Comparative Study - Retrospective Cohort

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Unraveling variations and enhancing prediction of successful sphincter-preserving resection for low rectal cancer: a post hoc analysis of the multicentre LASRE randomized clinical trial

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Background: Accurate prediction of successful sphincter-preserving resection (SSPR) for low rectal cancer enables peer institutions to scrutinize their own performance and potentially avoid unnecessary permanent colostomy. The aim of this study is to evaluate the variation in SSPR and present the first artificial intelligence (AI) models to predict SSPR in low rectal cancer patients.

Study design: This was a retrospective post hoc analysis of a multicenter, non-inferiority randomized clinical trial (LASRE, NCT01899547) conducted in 22 tertiary hospitals across China. A total of 604 patients who underwent neoadjuvant chemoradiotherapy (CRT) followed by radical resection of low rectal cancer were included as the study cohort, which was then split into a training set (67%) and a testing set (33%). The primary end point of this post hoc analysis was SSPR, which was defined as meeting all the following criteria: (1) sphincter-preserving resection; (2) complete or nearly complete TME, (3) a clear CRM (distance between margin and tumour of 1 mm or more), and (4) a clear DRM (distance between margin and tumour of 1 mm or more). Seven AI algorithms, namely, support vector machine (SVM), logistic regression (LR), extreme gradient boosting (XGB), light gradient boosting (LGB), decision tree classifier (DTC), random forest (RF) classifier, and multilayer perceptron (MLP), were employed to construct predictive models for SSPR. Evaluation of accuracy in the independent testing set included measures of discrimination, calibration, and clinical applicability.

Results: The SSPR rate for the entire cohort was 71.9% (434/604 patients). Significant variation in the rate of SSPR, ranging from 37.7 to 94.4%, was observed among the hospitals. The optimal set of selected features included tumour distance from the anal verge before and after CRT, the occurrence of clinical T downstaging, post-CRT weight and clinical N stage measured by magnetic resonance imaging. The seven different AI algorithms were developed and applied to the independent testing set. The LR, LGB, MLP and XGB models showed excellent discrimination with area under the receiver operating characteristic (AUROC) values of 0.825, 0.819, 0.819 and 0.805, respectively. The DTC, RF and SVM models had acceptable discrimination with AUROC values of 0.797, 0.766 and 0.744, respectively. LR and LGB showed the best discrimination, and all seven AI models had superior overall net benefits within the range of 0.3–0.8 threshold probabilities. Finally, we developed an online calculator based on the LGB model to facilitate clinical use.

Conclusions: The rate of SSPR exhibits substantial variation, and the application of AI models has demonstrated the ability to predict SSPR for low rectal cancers with commendable accuracy.

Keywords: artificial intelligence models, light gradient boosting, rectal cancer, successful sphincter-preserving resection

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Introduction

Curative resection remains the cornerstone of treatment for locally advanced rectal cancer (LARC) and involves either a sphincter-preserving resection (SPR) with anastomosis or an abdominoperineal resection (APR) with permanent colostomy. With the increased usage of neoadjuvant chemoradiotherapy (CRT), a keen understanding of tumour biology, and advancements in surgical techniques and stapling devices, SPR has become more frequent for patients with rectal cancer[1,2]. However, there is still a concern that there might be missed opportunities for sphincter preservation due to the overuse of APR[3]. A previous population-based retrospective cohort study from a Canadian province reported significant variation in the rate of sphincter-preserving surgery among 10 hospitals (12–73%)[4]. A similar result was observed in another UK population-based study, in which significant variation in the odds of receiving an APR over time and between individual surgeons was observed[3]. Thus, there is a need to provide a benchmark for SPR that other specialty centres may use to assess their own practice patterns and, therefore avoid missed opportunities for sphincter preservation.

Avoiding permanent stoma is an important quality-of-life issue for rectal cancer patients[5]. Several authors advocated for the use of APR rates as a quality indicator for rectal cancer services[6], whereas their opponents strongly cautioned against using SPR rates as a quality measure due to its potential disadvantage of compromising cure rates in borderline cases where complete resection is unfeasible[7]. Thus, a more comprehensive quality indicator reflecting not only SPR rates but also radical cure rates is needed. Quality of surgical resection metrics (QSRMs) or "successful resection", defined as a composite measure including complete or nearly complete quality of total mesorectal excision (TME) and negative circumferential resection margin (CRM) and distal resection margin (DRM), have been used as surrogates for long-term oncologic outcomes in two randomized studies [ALaCaRT trial[8] and ACOSOG Z6051 trial[9]] comparing laparoscopic and open surgery for rectal cancer. An updated meta-analysis including 3744 patients demonstrated that achieving successful resection was significantly associated with improved disease-free survival for rectal cancers[10]. Thus, we introduced a composite measure labelled "successful sphincter-preserving resection (SSPR)", in which all QSRM components were met in a SPR for rectal cancer.

By comparing variation in SSPR across centres, this process enables peer institutions to scrutinize their own performance. In addition, accurate prediction of SSPR could potentially avoid unnecessary APR. Accurately determining the feasibility of SSPR prior to surgery is also crucial for informing patients and preparing them for the procedure. However, most previous registry studies on this topic have used administrative databases, and detailed patient-level data were not typically available to achieve this goal[7]. Consequently, we first evaluated the extent of variation in SSPR rates among tertiary hospitals across China. Then, by using detailed patient-level data from a multicenter randomized clinical trial database, we presented the first artificial intelligence (AI) models built on preoperative features to predict the SSPR of patients with locally advanced low rectal cancer after neoadjuvant CRT. Finally, the impact of SSPR on the short-term outcome of low rectal cancer surgery was comprehensively evaluated.

HIGHLIGHTS

- The sphincter-preserving resection (SSPR) rate achieved by the overall cohort in the Multicenter LASRE Randomized Clinical Trial, as determined through Post Hoc Analysis, was 71.9% (434/604 patients).
- Notably, a significant variation in the SSPR rate was observed across different hospitals in China, ranging from 37.7 to 94.4%.
- The utilization of artificial intelligence (AI) models has demonstrated remarkable predictive capabilities in determining the likelihood of SSPR in cases of low rectal cancers.
- The findings of this study have important implications for forecasting SSPR in low rectal cancer cases, enabling peer institutions to assess their own outcomes and potentially mitigate the need for permanent colostomy procedures.

Materials and methods

Patients

This was a post hoc analysis of a multicenter, non-inferiority randomized clinical trial (LASRE, Laparoscopy-Assisted Surgery for Carcinoma of the Low REctum, NCT01899547) conducted in 22 tertiary hospitals across China[11]. The trial design of LASRE has been previously published[11]. The trial protocol and statistical analysis plan are provided in Supplement 1, Supplemental Digital Content 1, http://links.lww.com/JS9/C409. Briefly, patients scheduled for curative-intent resection of low rectal cancer were randomized at a 2:1 ratio to undergo laparoscopic or open surgery between November 2013 and June 2018. Preoperative CRT was recommended for patients with clinical stage II/III disease. All participating surgeons had performed more than 100 laparoscopic TME surgeries, and all surgeries occurred in a high-volume (at least 30 laparoscopic TME surgeries annually) tertiary centre. Ethical approval for this study was provided by the central ethics committees of Fujian Medical University Union Hospital, 29 Xin-Quan Road, Fuzhou, Fujian 350001, People's Republic of China on 28 Sep 2013 (IRB number: 2013051 for LASRE trial). All participants in the LASRE trial provided written informed consent before enroling, and all data were collected and analyzed anonymously. This present retrospective study qualifies for a waiver of informed consent by the ethics committee (IRB number: 2023KY210 for this post hoc restrospective study of LASRE trial).

