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Short-term and long-term results of a randomized study comparing high tie and low tie inferior mesenteric artery ligation in laparoscopic rectal anterior resection: subanalysis of the HTLT (High tie vs. low tie) study

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Abstract

Background In rectal anterior resection, a clear consensus regarding the optimal level of inferior mesenteric artery (IMA) ligation does not exist because of a lack of randomized trials. We conducted a randomized trial to determine if the IMA should be tied at the origin (high tie, HT) or distal to the left colic artery (low tie, LT) (HTLT study). This study is a subanalysis of HTLT study for laparoscopic surgery.

Methods All candidates were randomly divided into the HT or LT groups. The lymph node dissection around the origin of the IMA was performed in the LT group. The stratified factor was the approach (open or laparoscopy). Evaluation parameters were operative factors, short-term and long-term results. In the present study, laparoscopic surgeries were examined as subgroup analysis.

Results From June 2006 to September 2012, 331 patients were registered. Two hundred and fifteen patients (107 for HT: 108 for LT) underwent laparoscopic surgeries. There was no difference between the groups in background. The incidence of anastomotic leakage (HT: LT %) showed no significant differences for grade 2 or higher (11.2:9.3), and grade 3 or higher (2.8:4.6). There were no differences in operative time (200:205 min), blood loss (15:15 ml), number of dissected lymph nodes (22:20), and postoperative hospital stay (10:10 days). The incidence of bowel obstruction in HT was significant (3.7 vs. 0%, $p = 0.043$). There were no significant differences in overall survival (5-year: 91.3 vs. 90.2%, $p = 0.850$) and disease-free survival (5-year: 83.2 vs. 78.0%, $p = 0.525$). There were no differences in the first recurrent site and death reason between both groups. The risk factors for leakage were being male and an anastomotic level in a multivariate analysis by logistic regression.

Conclusion The IMA ligation level was unrelated to anastomotic leakage. No significant difference was detected in long-term results between HT and LT.

Used in rectal cancer surgery since 1908, Miles was the first to introduce the concept of the en bloc excision of lymph nodes associated with tumor and those responsible for the upward spread of cancer [1]. Miles suggested that the inferior mesenteric artery (IMA) was divided in the distal portion of the branching of the left colic artery (LCA). This

method corresponds to a low tie technique (LT) for the ligation of the IMA. Moynihan advocated for the division of the IMA at its origin from the abdominal aorta, including apical lymph node dissection, in the same year [2]. Moynihan's method corresponds to a high tie technique (HT) for IMA ligation.

With regard to radical cure resection and accurate pathological staging, the HT principle has been advocated [3–10]. In opposition to HT, recent studies recommended LT, where no significant difference in survival rates between HT and LT was observed [11–13]. Other studies recommended LT because of the decreased blood flow to the proximal colon

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stump in HT [14–16]. LT is recommended by the American Society of Colon and Rectal Surgeons in the textbook of *Colon and Rectal Surgery* because of the decreased blood supply observed to the sigmoid colon in HT. It was described that HT should be performed in patients with a clinical suspicion of involved nodes around the IMA or in patients who require additional vascular mobilization for the proximal colon to avoid the over tension of an anastomosis [17]. Japanese guidelines for the treatment of colorectal cancer outlined that upward lymph node dissection should be performed at the level of the IMA for clinical T2 or more advanced disease [18]. However, a description of the most appropriate portion for the division of the IMA was not made. There were several reviews that reported no difference of short- and long-term results between HT and LT and concluded with a description of the necessity of randomized controlled trials [19–21]. A clinical question that remains is whether preservation of blood supply by the left colic artery (LCA) improves anastomotic outcome. Therefore, we conducted a randomized controlled trial (HTLT study) in rectal cancer patients comparing HT and LT methods. The HTLT study included both open and laparoscopic surgeries. Regarding laparoscopic surgery, there are two retrospective studies that recommended LT for this problem from the viewpoint of bloodstream maintenance [22, 23]. The long-term results and short-term results of these studies were invariable between HT and LT. In the present study, the short-term and long-term outcomes of laparoscopic surgery were analyzed as a subanalysis.

Methods

Patients

The HTLT study was a randomized controlled trial conducted at a single institute, Yokohama City University Medical Center (Japan). We planned to enroll 400 patients over 5 years beginning in June 2006. Rectal cancer patients who were scheduled to undergo anterior resection registered preoperatively were included. The patients were randomly allocated to undergo an HT or LT ligation of the IMA.

