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review

Comparison of outcomes following intersphincteric resection *vs* low anterior resection for low rectal cancer: a systematic review

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SUMMARY: **Comparison of outcomes following intersphincteric resection vs low anterior resection for low rectal cancer: a systematic review.**

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Background. *Low Rectal Anterior Resection (LAR) is challenging when anal canal mucosa and/or internal sphincter are involved by very low tumors. In these cases, Intersphincteric resection (ISR) with the removal of the internal sphincter is designed to increase the distal margin of resection, thus preserving the external sphincter and pubo-rectalis muscle complex. Aim is to compare results after ISR with those of LAR, including subgroup analysis of open, laparoscopic and robotic ISR.*

Methods. *Studies published from January 1991 to January 2017 describing ISR and comparing results with LAR in adults were included irrespective of the technique. Tumor and surgical characteristics, clinical, functional and oncological results were collected.*

Results. *25 non-randomized studies were included. Postoperative mortality ranged between 0% and 2.3%. The hospital stay ranged from 5 days to 40 days, lower in robotic ISR group if compared with laparoscopic ISR. Patients avoiding permanent stoma with ISR accept a lower continence level as satisfactory. Furthermore, anorectal function after ISR often tends to improve. ISR and LAR presented not statistically significant differences. Oncological outcomes were not statistically different Morbidity, blood loss and need for blood transfusions were lower in the laparoscopic ISR if compared with open approach.*

Conclusions. *Morbidity could more frequently affect open ISR if compared with laparoscopic ISR. Functional outcomes were influenced by neoadjuvant CRT, but not by the surgical approach of reconstruction, while were positively influenced by partial ISR with respect to total ISR.*

KEY WORDS: Abdomino-perineal resection - Anterior resection of the rectum - Intersphincteric resection - Low rectal cancer.

Introduction

The surgical treatment of low rectal cancer has always been the subject of considerable controversy. The abdomino-perineal resection (APR) was the "gold standard" for many years in the treatment of low rectal cancer and was one of the most frequently performed operations. In 1948, Dixon proposed the anterior resection of the rectum (LAR) as an alternative to abdomino-perineal resection, allowing preservation of the sphincter apparatus and therefore continence (1). Subsequently, in 1979 Goligher introduced the use of the stapler in rectal surgery, thus greatly expanding the LAR application, allowing fashioning the anastomosis even at a very low level (2). In addition, the oncological results after LAR were greatly improved with the introduction of total mesorectal excision in 1982 by Heald (3). Although LAR allowed sphincter preservation, it is often associated with the development of the "anterior resection syndrome", which includes urgency, fragmentation and anal incontinence thus affecting quality of life significanlty. To overcome these symptoms, formation of J pouch reservoir and the coloplasty were proposed in 1990s. In the same period, the intersphincteric resection (ISR), as a further "sphincter-saving" method for the treatment of low and ultra-low rectal tumors, was introduced by Schissel (4).

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The ISR technique includes complete mobilization of the rectum up to the external sphincter anteriorly and up to the puborectalis muscle posteriorly by abdominal approach followed by total or partial excision of internal sphincter by perineal approach with subsequent fashioning of the colo-anal anastomosis. The removal of the internal sphincter is designed to increase the distal margin of resection, thus preserving the external sphincter and puborectalis muscle (5). The ISR can be considered in cases where anal canal mucosa and/or internal sphincter are involved while anterior resection is technically very challenging in these cases. The contraindications of ISR include infiltration of the external sphincter and/or puborectalis muscle and poor anal continence (6). The variations of original surgical technique include beginning of the operation with a perineal phase followed by abdominal phase and use of circular stapler anastomosis instead of "hand-sewn" to fashion coloanal anastomosis (7). The aim of this systematic review is to evaluate the current state of ISR in the treatment of low rectal cancer and to compare its results with those of LAR including laparoscopic and robotic LAR.

Methods

Randomized controlled trials, clinical trials, observation based trials and case series of ISR for low rectal cancers in patients >18 years of age were included in this review irrespective of the technique of ISR (abdominal/perineal) and LAR employed. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) model was used for this review (8). Defined search strategy ("intersphincteric" [All Fields] and "resection" [All Fields]) was used in Pubmed, Cochrane Register of Controlled Clinical Trials, Scopus and Publish or Perish from January 1991 to January 2017 to retrieve relevant articles. Data including patient characteristics and outcomes were collected from included studies in data extraction forms, developed on the basis of "Cochrane consumers and communication review group's data collection model".

Assessment of methodological quality of the included studies

The included comparative studies were assessed by authors for their methodological quality using the revised and modified grading system of the Scottish Intercollegiate Guidelines Network (9). The included case series and case reports were assessed using the checklist for the quality of case series of the National Institute for Health and Clinical Excellence (NICE) (10).

Results

In total, 444 studies were retrieved following search strategy. Of these, 248 were excluded because they were not relevant to the objectives of our study. Review of full text of the remaining 196 studies was performed, of which 171 studies were excluded. In total, 25 non-randomized studies were included in this review: 14 case series and 11 controlled clinical studies (comparative) (11-35) (Figure 1).

Characteristics of participants (Table 1)

All included studies reported age of the patients which ranged from 25 years (14) to 86 years (14, 30, 34) with mean age of 58.4 years. In the included case series, mean age of participants was 58.26 years [range 25 (14) - 86 years (14)] with male: female ratio of 62:38. The average age of participants in controlled clinical trials was 58.54 years [range 26 (26) - 86 years (30, 34)] with male to female ratio was 61:39. The mean follow up period was 54.12 months (range 9-185 months) in case series (15, 22) and 49.76 months (range 1-107 months) in controlled clinical trials (11, 32).

Tumor characteristics (Table 2)

In included case series and controlled trials, the tumor localization was reported variably ranging from 1 (15, 20, 30) to 6 cm (23, 30) from the anal verge. Different authors used different locations to measure its distance such as anal verge (15, 18, 20, 22, 23, 29, 30, 33), anorectal ring (14) and dentate line (12, 13, 16, 21, 28, 32). Methods other than digital examination used to measure this distance were proctoscopy/rectoscopy/sigmoidoscopy (12, 15, 17, 21, 22) or colonoscopy (19, 24, 26, 27, 35) or radiological imaging (30). The infiltration of internal sphincter was evaluated in only two studies (20%, 22%) (14, 30) while some studies did not report the number of cases with internal sphincter or intersphincteric space involvement (18, 22). There was variability in reporting of the tumour size in included studies. The average size of tumor was 3.5cm (range 1-12 cm) using transanal ultrasound (20).

