4. Definitions and criteria used in this study

TNM classification 5th edition (1997 UICC) and Japanese classification of colorectal carcinoma 6th edition (1998 Japanese Society for Cancer of the Colon and Rectum) are used for staging in this study.

4.1. Anatomic definitions

4.1.1. Definition and classification of the rectum and the anal canal

Rectum

Anatomically, rectosigmoid is not included in the rectum. In this study, rectosigmoid is included.

Rectosigmoid (Rs): The portion between the sacral promontory and the inferior border of the second sacral vertebra.

Upper rectum (Ra): The portion between the inferior border of the second sacral vertebra and the level of the peritoneal reflection.

Lower rectum (Rb): The portion between the level of the peritoneal reflection and the superior border of the puborectal muscle.

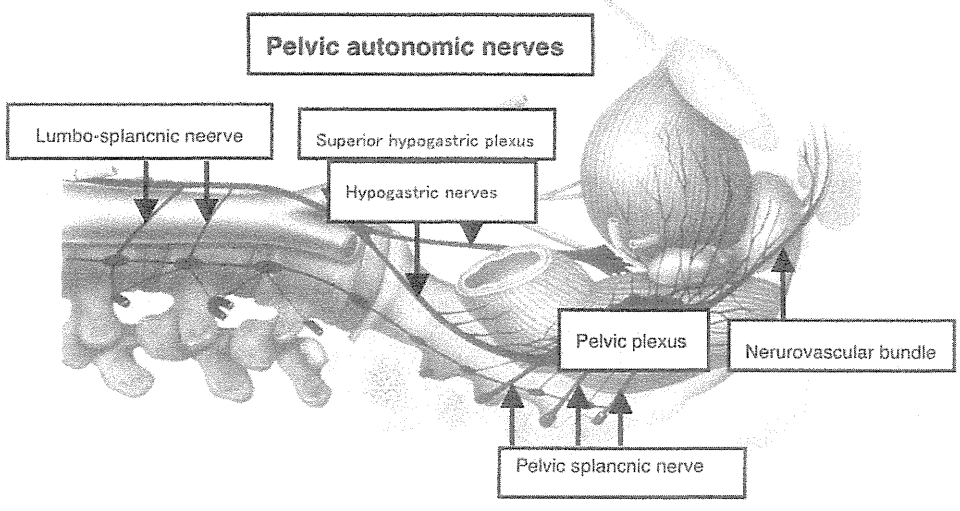
Anal canal

The tubular portion that extends from the superior border of the puborectal muscle to the anal verge.

4.1.2. Definition of the mesorectum

The lymphovascular, fatty and neural tissue that is circumferentially adherent to the rectum, starting the level of the sacral promontory.

4.1.3. Anatomy of the pelvic autonomic nerves



4.2. Stage classification

4.2.1. Clinical classification (TNM clinical classification)

T-Primary tumor

Tx Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis Carcinoma in situ: intraepithelial or invasion of lamina propria

T1 Tumor invades submucosa

T2 Tumor invades muscularis propria

T3 Tumor invades subserosa or into non-peritonealized pericoloc or perirectal tissue

T4 Tumor directly invades other organs or structures and/or perforates visceral peritoneum

N-Regional lymph nodes

Nx Regional lymph nodes cannot be assessed
N1 Metastasis in 1 to 3 regional lymph nodes
N2 Metastasis in 4 or more regional lymph nodes
M-Distant metastasis
Mx Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
Stage grouping

Stage 0		Tis	N0	M0
Stage I		T1	N0	M0
Stage II		T2	N0	M0
Stage III	Any T	N1, N2	M0	
Stage IV	Any T	Any N	M1	

pTNM pathological classification
The pT, pN, and pM categories correspond to the T, N and M categories. pN0 Hitological examination of a regional lymphadenectomy specimen will ordinaey include 12 or more lymph nodes. Although iliac lymph node and external lymph node are not regional lymph nodes in TNM classification, these lymph nodes are included in regional lymph nodes in this trial.

4.2.2. Pathological classification (Japanese classification of colorectal carcinoma)

Depth of tumor invasion
Intestine with serosa
m: Invasion confined to mucosa
sm: Tumor invasion to submucosa
mp: Tumor invasion to muscularis propria
ss: Tumor invasion to subserosa
se: Tumor invasion penetrating serosa
si: Direct tumor invasion of other organs or structures

Intestine without serosa
m, sm, mp: Same as Intestine with serosa
a1: Tumor invasion through to muscularis propria into non-peritonealized part
a2: Tumor invasion of non-peritonealized, pericolic, or perirectal tissues
ai: Direct tumor invasion of other organs or structures

Lymph node metastasis
n0 No lymph node metastasis
n1 Metastasis to Group 1
n2 Metastasis to Group 2
n3 Metastasis to Group 3
n4 Metastasis to Group 4

Peritoneal metastasis
P0 No peritoneal metastasis
P1 Metastasis only to adjacent peritoneum, which are removal by a combined resection
P2 A few metastases to distant peritoneum
P3 Numerous metastases to distant peritoneum

Liver metastasis
H0 No liver metastasis
H1 Metastasis limited to one lobe
H2 Some metastases to both lobes (4lesions or less)
H3 Numerous metastases to both lobes (5 lesions or more)

Distant metastasis, excluding liver and/or peritoneal metastasis

M (-) No distant metastasis
M (+) Distant metastasis

Stage	Depth of tumor invasion	Lymph node metastasis	Peritoneal metastasis	Liver metastasis	Distant metastasis
0	m	n0	P0	H0	M (-)
I	sm, mp	n0	P0	H0	M (-)
II	ss, se, a1, a2	n0	P0	H0	M (-)
IIIa	si, ai	n0	P0	H0	M (-)
	Any	n1	P0	H0	M (-)
IIIb	Any	n2, n3	P0	H0	M (-)
iV	Any	n4	P1, 2, 3	H1, 2, 3	M (+)

4.2.3. Curability of surgical resection (macroscopic)

Curability A (Cur A) No residual tumors
Curability B (Cur B) No residual tumors but not evaluable as Curability A
Curability C (Cur C) Definite residual tumors