The rectum is defined as the intestine between the level of the promontorium and upper edge of the puborectal muscle according to the seventh edition of the *Japanese General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus* [24].

Inclusion criteria were 20 years of age or over, histologically proven malignancy of the rectum, a clinical tumor that penetrated the visceral peritoneum (cT4a) or lower T factor, no metastasis (M0), elective operation, tolerable surgery under general anesthesia, no history of colorectal surgery except appendectomy, and provided written informed

consent. The clinical TNM classification for the staging of rectal cancer was based on the results of colonoscopy, thoracic, abdominal, and pelvic computed tomography (CT) scans, abdominal ultrasonography, or magnetic resonance imaging (MRI). Exclusion criteria were synchronous or metachronous (within 5 years) malignancy in another organ except for carcinoma in situ, multiple colorectal cancers; acute intestinal obstruction or perforation due to rectal cancer; and pregnant or lactating women. A past history of surgery on another organ was allowed for registration. The general condition of all elective surgery patients was assessed preoperatively by an anesthesiologist in our hospital. An abdominoperineal resection, Hartmann's operation, and rectal intersphincteric resection were excluded. The patients who underwent laparoscopic surgery from all candidates were analyzed in the present study. The protocol of this study was approved by the Ethics Committee of Yokohama City University and registered at http://clinicaltrials.gov. The trial number was NCT01861678.

Procedures

The surgeries were performed by the colorectal surgical treatment team. All surgeons were accredited as specialists from the Japan Society of Coloproctology. This specialty requires 6 years of clinical experience in an approved hospital and passing of the specialist qualifying examination [25]. Laparoscopic surgeons passed a skill accreditation examination system, which was established by the Japanese Society for Endoscopic Surgery in 2004 [26].

In deciding the approach method, conventional open surgery was performed for patients with a bulky tumor, 6 cm or greater in diameter. The other patients underwent laparoscopic surgery. A medial-to-lateral approach was performed in all laparoscopic surgeries. First, lymph node dissection around the IMA and a retroperitoneal dissection were carried out. The IMA was divided at its origin from the abdominal aorta in the HT group. In the LT group, the IMA was divided just after branching to the LCA with the dissection of lymph nodes around the IMA. Second, mobilization of the left colon was performed. Third, the distal rectum was cut by a linear stapler after rectal irrigation. In the fourth step, the specimen was removed via a small incision, and the proximal colon was cut approximately 10 cm from the lesion. A proximal margin of at least 10 cm is needed with a distal margin of 3 cm in upper rectal cancer and 2 cm in lower rectal cancer according to the *Japanese General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum, and Anus* [24]. Peritoneal reflexion divides the above part and the lower part of the rectum. Most patients had tumor-specific mesorectal excision (TSME), not full TME. A hemorrhage test of the marginal artery was performed to evaluate the blood flow of the proximal colon stump in both arms.

We judged it from the presence of the palmic hemorrhage of the artery. The resection of the proximal colon was added until confirmation of bleeding. The anvil of the circular stapler was installed and fixed to the stump of the proximal colon. A pelvic sidewall lymphadenectomy was performed after re-establishing pneumoperitoneum in clinical T3 or deeper cancers with a diagnosis of lymph node swelling by preoperative imaging examination. Finally, reconstruction was undertaken using a double stapling technique. All reconstructions were made in the straight fashion. A straight anastomosis is the most common reconstruction in Japan. To discover imperfections of the anastomosis, an air leak test was performed in all surgeries after reconstruction. The air leak test was performed using the following methods. The colon on the proximal side of an anastomosis is closed with forceps after firing of the circular stapler. A small quantity of saline was put in the pelvic cavity. The appearance of a bubble in the anastomotic region was determined by pumping air in from the anus. The anastomotic region was reinforced by the suture if there was a bubble.

The construction of a diverting stoma was intraoperatively decided by the surgeon in charge in patients with the narrow pelvis of a male, a positive air leak test, and an anastomotic level lower than 5 cm from the anal verge. An intraluminal drainage tube was inserted from the anus in the absence of a diverting stoma.

Randomization

After patient agreements were confirmed by written, informed consent, patients were randomly assigned to the HT or LT ligation groups. The randomization was performed by the Department of Biostatistics and Epidemiology Data Center of Yokohama City University immediately before the operation. To balance surgical backgrounds between the HT and LT groups, patients were stratified by the surgical approach (open or laparoscopic) with the minimization method.