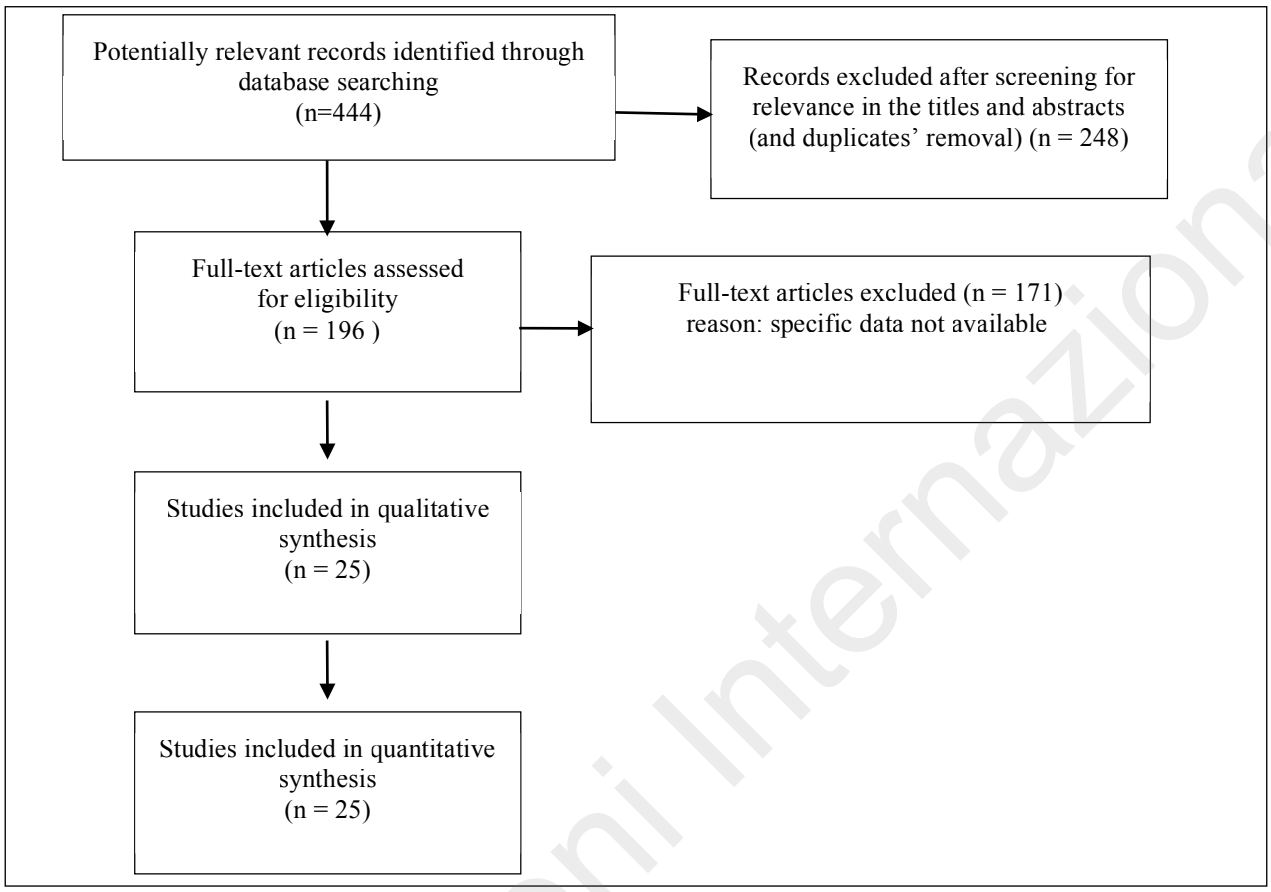

Figure 1 - PRISMA flow chart of literature search.

Other studies didn't use US (in particular this is contraindicated if stenosis is present) but CT and in most recent cases MRI (22, 26, 35). Two studies set the fixed maximum tumour size as inclusion criteria (16, 21). Regional lymphnode involvement ranged from 0% to 72% (23) with variation in the technique to measure this involvement (MRI vs Transanal Ultrasound) while one study used involvement of regional lymphnodes as an exclusion criteria (13). Distance metastasis was present in 3.3% cases (0%-6.5%) (14, 16, 29), but there was heterogeneity in the use of radiological investigation to detect and stage them. There was also variability in patient selection considering distance metastasis as an exclusion criteria irrespective of resectability of tumour (23, 29). The reporting of tumour differentiation (G1, G2) varied from 74% to 100% (13, 22, 29), while some studies excluded patients with poor differentiation (G3, G4) (15, 18, 21, 22, 24, 29). Out of the studies that reported TNM staging, some of those had excluded patients with T3 tumours (16, 17, 29). Only one study reported Duke's staging of tumours with equal distribution of Duke's staging between these studies (15). The neoadjuvant chemoradiotherapy and adjuvant chemotherapy were used in different extremes. Some studies used this as an exclusion criteria (15, 20, 29) and some studies included patients irrespective of their adjuvant treatment status (11, 22, 23), while some studies included patients selectively.

Surgical characteristics (Table 3)

In included case series and controlled trials, R0 resection (negative resection margin) was achieved in 89% to 100% case (11, 13-15, 18-20, 22, 23-25, 29, 32, 34). In one of the studies, histological examination of the margins was performed immediately (frozen section) after ISR resection and if distal or circumferential margin was positive, APR was performed in the same setting (22). Only few studies reported the number of lymph nodes removed during operation that ranged between 2 and 88 with mean of 16.25 (20, 25-28). The mean distal resection margin from tumour was 1.66 cm (range 0.5

TABLE 1. CHARACTERISTICS OF THE INCLUDED STUDIES.

Author Year	Type of study	Years of study	Follow-up [months]	Number of patients	Age [yrs]	Gender [n, %]	
						Male	Female
Bannon 1995 [11]	CCT	1984-1993	40 (1-107)[2]	65	59 (29-83)[2]	43 (66%)	22 (34%)
Kohler 2000 [12]	CS[3]	1985-1996	84 (24-144)[4]	31	59.7[2]	17 (55%)	14 (45%)
Vorobiev 2004 [13]	CS	1997-2002	38 (14-66)[4]	27	55 (26-75)[4]	16 (59%)	11 (41%)
Rullier 2005 [14]	CS	1990-2003	NR	92	65 (25-86)[4]	57 (62%)	35 (38%)
Schiessel 2005 [15]	CS	1984-2000	94 (24-185)[4]	121	63[4]	93 (77%)	38 (23%)
Chin 2006 [16]	CS	1995-2003	NR	18	62 (42-79)[4]	7 (39%)	11 (61%)
Hohemberger 2006 [17]	CCT	1985-2001	NR	65	NR	NR	NR
Saito 2006 [18]	CS	1995-2004	41 (10-84)[4]	228	58 (27-77)[4]	168(74%)	60 (26%)
Chamlou 2007 [19]	CS	1992-2004	56,2 (13,3-168,4)[4]	90	58,9 (27-82)[4]	59 (66%)	31 (34%)
Akasu 2008 [20]	CS	1993-2007	42 (11-140)[4]	120	57 (26-75)[4]	92 (77%)	28 (23%)
Han 2009 [21]	CS	2000-2007	43 (12-94)[4]	40	62 (34-73)[4]	24 (60%)	16 (40%)
Krand 2009 [22]	CS	1997-2007	67,5 (9-132)[4]	47	57 (27-72)[4]	31 (66%)	16 (44%)
Weiser 2009 [23]	CCT	1998-2004	47 (33-59)[6]	44	54 (28-78)[4]	25 (57%)	19 (43%)
Yamada 2009 [24]	CS	1994-2006	41 (12-110)[4]	107	NR	NR	NR
Funahashi 2011 [25]	CS	2006-2009	23,6 (12,2-56,7)[4]	20	66 (42-77)	15 (75%)	5 (25%)
Kuo 2011 [26]	CCT	2002-2009	55 (8-93)[4]	26	51 (26-71)[4]	16 (62%)	10 (38%)
Park 2011 [27]	CCT	1997-2009	NR	80	NR	53 (66%)	27 (34%)
Yamamoto 2011 [28]	CCT	2002-2011	NR	22	58 (35-69)[4]	16 (72%)	6 (28%)
Gong 2012 [29]	CS	2006-2009	20 (12-42)[4]	43	53[4]	27 (63%)	16 (37)
Laurent 2012 [30]	CCT	1990-2007	NR	65	64 (30-86)[4]	45 (69%)	20 (30%)
Baek 2013 [31]	CCT	2007-2010	NR	84	NR	NR	NR
Fu 2013 spostare [32]	CCT	2001-2011	56 (6-107)[4]	136	52 (37-60)[4]	70 (51%)	66 (49%)
2013 Konanz [33]	CCT	1999-2009	59[4]	33	NR	NR	NR
Park 2013 [34]	CCT	2010-2011	NR	8	58,9 (37-86)[2]	5 (63%)	3 (37%)
Tokoro 2013 [35]	CS	NR	NR	30	NR	NR	NR

