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Review Article

Laparoscopic intersphincteric resection for low rectal cancer: technique, oncologic, and functional outcomes

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Abstract

Intersphincteric resection (ISR) is a sphincter-saving procedure indicated for very low rectal cancer as an alternative to abdominoperineal excision (APE) in order to avoid permanent stoma that is associated with several complications and has negative influence on quality of life. Electronic databases including PubMed/Medline were queried to search the current literature for studies evaluating the technique and outcomes of ISR for distal rectal cancer. Some studies demonstrated that the oncologic outcome of ISR is comparable to APE. Other studies concluded good functional outcome of ISR, even comparable to low anterior resection. The most important functional problem after ISR is the development of fecal incontinence which improves by time and can be further improved by electric stimulation and biofeed back. Laparoscopic ISR had comparable outcomes to the open and robotic-assisted approaches. Predictors for poor oncologic and functional outcomes and for complications after ISR have been recognized which can help optimize the selection of patients with low rectal cancer for ISR.

Keywords: intersphincteric resection; low rectal cancer; technique; oncologic; functional; outcome.

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Background

Rectal cancer represents a true diagnostic and therapeutic challenge to colorectal surgeons. The treatment of rectal cancer is essentially based on the stage of disease at the time of diagnosis and the location of the tumor in the rectum. For early and localized stages (I-III) surgery is considered the standard of care, yet its role in advanced, metastatic rectal cancer is quite limited.

The distance of the tumor from the anal verge is also an authoritative factor for the decision making in rectal cancer. Rectal cancer is generally located within 12 cm from the anal verge according to the NCCN definition and is subdivided according to its location into upper, middle, and lower rectal cancer. The upper and middle rectal cancers are usually managed with sphincter-saving procedures including low anterior resection (LAR) and ultra-low anterior resection (ULAR). However, radical excision of the entire rectum and anal canal in the procedure of abdominoperineal excision (APE) is required in certain cases including lower-third rectal cancer infiltrating the anal sphincters, significant sphincter dysfunction, and pelvic fixation [1, 2].

Tumors located at the lower third of the rectum poses a unique challenge in management as the surgeon attempts to balance the need for achieving radical cure and maintaining the physiologic functions of the anorectum. For very distal rectal cancers with proximity to the anal sphincters, APE was applied in all cases on a routine basis. However, in order to avoid permanent colostomy along with its associated complications including retraction, prolapse, and ischemia, in addition to its negative

impact on the quality of life of patients [3], the intersphincteric resection (ISR) procedure was devised by Schiessel and colleagues [4].

Technique of ISR

The term ISR was initially devised by Lyttle and Parks [5] in 1977 to describe resection of internal anal sphincter (IAS) in management of inflammatory bowel diseases. Twenty years later, ISR was used for management of distal rectal tumors in 38 patients with rectal cancer, carcinoid tumor, or large villous adenoma [4]. Patients with T4 tumors infiltrating the pelvic floor muscles were excluded from the study. ISR was performed with patients placed in the Lloyd-Davies position by a team of abdominal and perineal surgeons.

The original technique of ISR was as follows: after the abdominal surgeon mobilizes the sigmoid and the rectum down to the pelvic floor level, the perineal surgeon evaluates the tumor synchronously with the abdominal surgeon. The anal mucosa is raised by injection of POR-8 solution, then is incised in a circular fashion to expose and divide the internal anal sphincter (IAS) either completely or partially if the cancer is above the anal canal or in benign conditions.

Dissection is carried out in the intersphincteric plane, guided by the abdominal surgeon. The tumor is then resected with a distal safety margin of at least 2 cm. The bowel continuity is restored by delivering the proximal end of the descending colon into the pelvis and performing a hand-sewn coloanal anastomosis. To protect the very low coloanal anastomosis, a covering transverse colostomy is done in all

patients.

While there was no mortality recorded in the original report, early complications occurred in seven patients, including hemorrhage, small bowel fistula anastomotic leakage (AL), and stricture. Late complications developed in four patients including intestinal obstruction and anastomotic stricture. Local recurrence developed in 13% of patients and liver metastasis in only one patient, all local recurrences were extramural.