Adjuvant therapy

All patients with stage III, IIb, and IIc cancer were recommended to undergo postoperative adjuvant chemotherapy by the surgeon in charge, and patients who agreed by written, informed consent underwent chemotherapy. For stage III, two regimens were used as follows: venous 5-fluorouracil (5-FU) plus l-leucovorin (l-LV) therapy and oral fluoropyrimidine (UFT) plus leucovorin (LV) therapy. For stage IIb and IIc, UFT therapy was undertaken.

Neither radiation therapy nor preoperative chemotherapy was given to any patient. Preoperative chemoradiotherapy was not standard treatment in Japan.

Follow-up schedule

Patients were followed up with outpatient examinations, including tumor marker measurements and chest, abdominal, and pelvic computed tomography (CT) scans every 6 months for the first 3 years. These examinations were done once a year during the fourth and fifth year. For stage IV, the follow-up schedule was decided according to the condition of each patient.

Assessment parameters

Preoperative parameters were as follows: the patient's background, including gender, age, height, and weight; previous history including prior abdominal surgery, concomitant disease, and American Society of Anesthesiologist score [27]; and tumor assessments, including histological diagnosis and clinical TNM stage [28]. Operative parameters were as follows: operating date, total operative time, time from skin-incision to ligation of the IMA, estimated amount of blood loss, operative procedure, intraoperative complications, and conversion to open from laparoscopic surgery. If the length of the abdominal incision was greater than 8 cm in laparoscopic surgery, it was assessed as a conversion to open surgery from laparoscopic surgery. The distance from the origin of the IMA to the branching of the LCA was measured in the LT group.

Postoperative parameters were as follows: early and late complications, grade of complication, and length of postoperative hospital stay. An early complication was defined as an occurrence within 30 postoperative days. The period of late complication was defined as the time of occurrence after 30 postoperative days. A leakage was detected by clinical findings of purulent discharge via the abdominal drainage tube or peritonitis. The terminology for complications used was in accordance with the *Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* [29], and grading was according to the Clavien–Dindo classification [30]. Grade 1 was defined as no need for pharmacological, surgical, or interventional treatment. Grade 2 required pharmacological treatment and total parenteral nutrition. Grade 3a required surgical, radiological endoscopic intervention without general anesthesia. Grade 3b required surgical, radiological endoscopic intervention under general anesthesia. Grade 4 was a life-threatening complication requiring intentional care. Grade 5 was death of the patient. If there was no clinical symptom of anastomotic leakage, contrast radiography via the drainage tube of anastomosis was not used in this study. Therefore, the grade 1 anastomotic leakage was not measured. In another early complication, a bowel obstruction was defined as a condition whereby the transportation of intestinal contents stopped at the distal side after recovery of intestinal movement. A patient who did not recover an

intestinal movement or defecation after operation and intestinal stasis within 7 days after operation were excluded as postoperative paralytic ileus. In addition, the patients with silent bowel sound on an occurrence were excluded from bowel obstruction.

In long-term outcomes, overall survivals and disease-free survivals were calculated by Kaplan–Meier method, differences were analyzed by log-rank test. The first recurrent mode and death reason were compared between both groups.

All pathological data were classified according to the 7th edition of the *Japanese General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus* [24] and the 7th edition for TNM classification [28].

Counting of dissected lymph nodes was performed as the total and each lymph node station. The lymph node stations were divided into the following three areas according to the 7th edition of the *Japanese General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus* [24]: the area of the IMA origin to the branch of the LCA (#253; lymph node station number), the intermediate area along the IMA (#252), and the perirectal area around the marginal vessels (#251). Pathological margins were measured for the proximal and distal length. The circumferential margin involvement was assessed as a histological exposure of a cancer cell at the vertical dissection surface.

Endpoints

The primary endpoint was the incidence of anastomotic leakage. Secondary endpoints were the operation time, amount of blood loss, and 5-year overall survival. To evaluate if a difference in the operative procedure influenced survival, overall survival was compared. The operating time and amount of bleeding were added to the list of secondary endpoints because these parameters could have influenced the selection of an operating technique if there were no differences in the overall survival.

Statistical analysis

A sample size of 362 patients was used to achieve a power of more than 80% to detect a difference between the groups using a two-sided Chi-square test with a type I error rate equal to 0.05 when the incidence of anastomotic leakage was 6 and 15% in LT and HT groups, respectively. Some dropouts were considered, and the number of accumulation targets was assumed to be 400 patients.

