Sphincter-preserving surgery for low-middle rectal cancer: Can we predict feasibility with high-resolution magnetic resonance imaging?

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Abstract
The study proposed to evaluate the feasibility of predicting sphincter-sparing surgery (SSS) preoperatively in low-middle rectal cancer by using magnetic resonance (MR).

The study included both retrospective and prospective design. In the retrospective design, the distance from lower edge of tumor to upper margin of the internal sphincter (Dis1) and distance to anal verge (Dis2) were measured on MR, the distance to anal verge recorded by colonoscopy (Dis3) and digital rectal examination (Dis4) were also obtained. ROC analysis was conducted and cut-off value was determined with overall and stratified analysis. The prospective part was designed to validate the predictive capability of the optimal distance.

The retrospective design included 278 patients with middle or lower rectal adenocarcinoma, the prospective design included 106 patients with neoadjuvant therapies. The primary outcome was the actual surgical method and pathological distal resection margin. Dis1 obtained from MRI presented better performance than other distances in determining the surgical approach, with AUC of 0.997 (95% CI, 0.994–1.000). Dis1 was selected as the optimal distance and a cut-off value of 2 cm was determined. Dis1 and the cut-off value were also validated in the prospective sample, with AUC of 0.996 (95% CI, 0.989–1.000) and an overall accuracy of 99.1%. MR-based distance from lower edge of tumor to upper margin of the internal sphincter could be used to help the surgeons to predict the feasibility of SSS preoperatively.

Abbreviations: APR = abdominoperineal resection, AUC = area under ROC, BMI = body mass index, CRM = circumferential resection margin, nCRT = neoadjuvant chemoradiotherapy, NPV = negative predictive value, PPV = positive predictive value, ROC = receiver operator characteristic, Sen = sensitivity, Spe = specificity, SSS = sphincter-sparing surgery.

Keywords: diagnostic accuracy, magnetic resonance imaging, rectal cancer, sphincter-sparing surgery

1. Introduction
Surgery for rectal cancer aims to completely resect the tumor and preserve the continuity of the bowel and the function of the anal sphincter. In recent decades, there has been great progress in the treatment of rectal cancer, which can be mainly attributed to 2 factors: the introduction of total mesorectal excision (TME) and neoadjuvant chemoradiotherapy (nCRT) for locally advanced cancers.[1,2] The combination of TME and nCRT not only significantly reduces local recurrence rates, but also provides greater possibilities for sphincter preservation in patients with low-middle rectal cancer.[1,3]

Previously, abdominoperineal resection (APR) was the optimal surgical approach for low-middle rectal adenocarcinomas. In recent years, because of better understanding of perirectal lymphatic drainage and advances in surgical techniques, the safe distal surgical resection margins have been reduced from 5 to 2 cm.[3–7] A safe distal margin of 1 cm is also accepted for patients after nCRT, as it does not seem to increase local recurrence rates.[8] Therefore, these advancements allow the shift from APR to sphincter-sparing surgery (SSS).

Intersphincteric resection has been shown to increase the chances of preserving the sphincter’s structure in patients with very low rectal cancers. However, because complete or partial resection of the internal sphincter leads to inferior defecatory control, this technique is still controversial.[9] Determining the feasibility of preserving the anal sphincter and its function is crucial when treating patients with low-middle rectal cancer. Although the feasibility of SSS can only be definitively established during surgery itself, preliminary assessment before surgery is still important for informing patients and preparing for the procedure. The decision to attempt SSS rather than APR for low-middle rectal cancer is often made after careful consideration of several factors, including sex, tumor stage, circumferential margins, health status, and patient intention. The
distance from the tumor edge to the anal verge is the most important factor in making surgical decisions. Traditionally, surgeons determined this distance preoperatively by colonoscopy and digital rectal examination.

