Table 3 Characteristics of six patients with local recurrence after intersphincteric resection (ISR)

Patient	TNM	T stage	Histological type	Surgical procedure	Distal resection margin, mm	Circumferential resection margin, mm	Localization	Distant metastases	Treatment	Outcome
1	IIA	T3	G2	tISR + pESR	7	2	Pelvic wall	NS	CRT	45 months, O
2	IIIB	T3	G2	sISR + pESR	25	2	Pelvic wall	NS	CRT	70 months, S
3	IIIB	T3	G2	pISR	12	5	Pelvic wall	Bone, lung	Cx	31 months, P
4	IIA	T3	G2	pISR	10	0.5	Lateral node	Adrenal gland	Cx	36 months, P
5	I	T2	G1	pISR	3	6	Anastomosis	NS	APR	22 months, S
6	IIB	T3	G1	pISR	3	0.5	Lateral node	NS	CRT	17 months, S

Distal resection margins and circumferential resection margins were measured on the histological slides.
APR = abdominoperineal resection; CRT = chemoradiotherapy; Cx = chemotherapy; ESR = external intersphincteric resection; ISR = intersphincteric resection; NS = not stated; O = other origin of death; P = primary death; S = survived.

respectively; $P = 0.14$), but an upward trend was observed in the Wexner scores at 6 months and 12 months (11.5 ± 4.9 vs 9.1 ± 5.6, respectively, $P = 0.06$). At 3, 6, and 12 months, the Wexner scores were not significantly different between patients who underwent partial and subtotal or total ISR (Table 4). In the patients without anastomotic stricture, the Wexner scores were significantly improved at 6 months and 12 months compared with those at 3 months. However, five patients, including the one with subtotal ISR and an additional partial ESR, required finger bougie, endoscopic balloon dilation, or stricture plasty for anastomotic stricture, no improvement in the Wexner score was observed.

Table 5 shows the anal function based on the questionnaires answered at 3, 6, and 12 months after stoma closure, with or without anastomotic stricture. At 12 months after stoma closure, patients without anastomotic stricture were showed improved urgency (from 12/14 to 3/12; $P = 0.008$) and nocturnal defecation (from 9/14 to 5/12; $P = 0.014$). However, patients with anastomotic stricture did not report improvement in any symptom. Compared to patients with anastomotic stricture, the non-stricture group showed significantly better results with regard to stool frequency (5.1 ± 2.9 vs 9.0 ± 5.3; $P = 0.02$), urgency (3/12 vs 4/5; $P = 0.04$), and fragmentation (4/12 vs 5/5; $P = 0.015$) at 12 months.

The results of the univariate analysis revealed that poor anal function, as assessed by the Wexner score, was significantly associated with gender (male; $P = 0.047$) and the presence of anastomotic stricture ($P = 0.018$) at 12 months. The surgical procedure (partial or subtotal/total ISR), type of reconstruction (straight or colonic J-pouch), and age (<70 or ≥70) were not significantly associated with anal function. The results of the multivariate analysis also showed that gender ($P = 0.283$) was not significantly associated with anal function and that the presence of anastomotic stricture ($P = 0.093$) only demonstrated a trend towards being significantly associated with anal function (data not shown).

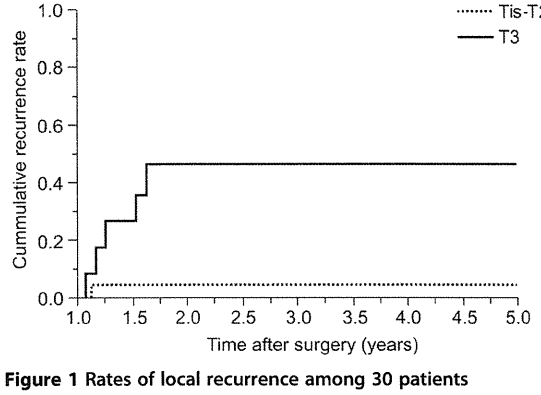

Figure 1 Rates of local recurrence among 30 patients undergoing intersphincteric resection according to the pathologic depth of the tumors (T stage).

Discussion

Although ISR is the sphincter-preserving procedure for very low rectal cancer, there are concerns regarding local control and defecatory function. In this study, we report the outcomes of ISR of very low rectal cancer, less than 2.5 cm from the dentate line, with a median follow-up period of 56 months. Our data show that this operation is feasible, with no postoperative mortality found in the study group. Moreover, it is associated with favorable

Table 4 Wexner scores at 3, 6, and 12 months in patients who underwent intersphincteric resection (ISR) followed by stoma closure

Procedure/findings	3 months	6 months	12 months
Surgical procedure			
Partial ISR (n = 9)	13.3 ± 3.1	12.1 ± 3.0*	11.8 ± 2.6
Subtotal or total ISR (n = 10)	13.0 ± 3.8	11.5 ± 4.9	9.1 ± 5.6
Anastomotic stricture			
Yes (n = 5)	15.4 ± 2.9	13.4 ± 4.5	13.6 ± 3.9
No (n =14)	12.4 ± 3.3	11.2 ± 3.9*	9.0 ± 4.5*

Data are shown as mean ± SD. Data at 6 and 12 months were statistically compared with those at 3 months using the Wilcoxon signed-rank test.
*P <0.05.