For continuous variables, data are presented as medians. For categorical variables, data are presented as frequencies and percentages. A comparison of the endpoints was based on an intention-to-treat principle; that is, the patients who switched to another group during surgery were treated as members of the allocated group. The Chi-square test was applied to evaluate the significance of differences in proportions, and a Mann–Whitney *u* test was used to evaluate the significance of differences in continuous variables. A *p* value of less than 0.05 was considered to be statistically significant. SAS® software version 9.2 for Windows® (SAS Institute, Cary, NC, USA) was used for these statistical analyses. The present trial is registered with *ClinicalTrials.gov*, number NCT01861678.

## Analyzed parameters in the present study

In the present study, to clarify short-term outcomes, early complications, operative parameters, and oncological qualities of surgery were analyzed in laparoscopic surgery. In particular, the incidence of anastomotic leakage of grade 2 or higher was analyzed. The oncological qualities of surgery were revealed by the surgical margin and the number of dissected lymph nodes in total and in each station. These findings were compared between the HT and LT groups. Moreover, the risk factors for anastomotic leakage were assessed by univariate and multivariate analyses using logistic regression.

Results

We planned to enroll 400 patients over 5 years beginning in June 2006. However, the number of candidates was insufficient, and we extended the registration period for 1 year. Even with this extension, the number of patients registered was 331 patients. One hundred and sixty-six patients were assigned to the HT group, and 165 patients were assigned to the LT group. In the HT group, two patients were excluded because of changes in operative procedures: an abdominoperineal rectal resection and a Hartmann's procedure. In the LT group, five patients were excluded because of changes in operative procedures: three intersphincteric rectal resections, an abdominoperineal rectal resection, and one patient's cancer could not be excised. One hundred and sixty-four patients in the HT group and 160 patients in the LT group were analyzed in the whole study. Fifty-seven patients of the HT group and 52 patients of the LT group underwent open surgery. Therefore, 107 patients in the HT group and 108 patients in the LT group were analyzed in the present study. In the LT group, the LCA of one patient was separated during the operation because of a high tension anastomosis. However, this patient was assigned to the LT group because this study was analyzed with an intention to treat (Fig. 1).

There were no significant differences between the HT and LT groups with regard to the patient and therapeutic characteristics. The distances of the anastomosis from the anal verge were approximately 6 cm in both arms. Two or more

Fig. 1 CONSORT diagram for sub analysis of HTLT study. *HT* high tie, *LT* low tie, *HTLT study* High tie versus Low tie study, *APR* abdominoperineal resection, *ISR* intersphincteric rectal resection
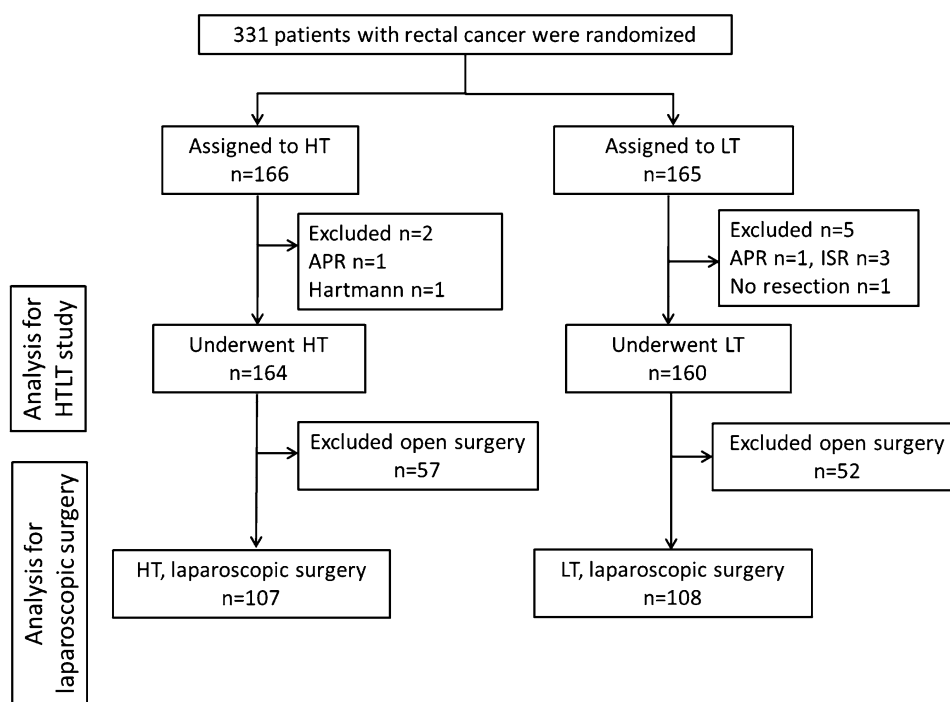
Short-term outcomes