ISR was technically classified into total ISR in which dissection is carried out in the intersphincteric space and the entire IAS is resected, subtotal ISR in which dissection is done between dentate line and intersphincteric plane with two-third resection of the IAS, and partial ISR in which dissection is conducted at the dentate line only with one-third resection of the dentate line [6]. Resection of IAS is what distinguishes ISR from sphincter-saving hand-sewn coloanal anastomosis [7].

Zhang et al. [8] compared total, subtotal, and partial ISR for low rectal cancer in regards oncologic and functional outcomes. Among 79 patients, partial ISR was used in 28 patients with tumors located less than one cm from the anal sphincter, subtotal ISR was used

Indications for ISR

ISR was initially indicated for non-metastatic, very distal rectal cancer located within five cm of the anal verge [4]. The surgical indication for ISR has been investigated by Bamba and colleagues [10] who evaluated the depth of anal canal invasion (DACI) by MRI to determine whether the assessment of the conjoined longitudinal muscle (CLM)

in 34 patients with tumors located between the dentate line and intersphincteric groove, and total ISR in 17 patients who presented with intra-anal tumors. The three groups had comparable 3-year disease-free survival rates and 3-year local relapse-free survival rates. Anal functions were assessed in 38 patients who did not receive neoadjuvant therapy and were followed after ileostomy closure, 73.7% of which had good continence with Wexner incontinence score ≤ 10 . Anal functions were worse in patients with chronic anastomotic stenosis compared to those without stenosis.

Although coloanal anastomosis was originally performed by hand sewn technique, some investigators advocated using stapled anastomosis alternatively. Cong et al. [9] compared laparoscopic ISR with hand sewn coloanal anastomosis ($n=22$) and ISR with stapled anastomosis ($n=93$) regarding anastomotic complications and functional outcome. The stapled anastomosis technique had significantly lower rates of AL and stenosis than the hand sewn technique. Both techniques had comparable functional results with no significant differences in Saito function questionnaire and Wexner continence score.

can guide the indication for ISR. Sixty-six patients with T1-T4 distal rectal cancer were evaluated by MRI to outline the CLM as clear, unclear, or absent which implied invasion by the tumor. In patients with T0-T2 tumors the CLM was clear in 30 patients and unclear in five. Whereas 25 patients with T3-T4 tumors showed invasion. The study found using clear CLM to predict T0-T2 DACI to have a sensitivity of

78.9% and specificity of 91.9%.

In an attempt to optimize patient selection for ISR, Narui et al. [11] retrospectively reviewed the specimens of 53 patients with T2-T3 rectal cancers who were treated with APE. The authors measured vertical invasion of the tumor which they defined as the shortest distance between the tumor and the striated muscle (T-SM). They assumed that if ISR was alternatively performed for these patients, the vertical invasion

Oncologic and functional outcomes of ISR

Akagi and associates published a systematic review [12] of the outcome of ISR for very low rectal cancer that included 14 published studies in addition to their local center experience. The review comprised 1217 patients with T1-T3 rectal adenocarcinoma located within five cm from the anal verge. Patients with rectal cancer infiltrating the external anal sphincter, fixed tumor, poorly differentiated carcinoma, distant metastasis, and poor anal functions were not candidates for ISR and were excluded from the studies.

The review demonstrated good oncologic outcome of ISR as the rate of R0 resection ranged between 92% and 100% across the studies reviewed. Positive circumferential resection margin (CRM) less than one mm was reported in 4-13.3% of patients. After a median follow-up of 40-94 months, local recurrence was detected in 0-22.7% of patients and distant spread was noted in 2.5-19% of patients. Overall survival rates were up to 97% and disease-free survival ranged from 69% to 86%.

Regarding the functional outcome, the majority of the studies reported high rates of urgency (up to 51.7%), fecal soiling at daytime and at night (up to 29%), and diarrhea (up to 79%), however medications for diarrhea were

would represent the surgical margin of ISR. Short T-SM was defined as equal or less than 2 mm. Infiltration of dentate line and intramural spread were significant predictors for short T-SM. The study concluded that ISR is recommended only in patients with low rectal cancer who have no intramural spread and with the inferior edge of the tumor above the dentate line.

required in less than one third of patients. Although fecal incontinence (FI) was documented in 7-33% of patients included, it was of minor to moderate severity with Wexner continence scores less than 12. Overall, about 72% of patients were completely satisfied with the outcome of the procedure [12].