Table 5 Anal dysfunction after stoma closure in patients with anastomotic stricture and those with no anastomotic stricture

Symptoms related to anal function	3 months		6 months		12 months	
	Non-stricture	Stricture	Non-stricture	Stricture	Non-stricture	Stricture
Stool frequency, times/day	6.4 ± 3.6	11.4 ± 3.0**	6.8 ± 2.8	7.0 ± 2.1	5.1 ± 2.9	9.0 ± 5.3**
Urgency	12/14	4/5	8/13	2/5	3/12*	4/5**
Fragmentation	10/14	5/5	7/13	4/5	4/12	5/5**
Dyschesia	2/14	3/5	2/13	0/5	2/12	0/5
Medication use	4/14	4/5	3/13	4/5**	2/12	3/5
Nocturnal defecation	9/14	5/5	5/13*	5/5	5/12*	4/5

Data associated with each anal dysfunction at 6 and 12 months were statistically compared with those at 3 months for each condition of anastomotic sites using Wilcoxon signed-rank test. *P <0.05.
Data associated with each anal dysfunction of the stricture group were statistically compared with those of the non-stricture group at 3, 6, and 12 months using the Mann–Whitney U test. **P <0.05.

oncological outcomes for Tis-T2 tumors. With regard to the Wexner score, total ISR did not produce worse outcomes than partial ISR did, with the exception that permanent stoma were necessitated by unfavorable anastomosis. However, anastomotic stricture, which occurred as a postoperative complication, was found to negatively affect anal function.

From an oncological point of view, local control of the disease remains the most important objective in rectal cancer surgery. The local recurrence rate of very low rectal cancer for ISR varied widely, ranging between 0% [23] to 31% [25]. With ISR, the rate of secure distal resection margin was in the range of 95% [23] to 100% [18], and our results showed a median distance of 7 mm, and a definite negative distal margin in all patients. Therefore, ISR was found to provide an optimal distal resection margin, which is difficult to attain by using only the abdominal approach for very low rectal cancer. Rate of positive CRM of the rectal cancer also influenced factor of local recurrence. In our study group, 6.7% of all patients had a CRM ≤1 mm, and similar results were reported in the range of 0% to 13.3% [18,26]. Preoperative CRT was considered useful for preventing local recurrence in low rectal cancer patients requiring ISR [14,23]. Kuo *et al.* [26] reported a positive CRM rate of 13.3%, but a local recurrence rate of 7.7% in their ISR series of 26 patients; 88.5% of these patients had undergone preoperative CRT. Paradoxically, Hohenberger and colleagues [27] reported that in ISR patients with lower-third rectal cancer without radiotherapy, the local recurrence rate was high, at 46.5%. In our study, local recurrence was significantly higher in patients with T3 tumors than in those with Tis-T2 tumors. Akasu *et al.* [28] reported that both T3 tumors and a positive microscopic resection margin in patients who underwent ISR were significantly associated with local recurrence. Because ISR involves dissection of the rectum between the internal sphincter muscle and the external sphincter muscle, in patients with T3 tumors with expanding microscopic tumor cells near the levator ani or the external sphincter muscles, during surgical resection, there is a considerable risk of cutting into the tumor or achieving a very short distance of a few millimeters to the CRM. Thus, for a group of patients with T3 tumors, ISR was applied to attain good responses to neoadjuvant CRT, leading to secure CRM.

Partial or total resection of the internal sphincter muscle resulted in defecatory dysfunction with frequent defecation, urgency, and fecal incontinence [16,18,29]. Moreover, preoperative radiotherapy against T3 tumors or lymph node involvement was found to have a negative impact on anal function after ISR [17,18,26]. In the study by Ito *et al.* [17], of all the patients who underwent ISR, 40% received radiotherapy and were found to have a mean Wexner score of 10 at 12 months. Moreover, Denost *et al.* [20] reported a median Wexner score of 11 in most of the patients who received radiotherapy.

It has been shown that colonic J-pouch reconstruction in conjunction with ISR can minimize the anal dysfunction-related side effects of a sphincteric resection [9]. Hida *et al.* [30] reported the long-term benefits of colonic J-pouch reconstruction suggesting that it improves reservoir function to a greater extent than straight anastomosis does, especially in patients in whom the anastomosis is less than 4 cm from the anal verge. In addition, Dennett *et al.* [31] reported that colonic J-pouch is effective in very low rectal cancer surgery, causing apparent reduction in the incidence of anastomotic leaks and in bowel frequency. In our study, the mean Wexner score was 11.5 in most patients with colonic J-pouch reconstruction, and none of the patients had received radiation therapy. In previous studies, total ISR was performed in 8.9% [29] to 33.7% [20] of all the ISR patients. A possible reason for the poorer outcomes about Wexner score in our study was that the number of patients who required total ISR accounted for approximately half the ISR patients (42.1%), because coloanal anastomosis using conventional DST was technically possible in a few patients who required partial ISR during our study period.

The outcome for continence is reported to be worse after total ISR than after subtotal or partial ISR [19,20]. In our results for Wexner scores, anal function between total or subtotal ISR and partial ISR were not different, but patients of partial ISR had earlier recovery than those of subtotal or total ISR. Our functional results are limited because of the differences in stoma closure rates between partial ISR and subtotal/total ISR patients. The rates of stoma closure in patients with subtotal or total ISR were lower than those in patients undergoing partial ISR. This result in itself indicates poor anal function outcomes for subtotal/total ISR. Especially with respect to the three patients with total ISR, stoma closure was not possible because of the high risk of major incontinence.

Postoperative complication rates varied between reported series from 18% to 64% [15]. Common complications included leakage, anastomotic stricture, fistula, pelvic sepsis, and prolapse. In a previous literature review, anastomotic leakage rates of 5% to 48% [32] were reportedly associated with ISR, and they varied depending on whether asymptomatic leaks were radiologically detected. Also, Tilney and Tekkis [9] reviewed 21 studies and reported an overall anastomotic leak rate of 10.5% and anastomotic stricture rate of 5.8%. Similar rates were reported in the current series: anastomotic leakage occurred in 7 of 30 patients (23.3%) and anastomotic stricture in 12% of the patients. Anastomotic leakage is an important feature since it has been found to lead to postoperative anastomotic stricture [33] and poor postoperative anorectal function [34]. However, in our study, there were no independent factors associated with anal dysfunction in the multivariate analysis, but patients with anastomotic stricture showed worse outcomes (frequency, urgency, and fragmentation) than patients without anastomotic stricture. In addition, symptoms related to anal function were not reduced in these patients. In our study, anastomotic stricture or occlusion occurred in five of seven patients with anastomotic leakage; thus, stricture formation could be attributed to leakage caused by ischemia or infection of the anastomotic site. Therefore, it is necessary to fully explain the possibility of fecal incontinence or of a permanent stoma to the patients before obtaining informed consent. Fecal QOL in our patients who had an anastomotic stricture was worse, and they might have little benefit from preserving the anal continuity with ISR.