[1] clinical controlled trial; [2] mean (range); [3] case series; [4] median (range); [5] not reported; [6] median (interquartile range).

cm - 4.0 cm) (14, 16, 19, 25). Three studies reported circumferential resection margin ranging from 0 to 15 mm with an average of 7mm (13, 14, 27). The neoplastic involvement of this margin varies from 0% (13, 25, 32, 34) to 12% (30) with an average of 4.5%. There was significant variability in reporting of duration of surgical procedure in included studies. The average duration of surgery was 245 minutes with a range of 150 minutes to 475 minutes (21, 27, 30, 32, 34). Most of the included studies reported hand-sewn anastomosis technique (11, 12, 14, 15, 17-19, 21-26, 28-31, 34, 35), while only one study reported the use of circular stapler (32). There was also significantly variability in the type of anastomosis performed; most frequently being reported as "straight end to end" anastomosis (12, 15, 17, 24, 26-28, 34). However, in some studies, J pouch was performed (14, 16, 17, 19, 21, 23, 24, 35) and in single study, S pouch reservoir (22), coloplasty (14, 23, 24) or latero-terminal anastomoses were performed in an attempt to improve postoperative functional outcomes. Except few studies (20, 21, 27, 29, 34), in most of the included studies, defunctioning stoma was performed in all the included patient. In the included case series and controlled trials, average frequency of permanent stoma (non-closure/reversal of diverting stoma) ranged from 0% (15, 16, 25, 29) to 36.5% (35).

Quality assessment of included studies (Tables 4, 5)

The methodological quality according to the modified grading system of the Scottish Intercollegiate Grading Network (SIGN) resulted in "fair" quality for each of the included clinical control trials (CCT) with mean score of 11.8 points out of 20 (Table 2). The included case series were evaluated with the NICE checklist and their methodological quality was "fair" (mean score 5.6 out of 8 points) (Table 3).

Clinical outcomes (Table 6)

Overall postoperative mortality (within the first 30 days after surgery) ranged from 0% (12-14, 16, 29) to 2.3% (23). The main causes of mortality included myocardial infarction, pulmonary embolism and anastomotic leak. The non-surgical morbidity was reported only in few studies in the form of myocardial infarction, pneumonia and heart failure (11, 23, 27) with an average incidence of 3.7%, thrombo-embolic events (11, 15, 18, 19, 21, 22, 24, 34) with an average incidence of 8.28 % and other complications such as sepsis (1.11%) (19) and dehydration (6.8%) (28). Surgical morbidity ranged from 9% (11) to 46% (30). Two studies also reported major morbidity (Dindo III-IV) of 5% (27) and 25% (30). The most frequent causes of surgical morbidity included anastomotic leak, pelvic abscess, postoperative bleeding, hematoma and wound infection. The frequency of anastomotic leak ranged from 1.5% (11) to 48% (12). The reported difference is attributed to the fact that some authors reported only symptomatic anastomotic leakage (20, 21) while others used clinical and radiological diagnosis of anastomotic leak (12, 19). Development of recto-vaginal fistula ranged from 1.11% (19) to 19% (12). Patients with recto-vaginal fistula were treated by different modalities including stoma formation, coloplasty and re-resection with neo-anastomosis. The pelvic or intra-abdominal collections/abscess developed in 0.95% (27) to 5.56% of cases (19) and were mainly secondary to anastomotic leak. These were treated with either laparotomy or percutaneous drainage. The wound infection rate ranged from 1.11% (19) to 22.2% (16). Bleeding and development of abdominal or pelvic hematoma were reported in five studies (11, 15, 18, 19) and their incidence ranged between 9.82% (18) and 6.52% (14) with an average of 2.32%. The re-laparotomy rate was reported in ten studies (11, 12, 14, 15, 18, 19, 22, 29) ranging from 0% (29) to 3.3% (15, 19). The indications of re-laparotomy included massive presacral bleeding, peritonitis, colonic necrosis, histologically positive margin (R1), recto-vesical fistula, ileus, anastomotic dehiscence and intestinal fistula. The late surgical complications were anastomotic stenosis and mucosal prolapse through the anal canal. Anastomotic stenosis was a relatively frequent complication in most of studies (11, 12, 15, 22, 23-27, 35) with incidence from 1.54% (11) to 15.9% (23). This was treated by dilation, sphincterotomy or permanent stoma. The hospital stay was reported in only five studies (13, 22, 27, 28, 30) that ranged from 5 days (27) to 40 days (28).

Functional results (Table 7)

In the included case series and controlled trials, the frequency of defecation varied from 2.2 to 3.8 per day. Most of studies used Kirwan classification to grade continence function. Grade I (excellent continence) ranged from 0% (15) to 80%-81% (13, 22) with an average of 47%. Two authors reported

TABLE 2 - TUMOR CHARACTERISTICS AND RADIOCHEMOTHERAPY.

