American College of Surgeons Oncology Group

Z6051

A Phase III Prospective Randomized Trial Comparing Laparoscopic-assisted Resection Versus Open Resection for Rectal Cancer

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ACOSOG protocols, Case Report Forms (CRFs) and Standard Operating Procedures (SOPs) are available on the ACOSOG home page at http://www.acosog.org. Members of ACOSOG are responsible for the compliance with ACOSOG SOPs. In some cases an ACOSOG SOP will refer to definitions and procedures defined by the Cancer Therapy Evaluation Program (CTEP). The URL for CTEP is http://ctep.cancer.gov/).

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Note: Direct all questions to the QA Specialist identified below.

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Cancer Trials Support Unit (CTSU) investigators. Note that patient enrollments from institutions that are not aligned with ACOSOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the CTSU. CTSU contact and logistical information is found in the Appendices.

The CTSU will use the ACOSOG-Z6051 number as required for reporting to ACOSOG and NCI, and when registering patients through the CTSU registrar. CTSU participants and institutions will be instructed to use the ACOSOG-Z6051 number on all data forms.

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1 Introduction

Rectal cancer in many circumstances is uniquely suited to treatment by minimally invasive approaches. Avoidance of any significant abdominal incision is potentially the end point of applying laparoscopic techniques to the treatment of even advanced (Stage II/III) rectal cancer. However, the laparoscopic technique for the resection of rectal cancer cannot go forward without solid Level I evidence which establishes its safety and equivalence to the standard open operative procedure. Surgical resection is the most important treatment modality for rectal cancer in terms of a curative resection, staging, prognosis and subsequent therapeutic decisions. Additionally, the surgical integrity and pathologic staging of the resection is the most important prognostic factor in recurrent rectal cancer. Laparotomy and total mesorectal excision (TME) are currently the standard of care. Laparoscopic resection of rectal cancer must achieve at least equivalent results in comparison with open laparotomy prior to becoming an established means of resection. A prospective, randomized trial is needed to establish the feasibility, reproducibility and oncologic applicability of minimally invasive techniques in the resection of rectal cancer.

There is no established Level I body of evidence investigating laparoscopic resection of rectal cancer. A single, prospective randomized trial of laparoscopic surgery has included both colon cancer and rectal cancer.[1] The laparoscopic data for rectal surgery revealed an increased risk of positive circumferential radial margins with laparoscopic-assisted low anterior resection. These findings raise concerns as to the level of precision which is achievable in laparoscopic surgery for rectal cancer. Numerous single institution case series support the safety and efficacy of laparoscopic resection of rectal cancer at their centers and in their hands. In order to establish the non-inferiority of the laparoscopic approach, all laparoscopic rectal resections should be completed in an environment where the outcomes can be meaningfully evaluated and the clinical relevance of laparoscopic resection can be established. A critical level of clinical equipoise has been reached and must be addressed with a prospective, randomized trial of laparoscopic-assisted surgery for rectal cancer.

Surgeons apply different surgical techniques to eradicate rectal cancer depending on the level of the cancer in the rectum and the oncologic distance necessary to obtain negative surgical margins. Abdominal perineal resection for low rectal cancers and low anterior resections for high rectal cancers are techniques which resect rectal cancer and establish adequate margins. The most appropriate and safe procedure for middle rectal cancer has not been adequately established. A clinical trial is required to standardize laparoscopic-assisted resection by stage of disease and the anatomic position of the rectal cancer.

Studies have shown that surgical technique and the adequacy of resection predicts local recurrence rates in open rectal surgery and the quality of surgical technique and resection should be as relevant in laparoscopic rectal resection.[2,3] Recently published results support non-inferior short term outcomes in open and laparoscopic-assisted surgical resections for colon cancer with regards to the quality of the resection and recurrence rates.[4] Similar findings may be revealed in rectal cancer, but technique, oncologic outcomes and recurrence patterns must first be systematically evaluated. A clinical trial is required to standardize laparoscopic-assisted resection by stage of disease and the anatomic position of the rectal cancer, and to assess the ability of the technique to produce adequate circumferential and distal margins, and complete TME.

These issues pose the question of whether laparoscopic-assisted resection is a safe, effective oncologic approach to rectal cancer.

1.1 Background

There has been a fundamental shift in the treatment of rectal cancer. Local excision, minimally invasive techniques and sphincter-sparing operations have created a new and broader spectrum of care for rectal cancer patients. In the future, the partnership of molecular markers and minimally invasive techniques will further shape treatment options. The development of safe laparoscopic approaches to the treatment of rectal cancer will be the key to bringing the benefits of these new modalities to rectal cancer patients.

Although most studies of laparoscopic-assisted colon resection exclude rectal cancer, there are several single institution studies which demonstrate the feasibility of laparoscopic-assisted resection of rectal cancer (LARR). Feliciotti et al. prospectively studied laparoscopic-assisted and open resections and found both

methods respected surgical oncologic principles with similar long-term outcomes.[6] Additional studies have mimicked these results.[7]

A number of single center case series have evaluated the morbidity and mortality in laparoscopic rectal resection. Prospective studies revealed that laparoscopic resection did not worsen survival or disease control for patients with rectosigmoid cancer when compared with open surgery.[8,9] Barlehner et al studied and reviewed the literature, demonstrating that laparoscopic resection for rectal carcinoma is not associated with a high morbidity or mortality.[10]

The initial report of the United Kingdom Medical Research Council Conventional versus Laparoscopic Assisted Surgery in Colorectal Cancer (UKMRC CLASICC) Trial, a prospectively randomized trial which included the laparoscopic and open resection of rectal cancer raised concerns regarding this technique.[1] The conversion rate was 29% (n=143 conversions, 61 colon and 82 rectal cases) for the laparoscopic cohort; comprising a conversion rate of 34% (82/242) for the rectal cases (total rectal cases n=242). In the rectal surgery subgroup, the circumferential radial margin positivity was greater in the laparoscopic group when compared with open surgery. This difference was not appreciated in the abdominal perineal laparoscopic procedure group but was specific to the laparoscopic low anterior resection procedure. While this difference did not reach statistical significance, the trend toward a higher margin positivity with laparoscopic LAR calls for further systematic investigation.

The UKMRC CLASICC Trial recently published long term survival data, local and distant recurrence rates and quality of life assessment on 794 patients enrolled from July 1, 1996, to June 28, 2002. The three year overall survival was similar for open and laparoscopic groups and for patients with rectal and colon cancer. There was no difference in three year overall survival for patients undergoing anterior resection or abdominal perineal resection in either technique group (AR-open 66.7%, laparoscopic 74.6%; APR-open 57.7%, laparoscopic 65.2%). This is despite the increase in number of positive radial margins for laparoscopic anterior resection of the rectum seen at the time of safety analysis. These findings held for the three year disease free analysis as well. There was no difference in three year local recurrence rates after anterior resection of rectal cancer (7% open, 7.8% laparoscopic) or abdominoperineal resection of rectal cancer (21% open, 15% laparoscopic). There were no differences in quality of life parameters for colon or rectal cancer. The CLASICC Trial did not confirm an advantage for laparoscopy in Stage III cancer patients. While differences were not significant, local recurrence rates for rectal cancer after APR was high. There was no standardization of the use of neoadjuvant chemoradiotheraphy within the rectal cancer group.[11]

Given the lack of Level I evidence from prospective randomized trials and the disparate evidence from small, single center studies, a large randomized trial is needed to establish the proper place of laparoscopic-assisted surgery in rectal cancer.

1.2 Quality of Life Background

Quality of life after resection of rectal cancer has not been adequately studied. A recent Cochrane Collaboration[73] Review found that there is no data available to compare laparoscopic and open laparotomy for rectal cancer and called for randomized control trials with Quality of Life Evaluation. Another Cochrane Review[79] confirmed that a meta-analysis was not possible to compare sphincter sparing and abdominoperineal resection of rectal cancer. Once again, randomized data is needed. There have been several prospective reports of Quality of Life Evaluations after resection of rectal cancer that suggest age, temporary and permanent stoma, ultra-low anterior resection, neoadjuvant therapy, colonic J pouch reconstruction and gender may influence the quality of life to differing degrees over time in the domains of sexual function, bowel and bladder function and global health related quality of life.[68-88] There are several instruments available which are validated questionnaires that focus on cancer (EORTC-C30) and colorectal issues (EORTC-C38).

When evaluating quality of life after resection of rectal cancer the population must be as uniform as possible in order to limit the confounding factors which may bias the outcomes. In order to compare two methods of surgical treatment such as laparoscopic resection and open laparotomy this is especially critical. Therefore, covariates such as presence of an ileostomy or colostomy, neoadjuvant therapy, disease stage, age and gender become very important for the analysis. Timing of quality of life assessment also seems to influence the comparison of different factors such as bowel function, sexual function and global health. Early comparison may show no difference in sexual function, but as time progresses there may develop real

improvement in patients with sphincter sparing procedures but not in patients after APR.[87] Sexual dysfunction may also be adversely affected over time as bowel function worsens.[80] Global quality of life is adversely affected by worsening sexual function and pain after APR and data suggest that multiple quality of life instruments evaluating sexual, bowel, urologic and global areas need to be used in a homogeneous population at multiple time points in the setting of randomized trials.

1.3 Human Aspects and Ethical Issues

Recent large, prospectively randomized trials have proven the safety and efficacy of laparoscopic-assisted resection for colon cancer. These studies confirm that this technique adheres to the principles of a standard oncologic resection as defined and confirmed by the pathologic examination of the specimen. Numerous case series and case-controlled studies have asserted the safety and efficacy of the laparoscopic-assisted technique in the resection of rectal cancer. These assertions must be critically evaluated to establish the appropriateness of this technique in regards to rectal cancer. This randomized trial will provide sufficient information to establish whether this procedure achieves a true oncologic resection of rectal cancer. Only by performing a large controlled prospective study which focuses on the oncologic parameters of circumferential and resected margins, and completeness of TME or nearly complete TME, will we be able to confidently assure our patients that they are receiving appropriate cancer care.

1.4 Significance

The current standard of treatment for rectal cancer involves resection of the involved bowel, an intact mesorectal fascial envelope and the accompanying lymph node tissue. Associated morbidities and mortality from open laparotomy and total mesorectal excision are well described. Since the introduction of laparoscopic-assisted resection for colon cancer, there has been mounting enthusiasm for applying this technique to rectal cancer. Proponents of the laparoscopic technique assert that the same cancer resection can be achieved with minimal access surgery and that this technique is associated with improved short term outcomes. The primary focus of this randomized trial will be to determine whether laparoscopic-assisted resection of rectal cancer is non-inferior in safety and efficacy to the open technique of total mesorectal excision. The study will determine whether laparoscopic rectal resection can provide comparable cancer outcomes and favorably impact the short term outcomes of recovery.

1.5 Objectives

1.5.1 Primary Objective

To test the hypothesis that laparoscopic-assisted resection for rectal cancer is not inferior to open rectal resection, based on a composite primary endpoint of oncologic factors which are indicative of a safe and feasible operation.

1.5.2 Changes to Primary Endpoint Oncologic Parameters in Amendment 4

1.5.2.1 Distal Margin

The current standard of care for all Stage II and III rectal cancer patients is neoadjuvant therapy. In the setting of neoadjuvant therapy, the clinical implications of a close distal margin compared to a negative distal margin are minor.[89] Also, efforts by surgeons to minimize the distance from the distal margin to the tumor in reconstructive procedures have not resulted in an increase in local recurrence.[89] However, true positivity of a distal margin is clearly an undesirable outcome. Therefore, the presence of a negative distal margin (as opposed to a distal margin of a certain distance from the tumor) as a success indicator is preferable and warranted as an endpoint.

1.5.2.2 Completeness of TME

Combining complete and nearly complete TME categories is based on emerging data that demonstrates that the incidence of (y)pCRM < 1 mm is the same for complete and nearly complete (14.6% and 11%, respectively) but significantly greater (28.2%) ($p<0.004$) for incomplete.[89] In a pooled analysis of the MRC CR07 and NCIC-CTG CO16 trials, local recurrence rates were nearly the same for complete and nearly complete TME (4% and 7%, respectively), but 13% for incomplete.[90]

The definitions of complete TME and nearly complete TME are subjective. Conversely the distinction between incomplete TME and complete or nearly complete TME is not subtle. The majority of the violations

of the mesentery are less than 5 mm, which is usually caused by traction injury rather than cancer surgery violations.[90] The patho-physiological implications of the small encroachment are negligible since there is no tissue left in the pelvis because of the encroachment. For these reasons, an endpoint for surgical success that includes both complete and nearly complete TME (rather than just complete TME) is appropriate.