Our study has some limitations: it was a retrospective study and the sample size was relatively small. There could be potential bias due to possible difference between those who were ambitious of receiving the anal sphincter preserving surgery and those who did not, which could affect the self-evaluation for gastrointestinal questionnaire. With regard to the additional partial ESR performed only in one patient with stoma closure, this was not taken into consideration while estimating anal function.

Conclusions

In summary, ISR is an oncologically safe procedure for pTis or pT2 tumors among very low rectal cancer patients. Also, total ISR, that is, complete removal of the internal sphincter muscles, carried risks of worse anal function or possibility of a permanent stoma. The complications associated with anastomosis, especially stenosis, resulted in poorer anal function. Larger studies are needed to evaluate functional results in ISR patients who suffer from anastomotic stricture.

Abbreviations

CRM: circumferential resection margin; DST: double-stapling technique; ESR: external sphincter resection; ISR: intersphincteric resection; TME: total mesorectal excision.

Competing interests

The authors declare they have no competing interests.

Authors' contributions

TT, KO, JH, KU, TY, KD, MT, FS: made substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data. TT, KO, JH: drafted the article and revised it critically for important intellectual content. TT, KO, JH, KU, TY, KD, MK, FS: responsible for final approval of the manuscript. All authors read and approved the final manuscript.

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References

1. Heald RJ, Ryall RD: **Recurrence and survival after total mesorectal excision for rectal cancer.** *Lancet* 1986, **1**:1479–1482.
2. Cohen Z, Myers E, Langer B, Taylor B, Railton RH, Jamieson C: **Double stapling technique for low anterior resection.** *Dis Colon Rectum* 1983, **26**:231–235.
3. Lavery IC, Lopez-Kostner F, Fazio VW, Fernandez-Martin M, Milsom JW, Church JM: **Chances of cure are not compromised with sphincter-saving procedures for cancer of the lower third of the rectum.** *Surgery* 1997, **122**:779–785.
4. Gamagami RA, Liagre A, Chiotasso P, Istvan G, Lazorthes F: **Coloanal anastomosis for distal third rectal cancer: prospective study of oncologic results.** *Dis Colon Rectum* 1999, **42**:1272–1275.
5. Berge A, Tiret E, Cunningham C, Dehni N, Parc R: **Rectal excision and colonic pouch-anal anastomosis for rectal cancer: oncologic results at five years.** *Dis Colon Rectum* 1999, **42**:1265–1271.
6. Schiessel R, Kamer-Hanusch J, Herbst F, Teleky B, Wunderlich M: **Intersphincteric resection for low rectal tumours.** *Br J Surg* 1994, **81**:1376–1378.
7. Teramoto T, Watanabe M, Kitajima M: **Per anum intersphinctric rectal dissection with direct coloanal anastomosis for lower rectal cancer: the ultimate sphincter-preserving operation.** *Dis Colon Rectum* 1997, **40**:S43–S47.
8. Köhler A, Athanasiadis S, Ommer A, Psarakis E: **Long-term results of low anterior resection with intersphincteric anastomosis in carcinoma of the lower one-third of the rectum: analysis of 31 patients.** *Dis Colon Rectum* 2000, **43**:843–850.
9. Tilney HS, Tekkis PP: **Extending the horizons of restorative rectal surgery: intersphincteric resection for low rectal cancer.** *Colorectal Dis* 2008, **10**:3–16.
10. Rullier E, Zerbib F, Laurent C, Bonnel C, Caudry M, Saric J, Parneix M: **Intersphincteric resection with excision of internal anal sphincter for**