Author	Tumour location (cm)	Largest tumour diameter (cm)	Lymph nodes involvement (N+)	Distant metastases	Differentiation [%]				Radiochemotherapy [%]	
					G1	G2	G3	G4	neoadjuvant	adjuvant
Bannon [11]	NR	NR	NR	NR	NR	NR	NR	NR	100	Dukes B,C
Kohler [12]	2,9 (1,4-4,2) DL[3]	NR	29%	NR	NR	NR	NR	NR	0	NR
Vorobiev [13]	1 (0,5-1,5) DL	NR	0%	NR	100		0	0	7	3,5
Rullier [14]	3 (1,5-4,5) AV	NR	NR	6,5% Rx thorax	NR	NR	NR	NR	8.8	N+
Schiessel [15]	3 (1-5) AV	NR	NR	NR	NR	NR	NR	NR	0	Dukes C
Chin [16]	(1-3) DL	5cm or less	17%	0% Rx thorax	NR	NR	NR	NR	T3,T4	NR
Hohemberger [17]										
Saito [18]	3,5 (2-5) AV	NR	NR	NR	NR	NR	NR	NR	NR	NR
Chamlou [19]	3,5 (2,2-5,2) AV	NR	16%	NR	NR	NR	NR	NR	41	Local recurrence
Akasu [20]	3 (1-5) AV	3,7 (1-12)	40%	2,5% CT	59	53	8	0	23	22
Han [21]	NR	< 5 cm	40%	NR	NR	NR	NR	NR	2.5	N+
Krand [22]	3,3 (1,5-5) AV	NR	53%	NR	100				100	N+
Weiser [23]	5 (3-6) AV	NR	72%	NR	95		5		100	NR
Yamada [24]	1,1 (-0,5-3,5) DL	NR	NR	NR	62	37	1	0	NR	T2,T3
Funahashi [25]	NR	4,2 (1,5-7,5)	60%	5% CT	NR	NR	NR	NR	10%	NR
Kuo 2011 [26]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Park [27]	4 AV	4	3.5%	NR	13	82	5	0	T3.T4 N+	NR
Yamamoto [28]	1,9 DL	3 (2,3-3,3)	24%	NR	NR	NR	NR	NR	11.8%	26.5%
Gong [29]	NR	NR	NR	0	100	NR	NR	0	NR	
Laurent [30]	4 (1-6) AV	NR	50%	NR	NR	NR	NR	NR	84.6%	53.8%
Baek [31]	NR	NR	NR	NR					NR	NR
Fu [32]	NR	2,6 (1,5-5,5)	NR	NR	NR	NR	NR	NR	NR	NR
Konanz [33]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Park [34]	3,5 (2-5) AV	NR	25%	NR	NR	NR	NR	NR	63%	NR
Tokoro [35]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

[1] anal verge; [2] not reported; [3] dentate line.

application of plastic with smooth muscle tissue of the colonic wall for repositioning internal sphincter after ISR (Krand technique, Vorobiev technique) (13, 22). Grade II continence (flatus incontinence) ranged from 0% (19) to 86.3% (15) while grade III (occasional minor loss of faeces) ranged from 0% (15) to 35% (19) with an average of 21%. The incidence of grade IV (frequent and greater loss of faecal

TABLE 3 - CHARACTERISTICS OF SURGERY.

Author	Radicalism of the surgery					Type of anastomosis				
	R0/R1 [%]	Number of Lymph nodes	Disatal margin [cm] (range)/positive %	Circumferential margin (range)/positive %	Average duration [minutes] (range)	J pouch	Trans coloplasty	Straight	Latero-terminal	S pouch
Bannon [11]	90.5/9.5	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kohler [12]	NR	NR	NR	NR	NR	0	0	100	0	0
Vorobiev [13]	100/0	NR	1,9 (1,5-2,6)/0	8 (6-15)/0	NR	NR	NR	NR	NR	NR
Rullier [14]	89/11	NR	2 (0,5-3)/2%	5 (0-15)/11%	NR	52 (56%)	26 (28%)	14 (15%)	0	0
Schiessel [15]	97/3	NR	NR	NR/3%	NR	NR	NR	NR	NR	NR
Chin [16]	NR	NR	1,5 (0,5-2)/NR	NR	NR	100%	0	0	0	0
Hohemberger [17]										
Saito [18]	98.7/1.3	NR	NR	NR	NR	51 (22%)	25(11%)	147 (64%%)	5 (3%)	0
Chamlou [19]	94.4/5.6	NR	1,2 (5-35)/ 5,6%	NR/ 4,4%	NR	100%	0	0	0	0
Akasu [20]	97/3	29(4-88)	NR	NR/3%	NR	NR	NR	NR	NR	NR
Han [21]	NR	NR	NR	NR	235 (160-390)	7 (17%)	0	33 (83%)	0	0
Krand [22]	98/2	NR	1.2	NR	NR	0	19(41%)	0	0	28 (59%)
Weiser [23]	92/8	NR	1,0 (0,9-1,3)/5%	NR/7%	NR	21 (48%)	6 (14%)	17(38%)	0	0

To be continued

Continued from TABLE 3.

Yamada [24]	NR	NR	NR	NR	NR	102 (95%)	2 (2%)	3 (3%)	0	0
Funahashi [25]	100/0	12,5	2,2 (0,7-4,0)/0	NR/0	NR	NR	NR	NR	NR	NR
Kuo 2011 [26]	NR	15	NR	NR	NR	NR	NR	NR	NR	NR
Park [27]	NR	NR	1.4/NR	NR/5%	299 (202-475)	NR	NR	N R	NR	NR
Yamamoto [28]	NR	NR	NR	NR	NR	4 (19%)	0	18 (81%)	0	0
Gong [29]	100/0	NR	NR	NR	NR	NR	NR	NR	NR	NR
Laurent [30]	NR	NR	NR	NR/12%	300 (210-470)	NR	NR	NR	NR	NR
Baek [31]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Fu [32]	100/0	13	1/0	NR/0	180 (150-210)	NR	NR	NR	NR	NR
Konanz [33]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Park [34]	100/0	8,5 (2-17)	1,35 (1-2)/0	8,25 (5-15)/0	210 (160-350)	2 (25%)	0	6(75%)	0	0
Tokoro [35]	NR	NR	NR	NR/6,67%	NR	NR	NR	NR	NR	NR

[1] Not reported.

TABLE 4 - EVALUATION OF METHODOLOGICAL QUALITIES OF COMPARATIVE INCLUDED STUDIES.

Items/author*	11	17	23	26	27	28	30	31	32	33	34
Inclusion criteria	1	1	1	1	1	1	1	1	1	1	1
Exclusion criteria	1	1	1	0	1	1	0	1	1	1	1
Comparable demographics?	1	0	1	1	1	1	1	1	1	1	1
Could the number of participating centers be determined?	1	1	1	1	1	1	1	1	1	1	1
Could the number of surgeons who participated be determined?	0	0	0	0	1	0	0	1	1	0	1
Could the reader determine where the authors were on the learning curve for the reported procedure?	0	0	0	0	1	0	0	1	1	1	0
Were diagnostic criteria clearly stated for clinical outcomes if required?	1	1	1	0	1	1	1	1	1	1	1
Was the surgical technique adequately described?	1	1	1	1	1	1	1	1	1	1	0
Did they try to standardize the surgical technique?	0	0	0	1	1	1	0	1	1	1	0
Did they try to standardize perioperative care?	0	0	0	1	0	0	1	0	0	0	0
Was the age and range given for patients in the Study group?	1	0	1	0	0	1	1	1	1	1	1
Did the authors address whether there were any missing data?	1	1	0	1	0	0	0	0	0	0	1
Was the age and range given for patients in the Control group?	1	0	1	1	0	1	1	1	1	1	1
Were patients in each group treated along similar timelines?	1	1	1	0	1	1	1	1	1	1	1
The patients asking to enter the study, did they actually take part to it?	0	0	0	0	0	0	0	0	0	0	0
Were drop-out rates stated?	0	0	0	0	0	0	0	0	0	0	0
Were outcomes clearly defined?	1	1	1	1	1	1	1	1	1	1	1
Were there blind assessors?	0	0	0	0	0	0	0	0	0	0	0
Were there standardized assessment tools?	1	1	1	1	1	1	1	1	1	1	1
Was the analysis by intention to treat?	0	0	0	0	0	0	0	0	0		0
Score	12	9	11	10	12	12	11	14	14	13	12