Revised primary endpoint oncologic parameters:

Circumferential margin > 1 mm

Negative distal margin

Completeness of TME

- A complete TME is defined as a rectal resection specimen that has an intact mesorectum and covering peritoneal envelope all the way to the level of rectal transection with no coning in of the mesorectum above the point of transection. The surface of the peritoneal covering should be smooth and shiny with no defects exposing the underlying fat.
- A nearly complete TME is defined as a rectal resection specimen where the mesentery is all present, without coning or missing fat. A < 5 mm deep defect may be present in the envelope covering the mesenteric fat caused either by a wayward incision or traction injury during extraction of the TME specimen through a small extraction site.

A patient will be considered to have a successful resection on either arm if and only if all oncologic parameters are satisfied. Based on historical data, we expect the rate of successful resection for the parameters for standard open resection to be 90% for the oncologic parameters. We will accept a 6% decrement from the successful resection rate of the open (laparotomy) arm of the study to be considered non-inferior.

1.5.3 Secondary Objectives

To assess patient-related benefit of laparoscopic-assisted resection for rectal cancer vs. open rectal resection (blood loss, length of stay, pain medicine utilization)

To assess disease free survival and local pelvic recurrence at two years.

To assess quality of life, sexual function, bowel and stoma function at scheduled time points throughout the trial.

1.6 Study Design

This is a prospective, randomized phase III trial evaluating the safety and efficacy of laparoscopic resection for rectal cancer.

1.6.1 Accrual Goal

This prospective, randomized phase III trial will require 480 patients, 240 patients per arm of the study. The anticipated accrual rate is 10 patients per month with a total accrual time period of 48 months.

If, after 36 months of accrual, the rate of accrual in the most recent 12 months exceeds 15 patients per month, and the total accrual at that time exceeds 400 patients, accrual will be extended to a total of 650 patients. Refer to Section 10.3, Sample Size Estimation and Patient Accrual.

1.6.2 Participation

Patient accrual will be accomplished at multiple centers, with 50 or more anticipated accrual sites. This study is limited to participation by pre-approved, credentialed surgeons (see Section 12.0, Surgeon Skill Verification).

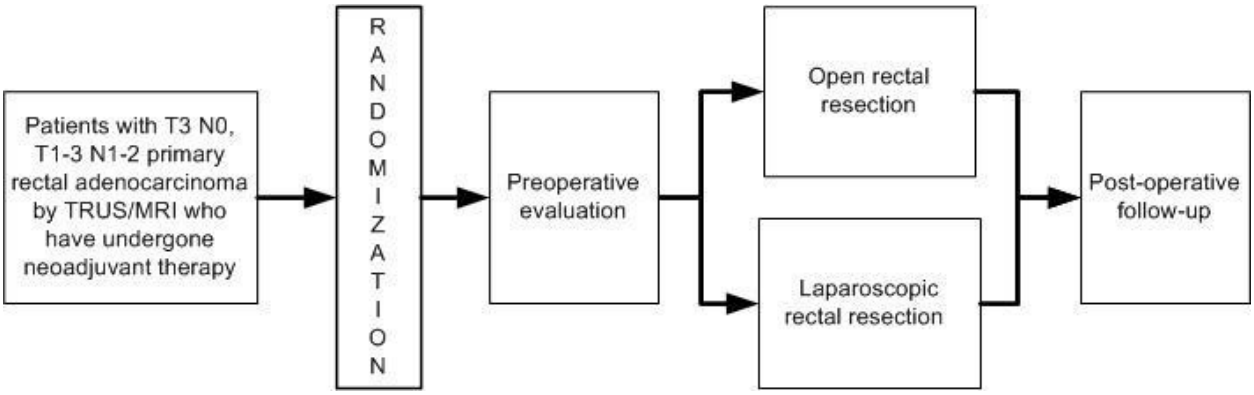
1.6.3 Stratification factors

Site of primary tumor: high, middle or low rectum.

Registering surgeon.

Planned operative procedure: low anterior resection, abdominal perineal resection.

1.7 Schema



2 Patient Selection

Each criterion must be addressed and documented in the patient's medical record. Patient eligibility must be determined by the investigator and confirmed by his or her dated signature. **No waivers or exemptions to any eligibility criteria are permitted.**

NOTE: Staging requirements for enrollment are based on pre-treatment clinical staging (prior to any pre-operative therapy or surgery).

2.1 Eligibility Criteria

1. Histologic diagnosis of adenocarcinoma of the rectum ($\leq$ 12cm from the anal verge).
2. T3 N0 M0, T1-3 N1-2 M0 disease as determined by pre-neoadjuvant therapy CT scans and pelvic MRI or transrectal ultrasound. Patients with T4 disease are not eligible.
3. Completion of pre-operative 5FU-based chemotherapy and/or radiation therapy. Capecitabine may be substituted for 5FU.
4. Age $\geq$ 18 years.
5. ECOG (Zubrod) Performance Status $\leq$ 2.
6. Body Mass Index (BMI) $\leq$ 34. NOTE: The same value applies to both male and female patients.
7. No evidence of conditions that would preclude use of a laparoscopic approach (e.g., multiple previous major laparotomies, severe adhesions).
8. No systemic disease (cardiovascular, renal, hepatic, etc.) that would preclude surgery. No other severe incapacitating disease, i.e., ASA IV (a patient with severe systemic disease that is a constant threat to life) or ASA V (a moribund patient who is not expected to survive without the operation).
9. No concurrent or previous invasive pelvic malignancy (cervical, uterine and rectal) within five years prior to registration.
10. No history of psychiatric or addictive disorders or other conditions that, in the opinion of the investigator, would preclude the patient from meeting the study requirements. NOTE: Incompetent patients are not eligible for this trial.

3 Study Calendar

	Prior to reg.*	REGISTRATION/RANDOMIZATION**	Pre-op***	SURGERY	Post-operative Follow-up‡									
					Day 3	1-2 weeks	4-6 weeks	3 mos.	6 mos.	9 mos.	12 mos.	18 mos.	24 mos.	Yearly #
Informed Consent/HIPAA	X													
H&P, vitals, ECOG PS	X		X[1]			X	X	X	X	X	X	X	X	X
Pregnancy test			X[2]											
BMI	X													
Colonoscopy	X										X			
CEA	X							X	X	X	X	X	X	
TRUS/MRI	X													
Chest CT or CXR			X[3]								X		X	
CT abd/pelvis	X												X	
WBC, ANC, Hgb, platelet, electrolytes, creatinine, bilirubin, AST, ALT, Alk Phos, albumin, total protein, LDH			X											
Adverse event assessment						X	X	X	X	X	X	X	X	
LASA, C30, CR38			X		X	X	X	X			X			
MBFQ (bowel function)			X								X			
SQOLS (stoma function)											X[4]			
Tissue submission for banking							X[5]							

* All patients must have had staging exams (e.g., colonoscopy, TRUS/MRI and CT abdomen/pelvis) conducted prior to neoadjuvant therapy at the time of diagnosis. All other baseline evaluations may be conducted anytime prior to registration.

** Patients may be registered/randomized anytime after completion of neoadjuvant therapy, but surgery must occur within 4-12 weeks (28-84 days) after completion of neoadjuvant therapy.

*** Pre-operative evaluation will occur after registration and within 2 weeks prior to surgery.

‡ Visits occurring from 3 months to 24 months may be done +/- 4 weeks from the due date. Yearly visits may be done +/- 8 weeks from the due date. After disease relapse, patients will be followed for survival at the intervals defined above until 5 years from date of surgery.

Long-term follow-up is required yearly until 5 years from date of surgery. Follow-up scans and tests should be conducted as clinically indicated. If follow-up scans or tests are conducted, then submit reports.

1 If the pre-registration H&P is within 2 weeks of surgery, then it does not need to be repeated after registration at the pre-operative assessment.

2 For patients of childbearing potential only. Women of childbearing potential must have a negative pregnancy test prior to surgery. If a pregnancy test is done prior to registration at the time of diagnosis or anytime during or after neoadjuvant therapy, then it does not need to be repeated after registration at the pre-operative assessment.

3 All patients must have a Chest CT or CXR prior to surgery. If a Chest CT or CXR is done prior to registration at the time of diagnosis or anytime during or after neoadjuvant therapy, then it does not need to be repeated after registration at the pre-operative assessment.

4 The 12-month SQOLS is required only for patients with a permanent stoma.

5 Tumor tissue submission for banking is required only for consenting patients when tissue is available. See Biospecimen Collection (Section 14).

4 Patient Registration/Randomization

Before registering patients, all investigators and study support staff must be registered members of the Cancer Trials Support Unit (CTSU). Please see the CTSU website (www.ctsu.org) for details on registering as a CTSU member.

All forms and documents associated with this study can be downloaded from the protocol-specific page of the ACOSOG website (www.acosog.org) or the protocol-specific page of the CTSU registered-member website (http://www.ctsu.org).

4.1 Assessment of Stratification Factors

The following stratification factors shall be observed throughout the enrollment period of the study:

Site of primary tumor: high, middle or low rectum.

Registering surgeon.

Planned operative procedure: low anterior resection or abdominal perineal resection.

4.2 Registration Requirements

The study is limited to participation by credentialed surgeons. The study chair will notify each surgeon or group involved in the study when approved. Randomization by that surgeon may not begin until documentation has been submitted and the study chair has approved his/her laparoscopic experience. See Surgeon Skill Verification (Section 12.0).

NOTE: To ensure proper stratification, the registering physician MUST be the surgeon intended to perform the assigned procedure.

4.3 Registration/Randomization Procedures

Patients may be registered/randomized anytime after completion of neoadjuvant therapy, but surgery must occur within 4-12 weeks (28-84 days) after completion of neoadjuvant therapy.

The patient or the patient‘s legally acceptable representative must provide a signed and dated informed consent prior to registration and prior to beginning any study-related procedure or intervention. (NOTE: Neoadjuvant therapy is not considered to be a study-related procedure). Faxed, emailed or verbal consents are not acceptable.

The patient or the patient‘s legally acceptable representative must provide signed and dated consent to the use of their Protected Health Information (this may be incorporated into the informed consent document). Note: this applies to all sites subject to US HIPAA requirements.

Prior to registering a patient to the study, the physician must verify that all of the eligibility criteria on the eligibility checklist have been met. **No waivers or exemptions to any eligibility criteria are permitted.** All eligibility criteria must be fully documented in the patient‘s chart.

Registration is available 24 hours a day via the CTSU‘s Oncology Patient Enrollment Network (OPEN) Portal system. All participating sites (ACOSOG and non-ACOSOG sites) will use OPEN to enroll patients to this study. OPEN can be accessed at https://www.ctsu.org/open/ or from the CTSU members' website OPEN tab.

Prior to accessing OPEN, site staff should verify the following:

All eligibility criteria have been met within the protocol stated timeframes.

All patients have signed an appropriate consent form and HIPPA authorization form (if applicable).

All pertinent forms and documents are on file with the CTSU.

Access requirements for OPEN:

Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' website.

To perform registrations, the site user must have been assigned the 'Registrar' role on the ACOSOG or CTSU roster.

- **ACOSOG Sites:** ACOSOG members intending to register patients have been assigned a 'Registrar' role on the group‘s roster.
- **Non-ACOSOG Sites:** Non-ACOSOG members intending to register patients must be assigned a 'Registrar' role on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' website.

Information required at registration:

Registering institution and investigator CTEP ID numbers

Patient demographic information (see the registration form)

Eligibility checklist (see the registration form)

Stratification factors

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records. Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.4 Randomization Arms

Patients will be randomized into one of the following treatment arms:

Arm 1: Open laparotomy and rectal resection

Arm 2: Laparoscopic-assisted rectal resection

5 Interventions

5.1 Neoadjuvant Chemoradiation Therapy

Patients eligible for this trial will have completed 5FU-based neoadjuvant chemotherapy/radiation therapy per the institution‘s standard of care or IRB-approved clinical trial. Capecitabine may be substituted for 5FU as the investigator‘s discretion.

Patients may be registered/randomized anytime after completion of neoadjuvant therapy, but surgery must occur within 4-12 weeks (28-84 days) after completion of neoadjuvant therapy.

5.1.1 Preoperative Evaluation

Patients will be seen for the preoperative evaluation within 2 weeks prior to surgery. Tests and evaluations should be conducted as required by the Study Calendar (Section 3.0).

5.2 Surgery

Surgeons are encouraged to treat all patients undergoing laparoscopic resection of rectal cancer on this protocol.

5.2.1 Preoperative Care

Patients will be admitted to the hospital the morning of the surgery or the day prior to surgery for complicating medical conditions (surgeon's discretion).

All subjects will receive bowel prep per institutional colorectal standard routine.

The site of the ileostomy/colostomy (potential or planned) will be marked preoperatively or per institutional standard routine.

5.2.2 Intraoperative Care

Anesthetic care will include general endotracheal anesthesia with gastric and bladder decompression.

Extent of colon and rectal resection will be determined by site of tumor on preoperative exam.