This study followed the STROCSS criteria[12] (Supplement 2: eFigure 1, Supplemental Digital Content 2, http://links.lww.com/JS9/C410 Supplement 3: STROCSS 2021 Guideline Checklist, Supplemental Digital Content 3, http://links.lww.com/JS9/C411). Patients who were treated with neoadjuvant CRT followed by curative-intent resection of low rectal cancer were included. Patients were excluded according to the following criteria: (1) patients who did not undergo neoadjuvant CRT; (2) patients with missing data regarding the quality of TME, CRM status, or DRM status; (3) patients who underwent total proctocolectomy, transanal excision, or posterior pelvic resection (Hartmann's procedure was rarely performed in the LASRE trial [$< 0.3\%$ of the entire cohort] and was therefore excluded); and (4) patients had missing data regarding important baseline

characteristics. Finally, a total of 604 patients were included in the current study.

Definitions

Low rectal cancer was defined as a tumour with a lower margin less than 5 cm from the dentate line at the time of initial diagnosis. SPR was defined as cancer-directed surgery involving an anastomosis between the colon and the rectum or anus, which included low or ultralow anterior resection (LAR/ULAR), ULAR via a pull-through procedure, and transabdominal or transanal intersphincteric resection (ISR). Patients diverted with loop ileostomy or loop transverse colostomy at the time of SPR were considered to have undergone SPR; non-SPR procedures included APR or extralevator abdominoperineal excision (ELAPE).

All tumours were clinically staged, both before and after CRT, through pelvic MRI or, if possible, the combined use of pelvic MRI and endorectal ultrasound. Parameters regarding patient demographics, tumour characteristics, laboratory test results, treatment factors and imaging report data were prospectively collected and maintained. A detailed list of the parameters used for model construction is provided in the Supplement 4 (eTable S1, Supplemental Digital Content 4, http://links.lww.com/JS9/C415). To assess the tumour distance from the anal verge for patients whose preoperative records noted distance from the dentate line rather than from the anal verge, 2 cm was added to each measurement. Clinical T downstaging was defined as any decrease in ycT stage after CRT. The degree of tumour regression was recorded based on the Dworak and colleagues regression system. Complications were graded according to the Clavien–Dindo classification[13].

The primary end point of this post hoc analysis was SSPR, which was defined as meeting all the following criteria: (1) SPR; (2) complete or nearly complete TME, (3) a clear CRM (distance between margin and tumour of 1 mm or more), and (4) a clear DRM (distance between margin and tumour of 1 mm or more). AI models built on preoperative features to predict SSPR were constructed and validated. An additional analysis was undertaken to investigate the extent of variation in SSPR rates among tertiary hospitals across China. For this analysis, only centres contributing at least 15 cases were included. A second additional analysis was performed to assess the potential difference between the short-term outcomes of the SSPR group and the non-SSPR group.

Sample size

Sample size calculations for prediction models were performed using the method of Riley *et al*.[14]. The anticipated Cox–Snell R2 squared was set at 0.10 (indicating a conservative, high anticipated signal-to-noise ratio), the shrinkage factor was set at 0.9 (recommended to decrease overfitting), and the mean absolute prediction error was set at 0.05. The calculation was done by considering 6 features selected through LASSO regression and the expected outcome proportion of 0.28 (representing the non-SSPR rate, 170 out of 604) in the target population. Thus, these assumptions rendered a minimum required sample size of 510 observations with 144 events, with 23.93 events per predictor parameter (Supplement 5, Supplemental Digital Content 5, http://links.lww.com/JS9/C417). The assumptions made for the sample size estimation were met.

AI model development

In this study, type 2A prediction models (random split-sample development and validation) were developed and evaluated following the checklist outlined in the Transparent Reporting of a model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines[15].

A schematic illustration of the working principle of AI model development is shown in Figure 1. The development of the supervised AI models was completed in the following four steps:

(1) Data preprocessing: missing values were imputed with abundances based on k-nearest neighbour imputation using $k = 20$. The dataset was split randomly into two groups: a training set (67% of the study sample) and a testing set (33% of the study sample). The training set was used to develop the AI models. Data normalization was performed using the scaler provided by the StandardScaler class of Sklearn on the training set and applied to the training and testing sets to avoid data leakage.

(2) Feature selection: a total of 77 features that were available before the operation, consisting of patient demographics, tumour characteristics, laboratory test results, treatment factors and imaging report data, were employed for feature selection. Feature selection was applied using the least absolute shrinkage and selection operator (LASSO) regression model with 3-fold cross-validation to shrink the small association coefficient to zero and then to identify important features for predicting SSPR. LASSO regression utilizes a penalty that operates as a function of the regression coefficients. The penalty function minimizes the residual sum of squares subject to a constraint on the sum of the absolute values of the coefficients and then reduces the variable numbers to avoid overfitting[16].

(3) Model training: A total of 7 different AI algorithms, including support vector machine (SVM), logistic regression (LR), extreme gradient boosting (XGB), light gradient boosting (LGB), decision tree classifier (DTC), multilayer perceptron (MLP), and random forest (RF) classifier, were used. Model hyperparameters were tuned using the Sklearn RandomizedSearchCV with 5-fold cross-validation on the training set to find the optimal parameters for the AI models and to avoid overfitting the data.

(4) Model validation: The predictive performance of the AI models was evaluated independently using measures of discrimination, calibration, and clinical applicability on the testing set. For discrimination assessment, receiver operating characteristic (ROC) curves were constructed, and area under the ROC curve (AUROC) values were calculated and compared by the method of DeLong *et al*.[17] on the testing set independently. An AUROC value between 0.7 and 0.8 was considered acceptable discrimination, between 0.8 and 0.9 was considered excellent discrimination, and greater than 0.9 was considered outstanding discrimination[18]. Calibration evaluation was performed by comparing predicted probabilities with observed probabilities in the testing set. One thousand replicates were used for bootstrap analysis. To evaluate the clinical applicability, decision curve analysis (DCA) was performed by quantifying the net benefits at different threshold probabilities in the testing set. Clinical impact curve analysis (CICA) was conducted by comparing the total number of patients who would be