Total score, 20; <8, poor quality; 8-14, fair quality; ≥15, good quality.
*Named by reference number and listed in chronological order.

matter) and grade V (complete incontinence) combined was 11%. A higher percentage of Grade V was reported in the study by Laurent with 6.9% incidence rate (30). This was probably attributed to the large number of very low cancer cases in his series that required total ISR. In few studies the degree of continence was evaluated by Wexner classification dividing patients into two categories: continent (score < 10) and incontinent (score > 10) (12, 13, 15, 16, 18, 30). In these studies, 76% (19) to 97% (32) of patients were satisfied with their anal continence. However, this may be explained by the fact that patients avoiding permanent stoma with ISR (impossible otherwise) were willing to accept a lower continence level as satisfactory continence function. The symptom of urgency (defined as inability to defer defecation for more than 15 minutes) ranged from 2% (22) to 50% (16). The fragmentation of

TABLE 5 - EVALUATION OF METHODOLOGICAL QUALITY OF THE INCLUDED CASE SERIES.

Items/author*	12	13	14	15	16	18	19	20	21	22	24	25	29	35
Case series collected in more than one centre, i.e. multi-centre study	0	0	0	0	0	1	0	0	0	1	0	0	0	0
Is the hypothesis/aim/ objective of the study clearly described?	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Are the inclusion and exclusion criteria (case definition) clearly reported?	1	1	1	1	0	1	1	1	1	1	1	1	1	1
Is there a clear definition of the outcomes reported?	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Were data collected prospectively?	0	0	0	1	1	0	0	1	0	1	0	0	0	0
Is there an explicit statement that patients were recruited consecutively?	0	0	0	1	0	1	0	1	0	0	1	0	1	1
Are the main findings of the study clearly described?	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Are outcomes stratified? (e.g., by disease stage, abnormal test results, patient characteristics)	1	1	0	0	1	1	1	1	1	1	1	1	1	1
Total Score	5	5	4	6	5	7	5	7	5	7	6	5	6	6

Yes=1 No (not reported, not available) = 0.
Total score, 8; ≤3, poor quality; 4-6, fair quality; ≥7, good quality.
* Listed by references.

defecation (2 and more evacuations per hour) was very variable between 23% (13) and 50% (21) and inability to discriminate faces and flatus ranged from 12% (13) to 50% (21). One study revealed an increase in grade I continence from 70% to 84% after 3 months (13). Use of antidiarrheal drugs was reduced in the same time period from 15% to 4% in one study (13) and from 22% to 0% in another study (22).

Oncological results of case series and controlled trials (Table 8)

In the included case series and controlled trials, distant metastases development varied from 0% [29] to 25% (16). Such high percentage (16) of distant metastases can be explained by inclusion of patients with advanced stage tumors along with comparatively longer follow up observation period (mean of 80 months) in one study while in other studies, patients with systemic (14, 20, 25) and/or regional metastases were excluded (12, 16, 20-23, 25, 30, 32). One of the studies performed a multivariate analysis to identify the factors that significantly increased the risk of distant metastasis development (20). These factors included involvement of regional lymph nodes, low-grade of tumor differentiation and low tumor localization. The majority of the authors reported local recurrence at five years after the ISR, while in other studies, the observation period was shorter. Only two studies reported local recurrence at six years after surgery (11, 12). The frequency of local recurrence ranged from 0% (13, 29) to 18% (17) with an average of 11%. In two studies, absence of local recurrence was contributed by inclusion of patients with early stage of disease (T1-T2, N0, M0) with good differentiation (G1, G2) and shorter mean observation period (38 months and 20 months respectively) (13, 29). One of the studies performed a multivariate analysis instead and identified the factors that significantly increased the risk of local recurrence in his study (20). These included neoplastic infiltration of resection margin (R1 and

TABLE 6 - CLINICAL OUTCOMES: EARLY COMPLICATIONS AND RELAPAROTOMY.

Author	Post operative mortality				Total Hospital Stay [days] (average)	Early complications					Relaparotomy/ causes
	Overall (%)	Causes				AD[3]			Infection[4]	Bleeding[5]	
		MI[1]	PE[2]	AD[3]		total	radiologic	clinical			
Bannon [11]	1(1,5%)	0	1	0	NR	1(1,5%)	NR	NR	2(3%)	1(1,54%)	1(1,54%)/ Pelvic bleeding
Kohler [12]	0	0	0	0	NR	15(48%)	15(48,3%)	NR	NR	NR	1(3,22%)/Ileus
Vorobiev [13]	0	0	0	0	14 (12-16)	2(7,4%)	2(7,4%)	NR	NR	NR	NR
Rullier [14]	0	0	0	0	NR	10(11%)	NR	NR	3(3,26%)	6(6,52%)	4(4,35%)/Bleeding, peritonitis, positive margin
Schiessel [15]	1(0,8%)	0	1	0	NR	5(4,13%)	NR	NR	NR	1(0,83%)	4(3,3%)/Fistula, bleeding, ileus
Chin [16]	0	0	0	0	NR	NR	NR	NR	NR	NR	NR
Hohemberger [17]											
Saito [18]	1(0,44%)	0	0	1	NR	23(10%)	NR	NR	10(4,39%)	3(0,82%)	9 (3,95%)/ Bleeding, necrosis or dehiscence
Chamlou [19]	NR	NR	NR	NR	NR	8(9%)	3(3,33%)	5(5,6%)	5(5,56%)	1(1,11%)	2(3,33%)/J pouch necrosis (APR), positive distal margin
Akasu [20]	1(0,83%)	0	0	1	NR	15(12,5%)	NR	6(5%)	NR	NR	NR
Han [21]	0	0	0	0	NR	1(2,5%)	NR	1(2,5%)	NR	NR	NR
Krand [22]					9 (6-22)	2(4,2%)	1(2,13%)	1(2,12%)	1(2,13%)	NR	1(2,13%)/AD
Weiser [23]	1(2,27%)	0	0	0	NR	2(4,5%)	NR	2(4,5%)	NR	NR	NR
Yamada [24]	0	0	0	0	NR	5(4,67%)	NR	NR	NR	NR	NR
Funahashi [25]	0	0	0	0	NR	NR	NR	NR	1(5%)	NR	NR
Kuo 2011 [26]											
Park [27]	1(0,48%)	0	0	1	18,1	10(5%)	NR	N R	2(0,95%)	NR	NR
Yamamoto [28]	0	0	0	0	14 (10-40)	1(2,27%)	1(2,27%)	NR	2(4,55%)	NR	NR
Gong [29]	0	0	0	0	NR	5(11,6%)	NR	NR	NR	NR	0/NR
Laurent [30]	0	0	0	0	16 (7-75)	41(23%)	NR	41(23%)	NR	NR	NR
Baek [31]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Fu [32]	0	0	0	0	NR	7(5,15%)	NR	7(5,15%)	NR	NR	NR
Konanz [33]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Park [34]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Tokoro [35]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

[1] Myocardial infarction; [2] Pulmonary embolism; [3] Dehiscence of anastomosis; [4] Intra abdominal, pelvic infection; [5] Abdominal, pelvic bleeding; [6] Not reported.