conservative treatment of very low rectal cancer. *Dis Colon Rectum* 1999, **42**:1168–1175.
11. Saito N, Ono M, Sugito M, Ito M, Morihiro M, Kosugi C, Sato K, Kotaka M, Nomura S, Arai M, Kobatake T: **Early results of intersphincteric resection for patients with very low rectal cancer: An active approach to avoid a permanent colostomy.** *Dis Colon Rectum* 2004, **47**:459–466.
12. Ueno H, Mochizuki H, Hashiguchi Y, Ishikawa K, Fujimoto H, Shinto E, Hase K: **Preoperative parameters expanding the indication of sphincter preserving surgery in patients with advanced low rectal cancer.** *Ann Surg* 2004, **239**:34–42.
13. Rullier E, Laurent C, Bretagnol F, Rullier A, Vendrely V, Zerbib F: **Sphincter-saving resection for all rectal carcinomas -The end of the 2-cm distal rule.** *Ann Surg* 2005, **241**:465–469.
14. Rullier E, Goffre B, Bonnel C, Zerbib F, Caudry M, Saric J: **Preoperative radiochemotherapy and sphincter-saving resection for T3 carcinomas of the lower third of the rectum.** *Ann Surg* 2001, **234**:633–640.
15. Tiret E, Poupardin B, McNamara D, Dehni N, Parc R: **Ultralow anterior resection with intersphincteric dissection-what is the limit of safe sphincter preservation?** *Colorectal Dis* 2003, **5**:454–457.
16. Bretagnol F, Rullier E, Laurent C, Laurent C, Zerbib F, Gontier R, Saric J: **Comparison of functional results and quality of life between intersphincteric resection and conventional coloanal anastomosis for low rectal cancer.** *Dis Colon Rectum* 2004, **47**:832–838.
17. Ito M, Saito N, Sugito M, Kobayashi A, Nishizawa Y, Tsunoda Y: **Analysis of clinical factors associated with anal function after intersphincteric resection for very low rectal cancer.** *Dis Colon Rectum* 2009, **52**:64–70.
18. Chamlou R, Parc Y, Simon T, Bennis M, Dehni N, Parc R, Tiret E: **Long-term results of intersphincteric resection for low rectal cancer.** *Ann Surg* 2007, **246**:916–922.
19. Yamada K, Ogata S, Saiki Y, Fukunaga M, Tsuji Y, Takano M: **Functional results of intersphincteric resection for low rectal cancer.** *Br J Surg* 2007, **94**:1272–1277.
20. Denost Q, Laurent C, Capdepont M, Zerbib F, Rullier E: **Risk factor for fecal incontinence after intersphincteric resection for rectal cancer.** *Dis Colon Rectum* 2011, **54**:963–968.
21. Colquhoun P, Kaizer R Jr, Efron J, Weiss EG, Nogueras JJ, Vernava AM, Vernava AM 3rd, Wexner SD: **Is the quality of life better in patients with colostomy than patients with fecal incontinence?** *World J Surg* 2006, **30**:1925–1928.
22. Sobin LH, Gospodarowicz M, Wittekind C: *UICC: TNM classification of malignant tumors*. 7th edition. New York, NY: Wiley-Liss; 2009:100–109.
23. Weiser MR, Quah HM, Shia J, Guillem JG, Paty PB, Temple LK, Goodman KA, Minsky BD, Wong WD: **Sphincter preservation in low rectal cancer is facilitated by preoperative chemoradiation and intersphincteric dissection.** *Ann Surg* 2009, **249**:236–242.
24. Jorge JM, Wexner SD: **Etiology and management of fecal incontinence.** *Dis Colon Rectum* 1993, **36**:77–97.
25. Yoo JH, Hasegawa H, Ishii Y, Nishibori H, Watanabe M, Kitajima M: **Long-term outcome of per anum intersphincteric rectal dissection with direct coloanal anastomosis for lower rectal cancer.** *Colorectal Dis* 2005, **7**:434–440.
26. Kuo LJ, Hung CS, Wu CH, Wang W, Tam KW, Liang HH, Chang YJ, Wei PL: **Oncological and functional outcomes of intersphincteric resection for low rectal cancer.** *J Surg Res* 2011, **170**:e93–e98.
27. Hohenberger W, Merkel S, Matzel K, Bittorf B, Papadopoulos T, Göhl J: **The influence of abdomino-peranal (intersphincteric) resection of lower third rectal carcinoma on the rates of sphincter preservation and locoregional recurrence.** *Colorectal Dis* 2006, **8**:23–33.
28. Akasu T, Takawa M, Yamamoto S, Fujita S, Moriya Y: **Incidence and patterns of recurrence after intersphincteric resection for very low rectal adenocarcinoma.** *J Am Coll Surg* 2007, **205**:642–647.
29. Barisic G, Markovic M, Popovic M, Dimitrijevic I, Gavrilovic P, Krivokapic Z: **Function after intersphincteric resection for low rectal cancer and its influence on quality of life.** *Colorectal Dis* 2011, **13**:638–643.
30. Hida J, Yoshifuji T, Tokoro T, Inoue K, Matsuzaki T, Okuno K, Shiozaki H, Yasutomi M: **Comparison of long-term functional results of colonic J-pouch and straight anastomosis after low anterior resection for rectal cancer: a five-year follow-up.** *Dis Colon Rectum* 2004, **47**:1578–1585.
31. Dennett ER, Parry BR: **Misconceptions about the colonic J-pouch: what the accumulating data show.** *Dis Colon Rectum* 1999, **42**:804–811.
32. Martin ST, Heneghan HM, Winter DC: **Systematic review of outcomes after intersphincteric resection for low rectal cancer.** *British J Surg* 2012, **99**:603–612.
33. Tuson JR, Everett WG: **A retrospective study of colostomies, leaks and strictures after colorectal anastomosis.** *Int J Colorectal Dis* 1990, **5**:44–48.
34. Nesbakken A, Nygaard K, Lunde OC: **Outcome and late functional results after anastomotic leakage following mesorectal excision for rectal cancer.** *Br J Surg* 2001, **88**:400–404.

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REVIEW ARTICLE

High ligation of the inferior mesenteric artery in rectal cancer surgery

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Abstract In rectal cancer surgery, it is unclear whether the inferior mesenteric artery (IMA) should be ligated as high as possible, at its origin, or low, below the origin of the left colic artery. We reviewed all relevant articles identified from MEDLINE databases and found that despite a trend of improved survival among patients who underwent high ligation, there is no conclusive evidence to support this. High ligation of the IMA is beneficial in that it allows for en bloc dissection of the node metastases at and around the origin of the IMA, while enabling anastomosis to be performed in the pelvis, without tension, at the time of low anterior resection. High ligation of the IMA does not represent a source of increased anastomotic leak in rectal cancer surgery and postoperative quality of life is improved by preserving the hypogastric nerve without compromising the radicality of the operation. More importantly, high ligation of the IMA improves node harvest, enabling accurate tumor staging. Although the prognosis of patients with node metastases at and around the origin of the IMA is poor, the survival rate of patients with rectal cancer may be improved by performing high ligation of the IMA combined with neoadjuvant and adjuvant therapy.

Keywords Rectal cancer · Inferior mesenteric artery · High ligation · Low ligation

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Introduction

In rectal cancer surgery, it is unclear whether the inferior mesenteric artery (IMA) should be ligated at a high position, flush with the aorta, or at a low position, below the origin of the left colic artery. The advantage of the high-ligation technique is that it allows for en bloc dissection of the lymph node metastases at and around the origin of the IMA, and enables anastomosis to be performed in the pelvis, without tension, at the time of low anterior resection. It also contributes to the accuracy of tumor staging. In contrast, the low-ligation technique allows for adequate blood supply to the colon proximal to the anastomoses at the time of low anterior resection [1]. There is also little or no risk of injury of the hypogastric nerve plexus and its possible consequence of ejaculation disorder [2, 3].

It has been reported that there is no significant difference in survival rates between the two techniques [4–8]. Based on these considerations, we set to identify, interpret, and discuss the available evidence related to performing IMA high ligation in rectal cancer surgery and identify future directions.