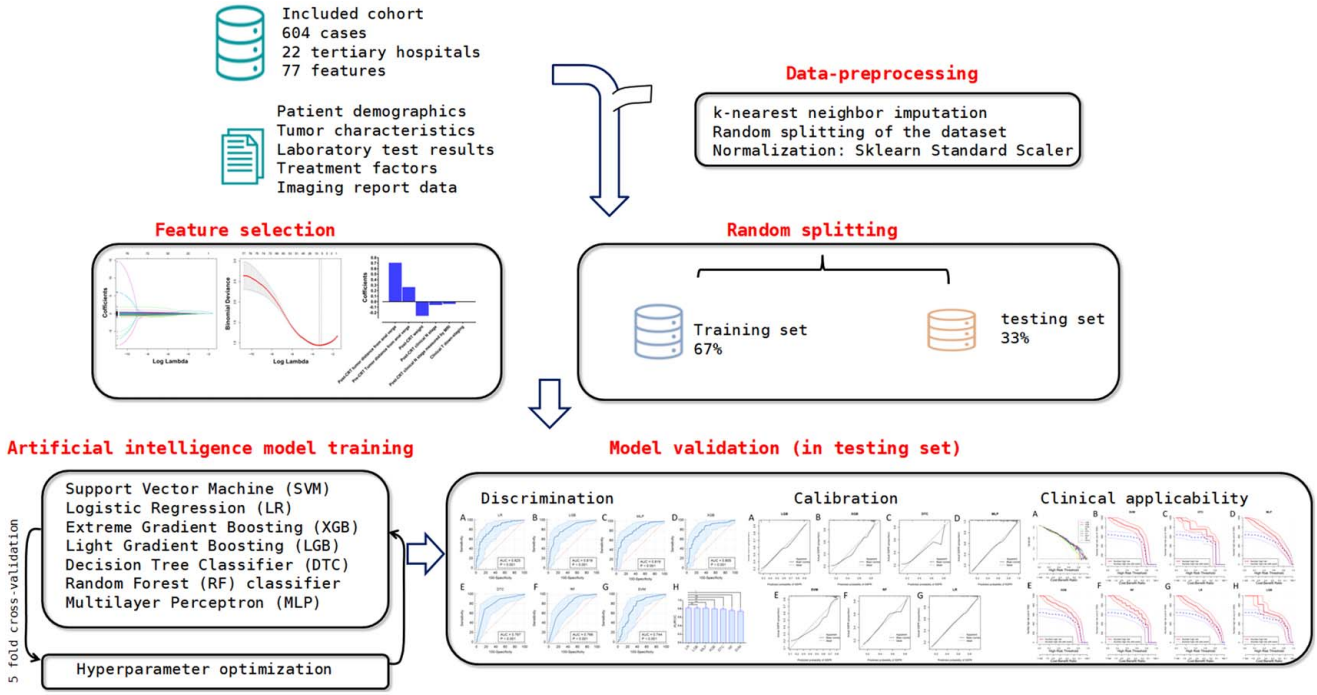

Figure 1. Schematic illustration of the working principle of artificial intelligence model development.

deemed high risk for each risk threshold and the number of those who would be true positives out of 1000 patients in the testing set. When the number of true positives and risk threshold were fixed, the fewer high-risk cases that were predicted, the better the clinical applicability of the model.

Statistical analysis

The analysis regarding data preprocessing and model development was performed with Python 3.4 (Jupyter Notebook) and libraries including Scikit–Learn, Matplotlib, Numpy, Pandas and Streamlit. Other statistical analyses were performed using R (version 3.6.2), STATA (version 15.0), MedCalc and GraphPad Prism (version 7.00). We compared continuous variables using the Wilcoxon test and categorical variables using the χ^2 test or Fisher's exact test. Maximum Youden index values were used to determine the optimal threshold for perfect classification of each model. The sensitivity and specificity of the models were calculated from the testing set independently using the optimal threshold. Propensity score matching (PSM) was employed to address the imbalanced covariates and selection bias in comparing short-term outcomes between patients in the SSPR group and non-SSPR group. The imbalanced covariates were incorporated into the PSM process, which involved one-to-one matching without replacement using a 0.01 caliper width. The level of statistical significance was set at two-sided *P* less than 0.05.

Results

Demographic data

A total of 604 patients who underwent CRT followed by radical resection of low rectal cancer from 22 tertiary hospitals across China were included in this study. The median age was 57.0 [interquartile range (IQR): 49.5, 63.0] years, and 395 (65.4%) patients were male. The SPR rate for the entire cohort was 73.3% (443/604 patients). Among patients who received SPR, positive DRM was present in 0.9% (4/443) of patients, 0.9% had a positive CRM (4/443), and 0.2% had incomplete TME (1/443). Based on the predefined study criteria, 434 (71.9%) patients had SSPR. Significant variation in the rate of SSPR, ranging from 37.7 to 94.4%, was observed among the 9 hospitals that provided more than 15 cases ($P < 0.001$, Fig. 2).

The baseline demographic and clinicopathological characteristics of patients who underwent SSPR and non-SSPR are compared in Table 1. Patients who underwent SSPR and non-SSPR were similar in terms of age, sex, comorbidities, and pathologic TNM stage. Patients who underwent SSPR had lower levels of pre-CRT and post-CRT BMI compared to those who underwent

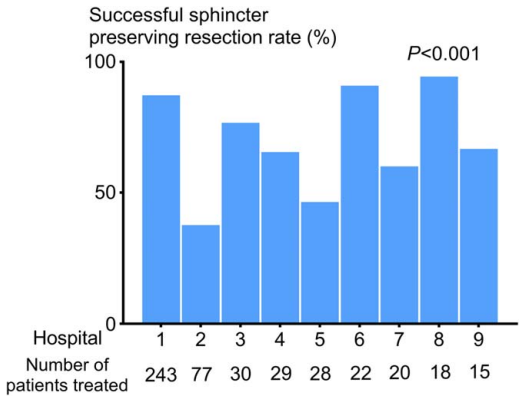

Figure 2. Variation in the rate of successful sphincter-preserving resection among the 9 hospitals that provided more than 15 cases.

non-SSPR. Tumour distance from the anal verge both before and after CRT was higher in patients who underwent SSPR than in patients who underwent non-SSPR. Moreover, the size of tumours in patients who underwent SSPR was significantly smaller, while the number of retrieved lymph nodes was similar between patients who underwent SSPR and non-SSPR. After PSM, the SSPR and non-SSPR groups were well-matched for all baseline demographic and clinicopathological characteristics.

Feature selection

A total of 77 features were collected from each patient for LASSO regression analysis. The optimal set of features selected by LASSO included 6 variables (Supplement 6; eFigure 2, Supplemental Digital Content 6, http://links.lww.com/JS9/C418). Of them, tumour distance from the anal verge before and after CRT and the occurrence of clinical T downstaging had positive coefficients, which implied that they were associated with higher SSPR rates. In contrast, higher post-CRT weight and higher clinical N stage, whether measured by MRI, had negative coefficients and were predictors of lower SSPR rates.

AI model development and validation

These 6 features were included in the development of 7 different AI algorithms in the training set. The optimal hyperparameters determined by RandomizedSearchCV are shown in Table 2. When applied to the independent testing set, the LR, LGB, MLP

Table 1

Baseline demographic and clinicopathological characteristics.