Anastomotic leakage

The incidence of grade 2 or higher anastomotic leakages was 11.2% in the HT group and 9.3% in the LT group. There were no patients with grade 3a anastomotic leakages in either group. Eight patients underwent emergent re-operation for the creation of diverting stoma in both groups. A grade 3b anastomotic leakage was detected in 4 patients of the LT group. A grade 4 anastomotic leakage was detected in three patients of the HT group. One patient death occurred because of multiple organ failure after the creation of a diverting stoma for anastomotic leakage in the LT group. This patient was classified as grade 5. The incidence of grade 3b or higher was 2.8% in the HT group and 4.6% in the LT group. No significant differences within each grade were observed (Table 2).

Early complication and operative parameters

The incidence of overall early complications including anastomotic leakage was 30.8% in the HT group and 24.1% in the LT group, and a significant difference was not observed. In terms of the details of early complications, a significant difference was detected in the incidence of bowel obstruction (3.7 vs. 0%, $p = 0.043$). There were no significant differences in the other early complications.

A significant difference in operating time was not observed (HT vs. LT = 200 vs. 205 min). However, the operating time of an IMA tie from the start of the operation in the LT group was longer than for the HT group (38 vs. 54 min, $p < 0.001$). No significant difference was observed between the groups in the estimated blood loss (15 vs. 15 ml). A blood transfusion was required for one patient in both groups. The conversion rate to open surgery was 5.7% in the HT group and 1.9% in the LT group, with no significant difference between the groups ($p = 0.142$). A significant difference in the postoperative hospital stay was not observed (10 vs. 10 days, Table 3).

Long-term outcomes

Survival rate

Five-year overall survival rates were 91.3% in HT group and 90.2% in LT group, respectively. There was no significant difference ($p = 0.850$). There was no significant differences in disease-free survival rate (5-year: 83.2 vs. 78.0%, $p = 0.525$) too. Both survival rates did not show the differences in the analysis according to the pathological stages (Table 4).

Table 1 Demographics and therapeutic characteristics of patient underwent laparoscopic surgery in HTLT study

	HT ($n = 107$)	LT ($n = 108$)	p
Age: years (min–max)	66 (30–86)	66 (35–88)	0.646
Gender [n (%)]			0.929
Male	68 (63.6)	68 (63.0)	
Female	39 (36.4)	40 (37.0)	
ASA score [n (%)]			0.124
1	29 (27.1)	53 (33.1)	
2	74 (70.1)	95 (59.4)	
3	4 (6.1)	12 (7.5)	
OPNI score (min–max)	53.0 (30.1–71.4)	52.6 (42.0–71.8)	0.433
Concomitant dis (general disease) [n (%)]	73 (68.2)	68 (63.0)	0.417
Cardiovascular disease	49 (45.8)	48 (44.4)	0.842
Diabetes	8 (7.5)	15 (13.9)	0.128
History of laparotomy	14 (13.1)	17 (15.7)	0.579
Body mass index: kg/m^2 (min–max)	23.1 (16.9–32.8)	22.3 (17.1–34.4)	0.149
Tumor location [n (%)]			0.696
Upper rectum	74 (69.2)	72 (66.7)	
Lower rectum	33 (30.8)	36 (33.3)	
Tumor diameter: mm (min–max)	30 (10–101)	35 (8-105)	0.371
Histology [n (%)]			0.757
Papillary adenocarcinoma	1 (0.9)	1 (0.9)	
Well-differentiated adenocarcinoma	53 (49.5)	54 (50.0)	
Moderately differentiated adenocarcinoma	50 (46.7)	45 (41.7)	
Poorly differentiated adenocarcinoma	1 (0.9)	1 (0.9)	
Mucinous adenocarcinoma	1 (0.9)	2 (1.9)	
Carcinoid tumor	1 (0.9)	4 (3.7)	
Small cell carcinoma	0 (0)	1 (0.9)	
Pathological TNM			0.953
Stage 0	3 (2.8)	5 (4.6)	
Stage 1	45 (42.1)	43 (39.8)	
Stage 2	20 (18.7)	20 (18.5)	
Stage 3	36 (33.6)	36 (33.3)	
Stage 4	3 (2.8)	4 (3.7)	
Anastomotic level from anal verge: cm (min–max)	6.0 (1.0–9.0)	6.0 (2.0–9.0)	0.711
Diverting stoma [n (%)]	18 (16.8)	23 (21.3)	0.404
Intraluminal per anal drain [n (%)]	6 (5.6)	14 (13.0)	0.063
Simultaneous resection of other organ [n (%)]	3 (2.8)	6 (5.6)	0.314
The number of linear stapler cartridge using [n (%)]			0.495
1	67 (63.2)	63 (58.3)	
2	35 (33.3)	36 (33.3)	
3	3 (2.8)	8 (7.4)	
4	1 (0.9)	1 (0.9)	
Pelvic side wall lymphadenectomy [n (%)]	12 (27.9)	8 (18.2)	0.281
Adjuvant chemotherapy [n (%)]	28 (26.2)	30 (27.8)	0.790
Follow-up time: month (min–max)	65 (1–129)	63 (1–116)	0.537