TABLE 7 - CLINICAL OUTCOMES: LATE COMPLICATIONS, PERMANENT STOMA, CONTINENCE.

Author	Late complications		Permanent stoma	Continence													
	Stenosis	Sugery for prolapse		Kirwan score					Wexner score			Satisfaction	Nocturnal incontinence	Antidiarrhoic drugs	Urgency	Fragmentation	Inability to discriminate
				I	II	III	IV	V	Continent	Incontinent	Colostomy						
Bannon [11]	1(1,54%)	NR	2(3%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kohler [12]	3(9,7%)	NR	5(16,1%)	29,6%	11,1%	29,6%	26%	3,7%	53%	48%	16%	87	NR	NR	NR	NR	NR
Vorobiev [13]	NR	NR	NR	81%	NR	NR	NR	NR	NR	NR	3.7%	NR	NR	4%	NR	23%	12%
Rullier [14]	NR	NR	N R	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Schiessel [15]	11(9%)	NR	0	0	86,3%	0	13,7%	0	86,3%	13,7%	NR	NR	NR	14%	NR	NR	NR
Chin [16]	NR	NR	0	NR	NR	NR	11%	NR	89%	11%	NR	80	NR	NR	50%	NR	NR
Hohemberger [17]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Saito [18]	NR	3	8(3,5%)	36%	32%	25%	7%	0	97%	3	NR	NR	NR	NR	NR	NR	NR
Chamlou [19]	NR	NR	1(1,11%)	41%	0	35%	22%	2%	NR	NR	NR	76%	29%	26.5%	19%	41%	25.3%
Akasu [20]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Han [21]	NR	NR	NR	43%	29%	22.5%	0	2.5%	NR	NR	NR	NR	NR	75%	25%	50%	50%
Krand [22]	1(2,13%)	NR	1(2,13%)	80%	9%	11%	0	0	NR	NR	NR	NR	NR	0	2%	NR	NR
Weiser [23]	7(15,9%)	NR	8(18,18%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Yamada [24]	9(12%)	4	3(2,8%)	42%	30%	25%	0%	2.8%	NR	NR	NR	NR	NR	NR	NR	NR	NR
Funahashi [25]	2(10%)	NR	2(10%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	N R	NR	NR	NR	NR
Kuo 2011 [26]	1/22	NR	1/22	NR	NR	NR	NR	NR	NR	NR	NR	90.8%	23.8%	About 1/3	19%	38.1%	NR
Park [27]	4(18%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Yamamoto [28]	NR	3(6,8%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	6%	NR	N R	NR	NR
Gong [29]	NR	NR	0	74.8%	11.6%	9%	4.6%	0	NR	NR	NR	95%	NR	NR	NR	NR	NR
Laurent [30]	NR	NR	NR	NR	NR	NR	NR	6.9%	87%	13%	NR	NR	NR	NR	NR	NR	NR
Baek [31]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Fu [32]	NR	NR	0	NR	NR	NR	NR	NR	NR	NR	NR	97.1%	8.8%	19.1%	NR	NR	NR
Konanz [33]	NR	NR	NR	NR	N R	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Park [34]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Tokoro [35]	2	2	11/29 (36.5%)	NR	NR	NR	NR	NR	NR	NR	NR	N R	5/12	8/19	3/12	15/19	NR

[1] Not reported.

TABLE 8. ONCOLOGICAL OUTCOMES.

Author	Number of treated patients	Average period of observation [months] (range)	Systemic metastasis development	Local recurrence at 5 years	Overall survival (5 years)	Cancer-free survival
Bannon [11]	65	40 (1-107)	12%	NR	85%	NR
Kohler [12]	31	82 (24-14)	12,90%	NR	NR	NR
Vorobiev [13]	27	38 (14-66)	11%	NR	NR	NR
Rullier [14]	92	NR	19%	2%	81%	70%
Schiessel [15]	121	94 (94-185)	NR	NR	87,60%	NR
Chin [16]	18	30 (18-47)	25%	12,50%	87,50%	75%
Hohemberger [17]						
Saito [18]			NR	18%	80%	69%
Chamlou [19]	90	56,2 (13,3-168,4)	8,80%	9%	82%	75%
Akasu [20]	120	42 (11-140)	13%	10%	91%	NR
Han [21]	40	43 (12-94)	2,50%	5%	97%	86%
Krand [22]	47	67,5 (9-132)	15,20%	2%	NR	70%
Weiser [23]	44	47 (33-59)	16%	0%	96%	83%
Yamada [24]	107	NR	NR	3%	NR	NR
Funahashi [25]	20	23,6 (12,2-56,7)	10%		NR	NR
Kuo 2011 [26]	26	NR	NR	7,70%	83%	76%
Park [27]	80	NR	NR	NR	NR	NR
Yamamoto [28]	44	NR	4,50%		100%	NR
Gong [29]	43	20 (12-42)	0	NR	NR	NR
Laurent [30]	65	NR	NR	3,40%	NR	NR
Baek [31]	84	31,5	NR	NR	NR	NR
Fu [32]	136	56 (6-107)	14,70%	7,20%	NR	NR
Konanz [33]	33	NR	NR	4(12,1%)	NR	NR
Park [34]	8	NR	NR	NR	NR	NR
Tokoro [35]	30	56,2	3(10%)	4(13,3%)	76,50%	68,40%

[1] Not reported.

R2), low degree of tumor differentiation and high levels of CA 19-9 in the preoperative phase. Overall survival was estimated at five years and ranged from 76.5% (35) to 100% (28, 29) while cancer-free survival ranged between 69% (17) and 100% (29). The significant variation of these results is likely due to the same factors indicated previously for local recurrence and distant metastasis.

Subgroup analysis

Laparoscopic vs. open ISR (Table 9)

Only four studies reported results comparing laparoscopic versus open ISR (26-28, 30). The characteristics of the patients and their tumours (mean age, gender, BMI, ASA score, previous abdominal surgery, tumour size, T stage, lymph node involvement, differentiation) were similar in both groups while the tumour localization in one of the studies was much higher in the open group (4.7cm vs. 3.6 cm from the anal verge) (27). The anastomosis fashioning technique, hand-sewn technique was reported only in three studies (26-28).

Results

Overall morbidity was significantly lower in the laparoscopic group (P = 0.02) (27, 28, 30). In laparoscopic group, there was no mortality, while in open group, there was single mortality attributed to

TABLE 9 - LAPAROSCOPIC VS ROBOTIC INTERSPHINCTERIC RESECTION; OPEN VS LAPAROSCOPIC INTERSPHINCTERIC RESECTION.