	Unmatched patients			Propensity-matched patients		
Variable	**Non-SSPR**	**SSPR**	***P***	**Non-SSPR**	**SSPR**	***P***
N	170	434		73	73	
Age (years), median (IQR)	56.5 (49.0, 63.0)	57.0 (50.0, 63.0)	0.96	57.0 (51.0, 64.0)	57.0 (49.0, 63.0)	0.49
Sex, *N* (%)			0.30			1.00
Male	117 (68.8)	278 (64.1)		50 (68)	50 (68)	
Female	53 (31.2)	156 (35.9)		23 (32)	23 (32)	
Pre-CRT BMI (kg/m^2), median, (IQR)	23.7 (21.5, 26.0)	22.8 (20.7, 24.8)	< 0.001	23.7 (21.5, 26.7)	24.1 (21.6, 25.9)	0.51
Post-CRT BMI (kg/m^2), median, (IQR)	23.7 (21.7, 26.3)	22.9 (20.8, 24.9)	< 0.001	23.7 (21.7, 26.7)	23.9 (21.7, 26.0)	0.65
ECOG performance status, *N* (%)			0.20			1.00
0	117 (68.8)	323 (74.4)		49 (67)	50 (68)	
1	52 (30.6)	103 (23.7)		24 (33)	23 (32)	
2	0	2 (0.5)		0	0	
Unknown	1 (0.6)	6 (1.4)		0	0	
Comorbidity, *N* (%)			0.64			0.47
No	113 (66.5)	278 (64.1)		53 (73)	48 (66)	
Yes	57 (33.5)	156 (35.9)		20 (27)	25 (34)	
Pre-CRT tumour distance from anal verge (mm), median, (IQR)	40.0 (30.0, 50.0)	50.0 (50.0, 60.0)	< 0.001	40.0 (30.0, 50.0)	40.0 (40.0, 50.0)	0.58
Post-CRT tumour distance from anal verge (mm), median, (IQR)	40.0 (30.0, 50.0)	60.0 (50.0, 70.0)	< 0.001	40.0 (30.0, 50.0)	40.0 (40.0, 50.0)	0.58
Pathologic TNM stage, *N* (%)			0.16			0.65
0/pCR	24 (14.1)	96 (22.1)		15 (21)	11 (15)	
I	49 (28.8)	119 (27.4)		19 (26)	19 (26)	
II	52 (30.6)	116 (26.7)		24 (33)	22 (30)	
III	45 (26.5)	103 (23.7)		15 (21)	21 (29)	
Tumour regression grade, *N* (%)			0.40			0.64
Grade 0	26 (15.3)	91 (21.0)		15 (21)	12 (16)	
Grade 1	39 (22.9)	109 (25.1)		15 (21)	24 (33)	
Grade 2	61 (35.9)	139 (32.0)		28 (38)	26 (36)	
Grade 3	22 (12.9)	46 (10.6)		6 (8)	7 (10)	
Grade 4	5 (2.9)	20 (4.6)		2 (3)	2 (3)	
Unknown	17 (10.0)	29 (6.7)		7 (10)	2 (3)	
Tumour size (mm), median (IQR)	25.0 (17.0, 31.0)	20.0 (15.0, 30.0)	< 0.001	25.0 (15.0, 31.0)	20.0 (15.0, 30.0)	0.19
Histopathology, *N* (%)			0.028			0.54
Tubular adenocarcinoma	99 (58.2)	202 (46.5)		48 (66)	49 (67)	
Papillary adenocarcinoma	1 (0.6)	3 (0.7)		4 (5)	4 (5)	
Mucinous adenocarcinoma	5 (2.9)	32 (7.4)		0	2 (3)	
Signet-ring cell carcinoma	2 (1.2)	1 (0.2)		2 (3)	0	
Adenocarcinoma or others	63 (37.1)	196 (45.2)		19 (26)	18 (25)	
Tumour differentiation, *N* (%)			0.90			0.69
Well differentiated	11 (6.5)	25 (5.8)		3 (4)	5 (7)	
Moderately differentiated	102 (60.0)	184 (42.4)		43 (59)	32 (44)	
Poorly differentiated	11 (6.5)	22 (5.1)		3 (4)	2 (3)	
Undifferentiated	1 (0.6)	1 (0.2)		1 (1)	0	
Unknown	45 (26.5)	202 (46.5)		23 (32)	34 (47)	
No. retrieved lymph nodes, median, (IQR)	12.0 (8.0, 16.0)	12.0 (8.0, 15.0)	0.75	12.0 (8.0, 17.0)	12.0 (9.0, 15.0)	0.72

CRT, neoadjuvant chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; pCR, pathological complete response; SSPR, successful sphincter-preserving resection.

Table 2

Set of parameters for designing the artificial intelligence models and the best value combination determined by RandomizedSearchCV.

AI models	Parameter	Best value combination
LR	C	3
	max_iter	1
	penalty	l1
	solver	saga
SVM	C	1
	gamma	1
DTC	max_depth	50
	max_leaf_nodes	10
RF	n_estimators	20
	max_features	log2
LGB	class_weight	balanced
	n_estimators	20
	num_leaves	5
	reg_alpha	0.001
XGB	n_estimators	50
	colsample_bytree	0.3
	max_depth	7
MLP	hidden_layer_sizes	100
	activation	relu
	solver	adam
	alpha	10
	max_iter	200

DTC, decision tree classifier; LGB, light gradient boosting; LR, logistic regression; MLP, multilayer perceptron; RF, random forest; SVM, support vector machine; XGB, extreme gradient boosting.

and XGB models showed excellent discrimination, with AUROC values of 0.825, 0.819, 0.819 and 0.805, respectively. The DTC, RF and SVM models had acceptable discrimination, with AUROC values of 0.797, 0.766 and 0.744, respectively. The AUROCs for LR and LGB were statistically superior to those of RF and SVM (LR or LGB vs. SVM or RF: each $P < 0.05$). Thus, LR and LGB showed the best discrimination. The resulting ROC curves in the independent testing set are shown in Figure 3. In the testing set, LGB, MLP, and LR showed excellent calibration, whereas DTC, SVM, XGB and RF suggested a predominance of lack of fit (Fig. 4). The results of the assessment of clinical applicability are shown in Figure 5. DCA and CICA visually showed that all 7 different AI models had superior overall net benefits within the range of 0.3-0.8 threshold probabilities. Finally, we developed an online calculator based on the LGB model in the Streamlit Python-based framework to facilitate clinical use (Supplement 7, Supplemental Digital Content 7, http://links.lww.com/JS9/C419 Streamlit needs to be installed on the user's computer).

Impact of SSPR on the short-term outcomes

The impact of SSPR on surgical details and short-term outcomes within 30 days is demonstrated in Table 3. Interestingly, laparoscopic surgery exhibited a higher SSPR compared to laparotomy (75.2% vs. 67.8%, $P = 0.009$). However, this disparity vanished after PSM. SSPR was found to be associated with several favourable outcomes compared to non-SSPR group. These included a shorter final incision length (53 vs. 80 mm, $P = 0.008$), reduced operative time (190 vs. 203 min, $P = 0.035$), lower estimated blood loss (50 vs. 100 ml, $P < 0.001$), and shorter hospitalization duration (7 vs. 10 days, $P < 0.001$). Notably, the SSPR group also exhibited significantly fewer postoperative complications (11.8% vs. 20.6%, $P = 0.007$) and a lower rate of incision complications (1.2% vs. 10.6%, $P < 0.001$) compared to the non-SSPR group. Even after conducting PSM, certain findings