	M	P	H	D:N	EW, OW, AW
Cur A	M (-)	P0	H0	D ≥ N	(-)
	No residual tumors				
Cur B	M (+)(Excision)	P1, 2 (Excision)	H1, 2 (Excision)	D < N	(-)
	No residual tumors				
Cur C	M (+)	P (+)	H (+)	D < N	(+)
	Residual tumors				

Classification of surgical resection according to lymph node dissection (D)

D0 No dissection or incomplete dissection of Group 1 lymph nodes
D1 Dissection of Group 1 lymph nodes
D2 Dissection of Group 1 and 2 lymph nodes
D3 Dissection of Group 1, 2 and3 lymph nodes

Tumor invasion of surgical margins

OW: Proximal cut end
AW: Distal cut end
EW: Surgical cut end

4.2.4. Comparison of TNM classification and Japanese classification of colorectal carcinoma

TNM	JSCCR
pTis	m
pT1	sm
pT2	a1, a2, ss
pT4	ai, si, se
pN0	n0
pN1	Metastasis in 1 to 3 lymph nodes in n1 or n2 or n3
PN2	Metastasis in 4 or more lymph nodes in n1 or n2 or n3
M0	H0 and P0 and M (-)
M1	H (+) or P (+) or M (+)
Stage 0	Stage 0
Stage I	Stage I

Stage II	Stage II or Stage IIIa (ai/si and n0)
Stage III	Stage IIIa (n1) or Stage IIIb (n2 or n3)
Stage IV	Stage IV

4.3. Classification of rectal cancer surgery

Surgical procedures in this protocol are classified as follows;

Mesorectal excision (ME)

The procedure is to excise mesorectum totally under direct vision. If mesorectum excision is performed correctly, pelvic autonomic nerves are not damaged. Dissection range is LD1 in Fig. 2.

Total mesorectal excision (TME)

The procedure is to excise mesorectum totally under direct vision.

ME with lateral lymph node dissection

After ME, lateral lymph nodes are dissected completely preserving pelvic autonomic nerves. Dissection range is LD3 in Fig. 2.

Fig. 2 Classification of lymph node dissection for rectal cancer

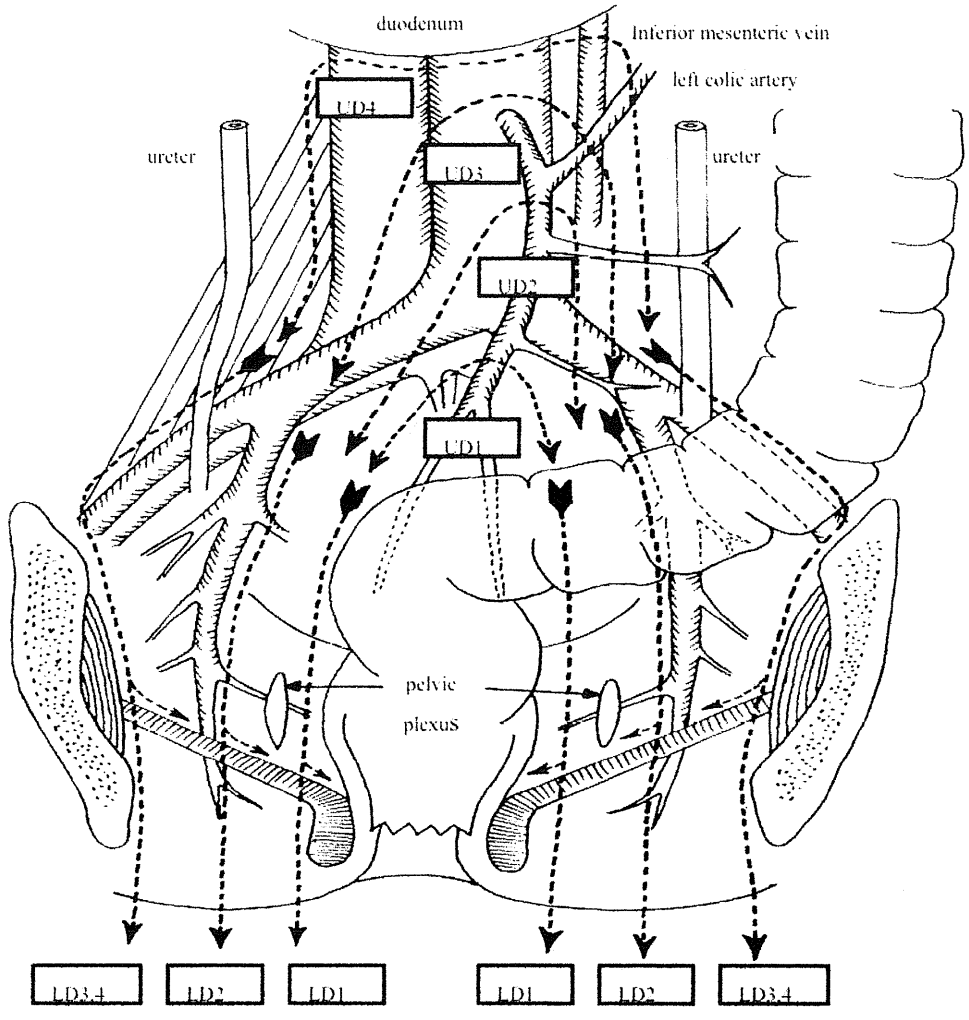
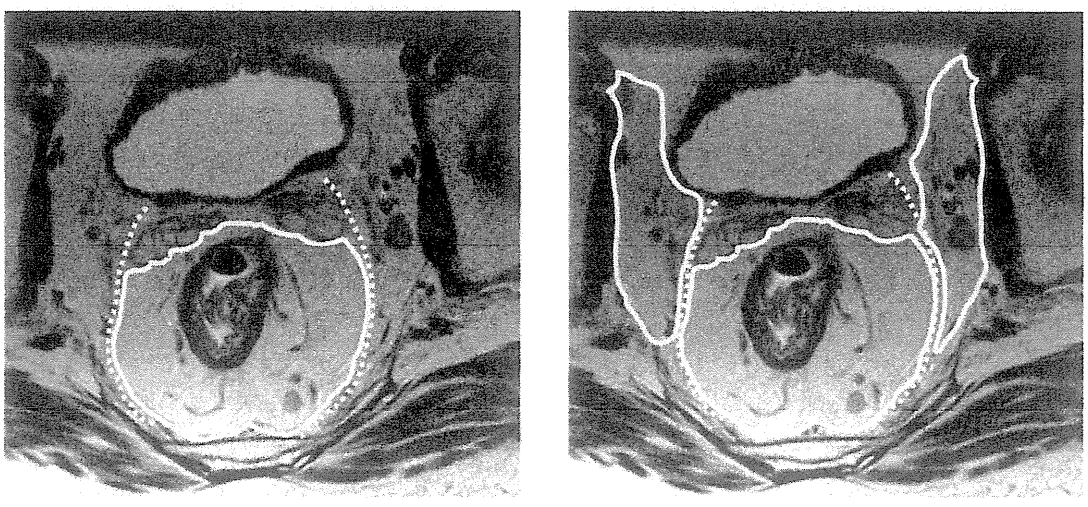