Dispute about the best position for ligation of the IMA

Since Miles [9] and Moynihan [10] proposed low- and high-ligation techniques, respectively, for rectal carcinoma surgery in the same year, 1908, the ideal position for arterial ligation has been debated. Miles introduced the concept of the upward spread of carcinoma and recommended division of the IMA just distal to the left colic branch with subsequent en bloc excision of the nodes and bowel below. Conversely, Moynihan argued that ligation and division of the IMA should be flush with the aorta to remove even more proximal nodes. When Dukes [11], Ault

et al. [12], State [13], and McElwain et al. [14] all demonstrated that the upward lymphatic extension of cancer was confined with remarkable consistency to the glands intimately related to the IMA right up to the aorta, Moynihan's high ligation became a logical extension of radical excision for rectal cancer. Furthermore, Gabriel et al. [15] and Morgan and Griffiths [16] reported that the survival of patients with Dukes C1 (the highest nodes encompassed by surgical resection, uninvolved) was better than that of patients with Dukes C2 (the highest nodes, involved). Thus, Moynihan's philosophy is still now supported by most colorectal surgeons. On the other hand, Dunphy and Pikula [17] proposed a modified procedure instead of high ligation, in which fatty tissues and nodes are dissected free and excised in the angle between the IMA and aorta, and the artery is ligated below the left colic branch.

Doubt was first cast on this approach by reports of poor survival after high ligation [4, 5]. Those patients with involved nodes above the left colic artery, for whom the high ligation was supposed to have been most advantageous, did not appear to have a better prognosis than others treated more conservatively. In other words, there was no significant difference in survival rates between the two techniques [4–8, 18, 19]. Because surgical cure is unlikely if cancer has spread to the nodes at the origin of the IMA, low ligation has been performed more frequently since 1970s [20].

Heald and Ryall [21] showed the world how total mesorectal excision (TME) following high ligation of the IMA can be readily affected with preservation of the inferior hypogastric plexuses and the hypogastric nerves. Local recurrence accounts for 34–45 % of recurrences after surgery for rectal cancer [22–24]. In fact, the local recurrence rates after TME reported by MacFarlane et al. [25], Arbman et al. [26], Enker et al. [27], Leo et al. [28], Law and Chu [29], Kapiteijn et al. [30], Tocchi et al. [31], Vironen et al. [32], Bülow et al. [33] and Wibe et al. [34] were 5.0, 3.3, 5.7, 9.2, 11.4, 8.2, 9.0, 9.0, 11.0, and 10.0 %, respectively. Considering that conventional operations are associated with an average local recurrence rate of 30 % worldwide [35–37], the local recurrence rate after TME is relatively low. Havenga et al. [38] reported that autonomic nerve preservation, in association with TME following high ligation of the IMA, reduced the local recurrence rate and minimized urinary and sexual dysfunction in patients undergoing rectal cancer surgery. Since 1990s, the goal of most specialist units has become TME with nerve preservation as standard practice [25–27, 39–42]. Our impression is that the vast majority of surgeons use high ligation to emulate the technique espoused by Heald. Furthermore, high ligation is advocated by many surgeons because in laparoscopic surgery it allows the easy creation of mesenteric windows [43–48].

The guidelines for the prevention, early detection, and management of colorectal cancer in Australia recommend high ligation, although this is based on weak evidence (Grade IV in the I-to-V scale) [49]. In contrast, the Guidelines for Colon and Rectal Cancer Surgery from the National Cancer Institute of the United States recommend low ligation [50]. However, the evidence to support low ligation is weak (level II–III in the I-to-V scale of evidence and grade C in the A-to-D scale of recommendation grades). These guidelines also recommend that all nodes suspicious for metastasis proximal to the origin of the left colic artery be biopsied or removed, or that the level of resection should be extended to include the nodes of concern [50].

One recent review article on the ligation level of IMA recommended high ligation because of improved node retrieval rates and accuracy of tumor staging [51]. Conversely, another recent review article recommended low ligation because it was anatomically less invasive with respect to circulation of the proximal colon limb of anastomosis [52]. This article also stated that the anatomic disadvantage of high ligation in relation to impaired perfusion of the proximal limb and anastomotic leakage has not been proven sufficiently [52].

The Japanese Classification of Colorectal Carcinoma [53] divides central regional node spread in colorectal cancer into two levels: central spread N3 (main node), with nodes at the origin of the primary feeding artery; and central spread N2 (intermediate node), with nodes other than the main nodes, which lie along the primary feeding artery. For invasive colorectal cancer, the Japanese Classification of Colorectal Carcinoma [53] recommends ligating the primary feeding artery at its origin. Therefore, in Japan, high ligation of the IMA is performed routinely for invasive rectal cancer; and widely in combination with lateral pelvic node dissection.

Ligation level and survival (Table 1)

In relation to 5-year survival rates, Grinnell [5] reported that high ligation resulted in a 7.3 % higher survival rate when only Dukes C tumors were considered. Similarly, Uehara et al. [54] reported no significant difference in survival rates between the two groups for lower rectal cancer and could not demonstrate any effect of prophylactic lymph node dissection at the root of the IMA on patients with any stage of disease. Moreover, they reported that lymph node dissection without the root of the IMA did not result in increased para-aortic or mediastinal lymph node metastases [high tie 1.9 % (4/207) vs. low tie 3.8 % (3/78)], which they had attributed to failing to perform lymph node dissection. Kawamura et al. [55] reported that

Table 1 Survival after high versus low ligation of the inferior mesenteric artery in rectal cancer surgery

References	Site of tumor	5-year survival (%)	
		High tie* (*n*)	Low tie (*n*)
Rosi et al. [4]	Rectum	65.1 (66)	56.0 (82)
	Rectosigmoid	58.3 (24)	47.0 (17)
Grinnell [5]	Rectum, sigmoid and descending colon	5.7 % higher than low tie (151)	(150)
Bacon et al. [6]	Upper rectum	58.3 (139)	52.3 (NA)
	Lower rectum	53.4 (118)	49.5 (NA)
Pezim and Nicholls [7]	Rectum, rectosigmoid	64.5 (543)	65.2 (690)
Surtees et al. [8]	Rectum, rectosigmoid (Dukes C ctage)	55.7 (150)	54.3 (100)
Slanetz and Grimson [59]	Rectum, colon	70.8 (1027)	68.1 (1053)
Adachi et al. [62]	Rectum, sigmoid colon	83.2 (134)	91.5 (38)
Uehara et al. [54]	Lower rectum	74.6 (133)	77.8 (78)

NA Not available

* *P* value not significant versus low tie

the incidence of local lymph node recurrence did not differ significantly between their high and low tie groups (2.3 % (3/132) vs. 1.8 % (7/379), respectively).