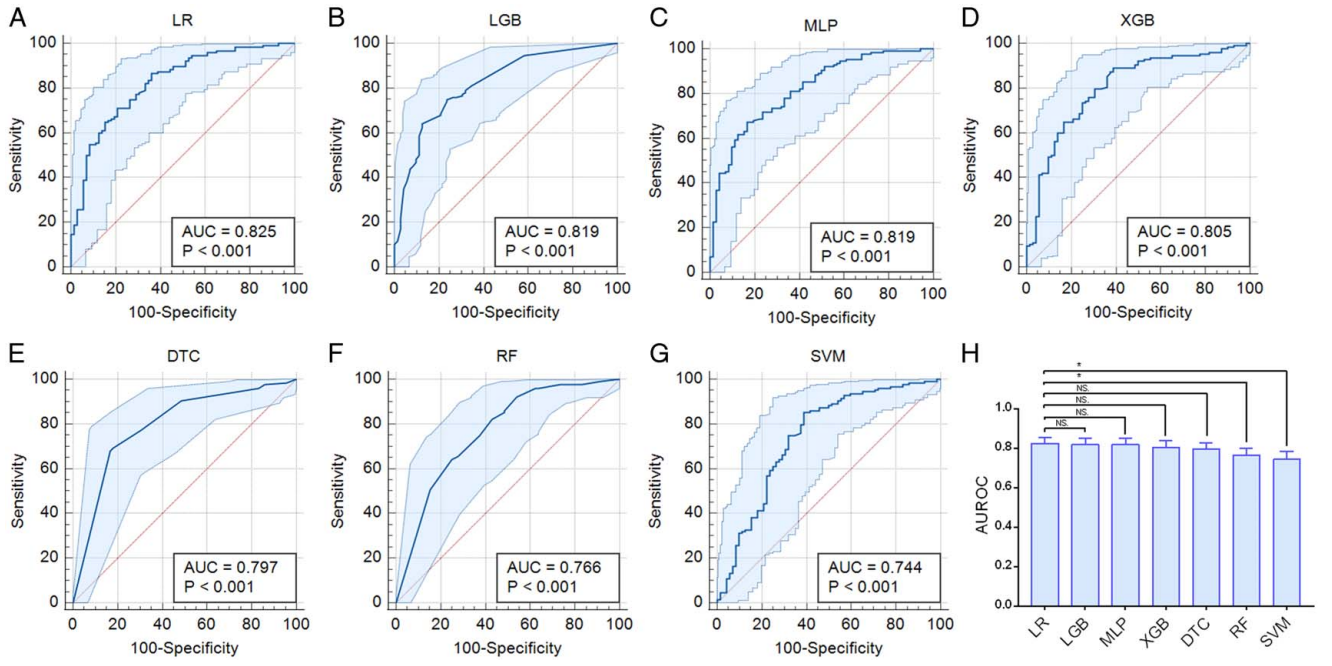

Figure 3. Receiver operating characteristic (ROC) curves for all models. DTC, decision tree classifier; LGB, light gradient boosting; LR, logistic regression; MLP, multilayer perceptron; NS, not significant; RF, random forest classifier; SVM, support vector machine; XGB, extreme gradient boosting; *statistical significance.

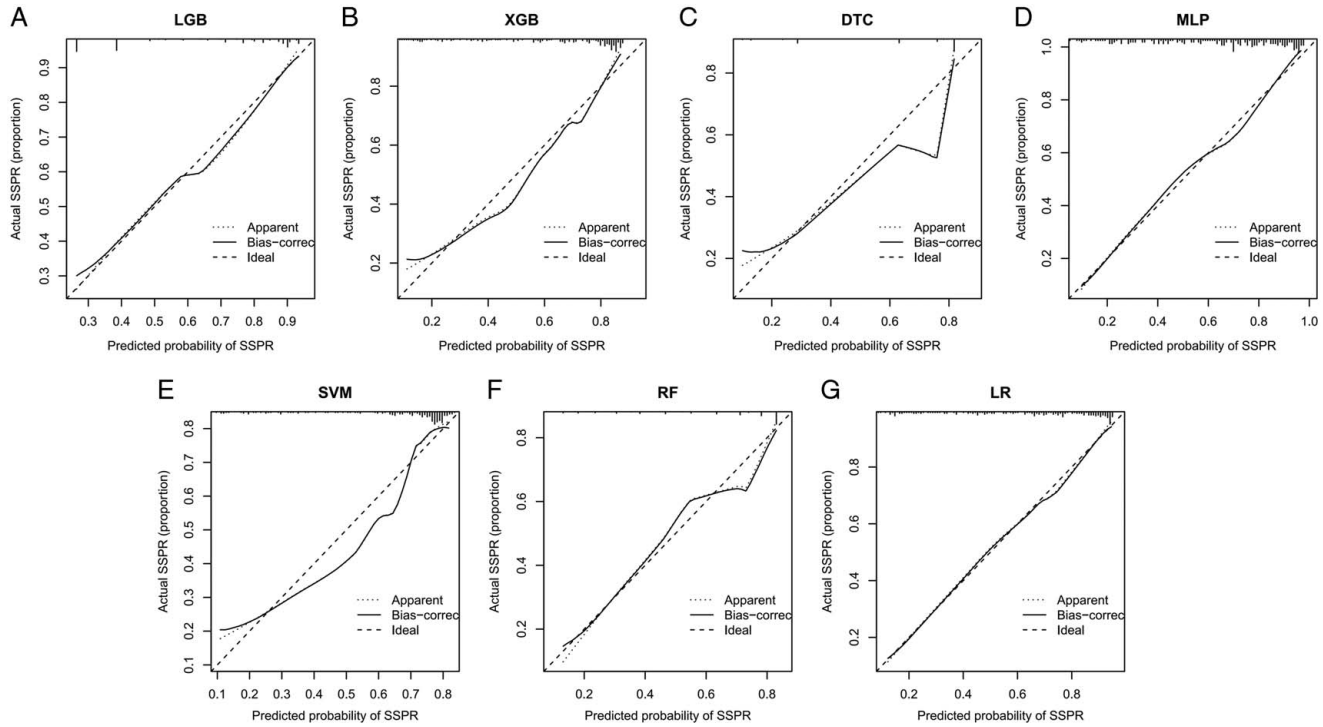

Figure 4. Assessment of calibration for all models.