The manner of anastomosis (stapled or hand sewn) will be based on the surgeon's preference.

5.2.3 Operative technique

Treatment on this protocol must commence by the accruing membership under the supervision of an approved credentialed surgeon. **NOTE: To ensure proper stratification, the registering physician MUST be the surgeon intended to perform the assigned procedure.**

Operative procedures will include laparoscopic, laparoscopic-assisted, hand-assisted, and open techniques for rectal tumor resection. Fascial incisions made earlier than expected during the procedure or greater than 10cm long will be considered open surgery (See Section 5.2.4, Conversion). The two randomization arms will be a laparoscopic-assisted procedure arm, including laparoscopic-assisted and hand-assisted techniques, and an open procedure arm.

Laparoscopic procedures must utilize laparoscopic techniques to accomplish the rectal dissection and cannot use blunt hand dissection of the rectum.

Robotic procedures used to perform the pelvic dissection will be considered laparoscopic or laparoscopic assisted procedures. The non-pelvic portion of the procedure must be performed by one of the accepted laparoscopic methods (hand assisted, assisted or pure laparoscopic). The surgeons performing robotic procedures must be credentialed for laparoscopic colon, laparoscopic rectal, and robotic rectal procedures as described in Surgeon Skill Verification (Section 12). Patients who fail robotic dissection of the rectum and are switched to a laparoscopy (laparoscopic-assisted or hand-assisted) approach will still be followed in the laparoscopic group. Patients who require conversion to an open operation (greater than 10 cm incision) will be considered as converted laparoscopic.

Although variation in technical approaches can be anticipated based on variation in patient's body habitus and surgical scars, the following technical descriptions will serve as guidelines.

Position: Lithotomy using a restraining system (e.g., beanbag and stirrups) (e.g., Allen or Lloyd-Davies).

Laparoscopy: Routine techniques for establishing pneumo-peritoneum should be used at the umbilicus. If hand-assisted laparoscopy is to be used, the access port can be placed first in the lower abdomen (midline suprapubic or left-lower quadrant transverse). The abdomen will be insufflated with CO_2 to achieve a pneumoperitoneum pressure $\leq$15 mm Hg. Additional appropriately sized trocars will be placed according to surgeon preference under direct vision with the laparoscope. The abdomen will be explored for evidence of advanced disease including inspection of the liver, retroperitoneum. para-aortic nodes, ovaries and peritoneal surface. The site and location of the tumor relative to the peritoneal cavity and adjacent structures will be noted. Advanced local disease (unsuspected T4 disease) at the time of initial examination will mandate conversion to celiotomy if the surgeon feels resectability with clear margins is questionable. Minimal tumor handling will be adhered to and contact of the tumor to the wound will be minimized by the use of wound protection or isolation of the specimen in a bag.

Low anterior resection/APR: The table is tilted head down and airplaned to the right. Mobilization of the left colon +/- splenic flexure, identification and protection of the left ureter, identification and ligation/division of inferior mesenteric vein and artery or superior hemorrhoidal vessels after bifurcation of the inferior mesenteric artery are essential features. Dissection of the rectum from the sacrum should occur in the avascular plane behind the fascia propria of the rectum and anterior to the presacral fascia in order to maintain intact the envelope containing the mesorectum. The pelvic nerves (right and left) at the pelvic brim should be identified and freed from the dissection plane unless

dictated otherwise by tumor involvement. The dissection posteriorly in the avascular areolar tissue plane should be carried out with sharp or energy dissection to maintain the fascia propria to a level well below the tumor or all the way to the pelvic floor depending on tumor level in the rectum. The lateral peritoneal and anterior cul-de-sac incision should be made outside the area of the tumor and, if possible, within the pelvic confines to avoid the ureters, nerves, prostate, seminal vesicles, vagina, pelvic floor and side wall muscles. Retraction of the sigmoid and rectum should be accomplished in such a way that injury to that area is avoided and contamination limited.

Transection of the posterior mesorectum 4 cm below the level of the tumor (or mesorectum should be removed entirely if necessary). Cautery, RF energy, clips or harmonic scalpel are all acceptable means of vascular control.

Transection of the distal rectum should be performed laparoscopically using an endocutter stapler or through the planned extraction wound (protected) using the appropriate stapling instrument. If an anastomosis is planned, the proximal bowel may be prepared for suturing or stapling either laparoscopically or through the access wound. The anastomosis should be performed using standard techniques via either the laparoscopic hand-assisted or laparoscopic-assisted approach.

Minimal acceptable margins should be obtained at the time of transection and evaluated on the fresh, unstretched specimen. A proximal margin of greater than 5 cm and a clear 1 cm margin distally will be considered adequate for low rectal lesions when sphincter preservation is a central issue. Upper and mid rectal lesions should have at least 2 cm distal margins. Inability to obtain adequate margins should be considered as a reason for conversion. The use of diverting loop ileostomy will be left to the surgeon‘s discretion and recorded.

Completion of the distal rectal and anal dissection for an APR may be started during the laparoscopic portion of the procedure and standard perineal dissection carried out. The rectal specimen can be extracted through the perineal wound (without any protective device). Trocar sites and extraction wounds should be closed per the surgeon's usual protocol.

Laparoscopic procedures will be videotaped beginning at pelvic dissection. Random audit of selected videotapes will be conducted by the study team. See Section 13.0, Performance Monitoring.

5.2.4 Conversion

Conversion will be defined as a change in operative approach to otherwise achieve the final goal; i.e. laparoscopic-assisted technique to a hybrid procedure, or any conversion to an open procedure. Conversion to a celiotomy will be at the discretion of the individual surgeon for concerns of patient safety, technical difficulties, inability to complete the planned procedure for sphincter sparing or associated conditions requiring treatment. Conversion will be defined as a fascial incision which is longer than 10 cm, utilized to achieve anything other than specimen extraction. (Largest handport size is ≈ 8 cm). Utilizing the extraction site for transverse stapler insertion to accomplish the distal anastomosis will not be considered a conversion. Identification of any grossly visible positive margins or extensions into adjacent organs will mandate conversion to an open procedure. Completion of the pelvic dissection through the extraction site also will be considered conversion.

5.2.5 Extent of resection

Extent of resection will be documented for all procedures in the operative report and on data forms.

5.3 Intraoperative Pathology and Pathologic Examination of Surgical Specimen

Surgeons will measure fresh, unstretched proximal and distal margins in the operating room. The completeness of the TME resection will be evaluated by the pathologist (and categorized as defined in the Evaluation of Outcomes section) in the operating room. Prior to opening the specimen, it should be prepared by the pathologist to evaluate radial margins by applying ink to the mesorectal surface in the area of the tumor.

Pathologists should make every effort to identify at least 12 lymph nodes in the surgical specimen. Efforts to locate lymph nodes (e.g., defatting) should be included in the pathology report.

NOTE: The mesorectal specimen must be photographed with the laparoscope or OR camera to verify the quality of the dissection. These photographs will be submitted for review by the study team as part of the pathology review that is required for all registered patients. See Section 7.4, Pathology Review Committee.

5.4 Documentation

Operative procedures and findings will be documented in the institutional operative and pathology reports and on required data forms. **Laparoscopic procedures will be videotaped beginning at pelvic dissection. Random audit of selected videotapes will be conducted by the study team. See Section 13.0, Performance Monitoring.**

5.5 Postoperative Care

Postoperative care will be according to current standards as directed by the operative surgeon.

Pain control will be provided using parenteral (intramuscular, intravenous or epidural) administration of narcotics or analgesics.

Oral analgesics will be offered ad lib when the patient has resumed oral intake.

Narcotic/analgesic use will be monitored and recorded for study purposes.

The initiation of oral intake and dietary advances will be made according to individual patient tolerance.

The day of first postoperative flatus and bowel movements will be monitored and recorded.

Intravenous fluids will consist of maintenance crystalloid solution in addition to blood products as needed until the patient is able to sustain oral intake.

Hospital discharge will occur only after the patient has shown diet tolerance, return of bowel function and able to resume self-care with minimal assistance.

5.5.1 Morbidity and Mortality

Early, in hospital and late (within 30 days) morbidity and mortality will be closely monitored and recorded using the study data forms with the following definitions:

Pyrexia will be defined as two or more documented patient temperatures $>38^0$ C that require any treatment intervention (excluding ambulation, incentive spirometer, or antipyretics) or that results in an increase in hospital stay.

Primary ileus will be defined as the condition of bowel dysfunction (NPO status) that occurs for greater than 10 days following surgery or that requires intervention including nasogastric tube, surgery, medication, etc.

Secondary ileus will be defined as bowel dysfunction that occurs in a patient that had been taking enteral nutrition, but that subsequently requires NPO status.

Pulmonary, urinary tract, wound (including perineal) and abdominal infections will be defined by the need for antibiotic treatment and/or drainage.

Urinary retention will be defined as the condition of urinary dysfunction that occurs for greater than 5 days following surgery or that requires intervention, including replacement of Foley catheter, surgery, etc.

Perioperative hemorrhage requiring blood transfusion(s) or reoperation will be considered as a complication. Correction of preoperative anemia will not be included as a complication. The decision to transfuse will be made at the surgeon's discretion.

Any documented medical or anesthetic complications that result in patient disability or that requires intervention will be recorded.

Problems with healing, function or management of the ostomy that requires intervention or additional hospital stay will be considered complication and recorded.

5.5.1.1 Perioperative Complications

Complications after laparoscopic rectal resection include:

- Death after laparoscopic rectal resection (0-2%)
- Anastomotic leak after sphincter-sparing rectal resection (20%)
- Perineal wound infection (24 %)
- Abdominal wound infection (0-3.4%)
- Stoma complications (2.6-18 %)

Complications after open rectal resections include: Death after open rectal resection (0-7.4%) Anastomotic leak after recta1 resection (1-17%) Perineal wound infection (8%)

- Abdominal wound infection (3-24%)
- Stoma complications (4-10%)

5.5.1.2 Late or Delayed Complications

Late or delayed complications such as bowel obstruction will be monitored and reported on data forms. Details of hospital admissions will be recorded in the patient‘s records, including dates, location, and admitting physician‘s name. The ―reason for admission‖ will provide guidance as to whether the hospitalization was related to the cancer diagnosis and surgery or for other reasons. See Section 8.0, Adverse Events Reporting for reporting guidelines for complications occurring >30 days after surgery.

5.6 Quality of Life

The impact of the disease and surgery on patient function and quality of life (QOL) will be evaluated at registration after completion of any preoperative chemoradiation therapy. These data will serve as our baseline data. Subsequent assessments will be collected post-operatively at day 3, one to two weeks, four to six weeks, 3 months and 12 months. These assessment timepoints have been chosen to gather information on short and long-term QOL-related deficits so that future interventions may be planned. The day 3 assessment will capture acute QOL deficits which may point us to interventions that could be incorporated into future surgical procedures. The 1-2 week time-point was chosen as a time at which immediate post-op symptoms should resolve and hence allow for identification of acute QOL-related deficits. The 4-6 week assessment will provide information relative to a time when recovery form the procedure itself should be complete. The 3 month and 12 month time points are included to gain information about long term impact on QOL. Not only will we be able to compare these different impacts on QOL between these two treatments, we will be able to gain knowledge about potential interventions to improve QOL for patients in this population.

A cross-comparison of instruments will be conducted, specifically to compare the single-item indicators to the more lengthy and detailed multi-item instrumentation (the EORTC-QLQ CR38, the SQOLS, and the LASA single-items). This is a core line of research that will allow ACOSOG to plan efficient QOL assessments for future ACOSOG trials. Dr. Sloan has done considerable research in this area, demonstrating that in general cancer patient populations, there is merit to the use of simple, single-item assessments.[45] No such work has been done, however, in surgical trials and so this study will be the first of its kind to carry out such work.

Functional status and the impact of the surgery and the disease will be assessed utilizing the instruments outlined below. Completion of the instruments will require no more than 20 minutes.

NOTE: QOL questionnaires for all patients should be completed as required in the Study Calendar, regardless of surgical outcome and/or conversion to open laparotomy. Questionnaires may be completed at any time during the day in the clinic, or they may be taken home by the patient for completion and then returned.

5.6.1 EORTC QLQ-C30 and QLQ-CR38

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)[44] is a 30-item questionnaire about patient ability to function (measured via five functional scales), symptoms related to the cancer and its treatment (via eight symptom scales/items), overall health and quality of life, and perceived financial impact of the cancer and its treatment. Each item is measured on a 1-4 scale (1=not at all; 4=very much).