Fig. 3 Mesorectal excision (ME) and ME with LLND
MR image of a male rectal cancer patient. Solid line indicates resection range and dotted line is the site of pelvic plexus.



ME

ME with LLND

5. Patients selection criteria

After ME procedure, patients are randomized intraoperatively to ME only or ME with LLND by phone call. If the patients fulfill the inclusion criteria and do not fulfill the exclusion criteria, they are judged to be eligible. TNM classification 5th edition (1997 UICC) is used for clinical staging and Japanese classification of colorectal carcinoma 6th edition (1998 Japanese Society for Cancer of the Colon and Rectum) is used for pathological staging.

5.1. Eligibility criteria

Preoperative criteria

1. Histologically confirmed adenocarcinoma
2. Clinical stage II or III
3. Preoperative findings:
   i) Main lesion of the tumor is located at the rectum
   ii) Lower tumor margin is below the peritoneal reflection
   iii) No extramesorectal lymph node swelling:
   iv) Shorter diameter is less than 10 mm by CT scan or MRI
   v) No invasion to other organ (s)
4. Patient age is more than 20 and less than 75
5. PS: 0, 1
6. No past history of chemotherapy, pelvic surgery or radiation
7. Written informed consent

Operative criteria

8. ME is performed
9. Operative findings:
   i) Main lesion of the tumor is located at the rectum
   ii) Lower tumor margin is below the peritoneal reflection
10. R0 after the ME procedure

5.2. Exclusion criteria

1. Synchronous or metachronous (within 5 years) malignancies other than carcinoma in situ or mucosal carcinoma
2. Pregnant or breast feeding women
3. Psychological disorder or severe mental disease
4. Currently treated with systemic steroid
5. History of myocardial infarction or unstable angina pectoris within 6 months
6. Severe pulmonary emphysema or pulmonary fibrosis
7. Doctor's decision for exclusion

6. Registration and randomization

6.1. Procedure of registration

Investigators or subinvestigators must confirm the IRB approval for the protocol of this study and that a patient fulfills all eligibility criteria and does not meet any of exclusion criteria, then fill out registration form and send it to the Data Center by facsimile or call.

Telephone and FAX, time open to accrual

JCOG Data Center

TEL : 03-3542-3373

FAX : 03-3542-3374

Weekday : 9 AM to 5 PM (not open in Saturday and holidays)

Quary for patient selection criteria

Study Coordinator :

Shin Fujita
Colorectal Surgery Division, National Cancer Center.
5-1-1, Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
TEL 03-3542-2511 (ext) 2284
FAX 03-3542-3815
E-mail sfujita@ncc.go.jp

6.2. Randomization and balancing factors for minimization

At the registration, patients are randomized to either group A (ME with LLND) or group B (ME only). Balancing factors for minimization are as follows:

1. N staging (N0/N1,2)
2. Sex(Male/Female)
3. Institution

7. Treatment schedule

7.1. Protocol treatment

After surgeons performed ME, the patients are randomized to Group A or Group B.

Group A : ME with LLND

LLND is performed preserving all the autonomic nerves. After LLND, surgical reconstruction is done.

Group B : ME only

Only surgical reconstruction is done.

Postoperative adjuvant chemotherapy

For pathological stage III (TNM classification) patients, adjuvant chemotherapy (5-FU+l-LV, RPMI regimen) is administered.

7.2. Completion and termination criteria of protocol treatment

Definition of completion of surgical treatment

ME with LLND:

When ME and lateral lymph node dissection with preservation of pelvic autonomic nerves is completed and pathological diagnosis is also completed, it is considered as completion of surgical treatment.

ME:

When ME is completed, and pathological diagnosis is completed, it is considered as completion of surgical treatment.

7.2.1. Definition of completion of protocol treatment

p-stage I or II:

When surgical treatment is completed, it is considered as the completion of protocol treatment. The day of pathological diagnosis is the day of completion of protocol treatment.

p-stage III:

When the postoperative adjuvant chemotherapy of three courses is completed, it is considered as the completion of protocol treatment. The day of day 56 of postoperative adjuvant chemotherapy is the day of completion of protocol treatment.

7.2.2. Termination criteria of protocol treatment

Protocol treatment is stopped after the following events.

1. Protocol treatment is invalid.
   i) Not Cur A in pathological diagnosis.
   ii) Recurrence during postoperative adjuvant chemotherapy
2. Protocol treatment can not be continued according to adverse events.
   i) Postoperative adjuvant chemotherapy can not be started less than nine weeks after the operation, because postoperative adjuvant chemotherapy starting criteria was not fulfilled.
   ii) Patient' conditions were not fulfilled with starting criteria of adjuvant chemotherapy, and adjuvant chemotherapy can not be started within 15 days from the scheduled date.
   iii) Drug reduction over the protocol limit is necessary
   iv) Grade 4 non-hematological toxicity is detected
   v) Physician decides the termination because of toxicity for a reason listed above.
3. Patient refuses due to the reason associated with toxicity.
4. Patient refuses due to the reason not associated with toxicity.
5. Patient dies during protocol treatment
6. Other reasons for off-protocol

Protocol violation, ineligibility revealed after registration etc.