At present, high-resolution magnetic resonance imaging (MRI) is accepted by surgeons as the best means of providing precise measurements of the distance from the tumor edge to the anal verge with multiplanar imaging. This study aimed to evaluate the accuracy of high-resolution MRI for predicting the feasibility of SSS in low-middle rectal cancer preoperatively. We aimed to discover a practical MRI indicator, and to compare the capabilities of MRI, colonoscopy, and digital rectal examination measurements for predicting the feasibility of SSS.

2. Methods

2.1. Study population

This study included both retrospective and prospective design elements (patient enrollment shown in Supplementary Fig. 1, http://links.lww.com/MD/B790). Both parts were approved by our institutional review board, and the requirement for informed consent was waived. First, we retrospectively collected the data of patients from June 2007 to December 2009 in our hospital. The inclusion criteria were patients with histologically confirmed primary adenocarcinoma located in the middle or low rectum (<10 cm from the anal margin by colonoscopy); patients who received colonoscopy, rectal digital examination, and preoperative MRI examinations; and patients who underwent radical tumor resection. The exclusion criteria were patients with other malignant tumors; patients who received non-radical resection surgery; patients whose MRI images could not be obtained or interpreted. MRI images after nCRT were necessary for patients who received neoadjuvant therapy. Data regarding 320 cases of rectal cancer were retrospectively collected. Forty-two cases were excluded (8 cases combined with other tumors, 29 cases of exploratory laparotomy or fistula (Hartmann), 5 of missing magnetic resonance (MR) images). Finally, 278 cases were included (195 cases of SSS and 83 cases APR). There were 196 men and 82 women, and the mean age was 59 ± 8 years.

Second, we prospectively enrolled consecutive rectal cancer patients who received nCRT in our hospital from January 2013 to February 2014. Patients with locally advanced rectal cancer and those scheduled to receive nCRT were also included. The other inclusion and exclusion criteria were the same as retrospective design. All eligible patients were assigned to undergo MRI both, before and after neoadjuvant therapy. A total of 106 patients were included, including 81 men and 25 women, with an average age of 57 ± 11 years.

2.2. MR data acquisition

Retrospective study: 1.5T MRI scanner (GE SignaEchoSpeed Plus with EXCITE II), 8-channel body phased array coil. Gradient field intensity: 33 mT/min, gradient switch rate: 120 mT/m/msec.

Prospective study: 3.0 T MRI scanner (GE Discovery MR 750), 8-channel body phased array coil. Scan parameters are shown in Supplementary Table 1, http://links.lww.com/MD/B790.

Ten milligrams of anisodamine (654-2) was administered by intramuscular injection 10 minutes before MRI examination to reduce bowel peristalsis.

All MRI images were evaluated independently by 2 radiologists (Zhu HB and Sun Y, who have 8 and 18 years’ experience, respectively). For the patients who received nCRT, the posttreatment MRI was selected as the definitive measurement images. The reviewers were blinded to all clinical information (digital examination and colonoscopy). The distance from the lower margin of tumor to the superior edge of the internal sphincter (the point at which the levator ani muscle attaches to the rectum) was measured (Dis1, Fig. 1). The surgeons preferred this landmark over the intersphincteric plane because it was easier to identify on MRI, particularly on sagittal and coronal T2-weighted images, using conventional workstation tools. In addition, because the lower rectum and the anal canal do not form a straight line, Dis1 and the length of the anal canal were added to determine the distance from the lower margin of tumor to the anal verge (Dis2, Fig. 2).

2.3. Digital rectal examination and colonoscopy

Digital rectal examination was performed after anesthesia during surgery. The value of the measurements was carried forward to the analysis (Dis3).

Figure 1. Sagittal (A) and short-axial (B) T2-weighted images obtained in a 56-year-old man with poorly differentiated rectal adenocarcinoma with local lymph node metastasis. The distance from the lower edge of the tumor to superior margin of internal sphincter (Dis1) by magnetic resonance imaging was 31 mm (arrowhead). Finally, the patient gave consent for low rectal anterior resection, and the tumor was staged as pT3N1c.
Fiber colonoscopy was conducted by professional endoscopic physicians (during 1 week before the surgery), and the distance from the lower edge of the tumor to the anal verge was recorded (Dis4).