The EORTC QLQ-CR38 is a 38-item colorectal cancer-specific questionnaire which covers symptoms and side-effects related to different treatment modalities, body image, sexuality, and future perspective with each item formatted the same as items of the EORTC QLQ-C30 (1-4 scale with 1=not at all; and 4=very much). It was developed to be used in conjunction with the EORTC QLQ-C30 following the EORTC guidelines for module development.[46] The EORTC QLQ-CR38 has been tested in cancer patients receiving chemotherapy or radiotherapy. Seven of nine scales had Cronbach's alpha greater than 0.70 at one or both of two assessments and the test-retest reliability for all scales and one single item was 0.78 or higher.[47]

These instruments are available in other languages upon request.

5.6.2 Stoma Quality of Life Scale (SQOLS)

The SQOLS is a 21-item questionnaire featuring three scales: Work/Social Function (6 items), Sexuality/Body Image (5 items), and Stoma Function (6 items). Additionally, 1 item (scored separately) measures the financial impact, 1 measures skin irritation, and 2 measure overall life satisfaction. The pair of overall QOL items asks patients to respond on a 0-100 scale. The remaining items ask patient to respond on a 5-point Likert-type scale (1=Never, 2=Seldom, 3=Occasionally, 4=Frequently, 5=Always). The questionnaire was validated using patients at the colorectal surgery clinic of the Mayo Clinic.[48]

This instrument is available in English only. It may be administered to non-English speaking patients via an interpreter.

Ostomy education may be provided to patients pre-operatively. Formal ostomy teaching by a Wound Ostomy Continence Nurse (WOCN) will be documented on the Perioperative Data Form as well as any other education provided to the patient. WOC Nurses are Registered Nurses who hold a baccalaureate degree or higher and complete a formal, accredited WOC full scope or specialty education program.

5.6.3 Mayo Bowel Function Questionnaire (MBFQ)

The Mayo Bowel Function Questionnaire is a simple 13-item assessment developed from prior studies of the effect of radiation treatment on bowel function[58,61] and has been used successfully in NCCTG trials.[59]

This instrument is available in English only. It may be administered to non-English speaking patients via an interpreter.

5.6.4 Linear Analogue Self Assessment (LASA)

The LASA consists of 6 single-item numeric analogue scales. One item measures overall QOL[62] while the five remaining items address the major domains of QOL (mental, physical, emotional, social, and spiritual well-being) on a scale of 0-10. LASA items such as these have been validated as general measures of global QOL dimensional constructs in numerous settings[53,54,57,66,67]. The six items have been validated at the Mayo Clinic for use in cancer patients and have been successfully used in numerous clinical trials[50]. Normative data for the LASA have recently been published (Brown et al, Locke et al, Sloan et al) so that the results of this trial can be compared relative to other patient populations.

This instrument is available in English only. It may be administered to non-English speaking patients via an interpreter.

5.7 Postoperative Adjuvant Therapy

Patients will be evaluated after surgery to determine the need for subsequent care based on the final pathology. All patients should be instructed to notify the operating surgeon of any additional therapy the patient will receive. Patients should not start treatment on any other investigative trial involving intervention or invasive diagnostic procedures $\leq$30 days following surgery to enable a complete evaluation of post-operative adverse events and complications occurring within 30 days of surgery.

6 Follow-up

Patients will be followed for recurrence and survival for 24 months for the primary endpoint, and then an additional 3 years, as required in the Study Calendar (Section 3.0). More frequent examinations may be performed as clinically indicated.

Postoperative contact will include a visit in the hospital or office at 3 days, one to two weeks, four to six weeks, 3 months, 6 months, 9 months, 12 months, 18 months and 24 months after surgery. Long-term follow-up will be conducted annually for an additional 3 years. Follow-up may be conducted through the patient's local physician, per surgeon discretion. Type and severity of activity restrictions will be documented on the Quality of Life forms.

6.1 Follow-up of Patients with Disease Relapse

If disease relapse is diagnosed, required data forms will be submitted to document the relapse. Patients will be followed for survival as required by the Study Calendar until 5 years.

6.2 Follow-up of Patients Who Receive Opposite Surgery or Refuse Surgery

Patients who are randomized but receive the opposite surgery from their randomized arm will be followed as required by protocol. Patients who are randomized but refuse all surgery will not be followed.

7 Evaluation of Outcomes

See Study Calendar (Section 3.0) for schedule of assessments.

7.1 Evaluation at the Time of Surgery

The primary endpoint for this study is a composite primary endpoint of oncologic factors which are indicative of a safe and feasible operation.

Circumferential margin > 1 mm

Negative distal margin

Completeness of TME (complete or nearly complete TME)

A patient will be considered to have a successful resection on either arm if and only if all oncologic parameters are satisfied.

If the tumor has completely resolved and if there is a scar present in the colon, the distal margin should be measured from the scar. The distal margin may not be measurable if there is no scar or tattoo ink present within the rectum. In that case, "not applicable" should be coded on data forms and source documents. The circumferential or radial margin only applies to the fat covered area of the rectum. Anterior lesions which are exposed to the peritoneum will have no radial margin to evaluate. Low rectal tumors will have a mesorectal fat which will be evaluable. The inked margin should be measured from the deepest point of invasion of the tumor and must be greater than 1 mm to be considered a clear margin.

Additional factors to be evaluated include:

Intact TME resection

Circumferential and distal margin positivity

Lymph node harvest and number of positive lymph nodes

Evaluation of surgical complications

7.2 Surgical Complications

Perioperative and postoperative complications will be collected and sent to ACOSOG. See Adverse Event Reporting (Section 8.0).

7.3 Pathologic Evaluation of the Resected Specimen

The resected specimen must be inspected fresh in the pathology department or operating room of each participating institution. Whenever possible, the pathologist should not be informed of the patient's treatment assignment.

The specimen should be oriented by the surgeon.

The quality of the mesorectal excision will be categorized as 1) complete, 2) nearly complete, or 3) incomplete, according to Dutch Colorectal Cancer Group methods[43]. It is imperative that this determination be made before the specimen has been inked or sectioned.

The specimen will be inked by the pathologist for margin determination, and fixed in 10% formalin.

It may be necessary to open the specimen at the time of surgery for intra-operative margin assessment, tumor banking, or other considerations. In those instances where the specimen must be opened, it is imperative that assessment of the mesorectal excision and inking of radial margins occurs prior to opening of the specimen. Prior opening of the specimen should not fundamentally alter the pathologic evaluation.

The size of the residual tumor or ulcer corresponding to the tumor site will be measured.

Dissection of the fixed specimen will consist of serial slicing of the rectal wall through the tumor and surrounding mesorectal fat in a plane perpendicular to the mucosa.

The deepest level of invasion in the rectal wall or mesorectal tissue will be determined and the distance measured from the overlying inked radial margin to the tumor.

Sections will be obtained at 5 mm intervals, embedded in paraffin, cut in 5 *u*m sections, and stained with H&E.

Although not strictly required, in cases where only a mucosal scar or ulcer is noted, we would strongly recommend submission of the entire scar/ulcer to evaluate for microscopic residual tumor.

A careful search will be conducted for any potential lymph nodes in the fragment of fat contained in the specimen.

Any lymph nodes identified should be submitted in their entirety.

Findings will be reported per the recommendations of the Association of Directors of Anatomic and Surgical Pathology [Pathology 1996].

7.4 Pathology Review Committee

A Pathology Review Committee (PRC) will review pathologic case report forms, pathology reports and photographic images of the TME specimen for all registered patients. The PRC will standardize the use of inking the mesenteric surface at the level of the tumor to determine the closest point of tumor invasion to the inked surface.

The PRC will evaluate the reports and provide education for failure to meet minimal standards of the pathology evaluation with potential site closure if minimal standards cannot be met. The parameters to be included in the reports are:

Distal margin of the unstretched fresh specimen

Proximal margins of the unstretched fresh specimen

Circumferential radial margin

Completeness of TME specimen

Number of lymph nodes in mesentery and number positive

7.4.1 Pathology Materials Submission Instructions

The following materials will be submitted for central review by the PRC. All materials must be identified with the study number and the patient's ACOSOG ID number:

Photograph of TME specimen (hard copy or burned to CD)

Pathology report

Final Pathology CRF

TME Specimen Photograph Submission CRF

All materials will be submitted to:

ACOSOG Site Coordinator

Mayo Clinic Cancer Center Research Office

200 First Street SW

Rochester, MN 55905

Phone: 507-284-9565

Fax: 507-293-1150

Email: rstacosogsite@mayo.edu

Note that submission of pathology materials for central review is in addition to submission of pathology reports, forms, etc. to CTSU, as required by the Schedule of Forms.

7.5 Evaluation of Disease Recurrence

The appearance of rectal carcinoma in the primary site, nodal basin or distant organ sites during follow-up will be classified as recurrent cancer. Recurrence will be classified as local or distant.

Suspected tumor recurrence within the surgical field should be documented histologically or cytologically. Pathological documentation of suspected distant metastasis is also recommended. The summary of local recurrence-free survival, disease-free survival and overall survival will be summarized graphically. Appropriate imaging should be used to document extent of disease (PET/CT, CT, MRI).

7.6 Data Safety and Monitoring

Patient data will be monitored by the ACOSOG Data Monitoring Committee for significant adverse effects on cancer outcomes, safety or feasibility. Accrual rate and feasibility shall be assessed. As described in Section 10, there will be a specific futility monitoring plan for the primary endpoint. In addition, the following rates are based on the current literature review and are provided to the DMC as guidelines for monitoring of additional safety related endpoints.

Rate of conversion greater than 20%.

Rate of anastomotic leak greater than a 6% increase compared to open procedure.

Rate of positive circumferential margins greater than a 6% increase compared to open procedure.

Surgical mortality greater than 5%.

Rate of rectal perforation greater than a 6% increase compared to open procedure.

8 Adverse Event Reporting

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations.

Toxicities/adverse events must be described and graded using the terminology and grading categories defined in the most current version of the NCI's Common Toxicity Criteria (CTCAE) version 3.0. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms, using the codes provided. **NOTE: CTCAE Version 3 will continue to be used for routine adverse event reporting. Effective January 1, 2011, CTCAE Version 4 will be used for expedited adverse event reporting only.**

8.1 Routine Adverse Event Reporting

All adverse events, regardless of grade or treatment attribution, must be recorded on AE case report forms (CRFs).

Some serious adverse events may require expedited reporting using the AdEERS reporting system, as defined below. **NOTE: All AEs including those submitted to NCI via the Adverse Event Expedited Reporting System (AdEERS) must be recorded on the AE CRF.** Expedited reporting is in addition to and does not supplant the reporting of AEs as part of the data submission requirements for the study.

8.2 Expedited Adverse Event Reporting

An expedited AE report is submitted via the AdEERS web application. Reports should be submitted within the timeframes specified below. Assistance for using AdEERS or for completion of the AdEERS templates is available at http://ctep.cancer.gov/.

What to Report:

AdEERS Expedited Reporting Requirements for Adverse Events Occurring Within 30 Days[1] of Surgery

	Grade 1	Grade 2	Grade 3	Grade 3	Grade 4	Grade 4	Grade 5	Grade 5
	Unexpected and Expected	Unexpected and Expected	Expected	Unexpected with or without Hospitalization	Unexpected with or without hospitalization	Expected with or without hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	Not Required	10 calendar days	Not Required	10 calendar days	10 calendar days
Possible Probable Definite	Not Required	Not Required	Not Required	Not Required	24-hour; 5 calendar days	Not Required	24-hour; 5 calendar days	10 calendar days

[1] Grade 4 unexpected and all grade 5 adverse events with attribution of possible, probable, or definite that occur greater than 30 days after surgery require reporting with AdEERS 10 calendar day report.

Expedited AE reporting definitions

–24 hours; 5 calendar days‖: The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.

–10 calendar days‖: A complete AdEERS report on the AE must be submitted within 10 calendar days of knowledge of the event.

Use the NCI protocol number and the protocol-specific patient ID provided at registration on all reports.

How to Report:

AdEERS reports are submitted electronically via the AdEERS web application. Paper templates are permitted only if the AdEERS Web-based application is unavailable. All AEs reported via paper report must be entered via the AdEERS system once connectivity is restored.

The AdEERS application and paper templates are available at: http://ctep.cancer.gov/reporting/adeers.html.

Secondary Malignancies

All cases of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) that occur in patients on NCI-sponsored trials following their treatment for cancer must be reported using the AdEERS web application.

Local IRB

All local AdEERS reports must be submitted to your Institutional Review Board (IRB) within 90 days of knowledge and reporting of the event. You should follow your IRB's policies and procedures in submitting external adverse events and safety reports.

8.3 Expected Adverse Events

More Frequent: Hemorrhage/bleeding, hematoma, infection/abscess, pain, anastomotic leak, urinary retention, stoma complications.

Less Frequent: Fistula, urethral injury, stricture, pelvic sepsis, perforation, fecal incontinence, thrombosis/embolism, infection/lung (pneumonia), cardiac ischemia/infarction (myocardial infarction), ileus, hernia, sexual dysfunction.