7.3. Surgery (ME with LLND, ME)

7.3.1. Common Part (before registration)

- Mesorectal excision (ME) with open laparotomy is performed.
- Under direct vision with sharp dissection, the rectum is mobilized keeping the plane around the mesorectum, and the attached mesorectum with at least a 4-cm clearance margin distal to the tumor is resected.
- If the length of the attached mesorectum distal to the tumor was less than 4 cm, the mesorectum is totally resected (TME).
- The rectum with at least a 2-cm clearance margin distal to the tumor is resected. When the distance from tumor to anal canal is less than 2 cm, 1-cm clearance margin in the anal canal is allowed.
- All of the autonomic nerves are preserved
- The inferior mesenteric artery (IMA) is ligated at its root, and then if the blood supply to the distal colon is considered to be inadequate as a result, preservation of the left colonic artery after lymph node dissection at its root was allowed

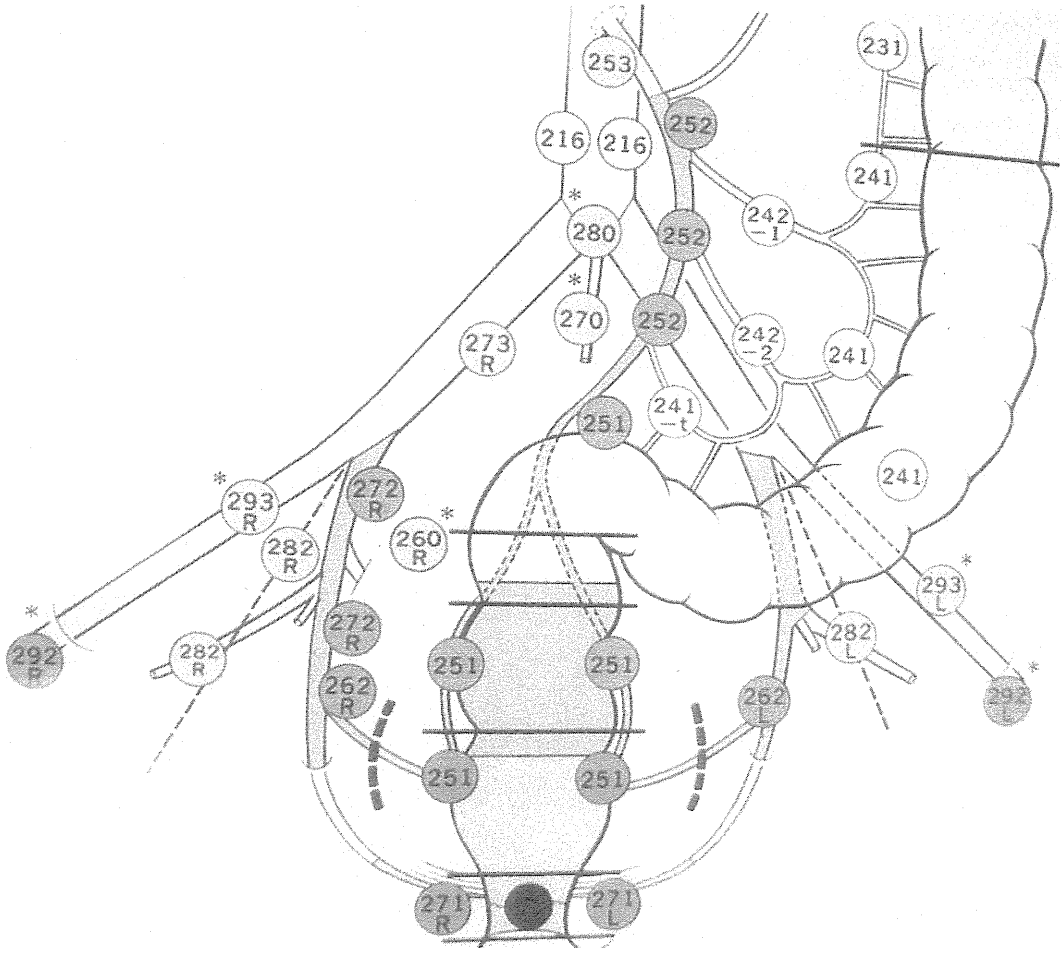
7.3.2. Group A: ME+LLND

When allocated to ME+LLND group, LLND is performed preserving the autonomic pelvic nerves. Lateral pelvic lymph nodes including the common iliac node (No. 273), internal iliac node (No. 262 and 272), obturator node (N0. 282) are dissected. After the LLND, surgical reconstruction is performed.

7.3.3. Group B: ME alone

When allocated to ME alone group, only surgical reconstruction is performed, because ME has been already performed.

Figure. Lymph node map and numbering



	Pericolic/perirectal lymph node	Intermediate lymph node	Main lymph node
Inferior mesenteric artery			
Sigmoid artery			
First	241-1	242-1	253
Second	241-2	242-2	
Terminal	241-t	252	
Superior rectal artery	251		
Iliac artery			
Middle rectal artery	251	262	
Internal iliac artery		272	
Common iliac artery			273
Obturator vessels			282
Inferior rectal artery	271		

7.3.4. Intraoperative photographs for surgical quality control and assurance

For surgical quality control and assurance, intraoperative photographs and the resected specimen are taken. Following sites are photographed during the surgery.