2.4. Neoadjuvant therapy and surgery
All patients underwent an MRI for initial staging. In total, 116 patients from the retrospective study and all patients from the prospective study proceeded to receive neoadjuvant therapy (long-course intensity-modulated radiochemotherapy, GTV 50.6 Gy/CTV 41.8 Gy, 22 fractions in total; capecitabine 825 mg/m²/bid by oral administration). At 8 weeks after the completion of neoadjuvant therapy, these patients underwent a second MRI scan. All patients underwent total mesorectal excision surgery in our hospital within 2 weeks.

2.5. Histopathology
Tumor stages were assessed using the 7th AJCC TNM classification.[13] Formalin-fixed specimens were examined macroscopically and microscopically by a pathologist who specialized in gastrointestinal pathological analysis (Dr. Li, 15 years’ experience). The pathological T and N stages and characteristic factors to predict the possibility for SSS, and area under the ROC curves (AUCs) were calculated and compared. A cut-off value was determined using the optimized Youden index method. Sex, BMI (body mass index), the location of the tumor (anterior, posterior, and circle of the rectal wall), pathological T stage, and neoadjuvant therapy were used as stratification factors to investigate discrepancies between cut-off values in the stratified population.

All retrospectively collected patients were followed up at 3-month intervals for 2 years, and then at 6-month intervals until death. Relapse-free survival (RFS) was measured from the date of surgery until local recurrence, and patients without local recurrence were censored at the last follow-up. The cut-off date was April 30, 2013. The median follow-up period was 44 months (1–90 months). The Kaplan–Meier method with log-rank estimates was conducted to compare RFS between patients in the SSS and APR groups.

All analyses were performed with SPSS software (version 22.0), and a P-value < .05 was considered statistically significant.

### 3. Results

#### 3.1. Evaluation of indicators associated with SSS

Perfect agreement was observed in the measurements of Dis1 and Dis2 (ICC = 0.9908, 95% CI, 0.9875–0.9941; 0.9314, 95% CI, 0.9166–0.9462, respectively). In the analysis of retrospective samples, patients in the SSS group had statistically higher Dis1, Dis2, Dis3, and Dis4 than patients in the APR group, and all differences had a P-value < .001 (Table 1). For the diagnosis of SSS, these 4 indicators produced AUCs of 0.997, 0.816, 0.866, and 0.919, respectively. Dis2, Dis3, and Dis4 showed similar AUCs, and Dis1 showed a statistically larger AUC than the other 3 indicators (Table 2). Thus, Dis1 was selected as the optimal indicator for assessing the feasibility of SSS (Fig. 1).

Pathologically clear distal resection margins were found in all patients who underwent SSS surgery. In patients who underwent APR, 2 patients (2.4%) were found to have distal resection margin involvement. Patients who underwent SSS showed similar RFS rates as those who underwent APR (univariate log-rank P = .881).

#### 3.2. Stratified analysis and determination of cut-off values

Stratified analysis yielded the cut-off value of 2 cm, which was selected from the different stratiﬁed groups (Table 3). Multivariate logistic regression with a backward stepwise method showed that only Dis1 was independent factors for determining SSS.

### Table 1

| Distance, cm | Dis1 | Dis2 | Dis3 | Dis4 |
|-------------|------|------|------|------|
| SSS group   | 4.82 ± 2.88 | 7.07 ± 3.55 | 5.23 ± 1.55 | 5.13 ± 2.78 |
| APR group   | 0.94 ± 2.61 | 4.27 ± 2.50 | 3.85 ± 1.46 | 3.51 ± 1.21 |
| P           | < .001 | < .001 | < .001 | < .001 |

APR = abdominoperineal resection, SSS = sphincter-sparing surgery.
Dis1/C2.0cm suggested that SSS was feasible, while Dis1/C2.0cm suggested that it was not (Figs. 1 and 2).