9 Data Considerations

Data management activities for Z6051 will be performed by the Cancer Trials Support Unit (CTSU). Please see the CTSU website: www.ctsu.org for details on registering as a CTSU member.

9.1 Case Report Form Completion and Submission Guidelines

All participating sites will submit patient data via the CTSU's Remote Data Capture (RDC) system. The CTSU RDC system allows sites to enter patient data into an Oracle Clinical ® database over a secure Internet connection. The RDC system also allows for data correction at the point of entry, and is used to communicate and resolve issues relating to discrepant data.

In addition to submitting patient data electronically via the RDC system, sites may be required to submit faxed clinical reports to CTSU. Clinical reports must be faxed to the CTSU Data Operations Center accompanied by a properly completed study-specific CTSU Data Transmittal Form. CTSU fax number is: 1-301-545-0406.

Data submission via fax also is allowed for sites unable to use RDC for technical reasons. See Submission via Hard Copy below.

The CTSU help desk is available to answer questions regarding data submission at 1-888-823-5923 or by email at ctsucontact@westat.com. Hours are between 9:00 A.M. and 7:00 P.M. Eastern Time, Monday through Friday (excluding holidays).

Required Case Report Forms are available on the ACOSOG website at www.acosog.org.

Submission via Hard Copy

Original and amended post-enrollment CRFs (including Specimen Bank Submission and Specimen Bank Consent CRFs), clinical reports, and responses to query and delinquency letters must be faxed to the CTSU Data Operations Center accompanied by a properly completed study-specific CTSU Data Transmittal Form. Copies of clinical reports submitted to the CTSU must include the Patient ID and protocol number on all pages of the report. The patient's name must be redacted.

A study-specific CTSU Data Transmittal Form must accompany all data submissions. Data submitted with an improperly completed CTSU Data Transmittal Form or without the correct study-specific CTSU Data Transmittal Form will be returned to the site for corrective action without being processed.

Documents will be faxed to:

Westat

Fax: 1-301-545-0406

9.2 Patient Data Quality Control

All data received will be subjected to various ACOSOG validation and quality-control measures. Issues arising from inaccurate, discrepant or incomplete data will be communicated to participating sites on a regular basis, along with patient status summaries. Any data submitted on case report forms is subject to audit against the patient's source documents. Consistent failure to complete and submit data in a timely fashion may subject a participating site to sanction up to and including the suspension of participation in the study.

10 Statistical Considerations

10.1 Study Design/Endpoints

The primary aim of this phase III trial is to test the hypothesis that laparoscopic-assisted resection for rectal cancer is not inferior to open rectal resection. The primary endpoint will be a composite endpoint of oncologic factors which are indicative of an adequate surgical resection based on pathologic evaluation.

Revised primary endpoint oncologic parameters:

Circumferential margin > 1 mm

Negative distal margin

Completeness of TME

- A complete TME is defined as a rectal resection specimen that has an intact mesorectum and covering peritoneal envelope all the way to the level of rectal transection with no coning in of the mesorectum above the point of transection. The surface of the peritoneal covering should be smooth and shiny with no defects exposing the underlying fat.
- A nearly complete TME is defined as a rectal resection specimen where the mesentery is all present, without coning or missing fat. A < 5 mm deep defect may be present in the envelope covering the mesenteric fat caused either by a wayward incision or traction injury during extraction of the TME specimen through a small extraction site.

A patient will be considered to have a successful resection on either arm if and only if all 3 oncologic parameters are satisfied. Based on historical data, we expect the rate of successful resection for the parameters for standard open resection to be 90% for the oncologic parameters. We will accept a 6% decrement from the successful resection rate of the open (laparotomy) arm of the study to be considered non-inferior.

10.2 Secondary Objectives

The secondary objective of this phase III trial is to test the hypothesis that laparoscopic-assisted resection for rectal cancer is not inferior to open rectal resection, from a patient-related benefit perspective (length of stay, operative times, use of pain medication).

Disease free survival and local pelvic recurrence are additional secondary endpoints. Based on the historical patterns of recurrence in rectal cancer, the analysis for these endpoints will focus on the disease-free survival and local recurrence rates after 2 years of follow-up. Patients will be followed for these endpoints, as well as for overall survival, for 5 years.

The tertiary aim of the study is to compare the effects of laparoscopic-assisted resection of rectal cancer and open resection on quality of life, sexual function, bowel function and recovery parameters. A number of

instruments are available to assess quality of life (QOL) in rectal cancer patients. Quality of life and sexual function will be evaluated using the EORTC function questionnaires and the Linear Analog Self-Assessment questionnaire. The trial will assess bowel and stoma functional outcomes with the Stoma Quality of Life Scale (SQOLS), the Mayo Bowel Function Questionnaire. These will be given preoperatively, immediately postoperatively and at regular follow-up intervals.

10.3 Sample Size Estimation and Patient Accrual

This prospective, randomized phase III trial will require 480 patients, 240 patients per arm of the study. The expected accrual rate is 10 patients per month, resulting in a 4 year planned accrual period. A single interim analysis for futility based on the primary endpoint, as described in Section 10.1 will be conducted after 240 patients are evaluable for oncologic success, using an O'Brien-Fleming stopping boundary. The specific rationale for a single interim analysis in this trial is based on the following considerations: (1) the primary endpoint of the study is not a time-to-event endpoint (the pathologic evaluation of the 3 parameters is available within a short time after the surgical resection); (2) the probability that there will be a very high rate of "non-success" early on with respect to the primary endpoint is considered to be very low since only surgeons skilled in this technique will be allowed to enroll patients; (3) since the study overall has only 80% power with the expected total sample size of 480 patients, one would not wish to decrease the power of the study overall by requiring additional interim analyses; and (4) as a non-inferiority trial, early stopping for "success" (i.e. non-inferiority) is not ethically necessary and may undermine the general acceptance of the result.

We realize that this is a relatively rare patient population and it is difficult to accrue a large number of patients, so the current study and statistical analysis plan is designed for 80% power. If accrual goes well, it would be scientifically desirable to increase the sample size to provide 90% power via an appropriate protocol amendment if the accrual rate is better than expected as specified in the protocol Therefore, after 36 months of accrual, the rate of accrual in the most recent 12 months exceeds 15 patients per month, and the total accrual at that time exceeds 400 patients, accrual will be extended to a total of 650 patients, allowing the primary hypothesis of non-inferiority to be conducted at a one-sided level of 0.05 as opposed to 0.10. Only accrual information will be considered in the decision to expand accrual to 650 total patients; no outcome data will be used to make this determination.

Patient accrual will be accomplished at multiple centers, with fifty or more anticipated accrual sites. Institutions should be capable of documenting >50 open or laparoscopic rectal cases each year and 20 laparoscopic rectal cases/per surgeon/per year, involving a laparoscopic, cancer-equivalent dissection.

10.4 Analytic Plan and Method

Assuming a baseline rate of 90% oncologic success for the open resection arm, this sample size provides 80% power to declare non-inferiority if the oncologic success rates are truly identical, using a 1-sided test with alpha = 0.10 for falsely declaring non-inferiority when the true oncologic success rate for the laparoscopic resection is 84%. If the trial's accrual is sufficiently rapid to satisfy the criteria outlined in Section 10.3, then this one-sided test for the definitive analysis will be performed at level 0.05. The calculations are based on a two-sample binomial non-inferiority calculation, performed using EAST version 4.0, with a 90% control group success rate, and a 6% non-inferiority margin. A single interim analysis for futility for the primary endpoint will be conducted after 240 patients are accrued, using an O'Brien-Fleming stopping boundary. The futility analysis will be performed based on an alpha level of 0.10, based on the target of the final accrual goal of 480 patients, since after 240 patients, per the protocol, it is very unlikely that it would be definitively determined whether the trial would be expanded.

The specific hypothesis test to be used for the primary analysis will proceed as follows. Let p_t denote the observed oncologic success rate for the laparoscopic arm p_c the observed rate for the open arm, and δ the non-inferiority margin (6%). The test statistic is then $Z = (p_c - p_t - \delta)/se(p_c-p_t)$, where se denotes the usual binominal standard error for the difference of proportions. Based on the single interim analysis and the boundaries specified above, if at the interim analysis the Z-statistic is >= -0.051, or at the final analysis the Z-statistic is >= -1.245, the hypothesis of non-inferiority will be rejected. Assuming that these analyses happen at the protocol specified number of events, the corresponding (p_c-p_t) values that will cause rejection of the non-inferiority hypothesis are >= 0.058 and >= 0.0254.

For the primary analysis, patients who are randomized to the laparoscopic procedure but during the operation are converted to the open procedure will be included in the laparoscopic arm for analysis. Patients who are randomized but then cancel and refuse any surgery on-trial will be excluded from the primary and secondary analyses. Patients who are randomized but from the initiation of surgery receive the opposite surgery to which they were randomized (this does not include the converted patients) will be included in the analysis according to the arm to which they were randomized. Based on the previous COST trial, the rate of refusal was very low (<1%), thus this should have minimal impact on the primary findings. Nonetheless, a sensitivity analysis using the fully intention to treat approach will be performed.

10.4.1 General Statistics and Survival/Recurrence Analysis

The patient-related benefit outcomes related to blood loss, etc. will be analyzed using a *t*-test or appropriate non-parametric equivalent. Time to event secondary endpoints of disease free and overall survival will be analyzed by Kaplan-Meier plots and log-rank testing; the cumulative incidence of local recurrence will be analyzed using cumulative incidence methodology.

10.4.2 Quality of Life

Bowel function, sexual functioning, and quality of life will be measured using the Stoma Quality of Life Scale (SQOLS), Mayo Bowel Function Questionnaire (MBFQ), EORTC C30 and CR38 Questionnaires, and the Linear Analogue Self Assessment (LASA). Research hypotheses include:

1. **There will be differences in QOL-related domains between the two treatment groups in terms of the patient's overall experience during the trial.**

   The AUC summary statistic will be calculated for each patient using the baseline and weeks 1-2 and 4-6 and at three months, and first year (12 month) data. AUC will be applied to all QOL endpoints. If a patient only provides baseline data, they will be excluded from the analysis. All QOL endpoints will be translated where appropriate onto a 0 – 100 point scale for comparability and ease of interpretability in the analysis phase.[62,63,64] Parametric procedures (e.g., *t*-tests) will be used unless there is evidence of non-normality via Shapiro Wilk testing[65], in which case non-parametric procedures (e.g., Wilcoxon tests) will be applied.

   Analysis of the AUC scores for the QOL endpoints will compare the average AUC for the laparoscopic arm to the average AUC for the open surgery arm using a single two-sample independent samples *t*-test. Confidence intervals will be constructed for mean reduction in total AUC score for the two arms. 240 patients per treatment arm will provide 80% power to detect a difference in the two groups in QOL endpoints of 0.5 standard deviations, a moderate effect size, using two-sided tests at level 0.05.

2. **The more brief measures of QOL-related domains will provide comparable information to what is provided by the longer assessments.**

   The EORTC-QLQ CR38, the SQOLS, and the LASA single-items will be compared via Bland-Altman procedures which have been established as the preferred methodology to compare assessments intended to measure the same concept.[49] Dr. Sloan's QOL team has experience in applying these procedures in cancer clinical trials.[56]

Supplementary analysis of QOL scores will involve *t*-tests and Wilcoxon procedures at each time point as well as a repeated measures analysis of variance (ANOVA) and general estimating equations (GEE) modeling using data from all time points.[60] Models will include covariates of patient characteristics as well as treatment arm to perform a conditional analysis of treatment comparison in the presence of potentially confounding variables.

Further analysis will involve an examination of the clinical significance for changes over time by calculating the percentage of patients on each arm that report an improvement of more than 10 points on the 0-100 point scale for any QOL endpoint. These percentages will be compared via chi-square testing.

Correlational analyses will be done on QOL endpoints to determine the relationships between various QOL endpoints. Such correlations will be done at single data points such as baseline or months 3, 12, or 24.

The extent of missing data will be explored for non-random influences.[52] Sensitivity analysis will be performed using various simple imputation techniques for which Dr. Sloan's QOL team has developed specific computer algorithms, to ensure results are not unduly influenced by the presence of missing data.[55,63]

We examine the impact of imputing using such methods as last-value-carried forward, nearest-neighbor imputation, zero-value imputation, minimum-value imputation, maximum-value imputation on the result of the primary analysis. The degree of variability in the results will allow for a calibration of the impact of the best and worst case scenarios in terms of patterns in the missing data on the stability of the analytical results.

11 Regulatory and Ethical Considerations

11.1 Registering Physician

The investigator intending to register a patient to this study must be a member in good standing of the American College of Surgeons Clinical Oncology Group (ACOSOG) or endorsed by another cooperative group (ECOG, SWOG, CALGB, etc), if applicable. The procedures for obtaining active status in ACOSOG are described in the membership information found on the ACOSOG web site at http://www.acosog.org.