Group A (ME+LLND)

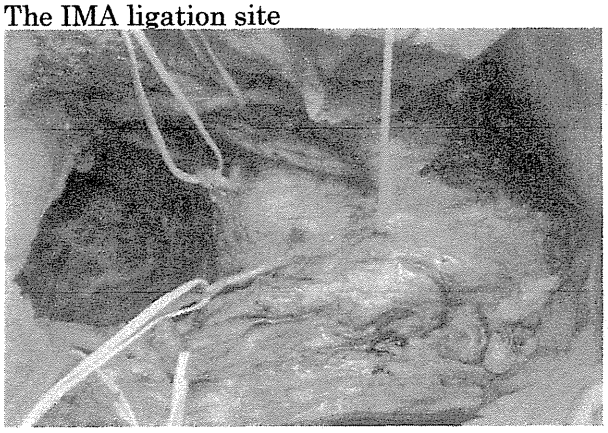
- The IMA ligation site
- The preserved right/left hypogastric nerves
- The anterior/posterior sides of the resected specimen
- The right/left internal iliac artery
- The right/left obturator fossa
- The right/left dissected fatty and connective tissues in the lateral pelvic lymph node area

Group B (ME alone)

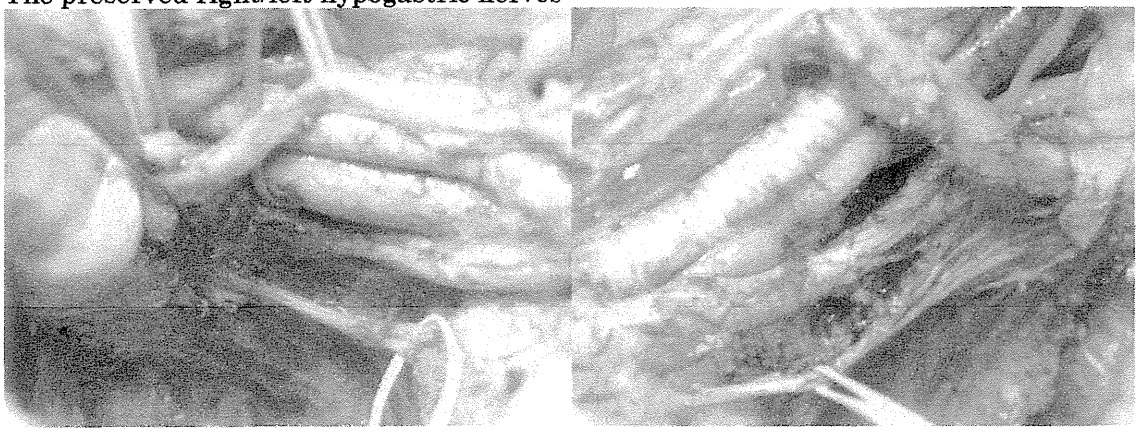
- The IMA ligation site
- The preserved right/left hypogastric nerves
- The anterior/posterior sides of the resected specimen

Group A

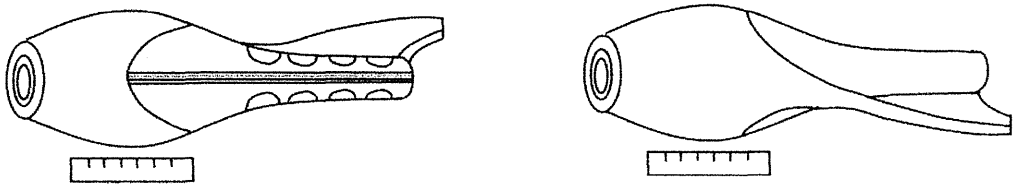
The IMA ligation site



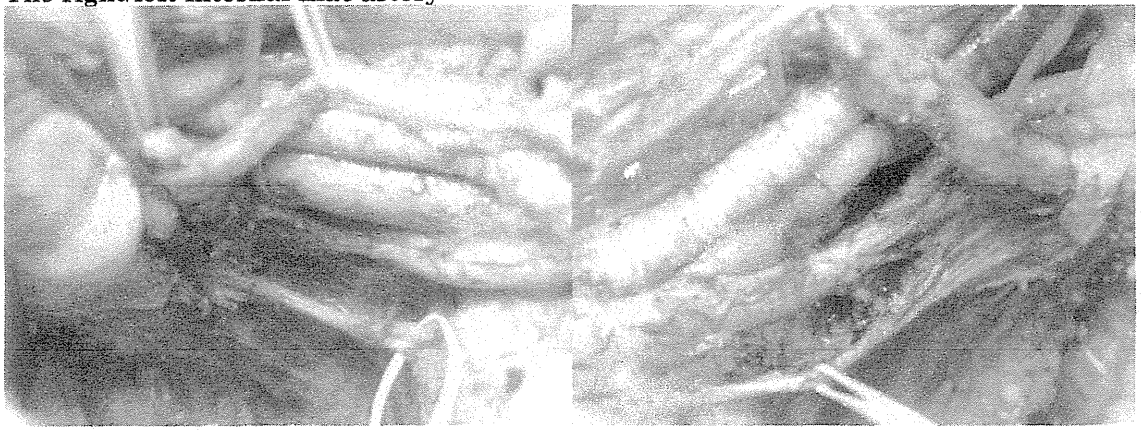
The preserved right/left hypogastric nerves



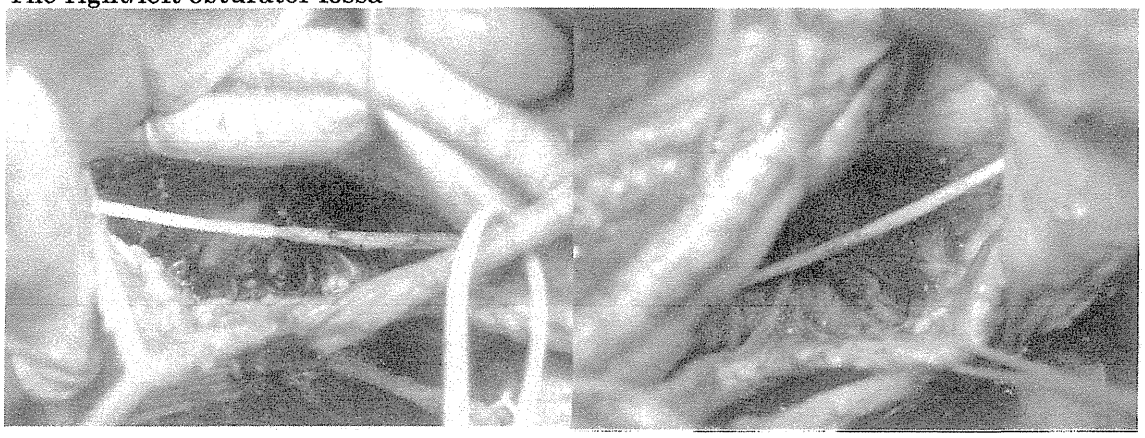
The anterior/posterior sides of the resected specimen