3.3. Prospective validation of Dis1 and the selected cut-off values

In analysis of the prospective sample, the AUC of Dis1 was 0.996 (95% CI, 0.989–1.000) for assessing SSS (Fig. 3). An accuracy of 99.1% (105/106) was obtained when a cut-off value of 2cm was used, with only one case of misdiagnosis reported. The actual proportion of SSS in this prospective study was 54.7% (58/106), while the proportion of MRI-determined nCRT was only 41.7% (45/108), meaning that nCRT afforded 13 patients the opportunity to receive SSS who previously would have lost their anal sphincter. nCRT raised the proportion of patients undergoing SSS by 13%. All patients obtained pathologically clear distal resection margins (Table 4).

4. Discussion

Surgeons usually make preoperative judgments of the feasibility of SSS for patients with low-middle rectal cancer depending on the results of rectal examination and colonoscopy. SSS is often considered infeasible if the distance between the lower edge of the tumor and the anal verge is <5 to 6cm. Conventionally, a safe distal resection margin (from the tumor to upper edge of the internal sphincter) is considered to be ≥2 cm (results were showed in the Supplementary Table 2, http://links.lww.com/MD/B790). Dis1/C2.0cm suggested that SSS was feasible, while Dis1/C2.0cm suggested that it was not (Figs. 1 and 2).

Table 2
Diagnostic performance for predicting sphincter preserving surgery using ROC curves.

| Parameters | Dis1 | Dis2 | Dis3 | Dis4 |
|------------|------|------|------|------|
| Mean±SD, cm | 3.61±3.32 | 6.23±3.51 | 4.68±1.69 | 4.54±2.08 |
| AUC (95% CI) | 0.997 (0.934–1.000) | 0.814 (0.692–0.903) | 0.866 (0.754–0.940) | 0.919 (0.819–0.974) |
| Cut-off value, cm | <.001 | <.001 | <.001 | <.001 |
| Sensitivity | 99.2% | 86.3% | 82.9% | 84.4% |
| Specificity | 95.0% | 91.1% | 81.8% | 79.9% |
| PPV | 96.8% | 93.5% | 81.0% | 80.8% |
| NPV | 98.7% | 81.8% | 83.7% | 76.6% |
| Accuracy | 97.5% | 88.3% | 82.3% | 84.0% |

Table 3
Stratified analysis of Dis1 toward gender, pathological T stage, and nCRT.

| Factors | No. | Dis1, cm | Cut-off value, cm |
|---------|-----|----------|------------------|
| Gender  |     |          |                  |
| Male    | 196 | 3.70±3.39 | 2.0              |
| Female  | 82  | 3.41±3.17 | 2.2              |
| Pathological tumor stage | | | |
| 0       | 7   | /        | All              |
| 1       | 9   | 3.69±3.73 | 2.0              |
| 2       | 58  | 2.58±4.00 | 2.0              |
| 3       | 172 | 3.06±3.33 | 2.0              |
| 4       | 32  | 4.99±4.20 | 2.0              |
| Pathological CRM+ | 62  | 2.29±3.27 | 2.0              |
| –       | 216 | 4.01±3.24 | 2.3              |
| Neoadjuvant therapy | | | |
| No      | 162 | 3.78±3.26 | 2.0              |
| Yes     | 116 | 3.45±3.09 | 2.0              |
| BMI, kg/m² | | | |
| <25     | 196 | 3.44±3.07 | 2.1              |
| 25–27.99 | 58  | 4.00±4.24 | 2.0              |
| ≥28     | 24  | 3.84±3.58 | 2.5              |
| Location |     |          |                  |
| Anterior | 72  | 4.04±4.28 | 2.4              |
| Posterior | 70  | 3.67±3.53 | 2.0              |
| Circle  | 136 | 3.45±3.29 | 2.0              |

BMI = body mass index, CRM = circumferential resection margin.