HT high tie, *LT* low tie, *ASA* American Society of Anesthesiologist, *OPNI* Onodera's Prognostic Nutrition Index

Table 2 Anastomotic leakage

	HT ($n = 107$)	LT ($n = 108$)	p
n (%)			
Leakage, grade 2 or higher	12 (11.2)	10 (9.3)	0.636
Leakage, grade 3 or higher	3 (2.8)	5 (4.6)	0.479
Grade of leakage [*n* (%)]			0.391
Grade 2	9 (8.4)	5 (4.6)	
Grade 3a	0 (0)	0 (0)	
Grade 3b	0 (0)	4 (3.7)	
Grade 4	3 (2.8)	0 (0)	
Grade 5	0 (0)	1 (0.9)	

HT high tie, *LT* low tie

Recurrence

The number of recurrence patients was 15 (14.0%) in HT group and 19 (17.6%) in LT group, respectively. The incidence of recurrence did not show a significant difference between both groups ($p = 0.473$). Six patients in HT group had two or more site of recurrences at first diagnosis. The number of patient who had multiple recurrent sites was four in LT group. HT group had 8 hepatic, 5 pulmonary, 3 lymphatic, 3 local, and 3 peritoneal metastases. LT group had 8 hepatic, 9 pulmonary, 2 lymphatic, 3 local, and 1 peritoneal metastases. There were no significant differences of the first recurrent site between both groups (Table 4).

Death reason

The numbers of death patients were 12 in HT group and 11 in LT group, and no significant difference was detected ($p = 0.807$). The numbers of rectal cancer death patients were 6 in HT group and 7 in LT group, and no significant difference was detected in death reason ($p = 0.815$) (Table 4).

Oncological quality of surgery

Significant differences in the total number of dissected lymph nodes and lymph nodes in each station were not observed between the groups. A significant difference in the number of lymph nodes involved between the HT and LT groups was not observed. There were also no differences in the pathological margins and the incidence of a positive circumference between the HT and LT groups (Table 5).

Risk factors for anastomotic leakage

The risk factors for an anastomotic leakage in the univariate analysis were being male, amount of blood loss, conversion to open surgery from laparoscopic surgery, and the anastomotic level from the anal verge. Being male and the anastomotic level from the anal verge were extracted as risk factors by multivariate analysis (Table 6).

Table 3 Early complications and operative parameters

	HT ($n = 164$)	LT ($n = 160$)	p
Mortality [*n* (%)]	0 (0)	1 (0.9)	0.318
Early complication [*n* (%)]	33 (30.8)	26 (24.1)	0.266
Early complication except leakage [*n* (%)]	24 (22.4)	17 (15.7)	0.212
Detail of early complication [*n* (%)]			
Surgical site infection	8 (7.5)	4 (3.7)	0.228
Ileus	6 (5.6)	1 (0.9)	0.053
Bowel obstruction	4 (3.7)	0 (0)	0.043
Enteritis	1 (0.9)	1 (0.9)	0.995
Lymphorrhea	2 (1.9)	4 (3.7)	0.414
Urinary tract infection	1 (0.9)	1 (0.9)	0.995
Urinary dysfunction	2 (1.9)	2 (1.9)	0.993
Conversion to Open from Laparoscopic surgery [*n* (%)]	6 (5.7)	2 (1.9)	0.142
Estimated blood loss: ml, median (max–min)	15 (1–2900)	15 (2–1400)	0.585
Blood transfusion [*n* (%)]	1 (0.9)	1 (0.9)	0.995
Operating time: minutes (min–max)	200 (110–535)	205 (110–415)	0.826
Duration of IMA tie from start: minutes (min–max)	38 (18–132)	54 (24–114)	<0.001
Duration of laparoscopic procedure: minutes (min–max)	158 (86–294)	160 (82–285)	0.608
Postoperative hospital stay: days (min–max)	10 (6–96)	10 (6–69)	0.327