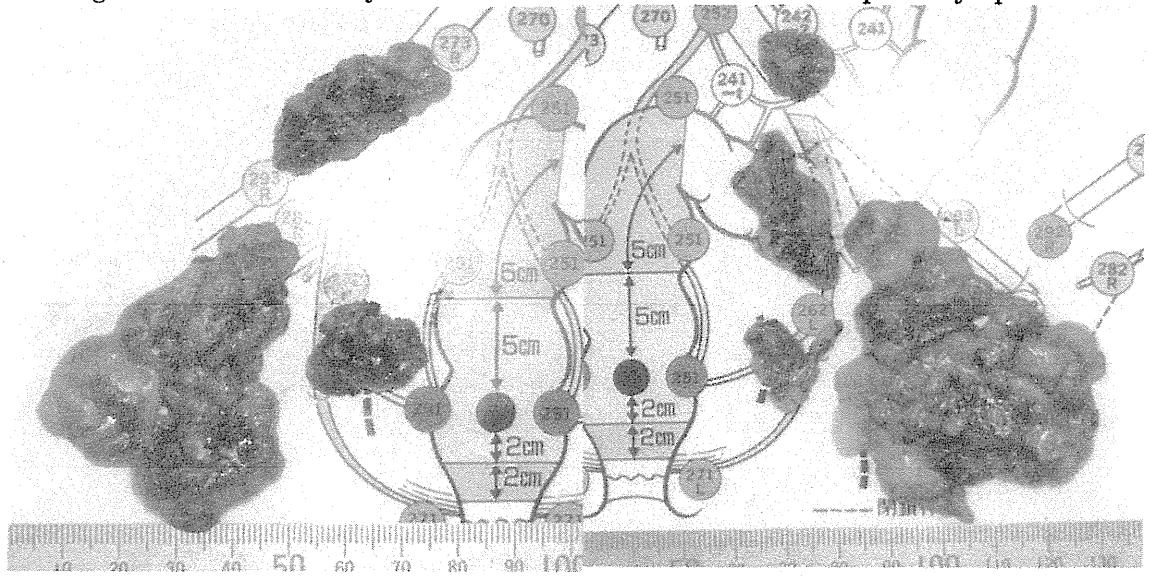
The right/left internal iliac artery



The right/left obturator fossa



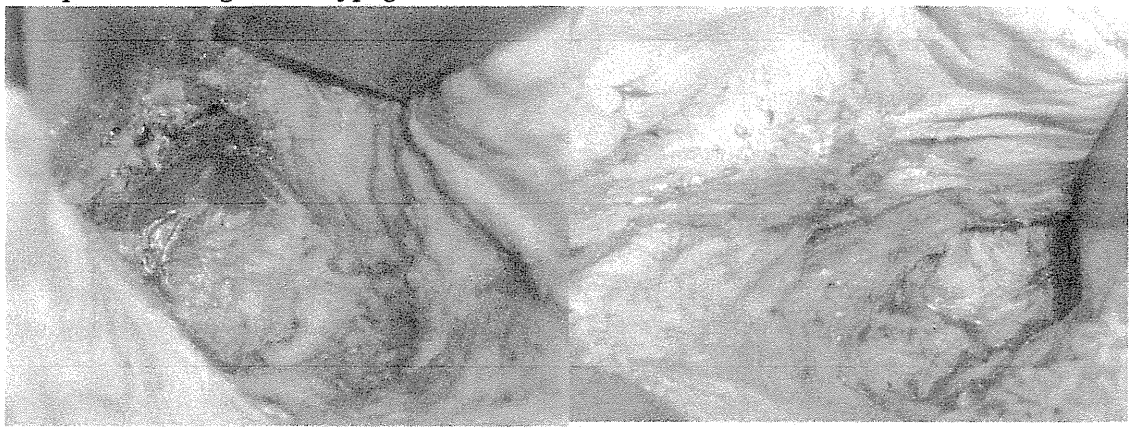
The right/left dissected fatty and connective tissues in the lateral pelvic lymph node area



Group B

The IMA ligation site

The preserved right/left hypogastric nerves



7.3.5. Surgical reconstruction and abdominal closure after ME or ME with LLND

After ME or ME with LLND, surgical reconstruction and abdominal closure is performed according to the institutional routine methods.

7.3.6. Change of surgical methods

In one of followings cases, protocol treatment of surgery can be changed.

Group A

1) Impossible to perform LLND because of intraoperative complications.
2) When lateral lymph node metastasis is found during LLND, ipsilateral autonomic nerves can be sacrificed. In necessary, ipsilateral iliac vessels can be resected.

In these cases, protocol treatment is not terminated and is continued.

7.3.7 Queries for surgical methods

Shin Fujita National Cancer Center Hospital Colorectal Surgery Division
5-1-1, Tsukiji, Chuo-ku, Tokyo, 104-0045
TEL: 03-3542-2511 (extension: 2284 or 7089)
FAX:03-3542-3815
E-mail: sfujita@ncc.go.jp

7.3.8. Perioperative management

Postoperative management is performed according to the institutional routine methods.

7.4. Postoperative adjuvant chemotherapy

When patients are diagnosed as pathological stage III (TNM classification), postoperative adjuvant chemotherapy (5-FU+l-LV treatment) is administered. The chemotherapy is started within nine weeks after the operation. One course is eight weeks, and repeats three times.

Drug	Dose	Method	Day
5FU	500 mg/m2	Bolus iv	Day 1, 8, 15, 22, 29, 36
l-LV	250 mg/m2	2hr div	Day 1, 8, 15, 22, 29, 36

7.4.1. Starting criteria of postoperative adjuvant chemotherapy

Postoperative adjuvant chemotherapy is started within nine weeks after the operation. When the chemotherapy is not able to be started less than nine weeks after the operation, protocol treatment is terminated.