Pezim and Nicholls [7] reported that patients with Dukes stage C2 in a high-ligation group fared significantly worse (22.2 vs. 52.2 % 5-year survival rate). They hypothesized that many of the Dukes stage C2 patients in the low-ligation group would have in fact had Dukes stage C1 cancer, had a high ligation been performed. A subsequent paper from the same institution [8] analyzed the survival of patients with Dukes stage C rectal cancers. The number of harvested nodes was higher in the high-ligation group (mean 14.2 vs. 11.9). The 5-year survival rate of patients with Dukes C1 cancers did not differ significantly between the high- and low-ligation groups (64 vs. 54 %, respectively). However, for those with Dukes C2 tumors, although there was an apparently improved survival rate after treatment by low IMA ligation, this was not significant. One explanation would be that many of the Dukes C2 cases in the low-ligation group would have in fact been staged C1, had a high IMA ligation been performed, thus creating a stage-migration phenomenon [56]. To minimize this effect, a subgroup of patients in the high-ligation group with involvement of the 12th node from the tumor was compared with a Dukes C2 tumor subgroup of patients in the low-ligation group, with no significant survival differences observed. They concluded that high ligation of the IMA did not improve survival. Rouffet et al. [57] favor low ligation because it yielded a 5-year survival rate of 64 %, comparable to high ligation (62 %), in a French multicenter, randomized trial of left colectomy and high ligation of the IMA versus segmental colectomy and low ligation of the IMA. The 12-year survival rates in this study were 54 versus 47 % for low versus high ligations, respectively. Because the survival rate after high ligation was only slightly higher, some colorectal surgeons now perform low ligation [52].

On the other hand, Leggeri et al. [58] reported a good prognosis after rectal cancer surgery with high ligation of the IMA, with 5-year survival rates of 68.1 % after sphincter-saving surgery and 57.5 % after abdominoperineal resection of the rectum. Slanetz and Grimson [59] reported a stage-specific survival benefit of high ligation. The level of IMA ligation had no influence on the 5-year survival rates of patients with Dukes stage A colon or rectal tumors. Patients with Dukes stage B colon cancers had significantly higher survival rates following high IMA ligation (83.9 vs. 73.9 %), but this trend was not seen in the rectal cancer subgroup. In patients with Dukes C colorectal cancers, high-IMA ligation significantly increased the 5-year survival to 52.9 versus 45.2 % of those who underwent low ligation. No significant advantage of high IMA ligation was evident in the survival rates of patients with Dukes C1 or C2 rectal cancers and Dukes C2 colon cancers, although those with Dukes C1 colon cancers fared better (58.6 vs. 49 %). However, when five or more nodes were involved, the level of ligation did not influence survival rates. This confirms previous findings that the positive effect of high IMA ligations is lost when the apical node is involved (Dukes stage C2) and with an increasing number of nodes being involved [5, 7]. Nevertheless, in patients with intermediate node involvement only, removing the uninvolved central nodes by performing high ligation of the IMA almost doubled the 5-year survival rate (41.7 vs. 25.9 %) and reduced the rate of death from recurrent cancer from 66.7 to 38.9 % [59]. Read et al. [60]

favored high ligation for left-sided colonic cancers based on multivariate analysis data, with high ligation of the IMA trending toward a good prognosis for both locoregional control at 5 years (96 %) and 5-year disease-free survival (84 %). More radical excision of lymphatic drainage may be more effective for carcinoma of the rectum; however, this has not been consistent for proximal lymphatic spread if data from retrospective studies are to be believed.

IMA root nodal metastasis and survival

Lymph node involvement is a major prognostic factor for survival after rectal cancer surgery. High ligation includes the apical group of nodes at and around the origin of the IMA within the resection; however, the incidence of metastasis to the IMA root nodes is reported to be relatively low, ranging from 0.3 to 11.1 % (Table 2) [6, 7, 54, 57–59, 61–66]. Bacon et al. [67] reported that positive nodes would have been left behind in 9 % (8/90) of patients operated on if a high ligation had not been carried out. Pezim and Nicholls [7] studied 5-year survival rates after the high-ligation technique and found it to be as low as 18.7 % of patients with IMA root nodal metastasis as opposed to 63.6 % of patients without IMA root nodal metastasis. Furthermore, Grinnell [5] and Uehara et al. [54] reported no survivors among their patients with IMA root nodal metastases; however, as many patients with IMA root nodal metastases had metastases in more proximal nodes, an operation with high ligation would result in a noncurative resection. Because the 5-year survival rate of patients with IMA root nodal metastases is low after high ligation, the low-ligation technique is used in rectal cancer surgery in some specialist units [20].