HT high tie, *LT* low tie, *IMA* inferior mesenteric artery

Table 4 Long-term results

	HT ($n = 107$)	LT ($n = 108$)	p value
5-year overall survival rate			
All stages	91.3%	90.2%	0.850
Stage 1	95.5%	100%	0.091
Stage 2	89.5%	83.1%	0.605
Stage 3	91.5%	85.2%	0.528
Stage 4	33.3%	75.0%	0.283
5-year relapse-free survival rate			
All stages	85.3%	81.2%	0.691
Stage 1	95.5%	87.8%	0.406
Stage 2	89.5%	73.3%	0.214
Stage 3	68.7%	77.8%	0.441
Recurrence [n (%)]			
All sites	15 (14.0)	19 (17.6)	0.473
Hepatic metastasis[a]	8 (7.5)	8 (7.4)	0.985
Pulmonary metastasis[a]	5 (4.7)	9 (8.3)	0.277
Lymphatic metastasis[a]	3 (2.8)	2 (1.9)	0.643
Local recurrence[a]	3 (2.8)	3 (2.8)	0.991
Peritoneal metastasis[a]	3 (2.8)	1 (0.9)	0.308
Death reason [n (%)]			
All reasons	12 (11.2)	11 (10.2)	0.807
Rectal cancer	6 (5.6)	7 (6.5)	0.815
Other organ malignancy	2 (1.9)	3 (2.8)	
Other disease except malignancy	4 (3.7)	2 (1.9)	

HT high tie, *LT* low tie

[a]Repetition was included

Discussion

The optimal level for IMA ligation in a rectal cancer operation has been re-examined for over 100 years and remains

controversial [1–16]. The reason of controversy appears to differ according to whether short-term or long-term results are valued. The achievement of a radical cure and accurate staging as a result of cancer therapy appeared excellent in studies that recommended HT ligation [5–10]. LT ligation was associated with excellent blood flow to the proximal colon and showed a survival benefit equivalent to that of HT ligation in studies that recommended LT ligation [11–16]. It is noteworthy that both LT and HT ligation proponents reached an opposing conclusion to each other. This study aimed to resolve this controversy.

The primary endpoint was the incidence of anastomotic leakage. Prior to this study, we expected to observe a decreased incidence of anastomotic leakage with LT compared with HT ligation. However, the methods showed equal incidences of anastomotic leakage. Anastomotic leakage does not appear to be a problem of blood flow from the IMA alone. Several studies have shown that colonic blood flow was lower in HT compared to LT ligation [14–16, 31]. However, there was a study that insisted that HT was not a risk for anastomotic leakage [32]. In our study, a hemorrhage test was performed to decide a proximal portion of colonic stump before anastomosis, and it was not a quantitative test. When the blood flow decreased, additional excision of the proximal colon was performed. However, no patients required an additional excision up to the transverse colon. Some studies recently reported that the intraoperative fluorescence angiography with indocyanine green was effective to evaluate the blood flow to the anastomosis [33–35]. Some quantitative evaluation of colonic perfusion might be necessary for the prevention of anastomotic leakage due to low blood flow in the near future.

However, the cause of the anastomotic leakage was not only a blood flow decrease of the stump of the proximal colon. Being male and the distance of the anastomosis from the anal verge were determined to be risk factors in

Table 5 Oncological quality of surgery

Number of lymph nodes harvested: n (max–min)	HT ($n = 164$)	LT ($n = 160$)	p
Total	22 (5–52)	24 (2–62)	0.131
IMA root nodes (#253)	2 (0–11)	2 (0–11)	0.981
Intermediate lymph nodes (#252)	4 (0–21)	4 (0–18)	0.130
Perirectal lymph nodes (#251)	14 (1–39)	13 (1–54)	0.553
Lymph node involvement ratio in each station [n (%)]			
IMA root node (#253)	3 (1.8)	5 (3.1)	0.452
Intermediate lymph node (#252)	10 (6.1)	8 (5.0)	0.666
Perirectal lymph node (#251)	58 (35.4)	55 (34.4)	0.852
#253 positive and #252 negative	0 (0)	1 (0.6)	0.311
#252 positive and #251 negative	1 (0.6)	1 (0.6)	0.986
Pathological distal margin: mm (max–min)	30 (1–80)	31 (1–90)	0.463
Positive of circumferential margin [n (%)]	2 (1.9)	4 (3.7)	0.414