All enrolling investigators must have an NCI investigator number and must maintain an ―active‖ investigator registration status through the annual submission of a complete investigator registration packet to the Pharmaceutical Management Branch.

11.2 Registering Institution

An ACOSOG member must enroll patients at clinical sites that have a valid assurance number from the United States Office for Human Research Protections (OHRP). Most institutions have a Multiple Project Assurance (MPA), Cooperative Project Assurance (CPA) number or Federalwide Assurance (FWA). If the clinical site does not have such an assurance, the clinical site must apply and obtain an assurance before patients can be enrolled to ACOSOG studies.

Unaffiliated Investigator Agreements (UIAs) are needed from investigators who independently accrue patients on ambulatory protocols outside an institution (e.g., in private practice) but who rely on an institution‘s IRB for review of ACOSOG protocols.

11.2.1 Submission of IRB Approval

IRB approval documentation must be submitted to CTSU for entry into the Regulatory Support System (RSS). This information is downloaded from RSS directly to ACOSOG and is required prior to enrollment of the first patient. Submission instructions are available on the RSS page of www.ctsu.org.

11.3 Inclusion of Women and Minorities

Minorities and non-pregnant women will be included in this trial. Observed incidence of rectal cancer suggests a slightly higher incidence of rectal cancer in males (58% of all rectal cancer patients) compared to female (42% of all rectal cancer patients). Therefore, we anticipate fewer female patients than the male patients in the trial.

We anticipate that the gender distribution and ethnic background of patients will be representative of the population of patients treated at the participating institutions. The ACOSOG has no basis for altering the proportions of minority patients to be expected, compared to the overall ACOSOG proportions.

Ethnic Category	Sex / Gender			
	Females	Males	Unknown	Total
Hispanic or Latino	21	14	0	35
Not Hispanic or Latino	211	234	0	445
Unknown	0	0	0	0
Ethnic Category: Total of all subjects*	232	248	0	480
Racial Category				
American Indian or Alaskan Native	1	1	0	2
Asian	9	17	0	26
Black or African American	24	38	0	62
Native Hawaiian or other Pacific Islander	1	1	0	2
White	197	191	0	388
More than one race	0	0	0	0
Unknown	0	0	0	0
Racial Category: Total of all subjects*	232	248	0	480

11.4 Clinical Site Audits

All clinical sites at which patients are enrolled are subject to an audit by ACOSOG in accordance with guidelines provided by and available from the Clinical Trials Monitoring Branch (CTMB) of the NCI. Information on these regulations may be obtained from the CTMB web site at http://ctep.cancer.gov/.

11.5 Clinical Monitoring

This study will be monitored by the current version of the Clinical Data Update System (CDUS). Cumulative CDUS data will be submitted quarterly by CTSU to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

12 Surgeon Skill Verification

Surgeons must be proficient at the proper open technique for total mesorectal excision for rectal cancer. **Surgeon credentialing in both laparoscopic colon and laparoscopic rectal surgery will be required for participation in this study.**

NOTE: For surgeons conducting laparoscopic surgery using robotics, credentialing in the use of robotics also is required.

12.1 Laparoscopic Colon Credentialing

Surgeons will be credentialed for laparoscopic colon surgery, having performed at least 20 laparoscopically-assisted or hand-assisted operations. Operative and pathology reports will be submitted for each of the 20 laparoscopic colon resections. COST trial participation will substitute for this credentialing.

12.2 Laparoscopic Rectal Credentialing

Surgeons will be credentialed for laparoscopic rectal surgery, having performed at least 20 laparoscopic, laparoscopically-assisted or hand-assisted operations. Surgeons will provide operative reports and pathology reports for these 20 rectal cases and an unedited videotape of their laparoscopic rectal technique. All videotapes submitted for this trial will be reviewed by designated investigators and approved for oncologic technique and practice.

12.2.1 Robotics Credentialing

Surgeons will be credentialed for robotic laparoscopic rectal surgery, having performed at least 20 pelvic dissections using robotics, or 10 pelvic dissections using robotics and 10 laparoscopic, laparoscopically-assisted or hand-assisted operations. Surgeons will provide operative reports and pathology reports for the 20 robotics cases, or the 10 robotic cases and 10 laparoscopic rectal cases and unedited videotapes of their robotic and/or laparoscopic rectal technique. All videotapes submitted for this trial will be reviewed by designated investigators and approved for oncologic technique and practice.

12.3 Submission Information (ACOSOG and Non-ACOSOG Investigators)

A completed Surgeon Skill Verification Checklist (available on the Z6051 page of www.acosog.org), plus complete operative reports, pathology reports, and video documentation must be submitted to:

ACOSOG Membership Coordinator
2400 Pratt Street
Room 0311 Terrace Level
Durham, NC 27705
Phone (919) 668-8836
Fax (919) 668-7156

12.4 Assessment Criteria

Criteria to be assessed include:

Proximal rectal vessel ligation (up to sigmoidal)
Left ureter identification
Splenic flexure mobilization
Division of anterolateral ligaments
Identification of pelvic nerves at pelvic rim
Transection of low rectum at sphincters
Intact total mesorectal excision

No registration will be accepted until skills verification and all credentialing requirements are completed, received and approved by the Study Chair or designee. Surgeons will have agreed to comply with study guidelines prior to completion of the credentialing process. Surgeons who fail to meet the criteria will be informed by the Study Chair or his/her designee and will be given the opportunity to respond to the evaluation within ten days.

13 Performance Monitoring

13.1 Study Chair Review

The Study Chair or designee will review each enrolled case for patient eligibility and intervention compliance (or a selection of cases, as required by ACOSOG policy). If an investigator has a possible performance issue, the Study Chair or designee will review the issue(s) and make recommendations to the investigator. It is expected that in most cases, the Study Chair or designee will work with the investigator to improve performance. However, the Study Chair or designee is empowered to suspend protocol participation, if necessary.

13.2 Monitoring of Surgical Performance

Video audit of laparoscopic procedures will take place for the first 100 patients randomized to the laparoscopic arm, with random audit of procedural videos after accrual of the first 50 and 100 patients. Sites will be contacted when patient cases have been selected for review. Required review materials and submission instructions will be provided.

14 Biospecimen Collection

Patients may consent to contribute tissue specimens from surgery for use in future research. Tissue not needed for current or future clinical management can be submitted for banking.

All specimens will be stored and governed by the ACOSOG Central Specimen Bank (CSB) at Washington University in St. Louis and the ACOSOG Central Specimen Bank and Pathology Committee.

All supplies for collecting and shipping specimens will be provided and distributed by the ACOSOG Central Specimen Bank (see Specimen Shipping, Section 14.3).

14.1 Required Specimens

14.1.1 Frozen Tissue Specimens for Banking

Snap frozen tissue specimens from the surgical resection (if tissue is available and the patient consents) should be collected using the procedures described below. **If resources are not available at the site to collect snap frozen surgical tissue, please contact the Central Specimen Bank to make other arrangements.**

14.2 Specimen Collection and Processing

Additional information regarding procedures for biospecimen collection and processing can be found in the ACOSOG Specimen Bank SOP, which is located on the ACOSOG web site: http://www.acosog.org. Procedures specific to this protocol are summarized here.

14.2.1 Frozen Tissue

After surgical resection, the specimen(s) should be brought to the pathology department as soon as possible (generally speaking, this means within 15 minutes after the time of tissue resection). **If possible, in order to accurately record the *ex vivo* ischemia time, the time at which the specimens are excised from the patient should be recorded.** The specimen(s) should be kept fresh and not put into any type of fixative, although it may be transported to pathology in a solution of normal saline or any other physiologic buffer. The specimens should be reviewed by the attending pathologist or other authorized individual (pathology resident, fellow, or qualified pathologist assistant). Material needed for diagnosis should be removed and processed according to the institution's standard procedures. Any remaining tissue may be sent to the ACOSOG Central Specimen Bank.

Where possible, representative and grossly apparent tumor tissue and organ-matched non-malignant tissue **at least 2 cm distal from the tumor margin** should be collected. Tissue that is grossly necrotic, hemorrhagic, or cauterized should be avoided. Tissue should be rapidly divided into segments no larger than 1 cm^3 (1 gram). As many segments as possible (but at least one) of this size should be collected. If appropriate, procurement of tissue can be facilitated by using a sterile skin punch biopsy tool included in the specimen kit. Areas identified by gross inspection can be ‗punched' with the disposable instrument. The resulting tissue ―plugs‖ can then be ejected from the punch. An independent punch tool should be used for each specimen type sampled (i.e. tumor versus non-malignant tissue) to avoid cross-contamination.

Place the tissue segments in the tissue cassettes provided (usually 2-3 segments of tissue per cassette). Use multiple cassettes if necessary - do not 'stuff' large amounts of tissue into a single cassette. Label the cassette with 'T' for tumor or 'N' for non-malignant tissue using the marker provided. Wrap each cassette in a piece of foil (provided in the kit). Place the cassette at one end of the foil and roll the foil around the cassette. Carefully fold over the ends of the foil and crease them tightly to create a sealed, compact packet. Immediately immerse the foil-wrapped cassette in liquid nitrogen for 5 minutes. If liquid nitrogen is not available, the specimen may be immersed in an isopentane cryobath available in most surgical pathology frozen section rooms. If using a cryobath, be certain that the temperature of the bath is at or below -40°C. As a last option, specimens may be frozen by complete immersion in an ethanol / dry-ice bath. Specimens should be left in the cryobath or dry ice bath for at least 15 minutes to ensure complete freezing. Specimens should not be frozen by placing fresh tissue in a -80°C freezer or inside a cryostat. **The time at which the tissue is frozen should be recorded so that, together with the recorded time of operative resection, the *ex vivo* warm ischemia time can be calculated.**

Once frozen, foil-wrapped tissue cassettes should be placed in one or more of the zip-lock bags provided. Be certain that the specimen bag is accurately and legibly labeled with the ACOSOG patient ID number. Once frozen, tissue may be stored in a -80°C mechanical freezer until shipping. Once frozen, take extreme care not to let the tissue specimen thaw.

If resources are not available at the site to collect snap frozen surgical tissue, please contact the Central Specimen Bank to make other arrangements.

14.3 Specimen Shipping

All biospecimen procurement and shipping supplies are available (at no cost) from the CSB. The submitting institution should contact the CSB at least 1 week prior to patient enrollment to request appropriate procurement and shipping materials. The CSB will provide up to three shipping kits to a site. Additional kits may be requested upon receipt at the CSB of a completed, returned kit. **Note that all components of the kit (including the outside box itself) are used for return shipment and are recyclable. Do not dispose of any kit component or shipping material.** Specific instructions for packing and shipping biospecimens are included in each biospecimen collection kit.

The de-identified surgical pathology report, coded with the ACOSOG patient ID number, and appropriate Case Report Form (see Schedule of Forms) must accompany all tissue sample submissions.

This protocol uses one kit and shipment to collect biospecimens.

A. Shipping kit to send frozen tissue

Specimens may be sent to the CSB on Monday through Friday for next day delivery. The CSB cannot receive specimens on Sundays or holidays. **Do not send specimens on Saturday or the day before a holiday.**

Arrange for Federal Express pick-up through your usual institutional procedure. Ship CSB specimens, required Case Report Form(s) and/or pathology reports to:

Mark A. Watson, M.D., Ph.D.

ACOSOG Central Specimen Bank

Room 2316 Kingshighway Bldg.

Barnes-Jewish Hospital North

216 S. Kingshighway

St. Louis, MO 63110

Phone: (314) 454-7615

Fax: (314) 454-5525

E-mail: watsonm@pathbox.wustl.edu

On the day that specimens are sent to the Specimen Bank, please contact the bank by phone, fax, or e-mail to notify what is being sent and when the shipment is expected to arrive.

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16 Appendices

16.1 Model Informed Consent Document

Z6051: A Phase III Prospective Randomized Trial Comparing Laparoscopic-assisted Resection Versus Open Resection for Rectal Cancer

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have rectal cancer which can be removed with surgical resection, and you have completed your chemotherapy and/or radiation therapy.

Why is this study being done?

This study is being done to compare two types of surgery currently used for rectal cancer. The two types of surgery are laparoscopic-assisted rectal resection and open laparotomy rectal resection. The two types of surgery are described below. Although laparoscopic-assisted rectal resection is being used for rectal cancer in some medical centers, there are still questions about whether this type of surgery is as effective as open surgery.