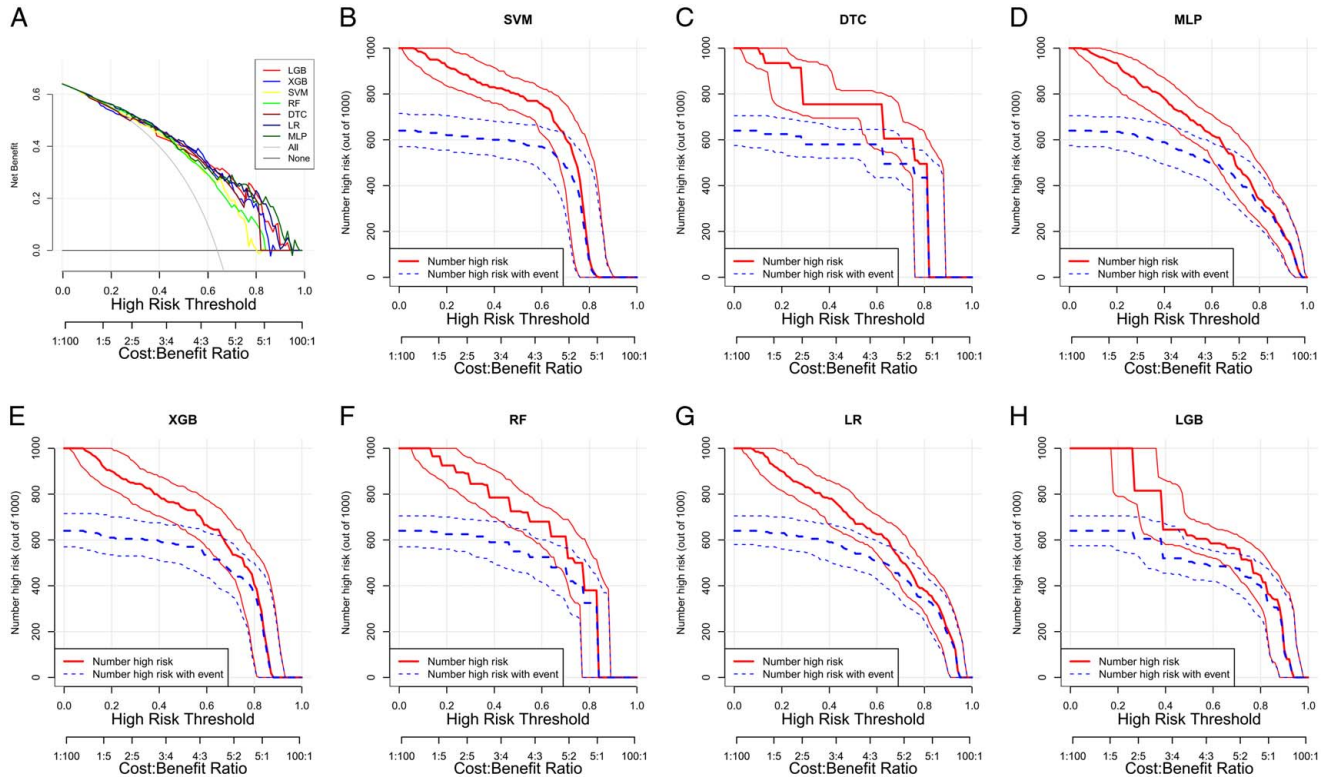

Figure 5. Assessment of clinical applicability for all models. (A) Decision curve analysis for all models. (B–H) Clinical impact curve analysis for SVM, DTC, MLP, XGB, RF, LR and LGB models. DTC, decision tree classifier; LGB, light gradient boosting; LR, logistic regression; MLP, multilayer perceptron; RF, random forest classifier; SVM, support vector machine; XGB, extreme gradient boosting.

Table 3

The impact of SSPR on surgical details and outcomes within 30 days.

Variable	Unmatched patients			Propensity-matched patients		
	Non-SSPR	SSPR	*P*	Non-SSPR	SSPR	*P*
N	170	434		73	73	
Approach method, *N* (%)			0.009			0.28
Open	68 (40.0)	125 (28.8)		25 (34)	18 (25)	
Laparoscopy	102 (60.0)	309 (71.2)		48 (66)	55 (75)	
Final incision length (mm), median (IQR)	80.0 (50.0, 150.0)	53.0 (47.0, 150.0)	0.008	80.0 (40.0, 150.0)	50.0 (40.0, 80.0)	0.017
Conversion to open surgery, *N* (%)	4 (2.4)	8 (1.8)	0.50	3 (4)	2 (3)	0.66
Operative time (min), median, (IQR)	203.0 (168.0, 245.0)	190.0 (150.0, 240.0)	0.035	210.0 (177.0, 257.5)	205.0 (170.0, 270.0)	0.98
Estimated blood loss (mL), median, (IQR)	100.0 (50.0, 100.0)	50.0 (35.0, 100.0)	< 0.001	100.0 (50.0, 100.0)	50.0 (40.0, 100.0)	0.006
Intraoperative transfusion, *N* (%)	2 (1.2)	2 (0.5)	0.32	1 (1)	1 (1)	1.00
Intraoperative complications, *N* (%)	1 (0.6)	1 (0.2)	0.48	0	0	
Duration of hospitalization (day), median, (IQR)	10.0 (7.0, 14.0)	7.0 (6.0, 9.0)	< 0.001	10.0 (8.0, 15.0)	7.0 (7.0, 9.0)	< 0.001
30-day postoperative complications, *N* (%)	35 (20.6)	51 (11.8)	0.007	14 (19)	7 (10)	0.16
Anastomotic bleeding	0	1 (0.2)	1.00	0	0	
Urinary disorder	4 (2.4)	8 (1.8)	0.75	2 (3)	1 (1)	1.00
Active intraabdominal bleeding	1 (0.6)	1 (0.2)	0.48	0	0	
Chylous leakage	0	3 (0.7)	0.56	0	0	
Anastomotic leakage	1 (0.6)	10 (2.3)	0.31	0	1 (1)	1.00
Ileus	5 (2.9)	11 (2.5)	0.78	2 (3)	3 (4)	1.00
Pneumonia	2 (1.2)	5 (1.2)	1.00	1 (1)	1 (1)	1.00
Incision complications	18 (10.6)	5 (1.2)	< 0.001	7 (10)	0	0.013
Abdominal infection	3 (1.8)	2 (0.5)	0.14	1 (1)	0	1.00
Stoma-related complications	1 (0.6)	3 (0.7)	1.00	0	0	
Clavien–Dindo classification, *N* (%)			0.011			0.11
No complication	135 (79.4)	383 (88.2)		59 (81)	66 (90)	
Grade 1	8 (4.7)	10 (2.3)		3 (4)	0	
Grade 2	25 (14.7)	38 (8.8)		10 (14)	6 (8)	
Grade 3a	0	2 (0.5)		0	1 (1)	
Grade 3b	0	1 (0.2)		0	0	
Grade 4a	2 (1.2)	0		1 (1)	0	

IQR, interquartile range; SSPR, successful sphincter-preserving resection.

remained unchanged, suggesting that the advantages of SSPR continued to be evident. These benefits included a decrease in incision length, reduced estimated blood loss, shorter hospital stay, and a lower incidence of incision complications in the SSPR group.

Discussion

Being free of a permanent stoma is one of the most important priorities for rectal cancer patients, ranked alongside a cure for the cancer itself[19]. There has been an increase in the use of SPR for rectal cancer without a decrease in pelvic local control over the past few decades[4,20]. The reported median rates of SPR in previous population-based studies for rectal cancer range from 62 to 77%[21], which is in line with the present result. However, statistically significant variation among hospitals regarding SPR receipt was observed[3]. Early investigations focused on this issue found that the rates of APR use varied from 20.1 to 39.3% across cancer networks in England, while the variation was even more noticeable across hospital trusts, with rates varying from 8.5 to 52.6%. In addition, there was substantial variation across surgical teams[3]. A study of 7 US cancer institutions found that the biggest variation in SPR rates was for tumours less than 8 cm from the anal verge. For instance, one institution performed SPR for only 22% of patients with 4–6 cm tumours, while another performed it for 83%[7]. In the present study, with a special focus on low rectal cancer, the magnitude of the variation in the rate of SSPR was more pronounced, ranging from 37.7 to 94.4%, among the tertiary hospitals included across China.