Interestingly, four studies on high ligation reported significantly positive 5-year survival data for patients with IMA root nodal metastases [58, 64, 66, 68]. Leggeri et al. [58] reported that the 5-year survival rate of Dukes stage C patients was clearly influenced by the level of proximal node involvement, being 68.2 % of patients with marginal node involvement, 25 % of those with intermediate node metastases, and 30 % of those with central node metastases. The survival rate of patients with IMA root node metastases was approximately half of that for those without IMA root node metastases. Because of the retrospective design of their study, it was impossible to find out what the survival rates of patient with IMA root positive node metastases would have been if those nodes were left in place. Furthermore, the impact afforded by the knowledge of nodal status may have altered the outcome. Conceivably, patients with IMA root nodal-positive metastases may have been treated in a more nihilistic manner, whereas those without IMA root nodal metastases may have been treated aggressively with adjuvant therapy, accounting for the twofold difference in survival. Cosimelli et al. [68] reported an overall 5-year survival rate of 58.5 % after rectal

Table 2 Inferior mesenteric artery root nodal metastasis and survival

References	Site of tumor	Metastatic Incidence[a] % (*n*)	5-year survival of pts with metastasis %
Morgan and Griffiths [16]	Rectum, sigmoid and descending colon	8.4 (18/214)	NA
Rosi et al. [4]	Rectum, rectosigmoid	8.3 (3/36)	NA
Grinnell [5]	Rectum, sigmoid and descending colon	10.6 (19/179)	No survivors who were free of cancer
Bacon et al. [6]	Rectum, sigmoid and descending colon	11.1 (11/99)	27.3
Pezim and Nicholls [7]	Rectum, rectosigmoid	5.5 (32/586)	18.7
Surtees et al. [8]	Rectum, rectosigmoid (Dukes C ctage)	NA	32.0
Leggeri et al. [58]	Rectum	4.2 (10/239)	30.0
Cosimelli et al. [68]	Rectum, sigmoid colon	5.6 (17/302)	42.7
Slanetz and Grimson [59]	Rectum	7.5 (22/294)	18.2
Hida et al. [66]	Rectum, rectosigmoid	8.6 (17/198)	38.5
Adachi et al. [62]	Rectum, sigmoid colon	0.7 (1/135)	NA
Steup et al. [61]	Lower rectum	0.3 (1/373)	NA
Kim et al. [71]	Rectum, sigmoid colon	3.6 (73/2040)	38.0
Kanemitsu et al. [64]	Rectum, sigmoid colon	1.7 (20/1188)	40.0
Uehara et al. [54]	Lower rectum	1.9 (4/207)	0
Chin et al. [65]	Rectum	2.9 (29/1002)	13.8
	Sigmoid colon	3.6 (14/387)	50.0

NA Not available

[a] No. of patients with metastasis/total no. of patients

cancer surgery with high ligation of the IMA. In this study, TME was performed, and systemic chemotherapy, with or without high-dose pelvic radiotherapy, was administered to selected Dukes B and C patients, suggesting that modern multimodality oncologic therapy combined with nerve-sparing TME, as advocated by Heald [69], can achieve high survival rates even for patients with Dukes stage C2 tumors, contrary to previous reports [5, 7]. Kanemitsu et al. [64] calculated that high-IMA ligation increased the curative resection rate by 9 %, but only 0.7 % of those patients were likely to be cured by this. Lymph node metastases at the root of the IMA were found in 1.7 % of the 40 % of patients who survived for 5 years, which compares well with data for patients with intermediate node metastases, who had a survival rate of 50 % at 5 years. This metastatic incidence (1.7 %) represented the frequency of residual metastatic nodes that would normally have been left behind in a low ligation. Furthermore, they reported that the high tie might save the occasional patient and prove helpful when nodal metastases are limited to below the level of the left colic artery by providing a greater margin of safety when the artery, including all the surrounding glands and lymphatics, is excised by a single block dissection. Liang et al. [70] postulated that the high tie would provide good and similar locoregional control of tumors with or without lymph node metastasis because 92.9 % of the recurrences in 28 patients developed within 3 years after surgery and all of those in patients with Dukes A/B, C1, or C2 cancers were distant metastases (recurrence rates: 20.0 % of 10 patients, 27.0 % of 74 patients, and 42.9 % of 14 patients, respectively; $P > 0.05$). Kim et al. [71] reported that high tie resulted in similar loco-regional recurrences among patients with and those without IMA root node metastasis (recurrence rates: 20.4 % of 54 patients and 16.0 % of 94 patients, respectively).

Based on these considerations, we set to clarify the indications for high ligation of the IMA in rectal cancer surgery [66]. First, we examined regional node metastases of rectal cancer, using the clearing method (xylene clearance), which makes it possible to identify nodes smaller than 4 mm in maximum diameter and to detect small metastatic nodes that would be undetected by the conventional manual method [72]. The mean number of nodes examined per patient was 73.5, being 14553 nodes in 198 patients. The incidence of metastasis was 56.6 % and the incidence of metastasis to the IMA root nodes was 8.6 %, which was higher than reported previously. These differences may be attributed to the detection of metastatic nodes smaller than 4 mm in maximum diameter by the clearing method. It is believed that the greater the number of nodes examined and the higher the incidence of metastasis, the more accurate the evaluation of the extent of node dissection for cancer control. IMA root nodal metastases developed more frequently in patients with pT3 and pT4 rectal cancer, at incidences of 9.4 and 20.8 %, respectively. For both pT1 and pT2 tumors, the incidence of metastasis to the IMA root nodes was 0 %. Among the 198 patients, 144 underwent curative resection. The 5-year survival rate of the 13 patients with IMA root nodal metastasis was 38.5 %, being significantly lower than the 73.4 % of those without IMA root node metastasis. The 5-year survival rate of patients with IMA root nodal metastasis was still higher than that reported in the literature, which could be because we examined metastatic nodes smaller than 4 mm in maximum diameter by the clearing method and performed extended node dissection following high ligation of the IMA. We concluded that although the survival rate of patients with IMA root nodal metastases was lower than that of those without metastases, IMA root nodal dissection should be performed after high ligation of the IMA for patients with pT3 and pT4 cancers. Upper lymphatic spread along the IMA was strongly related to the depth of tumor invasion. Kanemitsu et al. [64] reported that the incidence of IMA nodal metastasis for pT1, pT2, pT3, and pT4 tumors was 0, 0.4, 2.6, and 2.9 %, respectively. Chin et al. [65] reported that the IMA metastasis incidence for pT1, pT2, pT3, and pT4 tumors was 0, 1.0, 2.6, and 4.3 %, respectively. Nodal metastases at the origin of IMA occurred more frequently in patients with pT3 and pT4 tumors. In contrast, nodal metastases rarely developed at the origin of IMA in patients with pT1 and pT2 cancers. These studies [64–66] suggested that the low tie might be sufficient for pT1 and pT2 rectal cancers. However, according to an accompanying Invited Editorial by Wexner [43], high ligation should be performed for all patients with rectal carcinomas because it is impossible to know at the time of surgery, which patients have pT3 and pT4 lesions. Wexner also states that no method of preoperative or intraoperative assessment allows for 100 % sensitivity and specificity toward this issue. The problem with using preoperative staging to guide the extent of node dissection is that no imaging technique offers absolute staging accuracy [73, 74]. It has been our policy to perform high-tie procedure to cure patients with cancer of the rectum. However, its contraindications are an age of 85 years or more, advanced arteriosclerosis, and extreme obesity. Obviously, the high tie technique should not be used as a palliative procedure. The low-tie technique has been adopted as a standard procedure, when adequate exposure to allow ligation of the IMA on the aorta is considered too hazardous, such as after abdominal aorta replacement surgery for an aneurysm.