Figure 3. (A) Receiver operator characteristic curves of Dis 1 to 4 for predicting the feasibility of sphincter-sparing surgery. (B) Receiver operator characteristics curve of Dis1 for predicting sphincter-sparing surgery in the prospective sample. AUC=0.996 (95% CI, 0.989–1.000).
bleeding. However, it is impossible to obtain precise measurements from colonoscopy and digital rectal examination, which can only measure the distance from the lower edge of tumor to the anal verge. Therefore, surgeons cannot make accurate judgments based only on the results of colonoscopy and digital rectal examination.

Digital rectal examination is simple, convenient, and quick. However, it is imprecise, easily affected by sex, physical size, anesthesia status, patient’s position, and limited by the experience of the surgeon. The accuracy of assessing the distance using digital rectal examination is only 48.3% and 64% for middle and low rectal cancers, respectively. It is still controversial whether colonoscopy can accurately determine tumor location, and Piscatelli et al suggested that the accuracy was only 79%. Rigid straight sigmoidoscopy is thought to be more accurate than fiber colonoscopy, and enables adjustment of surgical options in 25% of patients. However, rigid straight sigmoidoscopy is an invasive examination and may cause mucosal injury or local bleeding.

In this study, the distance from the lower edge of tumor to the anal verge was measured using colonoscopy, digital rectal examination, and MRI. The results showed that we could accurately evaluate the feasibility of SSS by colonoscopy and digital rectal examination in more than 80% of patients using a cut-off value of 5 cm. An accuracy of 88% could be obtained for MRI using a cut-off value of 5.5 cm, which was very similar to the results of colonoscopy, digital rectal examination.

In this study, we tried to measure the distal margin directly using MRI. A cut-off value of 2 cm was obtained through the retrospective study, and produced an accuracy of 97.5% for predicting the feasibility of SSS, with an AUC of 0.997. MRI-determined distance to the upper margin of the internal sphincter presented higher accuracy in evaluating the feasibility of SSS compared to the distance to the anal verge, which could be acquired by colonoscopy, digital rectal examination, and MRI examination. Due to individual variation in the length of the anal canal, it is easy to understand why the distance to the upper margin of the internal anal sphincter acquired by MRI was more accurate.

Previous studies have suggested that the minimum safe distal margin is 2 cm. Although mucosal invasion occurs in as many as 40% of cases, mucosal invasion of >1 cm accounts for only about 4% to 6% of cases. We measured the linear distance on MRI images to ensure that the measurements were repeatable and convenient and obtained a cut-off value of 2 cm, which accorded with safe distal margins during surgery. The effectiveness of this cut-off value was validated using the prospective sample, with an AUC of 0.996 and a diagnostic accuracy of 99.1%. This cut-off value has good practical value and can be applied in a wide variety of situations.

In this study, we also established the cut-off value in subgroups divided by sex, BMI, the location of the tumor, preoperative T stage, CRM, and neoadjuvant therapies, and a cut-off value of 2 cm was selected in subgroup. SSS was considered becoming increasingly difficult as BMI rises or an anterior tumor compared to a posterior one, which many surgeons have suggested were important. However, only Dis1 was the most important factor in determining the possibility of SSS. BMI was significantly related with longer operative time and postoperative morbidity, however, it did not affect the option of the procedure, which was similar to the results of Gu et al.

This study has some limitations. First, the operations were not conducted by one surgeon, and thus the selection of surgical procedures may have been affected by subjective judgment. Second, the patients undergoing intersphincteric resection were not included. With the advancements in stapled anastomosis and improved transanal anastomosis techniques, intersphincteric resection has become more widely accepted in lower rectal cancer cases. Third, the relationship between anal sphincter function after SSS and MRI data was unclear. In this study, MRI was not used to evaluate anal sphincter function, which was mainly obtained from physical examination.

5. Conclusion

MRI-based distance from the lower edge of tumor to superior margin of the internal sphincter could be used to preoperatively evaluate the feasibility of SSS, and the distance of >2 cm suggests the feasibility of SSS. It is recommended that this distance should be regularly provided in clinical MRI reports. This might help surgeons to make accurate preoperative judgments.

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