               |          |        |                     |                        |                       |                       |
| No                                     | 361      | 98 (27.2) | 0.9 (0.4; 1.7) | 0.638                  | –                     | –                     |
| Yes                                    | 50       | 12 (24)  |                       |                        |                       |                       |
| Adjuvant chemotherapy                  |          |        |                     |                        |                       |                       |
| No                                     | 259      | 45 (17.4) | 3.6 (2.3; 5.6) | <0.001                 | 1.9 (1.1; 3.7) | 0.039 |
| Yes                                    | 152      | 65 (42.8) |                       |                        |                       |                       |
| Downsizing (<50%)                      | 215      | 67 (31.2) | 0.6 (0.4; 0.9) | 0.035                  | 0.9 (0.6; 1.6) | 0.881 |
| >50%                                   | 196      | 43 (21.9) |                       |                        |                       |                       |
| Perineural invasion                    |          |        |                     |                        |                       |                       |
| No                                     | 350      | 79 (22.6) | 3.5 (2.6; 2.3) | <0.001                 | 1.8 (0.9; 3.6) | 0.084 |
| Yes                                    | 61       | 31 (50.8) |                       |                        |                       |                       |
| Lymphovascular invasion                |          |        |                     |                        |                       |                       |
| No                                     | 355      | 82 (23.1) | 3.3 (1.9; 5.9) | <0.001                 | 1.4 (0.7; 2.9) | 0.351 |
| Yes                                    | 56       | 28 (50)  |                       |                        |                       |                       |
| Stage                                  |          |        |                     |                        |                       |                       |
| 0–I–II                                 | 278      | 51 (18.4) | 3.6 (2.3; 5.6) | <0.001                 | 1.5 (0.8; 2.9) | 0.219 |
| III                                    | 133      | 59 (44.4) |                       |                        |                       |                       |
| Resection margin                       |          |        |                     |                        |                       |                       |
| R0                                     | 370      | 91 (24.6) | 2.7 (1.4; 5.1) | 0.003                  | 1.7 (0.8; 3.5) | 0.174 |
| R1                                     | 41       | 19 (46.3) |                       |                        |                       |                       |
| Pelvic infectious complication         |          |        |                     |                        |                       |                       |
| No                                     | 327      | 72 (22)  | 2.9 (1.8; 4.8) | <0.001                 | 2.5 (1.5; 4.3) | <0.01 |
| Yes                                    | 84       | 38 (45.2) |                       |                        |                       |                       |

Values are n (%) unless otherwise indicated. OR, odds ratio; c.i., confidence interval.
A comparison of AUC values reveals an improvement equal to 0.10 (95 per cent Wald IC, 0.05 to 0.14).

Correlation between the nomogram score and time of recurrence
From this nomogram, we calculated the corresponding score for each patient who developed recurrence and categorized patients into three groups according to the evaluation of the risk of recurrence: low risk, less than 30 per cent (score 0–134); intermediate risk, 30–55 per cent (score 135–249); high risk, more than 55 per cent (score 250 or higher) (Table 4).

A high nomogram score had a statistically significant negative correlation with the delay in recurrence ($r = -0.214; P = 0.003$). When the nomogram score increases by 10 units, time of recurrence decreases by a mean of 12.2 days.
Table 4 Median time to local or metastatic recurrence in the overall cohort (n = 634) according to nomogram score

| Nomogram score | Low risk | Intermediate risk | High risk |
|----------------|----------|-------------------|-----------|
| Patients       | 434      | 122               | 78        |
| Events         | 79 (18.2)| 47 (58.5)         | 46 (58.9) |
| Local          | 8 (10.1) | 17 (14.9)         | 6 (13.5)  |
| Metastatic     | 55 (79.6)| 32 (68.1)         | 29 (63.1) |
| Local + metastatic | 16 (20.3) | 8 (17)          | 11 (23.9) |
| Time to recurrence (months), median (range) | 19.1 | 17.7 (1–99) | 10.8 (0.7–93) |

Values are n (%) unless otherwise indicated.

**Discussion**

Treatment strategies for LARC are becoming more complex and are evolving toward a personalized approach that goes beyond the TNM staging system, which is commonly used to predict disease-free and individual survival in patients with rectal cancer. Surgical and oncological treatment modalities are determined according to the characteristics of the patient, tumour, and imaging and therapeutic responses, which can vary greatly from one team to another. To address these new challenges, we constructed a nomogram based on eight factors to predict the recurrence risk in LARC following CRT and surgery to assist with medical decisions.

Several studies have attempted to develop a prediction score for recurrence following rectal cancer surgery, including both rectal and colonic surgeries, or for patients with and without neoadjuvant therapy. Van Gijn et al. developed a nomogram based on Dutch, Swedish, and Polish trials; however, half of the patients did not receive neoadjuvant radiotherapy. Yeo et al. developed a prediction model for recurrence based on radiological variables at diagnosis and did not consider any other criteria, including response to neoadjuvant therapy when administered, which significantly reduced the clinical significance of their results.