Type of comparison	**ISR laparoscopic (L) vs. robotic (R)**						**ISR Open (O) vs laparoscopy (L)**					
Author	**Park [34]**		**Baek [31]**		**Park [27]**		**Yamamoto [28]**		**Laurent [30]**		**Kuo [26]**	
Type of surgery	R	L	R	L	O	L	O	L	O	L	L	O
Number of patients	40	40	47	37	80	130	22	22	65	110	28	30
Time of surgery [minutes] (SD or CM)	235,5	185,4	352,7 (130,3)	360,7 (88,2)	297,8 (86,4)	281,8 (94,8)	299 (202-475)	385 (305-500)	300 (210-470)	390 (210-720)	374,3 (210-570)	416,5 (320-720)
Morbidity	6 (15%)	5 (12,5%)	9 (19,1%)	10 (27%)	14 (17,5%)	17 (13,1%)	13 (9%)	7 (32%)	35 (53,8%)	45 (40,9%)	NR[1]	NR
Dindo I-II	4 (66,7%)	4 (80%)	41 (87,2%)	30 (81,1%)	78 (96,2%)	127 (94,6%)	NR	NR	17 (26%)	20 (18,18%)	NR	NR
Dindo III-V	2 (33,3%)	1 (20%)	6 (12,8%)	7 (18,9%)	3 (3,8%)	7 (5,4%)	NR	NR	18 (27,7%)	25 (22,7%)	NR	NR
Mortality	0	0	0	0	1(1,3%)	0	0	0	0	0	NR	NR
Conversion	0	0	1 (2,1%)	6 (16,2%)	NR	0	NR	0	NR	24 (22%)	0	NR
Blood loss [mL]	45,7	59,2	190,9 (284,7)	302,7 (305,3)	155,2 (267.2)	59,1 (113,4)	434 (76-1108)	139 (45-477)	NR	NR	104 (30-250)	265 (100-800)
Protective stoma	14 (35%)	6 (15%)	40 (85,1%)	36 (97,3%)	6 (7,5%)	14 (10,7%)	NR	NR	65 (100%)	100 (100%)	NR	NR
Number of harvested lymph nodes	12,9 (7,5)	13,3 (8,6)	10,6	14,1	16,5 (10,6)	14,8 (9,2)	14 (5-29)	13 (3-27)	NR	NR	13,9 (5-31)	14,7 (2-42)
Distal margin [cm]	NR	NR	NR	NR	17,4 (13,3)	18,7 (16,5)	NR	NR	NR	NR	1,8 (0,1-6)	1,2 (0,1-4,5)
Distal margin involvment	1,4 (0,9)	1,3 (0,9)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

TABLE 10 - INTERSPHINCTERIC RESECTION VS LOWER ANTERIOR RESECTION.

Type of comparison		**ISR vs LAR**									
Author		**Kohler [12]**		**Weiser [23]**		**Kuo [26]**		**Fu [32]**		**Konanz [33]**	
Type of surgery		ISR	LAR	ISR	LAR	ISR	LAR	ISR	LAR	ISR	LAR
Number of patients		31	159	44	41	26	101	136	142	33	41
Time of surgery in min (SD or CM)		NR	NR	NR	NR	NR	NR	180 (150-210)	190 (156-210)	NR	NR
Morbidity		NR	NR	NR	NR	NR	NR	NR	NR	16 (48%)	12 (29%)
Mortality		0	0	NR	NR	NR	NR	NR	NR	NR	NR
Conversion		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Blood loss [mL]		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Protective stoma		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Number of harvested lymph nodes		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Distal margin [cm]		NR	2,2 (1-4)	1,0 (0,9-1,3)	1,1 (0,9-1,3)	NR	NR	NR	NR	NR	NR
Distal margin involvment		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Circumferential margin involvment		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hospital stay [days]		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Firs stool [days]		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
solid food resumption [days]		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Early complications	Anastomotic leak	15 (48%)	NR	2	0	NR	NR	7 (5,1%)	11 (7,7%)	NR	NR
	Wound infection	2 (6,5%)	NR	3 (6,8%)	3 (7,3%)	NR	NR	NR	NR	3 (9%)	5 (12%)
Overall survival		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
5Y DFS		NR	NR	83%	85%	76%	NR	NR	NR	NR	NR
Distant metastasis		12,90%	NR	16%	12%	NR	NR	14,70%	12%	NR	NR
Local recurrence		NR	NR	NR	NR	7,70%	NR	2,20%	11,30%	4 (12%)	0
Perfect continence by Kirwan classification		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

the anastomosis dehiscence and subsequent septic shock (27). The intraoperative blood loss was significantly greater in the open group (P = 0.0008) (26-28). The comparison of intraoperative blood transfusion was reported only in one study and it reported statistically significantly higher need of blood transfusion in the open group (P = 0.0004) (28). There was diversity in reporting of defunctioning stoma; one study reported slightly higher rate of diverting stoma in the laparoscopic group (7.5% vs 10.7%) (27), while in other study diverting stoma was fashioned in all patients in both groups (30). Distal margin was higher in the laparoscopic group, but this result was not significant (P = 0.25) (27, 28). Circumferential margin was also slightly higher in the laparoscopic group without any statistical difference (P = 0.77). Only single study reported local recurrence rate that was greater in the open group (7.7% vs. 2.6%) (P = 0.09) (27).

Robotic vs. laparoscopic ISR (Table 9)

Only two studiescompared robotic vs laparoscopic ISR (31, 34). Patient characteristics along with their tumour characteristics (mean age, sex, tumor size, tumor location, T stage, lymph node involvement, differentiation, BMI, colo-anal recon-

struction, application of neoadjuvant chemoradiotherapy and the percentage of patients undergoing abdominal surgery in the past) were similar in both groups.

Results

There was no mortality in either group. The hospital stay was significantly lower in robotic group (P = 0.01). The conversion rate to open surgery was significantly higher in the laparoscopic group (P = 0.05).

ISR vs. LAR (Table 10)

Only five studies performed comparison studies between ISR and LAR groups (12, 23, 26, 32, 33). The characteristics of the patients and tumour (mean age, sex, tumor size, T stage, lymph node involvement, differentiation, response to neoadjuvant chemotherapy) were similar in both group except higher BMI and lower location of tumour in the ISR group.

Results

There was no postoperative mortality (within 30 days after surgery) in either group (12). The postoperative morbidity (within 30 days after surgery) was reported only in one study and it was higher in the group of patients who underwent ISR (P = 0.09) (33). The wound infection was slightly higher in the ISR group (P = 0.56) (22, 23). Anastomosis dehiscence rate was similar in two groups (ISR group 5.1% vs LAR group 7.7%) (32).

Total vs. subtotal and partial ISR (Table 11)

Only four studies performed comparison of total ISR vs. subtotal and partial ISR (18, 21, 24, 35). Patient characteristics (gender, tumor size, TNM stage, lymph node involvement, differentiation, reconstruction) were similar across both groups. Only in one study, mean age was higher in the subtotal group compared to total (P = 0.02) (24). There was statistically significant difference in the location of tumor: patients undergoing total ISR had significantly lower tumors than those subjected to partial ISR (p = 0.8) (24, 35). This difference was statistically significant when comparing total ISR and subtotal ISR group ISR (P <0.0001).

Results

Morbidity was the highest in the total ISR group (25%) and lowest in the partial ISR group (11.3%) (P = 0.13). The rate of grade I continence after surgery was significantly lower in the total ISR group compared to the partial ISR group (P = 0.02) (24, 35).