Some research results suggest laparoscopic-assisted rectal resection could be an alternative to open laparotomy rectal resection for patients with rectal cancer, but today we do not know how the two compare. The results of this study will help make that comparison. We do not know whether laparoscopic-assisted rectal resection will be more effective, less effective or about the same as open laparotomy rectal resection. We do not know whether laparoscopic resection of rectal cancer will have any effect, positive or negative, on your overall health and quality of life. This study will compare:

- Safety and effectiveness of the surgeries: ability to remove the entire tumor plus an appropriate margin of surrounding tissue; amount of blood loss during surgery
- Recovery from surgery in the hospital: amount of pain medication required; length of hospital stay, nature of any surgical complications (problems)
- Overall recovery from surgery: general quality of life, sexual function, bowel function
- Cancer outcome: recurrence of cancer in the pelvis or other parts of the body

What are the two types of surgery?

The two types of surgery are laparoscopic-assisted rectal resection (LARR) and open laparotomy rectal resection.

Laparoscopic-assisted rectal resection is performed using small instruments on long handles introduced into the abdomen through small ports called trocars in 3 to 6 positions on the abdomen through incisions measuring 5 to 10 mm, under the guidance of a video camera. The

abdominal wall is held up with carbon dioxide under pressure. The piece of bowel or intestine is removed through another incision (about 8 centimeters), and the ends of the intestine are reconnected to provide normal bowel function.

Laparoscopic-assisted rectal resection is not currently considered standard care for rectal cancer, but it is used by some surgeons and is available outside of this study. In colon cancer, laparoscopic-assisted resections seem to be as good as open surgeries, but it remains to be seen if this will be the case for rectal cancer or not.

The standard form of surgery for your type of rectal cancer is open laparotomy rectal resection. During open laparotomy, the surgeon makes a large incision or cut in the abdomen, and goes in through that cut to remove the tumor and lymph nodes from the rectum. A laparoscope also may be used during the open procedure.

How many people will take part in the study?

About 480 people will take part in this study.

What will happen if I take part in this research study?

Before the study...

You will be randomly assigned (like flipping a coin) or "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in either group.

If you are in group 1 (often called "Arm A"), you will have an open laparotomy rectal resection of your rectal cancer.

If you are in group 2 (often called "Arm B"), you will have a laparoscopic-assisted rectal resection of your rectal cancer.

Before surgery…

You will need to have the following exams, tests or procedures. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study.

- History and Physical examination (including height, weight and vital signs),
- Laboratory studies and blood tests
- A pregnancy test (if you are of childbearing potential and have not already had a pregnancy test)
- Chest CT scan or chest x-ray (if you have not already had one).

You will need to have the following exams, tests or procedures as part of the study.

- Questionnaires regarding the function of your bowels and the quality of your life (Functional Status, Quality of Life and Sexuality Questionnaire). These questionnaires require about 20 minutes to complete and can be completed in the clinic at the time of your visit 2 weeks prior to surgery.

After surgery…

When you are finished with the surgical intervention, you will be followed closely by your study doctor. At your follow-up visits you will receive these tests and procedures as a part of your regular cancer care and to see how the type of surgery you had is affecting your body.

History and Physical examination (including height, weight and vital signs),

Laboratory studies and blood tests,

Colonoscopy,

CT scans and x-rays.

You will need these tests and procedures that are either being tested in this study or being done to see how the type of surgery you had is affecting your body.

Questionnaires regarding the function of your bowels and the quality of your life (Functional Status, Quality of Life and Sexuality Questionnaire). These questionnaires require about 20 minutes to complete and can be completed in the hospital or clinic at the time of your post-surgery visits.

If you receive a laparoscopic-assisted rectal resection, the procedure will be videotaped and may be selected for central review by study personnel. This is for quality control purposes. If the videotape is submitted for review, only your study number will appear on the recording. No other identifying information will be included. If the videotape is not selected for review, then it will be destroyed.

Optional Sample Donation for Future Studies

You may donate tissue samples from your surgery for use in future studies. More information about contributing samples for future research is included in a later section of this form.

Study Chart

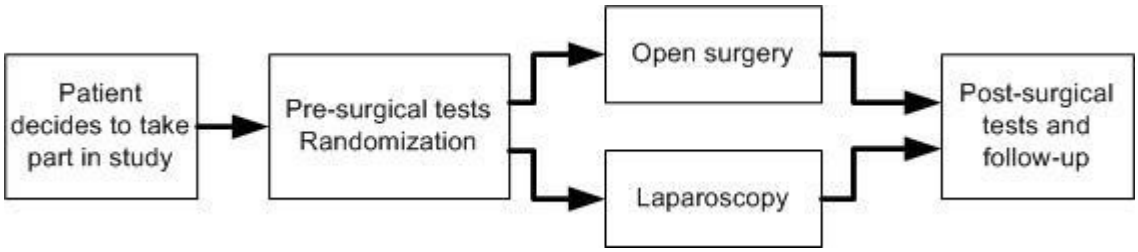
The chart below shows what will happen to you before and after surgery. The left-hand column shows the time period of the study and the right-hand column tells you what is scheduled to happen at that time.

Day	What you do
Before the study	Sign consent Randomization to laparoscopic-assisted rectal resection or open laparotomy rectal resection
2 weeks before surgery	Have history and physical exam Have routine blood tests, including pregnancy test (if needed) Have chest CT scan or chest x-ray (if you have not already had one) Complete questionnaires
Surgery	Have laparoscopic-assisted rectal resection or open laparotomy rectal resection Have tissue samples collected (optional)
3 days after surgery	Complete questionnaires
1-2 weeks after surgery	Have history and physical exam Complete questionnaires
4-6 weeks after surgery	Have history and physical exam Complete questionnaires

3 months after surgery	Have history and physical exam Have routine blood tests Complete questionnaires
6 and 9 months after surgery	Have history and physical exam Have routine blood tests
12 months after surgery	Have history and physical exam Have routine blood tests Have colonoscopy Have scans Complete questionnaires
18 months after surgery	Have history and physical exam Have routine blood tests
24 months after surgery	Have history and physical exam Have routine blood tests Have scans
Yearly x3	Have history and physical exam Have scans as needed

Study Plan

Another way to find out what will happen during the study is to read the Study Plan below. Start reading at the left and read across the list, following the lines and arrows.



How long will I be in the study?

You will be followed for up to 5 years after your surgery on this study. The study doctor will ask you to visit the office for follow-up exams at 1 to 2 weeks and 4 to 6 weeks after the surgery, then at 3, 6, 9, 12, 18 and 24 months after the surgery. After that, you will be seen once a year for 3 years. You will complete questionnaires at the visits occurring 1 to 2 weeks, 4 to 6 weeks, 3 months and 12 months after surgery.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

You may decide to stop completing the questionnaires and still continue with the study visits, or you may decide to stop all study-related activities.

It is important to tell the study doctor if you are thinking about stopping so any risks from the surgery can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may decide to take you off this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after the surgery. In some cases, side effects can be serious, long lasting, or may never go away. In some cases, surgery or other treatments may be needed to repair or correct some side effects. There also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to both laparoscopic-assisted rectal resection and open laparotomy rectal resection for rectal cancer include:

Likely

- Bleeding or bruising in, under or around the incision
- Wound infection/abscess
- Pain
- Suture line leak/separation
- Difficulty emptying the bladder

Less Likely

- An abnormal connection between rectum and another organ
- Injury to the ureter (tube between the kidney and bladder)
- Abnormal narrowing of the rectum
- An abnormal hole in the rectum
- Loss of bowel control/ incontinence
- Formation or presence of a blood clot inside a blood vessel
- Lung infection/ pneumonia
- Decreased blood supply to the heart/ heart attack
- Abnormally slow bowel contraction
- Blood infection/ sepsis
- Sexual problems/ dysfunction due to injury of nerves to sexual organs

Rare but serious

- Bleeding/Hemorrhage possibly requiring blood transfusion or surgery
- Blood clot in the lung
- Death

Additional risks and side effects related to laparoscopic-assisted rectal resection include:

- Air bubbles in the bloodstream (air embolism)

Possible need to convert the laparoscopic procedure to an open procedure
Increased likelihood that the entire tumor may not be removed completely (positive margin)
Injury to the abdomen due to the trocars
Tumor recurrence at the small wounds made to insert the trocars
Reduced blood flow to the kidneys if the abdominal pressure is too high

Reproductive risks
You should not be or become pregnant at the time of your surgery. After your surgery, if you require additional, non-surgical treatments such as chemotherapy or radiation, you should talk with your doctor regarding the risks of these therapies to a pregnancy or to fathering a child.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope laparoscopic-assisted rectal resection will be as effective in removing your rectal cancer as open laparotomy rectal resection, we do not know this at this time. We do know that laparoscopic-assisted resection for colon cancer seems as safe and effective as open laparotomy resection, and that laparoscopic-assisted resection seems to shorten recovery times in resections for colon cancer. We do know that the information from this study will help doctors learn more about laparoscopic-assisted rectal resection as a treatment for rectal cancer. This information could help future cancer patients in choosing the method by which their rectal cancer will be removed.

What other choices do I have if I do not take part in this study?

Your other choices may include:

Getting treatment or care (including laparoscopic-assisted rectal resection or open laparotomy rectal resection) for your cancer without being in a study
Taking part in another study
Getting no treatment

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

The American College of Surgeons Oncology Group (ACOSOG)
The local Institutional Review Board (IRB) at the hospital where you are being treated. The IRB is a group of people who review the research study to protect your rights as a patient

The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA) and the Office for Human Research Protection (OHRP), involved in keeping research safe for people

The Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

You will not be required to pay for the cost of the questionnaires which you fill out as part of this study.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site. Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *investigator's name(s),* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study makes no provisions for payment for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

A Data Monitoring Committee, an independent group of experts, will be reviewing the data from this study on an ongoing basis.

Your doctor will tell you about any new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____2030_____ *[name(s)]* at _____2032_____ *[telephone number]*. 2031

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____2038_____ *(telephone number).*

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only).

Optional Banking of Specimens for Future Research

This section of the informed consent form is about contributing tissue samples from your surgery for future studies, if samples are available. You can still be a part of the main study even if you say ‗no' to contributing tissue samples for future studies.

About Contributing Specimens for Future Research

As a part of your surgery, your doctor will remove your rectal tumor. If there are tissue samples available from your surgery, we would like to have the tissue for future research. If you agree, these samples will be stored (or ―banked‖) by ACOSOG and may be used in future research to learn more about cancer and other diseases. If all the tissue is needed by your doctor for current or future treatment decisions, then no tissue will be sent for banking.

Your tissue samples are called ―biological specimens‖. You can learn more about how biological specimens are used for research at http://biospecimens.cancer.gov/patientcorner/.

The research that may be done with your specimens is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your specimens will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the specimens for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your specimens can be used for future research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens. Then any specimens that remain will no longer be used for research and will be discarded.

In the future, people who do research may need to know more about your health. While the ACOSOG may give those people reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Your specimens will be used only for research and will not be sold. The research done with your specimens may help to develop new products in the future, but you will not be able to benefit financially from the new products.

Genetic Research

Sometimes specimens are used for genetic (DNA) research.

The purpose of doing genetic research is to discover changes in genes (or DNA) associated with the development or outcome of cancer. This could lead to better ways to prevent, detect, and treat cancer and, perhaps, other diseases as well. Due to advances in the techniques and tests used to analyze genetic material in specimens (DNA), it is likely that your specimens could be used for this type of research, if you allow it.

Body tissues are made up of cells. Cells contain DNA, which is part of your unique genetic material that carries the instructions for your body‘s development and function. DNA can be analyzed so that your unique, exact genetic code or the altered genetic code of your tumor cells can be identified and compared to other patients. Cancer can result from changes in a person‘s genetic material (DNA) that causes cells to divide in an uncontrolled way and, sometimes, to travel to other organs. Currently, researchers and doctors know some of the genetic changes that can cause cancer, but they do not know all of the genetic changes that can cause cancer.

By studying the genetic code of cancer cells and the people who have cancer, scientists expect to identify most of the genetic changes associated with different kinds of cancer. ACOSOG and scientists who work with ACOSOG members, such as your doctor, would also like to compare genetic information obtained from your biological specimens with information available from your progress on the ACOSOG study, such as the outcome of your treatment and your long term health. With this knowledge, future treatments for cancer could become customized to a patient‘s unique genetic make-up (this is known as personalized medicine).

Your specimens and medical information collected as part of the ACOSOG study will be labeled with a code.

Only ACOSOG will have the information that matches the code to traditionally-used identifying information, such as your initials, birthdate or medical record number. ACOSOG will keep the information that matches the code to this traditionally-used identifying information in a safeguarded database. Only very few, authorized people, who have specifically agreed to protect your identity, will have access to this database. All other researchers and personnel, including those who will be working with your samples and medical information, will not have access to any of the traditionally-used identifying information about you.

Information from analyses of your coded specimens and your coded medical information will be put into databases along with information from other research participants. These databases will

be accessible by the Internet. The purpose of making sequence and medical information available is so that they can be used by scientific researchers throughout the world to study cancer and other diseases.

Please note that traditionally-used identifying information about you, such as your initials, birthdate or medical record number would NOT be put into the databases.