Complications after ISR were reported in 7.5-38.3% of patients in the studies reviewed. Recorded morbidities included AL in 4.3-48% of patients, colonic necrosis in up to 2%, pelvic abscess in up to 5.6%, pelvic hematoma in up to 6.5%, and anastomotic stricture in 8.4-15.9%. The mortality rates ranged from zero up to 1.7% and surgical reintervention was required in 0-12.9% of patients [12].

Laparoscopic ISR has been assessed in a multitude of studies with encouraging results. Pai et al. [13] reviewed the results of 19 patients with rectal cancer who underwent laparoscopic ISR. The mean distance of the tumor from anal verge was four cm and around 75% of tumors were of stage T3-T4. The study reported excellent oncologic outcome with 100% of patients having complete TME and 95% having free CRM. The median number of lymph nodes harvested was 11. No patient required conversion to open surgery and complications including AL and chyle leak developed in only 10% of the patients studied.

Beppu et al. [14] investigated the

outcome of laparoscopic ISR in 20 patients with low rectal cancer located at a median distance of 2.5 cm from the anal verge. The study used colonic J-pouch for restoration of the bowel continuity instead of conventional hand sewn anastomosis. Three patients developed pelvic infection, however no pouch-related complications were recorded. All patients had a diverting stoma. Immediately after closure of stoma the anal functions were assessed and the median Wexner score was 12 then dropped to 6 at 18 months postoperatively.

The anorectal dynamic functions after laparoscopic ISR for very low rectal cancer were assessed by Yu and associates [15]. Twenty-six patients underwent laparoscopic ISR and were compared with 30 patients who underwent laparoscopic LAR in regards Wexner continence score, resting and squeeze anal pressures, and rectal maximal tolerable volume. The two groups were well matched with no significant differences in the clinical baselines data and preoperative anal pressures. At three months postoperatively, the ISR group had significantly higher defecation frequency, Wexner score and remarkably lower resting and squeeze anal pressures and rectal maximal tolerable volume. Nonetheless, at 12 months after surgery the functional parameters of patients in the ISR group were normalized and the significant differences between ISR and LAR in anorectal functions were no longer observed.

Long-term outcomes

The long-term outcomes of ISR were studied by Satio and affiliates [16] who reviewed the records of 199 patients with low-lying rectal cancer who underwent ISR with or without partial resection of the external anal sphincter. The 7-year overall survival rate was 78% and the disease-free survival was 67%, however these rates were

significantly lower in patients who underwent partial external sphincter resection or who had positive CRM. At five years, the functional outcome of ISR was evaluated using Wexner continence score which was 8 in patients who had surgery without preoperative chemoradiotherapy versus 10 in the neoadjuvant group. The FI quality of life scores were relatively good, again patients who had surgery without preoperative neoadjuvant therapy had significantly better quality of life scores than patients who received neoadjuvant therapy.

Koyama and colleagues [17] also investigated the long-term outcomes of ISR in 77 patients with low rectal cancer in comparison with APE and LAR. Compared to APE, ISR had equivalent rate of local recurrence (12.1% Vs 11.7%) and better five-year survival (76.4% Vs 51.2%). On another hand, ISR had similar functional outcomes to LAR with no significant differences between the two procedures with regard defecation functions and FI quality of life scores. The findings of this study suggests that “ISR may be the optimal sphincter-preserving surgery for patients with low rectal cancers who cannot be treated with a double-stapling technique”.

Maglio and coworkers [18] illustrated a single-surgeon experience with laparoscopic ISR in 30 patients with ultra-low rectal cancer. All patients had a manual coloanal anastomosis with coloplasty and diverting ileostomy. The operation time ranged from 240-360 minutes with no recorded conversion to open surgery or in-patient mortality. The study concluded that ISR is a feasible procedure that provides radical cure of ultra-low rectal cancer while maintaining good anal functions.

Open versus laparoscopic ISR

Chi et al. [19] used a completely abdominal approach partial ISR and compared the open with the laparoscopic

approaches in 48 and 89 patients with low rectal cancer, respectively. The study demonstrated less intraoperative blood loss and shorter hospital stay in favor of the laparoscopic approach which had a longer operation time than the open group. The authors could not find any significant differences between the two approaches in regards local tumor recurrence, 3-year disease-free survival, and Wexner continence score. Overall, the study asserted that the laparoscopic approach had equivalent oncologic and functional outcomes to the open approach, yet with shorter stay and quicker patient recovery.