Only Valentini et al. developed nomograms to predict DM, LR, and overall survival in patients undergoing rectal cancer surgery based on five large European RCTs; however, the results are difficult to adapt to current practice, as the 2795 patients included were treated between 1993 and 2003 with different modalities of pre- and postoperative radiotherapy, surgery (TME was introduced in 1999), and adjuvant chemotherapy. They claimed that ypN and ypT are associated with distant and local recurrences. Compared with other surgical procedures, APE was a risk factor for metastatic recurrence but not for LR. Adjuvant therapy significantly decreased the risk of LR but not the risk of metastatic recurrence. More recent studies have shown that the worse prognosis after APE in comparison with restorative resection was not related to the surgical technique itself but to the patient and tumour characteristics with more frequent margin involvement. After adjusting for clinical stage, tumour distance from the anal verge, and tumour size, Lee et al. described comparable local and distant recurrence rates after APE. Consequently, we did not consider surgical intervention in our analysis but rather the tumour location, pathological stage, and resection margins (R0 versus R1).

We also collected clinical data often unavailable in studies evaluating the risk factors for recurrence rectal cancer surgery, including postoperative complications, especially PICs. We found a strong independent association between PIC and recurrence (OR 2.50, 95 per cent c.i. 1.45 to 4.32; P = 0.001), and it seemed to have a similar impact on local and distant recurrences. The data in the literature are contradictory; however, a recent meta-analysis showed that AL was associated with increased LR and reduced disease-free survival. The impact of PICs has recently been highlighted; PICs have a worse impact on the prognosis following the resection of rectal cancer and colorectal liver metastasis compared with non-infective postoperative complications. Poor oncological outcomes can be attributed to viable tumour cells released during sepsis or soluble factors released during the inflammatory response, which may increase tumour aggressiveness and reduce the effectiveness of the immune system. Including PICs in our model increases its strength and provides a clinically relevant patient-specific risk of recurrence. Some measures can be implemented to reduce PICs, including the correction of preoperative malnutrition, sarcopenia, or anaemia.

Contrastingly, adjuvant chemotherapy was associated with a poorer prognosis in our study. Contrary to that observed in patients with colon cancer, the benefit of adjuvant chemotherapy has never been proven in patients with LARC after preoperative CRT. Currently, CRT is recommended for patients with ypT1–3 (stage III); poor responders after CRT and TME are correlated with a poorer prognosis. We excluded patients who underwent local excision to analyse the most homogeneous population; however, we excluded the best responders, which could introduce bias in the adjuvant treatment effect analysis. Collette et al. demonstrated that only patients with a good prognosis (ypT0–2) benefit from adjuvant chemotherapy with increased disease-free survival. The same prognostic factors could determine tumour sensitivity for preoperative and additional adjuvant therapy.

Our study does not allow us to conclude on the role of adjuvant chemotherapy in LARC; however, it raises the question of the possibility of predicting the therapeutic response and/or intensification of the preoperative treatment. Recent RCTs have shown significant improvements in DM and survival rates in patients with LARC using the TNT approach. This strategy increases the rate of complete histological response and decreases chemotherapy neurotoxicity.

In our study, all patients received long-course CRT, according to the same protocol, using the same dose, enabling us to evaluate the most homogeneous population. However, neoadjuvant CT (FOLFIRINOX—four cycles as per the GRECCAR 4 trial) was administered in 71 patients (11.2 per cent). This variable was included in our multivariable analysis to avoid bias and was not significant. TNT has become the standard treatment for LARC, however, the impact of postoperative chemotherapy remains unclear. In the PRODIGE 23 trial, 3 months of adjuvant chemotherapy was planned systematically, but 90 patients (22 per cent) did not receive any treatment, and 115 patients (28.2 per cent) received at least 80 per cent of the planned doses.

Our nomogram is a simple tool for assessing the risk of LARC recurrence after CRT and surgery. The strength of our study is the size and homogeneity of the patients included, allowing for model validation in an internal cohort. The statistical performance of the nomogram was good, with an AUC of 0.74 and 0.75 in the training cohort and validation cohorts respectively, providing a better prediction model than TNM staging alone.

Our nomogram score also correlated with the time to recurrence. Although early detection of recurrence may potentially favour surgery with curative intent and improve survival, studies evaluating intensified follow-up programmes of patients with rectal cancers after curative treatment are contradictory and
show no improvement in overall survival. These studies involved all patients, regardless of tumour stage or prognostic factor. We believe that patients identified as high risk for recurrence according to our nomogram would benefit from a closer follow-up. As we found similar risk factors being responsible for local and distant recurrences, the two possible follow-up options are liver and pelvic MRI or positron emission tomography, either in place of or alternating with CT.

Our study had several limitations. First, selection bias because of the retrospective nature and inclusion of patients with complete information only; however, only 21 patients were excluded due to missing data or were lost to follow-up before 3 years. Some variables were not included in the analysis due to a significant amount of missing data, although they may have prognostic value, such as MRI criteria (extramural vascular invasion and predictable CRM) or genetic biomarkers (KRAS and BRAF mutations and MMR status). Second, the nomogram was constructed based on our single-centre experience. Although internally validated in the validation cohort, external validation of our nomogram in a prospective multicentric cohort is necessary.

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**Disclosure**

The authors declare no conflict of interest.

**Supplementary material**

Supplementary material is available at BJS Open online.

**Data availability**

Data are available on request from the authors.

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