Although it is widely accepted that IMA high ligation does not improve survival, most data originated from studies on operations performed 4–5 decades ago, when TME and adjuvant chemo- and radiotherapy were not common practice. More recent reports challenge this belief [59, 62, 64, 66]. However, most of these studies originate in Japan, where IMA

high ligation is often combined with lateral pelvic lymphadenectomy, which makes interpretation of the results difficult. The 40 % 5-year survival rate reported for patients with Dukes C2 tumors [64, 66] has been replicated in two European series [58, 68], but it is unknown whether this can be widely matched. While there is no solid evidence of improved survival directly attributable to IMA high ligation, the majority of published studies report that patients who underwent this procedure had better survival rates [5, 7, 59], but the difference was not significant.

Ligation level of the IMA and staging

Although there may be no survival advantage, ligating the IMA at its origin from the aorta seems to increase the number of nodes harvested significantly [55], considering that as many as ten nodes have been found along the segment of the IMA between the aorta and the origin of the left colic artery [5]. In all published series disclosing node retrieval rates, high IMA ligation retrieved more than 12 nodes; [8, 60, 61, 66, 71, 75] thought to be the minimum necessary for accurate tumor staging [50] (Table 3).

The most important aspect of node staging is the presence or absence of apical node involvement [76, 77]. Patients with apical node metastases have 5-year survival rates comparable to those presenting with distant metastases and are 2.5 times more likely to die from their cancer than patients with an uninvolved apical node [78]. This was recently confirmed by Kim et al. [71], who reported that metastases at the root of the IMA were an independent prognostic factor.

That high ligation allows for the sampling of more nodes is inherently logical. Somewhat more debatable is that these additional harvested nodes improve prognostication [79, 80]. The ability to examine these nodes and to increase their yield is dictated only in part by the surgical procedure. Specifically, with more colons harvested and a higher the level of ligation, more nodes will be sent to the pathologist; however, the diligence with which the pathologist searches for nodes will impact greatly on the number of nodes reported. Moormann et al. [81] compared the conventional manual and clearing methods used in surgery for carcinoma of the colon and rectum and reported that the mean number of detected nodes increased from 3.1 to 10.6 per patient when the clearing method was used. Cohen et al. [82] reported that standard histopathologic evaluation revealed a mean of 13 (range 0–43) nodes after segmental colectomy, but a mean additional 4 (range 0–12) nodes were found after xylene clearance. A similar increase, from 10.5 to 23.1 nodes, was reported when the clearing method was used in patients with carcinoma of the rectum [83]. Scott and Grace [84] reported a threefold increase in the number of nodes harvested versus traditional sectioning (6.1 vs. 18.9), respectively, which led to a change of stage in 8.6 % of their patients, from Dukes B to Dukes C. Haboubi et al. [85] reported similar results in their analysis of colorectal specimens from 47 patients, 41 of whom had carcinoma. The mean number of nodes harvested at initial dissection from these 41 patients was 7 (range 1–20), which increased almost sevenfold to a mean of 48 (range 10–295) after xylene clearance. They estimated that 88 % of nodes were not recovered by traditional methods. Subsequently, 3 of the 41 (7 %) patients who had initially been staged as Dukes B were subsequently restaged as Dukes C. We reported increasing the mean number of nodes recovered by the clearing method, from 21.2 nodes/patient to 73.7 nodes/patient; however, the incidence of metastasis also increased from 50 % to 57.1 % in patients with rectal cancers [72]. Furthermore, when the clearing method was used, metastatic nodes smaller than 4 mm in diameter accounted for as many as 32.6 % of the total number of metastatic nodes, but only 14.8 % when the manual

Table 3 Level of ligation of the inferior mesenteric artery and staging

References	Results
Morgan and Griffiths [16]	Routine high tie may result in conversion of one in eight C2 cases into C1 cases
Pezim and Nicholls [7]	Some C2 low tie cases might have been C1 had high tie been done
Surtees et al. [8]	Mean no. of lymph nodes examined (*n*), high tie 14.2 (150) vs. low tie 11.9 (100)
Kawamura et al. [55]	Mean no. of lymph nodes examined (*n*), high tie 23* (132) vs. low tie 16 (379)
Kanemitsu et al. [64]	High tie allowed for the upstaging of cancer
	Of the 20 patients with IMA root node (central node) metastasis, 8 did not have intermediate node metastasis
Uehara et al. [54]	Mean no. of lymph nodes examined (*n*), high tie 39 (133) vs. low tie 31 (78)
	Incidence of Dukes C % (*n*), High tie 71.4 (95/133) vs. Low tie 62.8 (49/78)
Liang et al. [70]	High tie allowed for upstaging of cancer (from Dukes B to C2) in five patients (5.1 %)
	Sixteen patients (18.2 %) had skip lymph node metastases

IMA Inferior mesenteric artery

* Significant