In concordance with the previous study, another case-matched study [20] compared the outcome of open and laparoscopic ISR in an equal number of patients with low rectal cancer. The oncologic and functional outcomes of both approaches were comparable. Furthermore, there were no significant differences between the two approaches in the total complication rate or the incidence of anastomotic complications. Again, the laparoscopic approach had shorter hospital stay and less median blood loss, yet with longer operation time than the open approach.

Laparoscopic versus robotic ISR

A recent retrospective study [21] compared the outcome of laparoscopic ISR with robotic ISR in 26 and 44 patients with low rectal cancer, respectively. Although the two groups were not well matched as the robotic group had higher BMI, more advanced N staging, and lower tumor location, the two groups had similar oncologic outcomes, comparable overall survival and disease-free survival rates and equivalent functional outcomes implying no definitive superiority of one approach over the other.

Kuo et al. [22] also compared the laparoscopic and robotic-assisted in ISR in 28 and 36 patients with low rectal cancer, respectively. Although the

robotic platform achieved similar oncologic and functional outcomes to the laparoscopic approach, it had a significantly longer operation time of a mean of 485 minutes. It was also notable that protective stomas were required in patients who underwent robotic ISR far less than patients who underwent laparoscopic ISR (19.4% Vs 46.4%, $P=0.02$) which can be regarded as a benefit of the robotic approach.

Standard versus extended ISR

Kim and colleagues [23] compared the long-term outcome of standard and extended ISR for low rectal cancer within four cm of the anal verge. Standard ISR was used in 24 patients with T2 rectal cancer, and extended ISR in 38 patients with T3 tumors. Extended ISR involved quadrant resection of the upper external anal sphincter. The 5-year overall survival and disease-free survival rates were comparable in both groups (95.8% Vs 94.7% & 87.5% Vs 86.6%, respectively). At one and two years after ileostomy closure, the functional outcome was assessed. Patients who underwent extended ISR had significantly higher frequency of bowel evacuation at 12 months, yet at 24 months no significant difference was detected between the two groups with similar Wexner continence scores (7.33 Vs 8.18).

ISR versus APE for very low rectal cancer

The oncologic and functional outcomes of ISR (n=60) were compared with APE (n=83) in a recent retrospective case-matched study [24]. Both procedures had comparable disease-free survival and recurrence-free survival rates and similar morbidity rates with no recorded mortality in either group. Around two-thirds of patients who underwent ISR complained of FI with Wexner score greater than 10, however it did not affect quality of life of patients which was significantly better than patients who had APE. Klose

and colleagues concluded that although ISR is technically feasible with acceptable complication rates, the postoperative incontinence can compromise the functional outcome of the procedure.

Two other studies [25, 26] also compared the outcomes of ISR and APE for very low rectal cancer and both studied concluded lower rates of local recurrence, and higher rates of disease-free survival and overall survival in favor of ISR, however the difference between the two procedures was not statistically significant.

Tsukamoto et al. [27] compared the oncologic outcome of ISR (n=128) and APE (n=149) for very low rectal cancer. The 5-year relapse-free rate of ISR was higher than APE for T1-T2 tumors, yet it was lower for T3-T4 tumors. Similarly, local recurrence rate for T3-T4 tumors was higher in the ISR group (13.2% Vs 3.8%). When classified according to TNM staging, the 5-year relapse-free survival rates of ISR were lower than APE in stages I, II, and III. These findings suggest that while ISR can be a feasible option for T1-2 tumors, however the same conclusion cannot be made for T3-T4 tumors. In line with the previous study, other authors concluded that ISR can be an oncologically safe alternative to extralevator APE for stage I-III low rectal cancer [28].

Predictors of outcomes after ISR

Predictors of oncologic outcomes

Lee et al. [29] studied 163 patients with stage I-III primary rectal cancer who underwent ISR after neoadjuvant therapy. Cox regression analysis was performed to determine the predictive factors for survival after surgery. The analysis revealed that T3-T4 staging and N1-2 staging were associated with lower disease-free survival, whereas N1-2 staging, tumor size > 3.5cm, and tumors

located at or less than 2 cm from the anal verge were associated with lower rates of local relapse free-survival. The study came to a conclusion that ISR is feasible for stage I-II low rectal cancer patients, but not for stage III disease where the oncologic outcomes can be predictably poor.