1) pStage III
2) Performance status: ECOG 0 or 1 at day 1 of the chemotherapy
3) Laboratory data within 14 days before day 1
   i) WBC >= 3000/mm3
   ii) Platelets >= 10X104/mm3
   iii) T.Bil <=2.0 mg/dl
   iv) GOT<=100 IU/l
   v) GPT<=100 IU/l
   vi) Cr<=1.5 mg/dl
4) The patient does not have the following complications.
   i) Poorly controlled diabetes
   ii) Poorly controlled Hypertension
   iii) Interstitial pneumonia, pulmonary fibrosis, advanced pulmonary emphysema.
5) Non-hematological complications except GOT, GPT, T.Bil, constipation, and depilation are less than grade 1

7.4.2. Dose reduction and termination criteria of adjuvant chemotherapy

Dosage level

Level	Drug	Dosage
Level 0	5FU	500 mg/m2
	l-LV	250 mg/m2
Level -1	5FU	400 mg/m2
	l-LV	250 mg/m2

Starting criteria of chemotherapy

The chemotherapy is started after confirming all the following criteria are fulfilled. When all of the criteria are not fulfilled, the start is delayed by the week. Protocol treatment is discontinued when the criteria are not fulfilled within the 15day from the planned start date.

1) Laboratory test
   i) WBC>=3,000/mm3
   ii) PLT>=100,000/mm3
   iii) GOT<=100 IU/l
   iv) GPT<=100IU/
   v) T.Bil<=2.0 mg/dl
2) Non-hematological complications except GOT, GPT, T.Bil, constipation, and depilation are less than grade 1
3) 21 days or more have passed by the planned 2nd or 3rd course start day (day 1) from the final medicated day of the previous course.
4) Doctor in charge judges that chemotherapy is possible.

Dose reduction criteria

When the patients fulfill the following criteria, the dose of 5FU in the next administration is

reduced to level -1. If the second dose reduction is necessary, protocol treatment is terminated.

1) WBC < 1,000/mm3
2) PLT < 25,000/mm3 i
3) Grade 3 non-hematological toxicity (When grade 4 non-hematological toxicity is detected, protocol treatment is terminated)
4) The delay of the planned start date is form nine days to 15 days

7.4.3. Queries for adjuvant chemotherapy

Yasuhiro Shimada and Tetsuya Hamaguchi
National Cancer Center central hospital
Internal medicine
TEL: 03-3542-2511 (extention: Shimada 7056, Hamaguchi 7375),
FAX:03-3542-3587

7.5. Combined therapy and supportive care

7.5.1. Surgery

Although a combined therapy and supportive care are not specified but it carries out based on the standards of each institution.

7.5.2. Chemotherapy

Recommended combined therapy and supportive care

- Medication for critical diarrhea

Permitted combined therapy and supportive care

- Prevention of nausea and vomiting using 5HT3 antagonist, Dexamethasone, etc.
- Management of fever during neutropenia
- Antibiotics or G-CSF should be used, if necessary.

7.6. Subsequent treatment after off-protocol treatment

Patients are observed without treatment until recurrence is detected.
Any subsequent treatment is allowed in case of recurrence, or protocol treatment termination.

8. Expected adverse events and treatment modification

9. Evaluation schedule and study calender

9.1. Baseline evaluation before registration

Patient backgrounds, Physical examination

1) Clinical history
2) Physical examination
3) Performance status: PS (ECOG), height, body weight
4) International erection functional score (IIEF5) (for only male patient)

Laboratory test (within 14 days before registration)

1) Complete blood count: RBC, Hb, Ht, WBC, platelet, WBC differential count
2) Biochemical exam: Total protein, albumin, total bilirubin, GOT, GPT, BUN, creatinine, Na and K, Cl, Ca, CRP, LDH, ALP, FBS (fasting blood sugar)
3) Tumor marker: CEA, CA19-9
4) Urinalysis: urine sugar, urine protein

Electrocardiogram and respiratory function test (within 56 days before registration)

1) ECG
2) Respiratory function test

Evaluation of tumor

Evaluation of distant metastasis

1) Chest and abdominal CT or chest X-ray + abdominal CT

Evaluation of regional lymph node metastasis

2) Pelvic CT or MRI (less than 5 mm of slice width)

Evaluation of depth of invasion

3) Digital examination
4) Endorectal ultrasound or MRI (less than 5 mm of slice width)

Evaluation of lower margin of tumor

5) Barium enema or MRI (sagittal, less than 5 mm of slice width)

Confirmation of diagnosis

6) Biopsy of the primary tumor

Evaluation of multiple colorectal cancer

7) Barium enema or colonoscopy

Intraoperative evaluation

8) Tumor location, clinical stage, depth of tumor invasion

9.2. Intraoperative and postoperative evaluation

9.2.1. Intraoperative evaluation

Operation time, bleeding, type of surgery, reconstruction, resected organ, tumor location, distance from anal verge, tumor size, resected margin, depth of invasion, number of metastatic lymph nodes, number of dissected lymph nodes

9.2.2. Pathological evaluation

Pathological depth of invasion, peritoneal dissemination, vascular invasion, pathological lymph node metastasis, pathological resected margin, tumor differentiation, pathological stage, pathological curability

9.2.3. Assessment of intraoperative complications

Complications during operation

Bleeding, thrombosis, injury of ureter or bladder, other fetal complications

9.2.4. Assessment of postoperative complications

In-hospital complications

Fever, anastomtic leakage, pelvic abscess, wound infection, melena, fistula, bowel obstruction, urinary retention, urinary frequency, infection with normal absolute neutrophil count

Postoperative late complications (After first discharge and until 5 years after operation)
Constipation, diarrhea, urinary frequency, urinary retention, urinary obstruction, erectile dysfunction, decrease of libido, bowel obstruction

9.2.5. Postoperative evaluation, if necessary (within 6 months after operation)
Barium enema or colonoscopy
If preoperative colorectal evaluation is inadequate, these examinations are mandatory.