Although some patients will always require an APR due to the closeness of the tumour to the anal verge or direct invasion of the sphincter, in a larger proportion of patients, either APR or SPR may be appropriate from the perspective of surgical oncology. A previous study showed that infiltration of the external anal sphincter is extremely rare for low rectal cancer (~5%)[22]. This may result in some patients needlessly undergoing an APR. For instance, a population-based retrospective cohort study from Canada found that 29% of patients underwent a potentially inappropriate permanent colostomy[4]. In fact, hospital was a stronger predictor of SPR receipt than any patient characteristic, explaining 32% of procedure choice based on SEER-Medicare linked data[21]. Thus, identifying the potential missed opportunities for sphincter preservation might offer the potential for performance improvement. Some researchers advocate for the use of the APR rate as a national performance measure, and there has been a growing appreciation of the importance of undertaking national comparative audits to monitor surgical performance[3]. On the other hand, identifying borderline cases where complete SPR is unfeasible is an equally important question. Thus, SPR adherence to oncological standards, namely,

SSPR, instead of SPR alone was employed as the primary end point of this post hoc analysis.

SSPR was defined by SPR with clear DRM and CRM and complete or nearly complete mesorectal excision. Uncertainty remains on the prudence of performing SPR. Minimizing DRM while maintaining survival may enable offering SPR. Retrospective analysis shows excellent results with R0 resection of LARC after CRT, even with DRM less than 1 cm[23]. The completeness of the resected mesorectum is a quality metric in rectal cancer surgery and is an important predictor of local and overall recurrences[24,25]. The prognostic association between CRM and oncological outcomes has been widely confirmed[26]. It is noteworthy that CRM is influenced not only by operative techniques but also by the incorporation of a multidisciplinary treatment strategy[27]. The quality metric included a composite of DRM and CRM status, and intact mesorectal excision has been recognized as a measurement to identify gaps in surgical quality[8].

There is evidence suggesting that clinical parameters can predict the probability of SPR in rectal cancer[28]. Understanding these parameters is crucial to ensuring equitable availability of sphincter preservation. The present multicenter study identified several baseline and early post-CRT predictors for SSPR, including lower pre-CRT and post-CRT BMI, higher tumour distance from the anal verge both before and after CRT, the occurrence of clinical T downstaging, lower clinical N stage whether measured by MRI and smaller tumour size. Currently, evidence is mounting to show that the distance of the tumour from the anal verge represents an important predictor of sphincter-preserving surgery[7,20,29]. Moreover, tumour distance from the anal verge was the only preoperative determinant of permanent stoma creation, including patients who underwent permanent ileostomy formation after sphincter-preserving surgery[30]. Previous studies have found a link between clinical T-size and sphincter preservation[31], while depth of invasion was also demonstrated to be strongly associated with SPR[29].

Notably, the effect of CRT on the rate of SPR use in rectal carcinoma patients is still a controversial topic. In general, the improvement in the rates of SPR after CRT was most striking among patients with low-lying LARC[20]. Previous investigations have shown that patients with distal tumours 3 cm or less from the anal verge have a higher SPR after the clinical complete response (cCR) following CRT[20]. Patients with cCR had a 44% chance of undergoing a sphincter-preserving procedure, compared to 22% for those without cCR. In this study, all patients with clinical stage II/III rectal cancer received preoperative CRT. However, patients with pathological complete response (pCR) had a similar SPR rate to those without pCR (22.1% vs. 14.1%, $P = 0.16$). Since pCR status is not known before surgery, it is not useful for determining the feasibility of SPR. Instead, the occurrence of clinical T downstaging, which can be assessed before surgery, was used to construct AI models for predicting SPR in the present study. In addition, the present results highlighted the importance of clinical N stage as a potential indicator of SSPR. In addition to its value in predicting SSPR, our previous single-centre study suggested ypN1–2 stage as an independent poor prognostic factor for worse disease-free survival in low rectal cancer patients who underwent ISR[32]. A previous post hoc analysis of the CAO/ARO/AIO-04 randomized phase III trial showed that obesity was associated with an increased risk of APR[33], which is congruent with the present findings. In clinical practice, the assessment of which patients may have a difficult pelvis to surgically dissect relies empirically on the BMI level. A previous single-centre study revealed that sphincter preservation was more likely to succeed when the distance from the anal verge was greater than or equal to 5 cm and BMI was less than 25 kg/m^2[34].

An accurate prediction model of SSPR before surgery is patient-centred and an essential part of preoperative counselling. This study found that different AI models were able to predict SSPR, with the LR and LGB models outperforming qualitative analysis in independent testing. Machine learning, a subdomain of AI, involves the analysis of data to identify statistical patterns and make predictions on unseen data. AI, on the other hand, refers to machines that can perform tasks typically done by humans. In this study, we have developed an online calculator using the LGB model in the Streamlit Python-based framework to aid in clinical decision-making (Streamlit installation required). This tool can automatically predict the feasibility of SSPR for patients with locally advanced low rectal cancer after neoadjuvant CRT when the necessary six parameters are provided. These parameters consist of post-CRT weight, tumour distance from the anal verge before and after CRT, the occurrence of clinical T downstaging, as well as clinical N stage determined by MRI and clinical assessment. It is crucial to emphasize that machine learning models do not consider specific cutoff points for each parameter. Instead, these models utilize non-linear manifolds in higher-dimensional spaces to effectively analyze relevant data. By treating parameters as a black box, these models assess subsets of variables based on their predictive capability. As a result, they draw comprehensive conclusions regarding the feasibility of achieving SSPR. To demonstrate how surgeons can utilize AI in patient selection for SPR, we have presented three cases (Case 1 shown in Fig. 6, Supplementary 8: video, Supplemental Digital Content 8, http://links.lww.com/JS9/C420 for all three virtual cases). With the aid of the LGB model, surgeons could support patients by providing estimates of the potential chance of SPR and its oncological safety. On the other hand, this LGB model system enables other specialty centres to assess the need for additional specialized colorectal training by providing a benchmark for SPR. Heldenberg *et al*.[35] reported that special training in colorectal surgery facilitated the surgeon, in keeping with the principles of oncologic surgery, to preserve the anal sphincter mechanism.

The present study showed that patients with SSPR have better short-term outcomes within 30 days than non-SSPR patients, as it may reflect better surgical technique. In addition, a retrospective cohort study found that APR was associated with higher rates of postoperative complications (wound infections and wound dehiscence) and longer hospital stays than low anterior resection[36]. Interestingly, our data revealed that laparoscopic surgery had a higher SSPR than laparotomy, which was consistent with a previous study[37]. This was probably because the laparoscopic system provides greater visibility and access to the dissection planes deep in the lower pelvic cavity when compared to open surgery.