Predictors of functional outcomes

Hunag et al. [30] used Wexner continence score to evaluate the functional outcome of 96 patients with distal rectal cancer who underwent ISR. After a mean follow-up of 32 months, 86.5% of patients reported good continence state with Wexner score less than 10. The Wexner score was negatively correlated with the follow-up duration (-0.078, p=0.003). Univariate analysis revealed that the predictors for poor functional outcome after ISR were tumors located less than 5 cm from anal verge, height less than 2 cm from anastomotic line to anal verge, and neoadjuvant chemoradiotherapy. On multivariate analysis, only low anastomosis and neoadjuvant therapy were significant independent risk factors for FI.

Furthermore, Yokota et al. [31] demonstrated that AL after ISR can negatively impact the functional outcome of surgery. After evaluating 341 patients who had ISR, patients were classified into three groups: anastomotic dehiscence (AD), major AL, and control group. Overall, AL developed in 59 (17%) patients, 36 of which had major AL. The AL and AD groups had lower rates of stoma reversal within three years and higher rates of anastomotic stricture compared to the control group. The major AL group had poorer functional outcome with higher Wexner

continence scores than controls, however at 24 months of follow-up the AL group exhibited remarkable improvement in the continence scores and were comparable to the control group.

Post-ISR FI can be improved by the application of pelvic rehabilitation programs involving electric stimulation and biofeed back strategies. Kuo et al. [32] published a prospective observational study on 32 patients with FI after ISR who were managed with pelvic rehabilitation. Electric stimulation and biofeed back managed to increase the maximum squeeze anal pressure and to decrease the mean stool frequency from 18.8 to 7.8 per day and the mean Wexner score from 17.7 to 12.9. Furthermore, the need for anti-diarrheal medications was reduced from 84.3% to 28% after electric stimulation and biofeed back therapy. The authors concluded that pelvic rehabilitation is effective in the treatment of post-ISR FI and in improving quality of life of patients.

Predictors of AL after ISR

Risk factors for AL after ISR without protective defunctioning stoma were studied by Koyama and coworkers [33] on 131 patients with low rectal cancer. Clinical and radiologic AL was detected in 17% of patients. Significant predictors for AL included male gender, preoperative chemotherapy, partial ISR, lateral lymph node dissection, distal tumor distance from the dentate line, and straight reconstruction. After adjustment for confounders in multivariable logistic regression analysis, partial ISR and straight reconstruction were found the most significant independent predictors of AL with odds ratio of 6.7 and 5.5,

respectively. The authors recommended constructing diverting stoma in patients with the risk factors identified in their analysis.

Delayed AL after ISR was reported by Iwamoto et al. [34] in four patients with low rectal cancer. Two patients developed fistula between the anastomosis and the urethra at 57 and four months postoperatively. Another female patient developed fistula between anastomotic line and vagina which was diagnosed at 14 months after ISR. The last patient developed fistula between the anastomosis and perineum at 9 months after ISR. All patients had partial ISR except one who had subtotal ISR. Operative treatment of the anastomotic fistulas and diverting stoma were conducted in all patients.

Summary and conclusions

ISR is a sphincter-saving procedure performed for very low rectal cancer located within 5 cm from the anal verge. The aim of this procedure is to avoid permanent stoma that negatively impact the quality of life of patients.

The oncologic outcome of ISR is comparable to APE which is regarded as the traditional surgical management for very distal rectal cancers. The functional outcome of ISR can be comparable to low anterior resection, however FI is the most important functional limitation after ISR. FI tend to improve with time, pelvic rehabilitation involving electric stimulation and biofeed back can hasten the improvement in continence state and improve quality of life.

Laparoscopic ISR had comparable oncologic and functional outcomes to the open and robotic-assisted approach. Nonetheless, the laparoscopic approach

is superior to open approach as it provides the unique advantages of minimally invasive surgery, yet with shorter operation time than the robotic approach.

Predictors for poor oncologic and functional outcomes and for complications after ISR have been recognized which can help optimizing selection of patients with distal rectal cancer for ISR to attain the best survival and anal functions with the least possible morbidity.

Conflict of interest

The authors have no potential conflicts of interest to disclose.

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