HT high tie, *LT* low tie, *IMA* inferior mesenteric artery

Table 6 Risk factors for anastomotic leakage

	Leakage (n=22)	No leakage (n=193)	Univariate analysis		Multivariate analysis	
			p	Odds ratio (95% CI)	p	Odds ratio (95% CI)
Gender [n (%)]						
Male	19 (14.0)	117 (86.0)	0.027	4.114 (1.177–14.380)	0.046	3.712 (1.024–13.456)
Female	3 (3.8)	76 (96.2)				
Anastomotic level from the anal verge: cm (min–max)	6.0 (1.5–8.0)	6.0 (2.0–9.0)	0.028	0.973 (0.949–0.997)	0.042	0.971 (0.845–0.999)
Estimated blood loss: ml (min–max)	26 (5–2900)	12 (1–740)	0.042	1.002 (1.000–1.003)	0.358	1.001 (0.999–1.003)
Conversion to open [n (%)]						
Yes	3 (37.5)	5 (62.5)	0.021	5.937 (1.315–26.797)	0.435	2.259 (0.292–17.495)
No	19 (9.2)	188 (90.8)				

CI confidence interval

our analysis of anastomotic leakages. Both of these factors make it difficult to operate in the pelvic cavity. Therefore, it is incontrovertible that a technical factor is involved in anastomotic leakages. There might be some complex factors for the anastomotic leakage such as low blood flow to the distal rectum and the high tension of the anastomotic region.

Regarding early complications other than anastomotic leakage, the incidence of bowel obstruction in HT was significantly higher than in LT. This reason is uncertain. The dissected range of retroperitoneal surface in HT could be wider than it was in LT. However, it is uncertain, because these accurate data did not exist.

The IMA tie time in LT ligation was longer than for HT ligation. This difference appears to reflect the technical complexity in the preservation of the LCA in the LT method. Several studies reported that an IMA branching pattern and a long distance between the origins of the IMA and LCA caused technical difficulties [36, 37]. Several reports exist regarding the development of tension in the anastomosis in the LT ligation because the proximal colon limb was shorter than for HT ligation [38, 39]. In a case that displayed tension in the anastomosis, a transection of the descending branch of the left colic artery was necessary to gain enough length in the LT technique [38].

Differences in the numbers of dissected lymph nodes around the IMA root and total lymph nodes were not apparent between the two arms of this study. Differences in the incidences of lymph node involvement in each station were also not noted. The numbers of dissected lymph nodes in this study were similar to past reports [5, 6]. Therefore, the oncological qualities of both arms appeared to be equal. However, the mesenteric package near the apical node was torn in LT, whereas that of HT was similar to an enveloped package [8]. LT might also have the risk of tumor spillage.

This study had several limitations. First, the study was not able to reach the enrollment targets, although the registration period was extended. This was a very regrettable problem. Three hundred and thirty-one patients were registered, and there were seven dropouts. Therefore, 324 patients were analyzed. A sample size of 362 patients was needed to achieve a power of more than 80% to detect a difference. Actual number was 89.5% of required number calculated beforehand, and corresponds to approximately 75% power to detect a difference between the groups. The influence of age might affect the data quality when the registration period of the study is long. Therefore, we did not prolong the registration period any longer and judged that the results were almost same. Second, this study was performed in a single institute. A prospective multicenter cohort study reported that the incidence of anastomotic leakage was lower in LT than in HT [40]. Third, there is a difference in the patient background in Western countries. No patients underwent chemoradiotherapy in this study because chemoradiotherapy was not standard treatment in Japan during the registration period of this study. However, the report of the result of CRT from Japan has increased gradually in recent years. One retrospective study reported that HT is a risk factor for anastomotic leakage in patients treated with preoperative radiotherapy [41]. Fourth, we had no data about the splenic flexure mobilization. We understand that this point was very important in the result. Mobilization of splenic flexure is not needed for anastomosis in most of Japanese patients, because their sigmoid colon is long. Mobilization of splenic flexure is 10% or less by my clinical experience. Fifth, we did not have any functional data.

LT was not an effective technique for the prevention of anastomotic leakage in an anterior resection. There were no significant differences in the long-term results between HT and LT. The procedure of LT is technically complex. It is necessary to treat HT as a standard procedure.

Compliance with ethical standards

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