The strengths of this study include the multicenter cohort of patients with comprehensive detailed patient-level data. However, several limitations are associated with the present study that should be considered. First, this study is a retrospective post hoc analysis of prospectively sampled data from the LASRE trial, which had a different end point. As a result, important

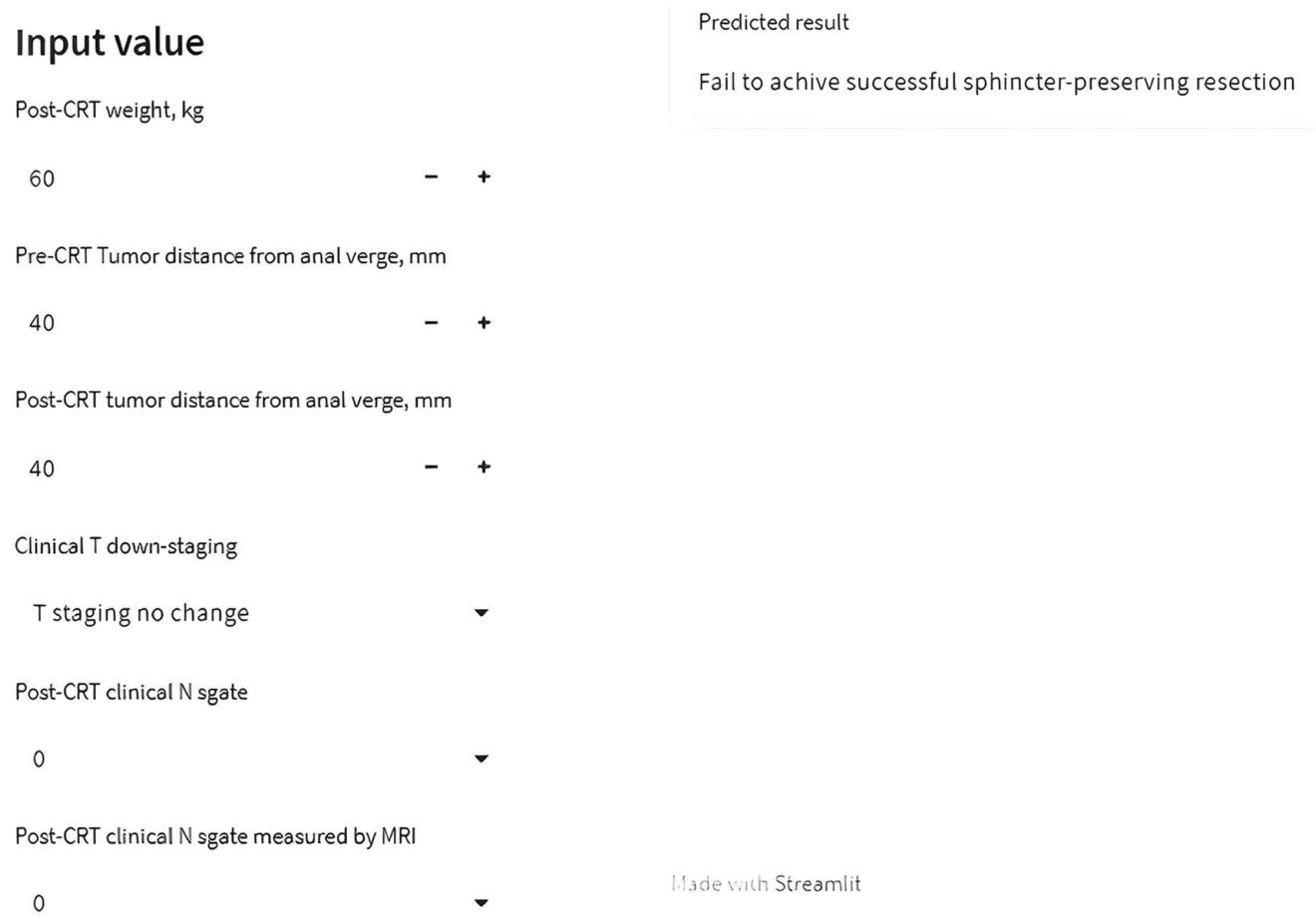

Figure 6. The practical implementation of a light gradient boosting (LGB) model. It demonstrates the use of the LGB model in a specific case (case1 in the video). The case involves a rectal cancer patient with a weight of 60 kg and a tumour located 4 cm away from the anal verge. Despite receiving neoadjuvant chemoradiotherapy, the tumour remains at the same distance, and there is no significant downstaging in the clinical T stage. The clinical N stage, determined through MRI and clinical assessment, is stage 0. By inputting the example values of these six required features into the LGB model, it predicts that successful sphincter-preserving resection is unachievable in this particular case.

variables related to SSPR, such as tumour fixation, patient willingness for sphincter preservation, and preoperative evaluation of anal function, were not specifically collected or analyzed in this study. Conducting a randomized controlled study that randomly assigns patients to undergo sphincter-saving surgery or not is challenging due to ethical and oncological concerns. Therefore, future studies should focus on conducting more detailed evaluations of critical variables associated with sphincter preservation to enhance the accuracy of the models. Secondly, another limitation of our study is the presence of selection bias inherent in retrospective studies. It is important to acknowledge that comparing the baseline demographic and clinicopathological characteristics of patients who underwent SSPR and those who did not is a traditional univariate analysis of predictors for SSPR. In this specific case, there were imbalanced covariates observed between the groups, including the distance of the tumour from the anal verge. This variable holds the potential to predict SSPR. However, when evaluating the short-term outcomes between the SSPR and non-SSPR groups, there is a selection bias due to the uneven distribution of covariates. Moreover, there was a significant variation in the rate of SSPR among the included hospitals, which may not be fully accounted for by statistical operations. To address this bias, we conducted widely recognized PSM analyses, adjusting for a comprehensive range of measured confounders. The outcomes of our study revealed that the advantages of SSPR remained significant even after conducting PSM. Third, the most important factor in assessing the quality of rectal cancer surgery should be the rate of local recurrence, which was not available in this post hoc analysis. With longer follow-ups, we will be able to determine this in our cohort after the publication of long-term outcomes of the ongoing LASRE trial. It is crucial to emphasize that the inclusion criteria used to define a SSPR are the absolute minimum parameters necessary for sphincter preservation; otherwise, the procedure should not be undertaken. In addition, the long-term functional outcomes, quality of life, and permanent stoma risk of SPR performed in this trial were not evaluated. Although patients avoiding permanent stoma with ISR accept a suboptimal continence level[38], a minority of patients wished that they had had a permanent stoma rather than anastomosis due to impaired faecal continence[39]. Thus, a more comprehensive metric regarding SPR that estimates both oncological clearness and functional satisfaction might be needed.

In conclusion, the rate of SSPR exhibits substantial variation, and the application of AI models has demonstrated the ability to predict SSPR for low rectal cancers with commendable accuracy.

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Ethical approval

Ethical approval for this study was provided by the central ethics committees of Fujian Medical University Union Hospital, 29 Xin-Quan Road, Fuzhou, Fujian 350001, People's Republic of China on 28 Sep 2013 (IRB number: 2013051 for LASRE trial). All participants provided written informed consent before enrolment. A copy of the written consent is available for review by the Editor-in- Chief of this journal on request. Moreover, all participants in the LASRE trial provided written informed consent before enroling, and all data were collected and analyzed anonymously. This present retrospective study qualifies for a waiver of informed consent by the ethics committee (IRB number: 2023KY210 for this post hoc restrospective study of LASRE trial).

Consent

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Author contribution

Study concept or design: X.W., W.J. Data collection: X.W., W.J., Y.D., Z.C., Z.Z., Y.S., Z.X., X.L., S.H., Y.L., Y.H., and P.C. Data analysis or interpretation: X.W. Writing the paper: X.W. Paper reviewed: Y.H., and P.C.

Conflicts of interest disclosure

The authors declare no competing interests.

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Guarantor

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Data availability statement

The data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Provenance and peer review

None.

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