Discussion

The treatment of low rectal cancer still represents a therapeutic challenge. On one side, surgeons face the obvious patients' desire for preservation of continence and thus quality of life, on the other side, they have to pursue the optimal oncological outcome. While waiting for the assessment of consistent long-term results of transanal excision combined with neoadjuvant therapy, the aim to reduce more and more surgical invasiveness is restricted to the different abdominal techniques. APR has been the "gold standard" for many years and it is still the most frequently performed operation for low rectal cancer, now in the most common extra-levator fashion, to achieve wider free resection margins (36). With the same intent, but at the same time with the aim to preserve the anal sphincter function, in the 90's Schissel proposed inter-sphincteric resection (ISR) for the treatment of low and ultra-low rectal tumours (4) In order to improve conventional LAR, the removal of the internal sphincter is designed to increase the distal margin of resection, thus preserving the external sphincter and pubo-rectalis muscle complex (5). This technique theoretically restricts the need of rectal amputation to those cases with infiltration of the external sphincter or the pubo-rectalis muscle (14). Although technically challenging, in the past two decades ISR attracted a growing interest of colo-rectal surgeons so that several series and comparative studies with alternative techniques were published. This systematic review evaluated the published results of ISR series in the treatment of low rectal cancer and compares them with those of laparoscopic and robotic LAR. Although we followed the method suggested by PRISMA (37), the quality of surgical studies including clinical trials have often been quite poor and this has reflected on the quality of this systematic review (38). The reporting of outcomes in studies included in this review was not consistent. While oncological out-

TABLE 11 - TOTAL VS SUBTOTAL VS PARTIAL INTERSPHINCTERIC RESECTION.

Type of comparison		**Total vs subtotal vs partial ISR**											
Author		**Saito [18]**			**Han [21]**			**Yamada [24]**			**Tokoro [35]**		
Type of surgery		Total	Subtotal	Partial	Total	Subtotal	Partial	Total	Subtotal	Partial	Total	Subtotal	Partia
Number of patients		69	124	35	5	23	12	20	16	71	14	4	12
Duration of surgery [minutes]		NR[1]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Morbidity		NR	NR	NR	NR	NR	NR	5 (25%)	3 (18,8%)	8 (11,3%)	NR	NR	NR
Dindo I-II		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Dindo III-V		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mortality		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Conversion		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Blood loss [mL]		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Protective stoma		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Number of harvested lymph nodes		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Distal margin [cm]		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Distal margin involvment		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Circumferential margin involvment		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hospital stay [days]		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Firs stool [days]		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Early complications	Anastomotic leak	NR	NR	NR	NR	NR	NR	3 (15%)	0	2 (2,8%)	NR	NR	NR
	Wound infection	NR	NR	NR	NR	NR	NR	2 (10%)	2 (12,5%)	0	NR	NR	NR
Total survival		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
5Y DFS[2]		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Distant metastasis		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Local recurrence		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Perfect continence by Kirwan classification		NR	NR	NR	NR	8 (40%)	7 (64%)	5 (19)	4 (16)	35 (69)	9,1 (5,6)	NR	11,8 (2,6)

comes after ISR were relatively well documented, it was not the same for functional outcomes and mainly quality of life scores. All series and trials included selected patients, although not always with similar selection criteria. The major bias was probably consisting of the patient's willing to accept the reduction in life expectancy and imperfect continence that may result from a coloanal anastomosis, in order to preserve their anal function (39, 40). Overall mortality was reported in less than 1% of patients considered in our analysis, which overlaps results of standard LAR, as well as overall morbidity. When comparing results of laparoscopy and open surgery we could demonstrate that similar to standard Total

Mesorectal Excision (TME) (41), overall morbidity, as indicated by Park, Yamamoto and Laurent, was significantly lower in the laparoscopic group (27, 28, 30). Similarly, other advantages of a minimally invasive approach were verified in this field too, such as a reduction in blood loss and need of blood transfusion, which were significant lower in the laparoscopic ISR group. Here too, as in standard TME procedures, conversion to open surgery was significantly higher in the laparoscopic ISR group compared to robotic cases, which probably was reflected in terms of shorter hospital stay. This systematic review cannot exclude that oncological outcomes could be adversely affected with the sphincter-saving technique. Pathology results showed that distal margin was positive in up to 5.6%, while the more important, circumferential resection margin was positive in up to 12%. These consistently low average rates are compatible with those following standard TME. The 5-year disease-free survival rate after ISR was around 75% and the overall survival rate was around 85%, also in line with standard TME results. Similarly, the mean local recurrence rate in this review was 7%. The overall survival at 5-years as indicated by Weiser (23, 42), was significantly higher in the ISR group, compared to APR group, however this might be attributed to selection bias in these studies in favour of less invasive cases, as well as a shorter hospital stay (33, 43). Hohenberger reported the local recurrence rate as high as 23% after ISR, despite R0 resection rate achieved in 92% of cases (17). In this study, 35 of 53 patients received neoadjuvant CRT of whom four (11%) developed local recurrences. Of those who did not receive neoadjuvant treatment, seven patients (39%) developed local recurrences. This and other reports demonstrated that neoadjuvant CRT undoubtedly decreased the local recurrence rate in patients undergoing ISR. On the other side, neoadjuvant CRT is likely to have a deleterious effect on the long-term functional outcomes. In general (44-47), anorectal continence improved significantly along the time reaching patients'satisfaction in more than three fourths of the patients, as reported in our analysis. Nevertheless, neoadjuvant CRT is currently performed before ISR as standard TME with similar criteria. It has to be acknowledged that patients undergoing ISR were probably more motivated to care about their anal continence. Another major contributory factor that might influence continence is the surgical approach used for reconstruction. This was almost equally divided between J-pouch and straight reconstruction, with or without transverse coloplasty. However, the only comparative study that evaluated continence after these two reconstruction techniques did not find any significant differences between the two groups (21). Partial ISR or J-pouch reservoir for coloanal anastomosis has also been shown to improve the functional outcomes, particularly in the first year of surgery. The rate of perfect continence (grade I) after surgery was significantly lower in the total ISR group compared to the partial ISR group. The rate of stoma, either temporary or permanent was also analyzed in this study. Almost all included patients had a temporary loop ileostomy for an average of 3 months, which was transformed into a permanent one in less than 5% of cases if three studies were excluded (12, 23, 25). The main reason for permanent stoma was persistent anastomotic leak. Kohler reported rates of permanent stoma as high as 48% as they checked all anastomosis by contrast enema (12), while Laurent reported rates as high as 23% as they considered only clinically evident anastomotic leaks (30). The rate of re-laparotomy was reported in all the included studies and that was less than 5%.

Conclusion

The critical question that we must consider before deciding on ISR or APR is whether the imperfect functional outcomes in terms of continence status and frequent defecation are preferable to living with a colostomy or vise versa. No randomized trial could realistically be performed to compare ISR and APR, as anyone would opt for a restorative procedure if possible. This systematic review from available data of case series and comparative studies, with potential for selection bias, suggested that oncological outcomes after ISR were comparable to LAR but it didn't reach statistically significant conclusions about. Functional outcomes were influenced by neoadjuvant CRT, but not by the surgical approach of reconstruction, while were positively influenced by partial ISR with respect to total ISR. The functional outcomes following ISR are widely accepted by many patients who avoid a permanent stoma this way. This data indicates that the anorectal function after ISR tends to improve during the first 24 months after surgery, and in most cases, reaches acceptable levels.

Disclosure statement

The Authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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