9.2.6. Postoperative evaluation
Post voiding residual urine volume is examined three times between POD 10 and 14. If sum of voiding urine and residual urine is less than 150 ml, post voiding residual urine volume should be examined again.

Between 4 and 6 weeks after operation (for the patients without adjuvant chemotherapy).
Complete blood count: WBC, RBC, Hb, Ht, platelet, WBC differential
Blood chemistry: T.Bil, ALP, GOT, GPT, BUN, Cr, Na, K, Cl, CRP
Every four months till 2 years after operation and every six months beyond 3 years after operation

Imaging examination: chest CT, abdominal CT, pelvic CT (below helical CT and slice width 5 mm) or MRI (below slice width 5 mm)
Complete blood count: WBC, RBC, Hb, Ht, Platelet, WBC differential
Blood chemistry: T.Bil, ALP, GOT, GPT, BUN, Cr, Na, K, Cl, CRP
Tumor marker: CEA, CA19-9

9.3. Evaluaion during and after adjuvant chemotherapy (for the patients treated with adjuvant chemotherapy)

9.3.1. Evaluation before postoperative adjuvant chemotherapy (within 14 days before the start of chemotherapy)
1) General status: PS (ECOG), body weight
2) Complete blood count: RBC, Hb, Ht, WBC, platelet, WBC differential
3) Biochemical examination: T-Bil, ALP, GOT, GPT, BUN, Cr, Na, K, Cl, CRP
4) Tumor marker: CEA, CA19-9

9.3.2. Evaluation during chemotherapy
Weekly evaluation
Fever without neutropenia, hand-and-foot skin reaction, pigmentation, loss of appetite, diarrhea, nausea, disorder of smell, stomatitis/pharyngitis, taste disorder, vomiting, febrile neutrophil depletion, and the neutrophil depletion of G3-4, infection without neutrophil depletion, neuropathy (motor), PS

Complete blood count: RBC, Hb, Ht, WBC, Platelet, WBC differential
Biochemical examination: T.Bil, ALP, GOT, GPT, BUN, Cr, Na, K, Cl, CRP

9.3.3. Evaluation during chemotherapy, if necessary
Neurotoxicity (cerebellar syndrome (headache and cerebellar ataxia)), circulatory systems (angina, ischemic heart disease)

9.3.4. Evaluation after chemotherapy (within 4 weeks after the end of chemotherapy)

Fever without neutropenia, hand-and-foot skin reaction, pigmentation, loss of appetite, diarrhea, nausea, disorder of smell, stomatitis/pharyngitis, taste disorder, vomiting, febrile neutrophil depletion, and the neutrophil depletion of G3-4, infection without neutrophil depletion, neuropathy (motor), PS

Complete blood count: RRBC, Hb, Ht, WBC, Platelet, WBC differential
Biochemical examination: T.Bil, ALP, GOT, GPT, BUN, Cr, Na, K, Cl, CRP
Tumor marker: CEA, CA19-9

9.3.5. Evaluation of reccurence during chemotherapy

Every four months after operation
Imaging examination: chest CT, abdominal CT, pelvic CT (below helical CT and slice width 5 mm) or MRI (below slice width 5 mm)
Tumor marker: CEA, CA19-9

9.4. International Erection Functional Score (International Index of Erectile Function-5: IIEF-5) (For only male)

1) Investigation schedule

Investigation is conducted at the following two times.

i) After informed consent and before registration
ii) One year after the registration

2) Questionnaire: A total of five items of an international erection functional score (IIEF5) are used as an investigation item.

IIEF-5

Select the answer that best describes your condition over the past six months. Write the score into the box.

1. How do you rate your confidence that you could get and keep an erection?

Very low	1 point
Low	2 points
Moderate	3 points
High	4 points
Very high	5 points

2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?

Almost never or never	1 point
A few times	2 points
Sometimes	3 points
Most times	4 points
Almost always or always	5 points

3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?

Almost never or never	1 point
A few times	2 points
Sometimes	3 points
Most times	4 points
Almost always or always	5 points

4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?

Extremely difficult	1 point

Very difficult	2 points
Difficult	3 points
Slightly difficult	4 points
Not difficult	5 points

5. When you attempted sexual intercourse, how often was it satisfactory to you?

Almost never or never	1 point
A few times	2 points
Sometimes	3 points
Most times	4 points
Almost always or always	5 points

9.5. Study calender

Course	Before registraitoin	Intaraoperative		Beforeadjuvant chemotherapyore	1、2、3 course								After chemotherapy	Follow-uo period
Week					1 9 17	2 10 18	3 11 19	4 12 20	5 13 21	6 14 22	7 15 23	8 16 24		
General condition														
Body weight、PS	o			o	o									
Laboratory data														
WBC、Hb、Platelet	o		o	o	●	●	●	●	●	●			o	Every 4 months Every 6 months
Neutrophil	o		o	o	●	●	●	●	●	●			o	
Laboratory	o		o	o	●	●	●	●	●	●			o	
CEA, CA19-9	o			o	*	*	*	*	*	*			o	
FBS	o													
Urine analysis	o													
ECG	o													
Respiratory function	o													
Imaging diagnosis	o													
Chest CT/X-P	o				*	*	*	*	*	*				Every 4 months Every 6 months
AbdominalCT	o				*	*	*	*	*	*				
PelvicCT/MR	o				*	*	*	*	*	*				
Transanal ultrasonography/MR	o													
Barium enema/MR	o													△
Colonoscopy	o													△
Pathology			o											
Post-voiding residual urine			o†											
Toxicity														
Symptoms	o	o	o	o	o	o	o	o	o	o			o	Every 4 months Every 6 months
Clinical signs	o	o	o	o	o	o	o	o	o	o			o	
IIEF5	o													One year after registration
Neurotoxicity					△	△	△	△	△	△			△	
Cardiovascular toxicity					△	△	△	△	△	△			△	
Adjuvant chemotherapy														
5FU					o	o	o	o	o	o				
l-LV					o	o	o	o	o	o				

○: Do, ●: Once or more a week, △: If necessary, *: Every 4 months, †: Three times

10. Data collection

11. Adverse Event Reporting