Even if your specimens are used for this kind of research, the results will not be put in your health records and although you can learn more about this type of research, individual information about your genetic code or your tumor will not be available to you.

Benefits

The benefits of research using specimens include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

Your privacy is very important to us and we will use many safety measures to protect your privacy. However, in spite of all of the safety measures that we use, it is impossible to guarantee that links between you and the genetic information we would obtain will never become known. Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters, and other relatives. Consequently, it may be possible that genetic information from them could be used to try and identify your sample from the publicly available information. Similarly, it may be possible that genetic information from you could be used to help identify them.

While the databases used to store your genetic information would not contain information that is traditionally used to identify you, such as your initials, birthdate or medical record number, people may develop ways in the future that would allow someone to link your genetic or medical information in our databases back to you.

We would like to emphasize that we will do everything we can to protect your private information. However because of the nature of the issues, we feel that we should explain these issues to you carefully.

An additional risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at _____ *[IRB's phone number]*.

No matter what you decide to do, it will not affect your care.

1. My tissue specimens (if available) may be kept for use in future research to learn about, prevent, or treat cancer.

Yes No

2. My tissue specimens (if available) may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes No

3. My tissue specimens (if available) may be kept for use in future genetic research.

Yes No

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of all pages of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Patient Signature _____Date ___/___/___

16.2 Staging Reference

Rectal Cancer Staging Reference (Adapted from AJCC Cancer Staging Manual, 7th Ed., 2010)	
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 through the muscularis propria into the subserosa, or into non-peritonealized pericolic or perirectal tissues
T4a	Tumor penetrates to the surface of the visceral peritoneum
T4b	Tumor directly invades or is adherent to other organs or structures
REGIONAL LYMPH NODES (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 3 regional lymph nodes
N1a	Metastasis in 1 regional lymph node
N1b	Metastasis in 2-3 regional lymph nodes
N1c	Tumor deposits in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in 4 or more regional lymph nodes
N2a	Metastasis in 4 to 6 regional lymph nodes
N2b	Metastasis in 7 or more regional lymph nodes
DISTANT METASTASIS (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Ultrasound Staging References

ID	Reference
Hildebrandt 1985	Hildebrandt U, Feifel G. Preoperative staging of rectal cancer by intrarectal ultrasound. Dis Colon Rectum 1985; 28:42-46.
Greene 2002	Greene FL, Page DL, Fleming ID, Fritz IG, Balch CM, Haller DG, Morrow M Editors Cancer Staging Manual. Sixth Edition. Springer, New York. 2002

16.3 ECOG (Zubrod) Performance Status

ECOG (Zubrod) Scale	
0	Fully active; able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory
2	Ambulatory and capable of self-care; confined to bed or chair more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled

16.4 Cancer Trials Support Unit (CTSU) Participation Procedures

Data management activities for the study will be performed by CTSU. All sites, ACOSOG and non-ACOSOG alike, will submit data electronically using the CTSU's Remote Data Capture (RDC) system or via fax. For this reason, investigators and study support staff involved in the collection and reporting of study data must be registered members of the CTSU.

To submit site registration documents:	**For patient enrollments:**	**To fax study forms or data:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone: 1-888-823-5923 Fax: 215-569-0206	See Section 4.0.	Westat Fax 301-545-0406
For patient enrollments that must be completed within approximately one hour or for extenuating circumstances, call 301-704-2376. For all other CTSU patient enrollments, please use 1-888-462-3009. **No exemptions or waivers will be granted for patients who do not meet the eligibility criteria.**		
For data submission: **This is a CTSU Remote Data Capture (RDC) study.** All sites, ACOSOG and non-ACOSOG alike, will submit data and respond to all queries electronically via CTSU's Remote Data Capture (RDC) system or via fax. **Please see the guidelines on the protocol-specific page on the CTSU Web site for details on submitting hard-copy data for quality assurance or other reasons.**		
For patient eligibility or treatment-related questions: Contact the ACOSOG Study Chair and copy the ACOSOG QA Specialist. The option remains to contact CTSU Help Desk for assistance in obtaining a response from the Group.		
All other questions (including forms-specific questions): Contact the CTSU Help Desk at: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at: www.ctsu.org.		

15.4.1 Registration and Randomization

Registration is available 24 hours a day via the CTSU's Oncology Patient Enrollment Network (OPEN) Portal system. All participating sites (ACOSOG and non-ACOSOG sites) will use OPEN to enroll patients to this study. See Section 4.0.

15.4.2 Other Protocol Requirements

CTSU sites will follow the requirements of the protocol for eligibility, data submission, surgeon skills verification, study treatment, adverse event reporting and all other protocol requirements.

17 Revision History

Date	Section	Description
08/15/2011	**Z6051 A4**	**ACOSOG activation**
07/25/2011	**Z6051 A4**	**CTEP approval**
Begin A4 changes:		
	Title page	**Updated:** Version number, version dates
	All pages	**Updated:** Footers, page numbering
	Pg 2 **Contact Information**	**Updated**: Research Coordinator for Study Chair
	Pg 2 **Contact Information**	**Added**: GI Committee Co-chair, Central Specimen Bank contact
	Pg 3 **Participants**	**Full name of CALGB has been added.**
	Sec 1.5.2, pg 7 **Changes to Primary Endpoint Oncologic Parameters in Amendment 4 (new)**	**New Section 1.5.2 has been added to describe changes in the endpoint oncologic parameters and the reasoning behind the changes. Two new subsections 1.5.2.1 and 1.5.2.2 are included.** **Subsequent section has been renumbered.**
	Sec 3, pg 10 **Study Calendar**	**Tissue submission for banking has been added as the last row of the table. The sub missi on ti me p oint ha s be en ma r ke d in t he " 4 -6 w eeks" colu mn w ith a refere nce**
	Sec 3, pg 10 **Study Calendar**	**Adde d to th e ‡ fo otn ote:** Visits occurring from 3 months to 24 months may be done +/- 4 weeks from the due date. Yearly visits may be done +/- 8 weeks from the due date.
	Sec 3, pg 10 **Study Calendar**	**Added new footnote:** 5 Tumor tissue submission for banking is required only for consenting patients when tissue is available. See Biospecimen Collection (Section 14).
	Sec 5.2.3, pg 14 **Operative technique**	**Deleted from second sentence of last bulleted item: and photos of the mesorectum**
	Sec 5.3, pg 15 **Intraoperative Pathology and Pathologic Examination of Surgical Specimen**	**Last paragraph NOTE has been changed from:** **NOTE: The mesorectal specimen must be photographed with the laparoscope or OR camera to verify the quality of the dissection. These photographs should be retained in patient's research records. Random audit of selected pathology documentation will be conducted by the study team. See Section 7.4, Pathology Review Committee.** **Last paragraph NOTE has been changed to:** **NOTE: The mesorectal specimen must be photographed with the laparoscope or OR camera to verify the quality of the dissection. These photographs will be submitted for review by the study team as part of the pathology review that is required for all registered patients. See Section 7.4, Pathology Review Committee.**
	Sec 5.4, pg 15 **Documentation**	**Deleted from last sentence: and photos of the mesorectum**
	Sec 5.6.2, pg 17 **Stoma Quality of Life Scale (SQOLS)**	**In the second sentence of the last paragraph, the Registration Form has been corrected to read the Perioperative Data Form.**
	Sec 7.1, pg 18 **Evaluation at the Time of Surgery**	**Revised endpoint oncologic parameters and guidelines for evaluating resection margins have been added to this section.**
	Sec 7.4, pg 19-20 **Pathology Review Committee**	**This section has been revised and expanded to require central review of pathology documentation for all patients. Submission instructions have been added in the new subsection 7.4.1.**

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	Sec 8, pg 21 **Adverse Event Reporting**	**Added to the end of the second paragraph:** **NOTE: CTCAE Version 3 will continue to be used for routine adverse event reporting. Effective January 1, 2011, CTCAE Version 4 will be used for expedited adverse event reporting only.**
	Sec 8.2, pg 21 **Expedited Adverse Event Reporting**	**Added to Grade 2 column in AdEERS reporting requirements table:** and Expected
	Sec 8.2, pg 22 **Expedited Adverse Event Reporting: Secondary Malignancies**	**The reporting instructions for secondary malignancies have been revised to include use of the AdEERS application.**
	Sec 10.1, pg 23 **Study Design/Endpoints**	**This section has been updated to include the revised endpoint oncologic parameters.**
	Sec 12.2.1, pg 27 **Robotics Credentialing**	**The first paragraph has been updated to allow either 20 robotics cases or 10 robotics and 10 laparoscopic cases to be submitted for credentialing.**
	Sec 13.1, pg 28 **Study Chair Review**	**Added to the end of the first sentence:** (or a selection of cases, as required by ACOSOG policy)
	Sec 14, pgs 29-30 **Biospecimen Collection (new)**	**New Biospecimen Collection section has been added to provide guidelines for processing and submission of frozen tissue for banking.** **All subsequent sections have been renumbered**
	Sec 16.1, pg 38 **Model Consent: "After Surgery"**	**Added to end of section:** **Optional Sample Donation for Future Studies** You may donate tissue samples from your surgery for use in future studies. More information about contributing samples for future research is included in a later section of this form.
	Sec 16.1, pg 38 **Model Consent: "Study Chart"**	**Added to "Surgery" row:** Have tissue samples collected (optional)
	Sec 16.1, pgs 43-46 **Model Consent: "Optional Banking of Specimens for Future Research" (new)**	**Added new section:** –Optional Banking of Specimens for Future Research‖
End A4 changes		
05/14/2010	**Z6051 A3**	**ACOSOG activation**
05/14/2010	**Z6051 A3**	**CTEP approval**
Begin A3 changes:		
	Title page	**Updated:** Version number, version dates
	All pages	**Updated:** Footers, page numbering
	Pg 2 **Contact Information**	**Added above table:** **Note: Direct all questions to the QA Specialist identified below.**
	Pg 2 **Contact Information**	**Updated**: Statistician name, QA Specialist title and fax
	Sec 2.1, pg 9 **Eligibility Criteria**	**Criterion #2 changed from**: T3 N0 M0, T1-3 N1-2 M0 disease as determined by pre-treatment CT scans... **Criterion #2 changed to**: T3 N0 M0, T1-3 N1-2 M0 disease as determined by pre-neoadjuvant therapy CT scans...
	Sec 2.1, pg 9 **Eligibility Criteria**	**Deleted criterion:** Non-pregnant and non-lactating, as confirmed by pre-treatment pregnancy test for patients of child-bearing potential. Patients must be amenorrheic for ≥ 12 months to be

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		considered not of child-bearing potential.
	Sec 2.1, pg 9 **Eligibility Criteria**	**Renumbered:** Criteria 10 and 11.
	Sec 3, pg 10 **Study Calendar**	**"Prior to tx /reg" column heading changed to "Prior to reg."**
	Sec 3, pg 10 **Study Calendar**	**Added to list of required tests and "Prior to reg" column:** BMI
	Sec 3, pg 10 **Study Calendar**	**Deleted from "Prior to reg" column:** Pregnancy test
	Sec 3, pg 10 **Study Calendar**	**Added to H&P in "Pre-op" column:** footnote 1 reference
	Sec 3, pg 10 **Study Calendar**	**Added to "Pre-op" column:** Pregnancy test and footnote 2 reference
	Sec 3, pg 10 **Study Calendar**	**Deleted from "Pre-op" column:** SQOLS
	Sec 3, pg 10 **Study Calendar**	**Added to SQOLS in "12 mos" follow-up column:** footnote 4 reference
	Sec 3, pg 10 **Study Calendar: Footnotes**	*** footnote changed from:** Pre-registration tests and evaluations will be conducted prior to neoadjuvant therapy at the time of diagnosis. Consent will be signed after neoadjuvant therapy is completed and prior to registration. *** footnote changed to:** All patients must have had staging exams (e.g., colonoscopy, TRUS/MRI and CT abdomen/pelvis) conducted prior to neoadjuvant therapy at the time of diagnosis. All other baseline evaluations may be conducted anytime prior to registration.
	Sec 3, pg 10 **Study Calendar: Footnotes**	**New footnote 1 added:** If the pre-registration H&P is within 2 weeks of surgery, then it does not need to be repeated after registration at the pre-operative assessment.
	Sec 3, pg 10 **Study Calendar: Footnotes**	**Renumbered:** Footnotes for pregnancy test and SQOLS
	Sec 3, pg 10 **Study Calendar: Footnotes**	**Added to Footnote 2**: Women of childbearing potential must have a negative pregnancy test prior to surgery. If a pregnancy test is done prior to registration at the time of diagnosis or anytime during or after neoadjuvant therapy, then it does not need to be repeated after registration at the pre-operative assessment.
	Sec 3, pg 10 **Study Calendar: Footnotes**	**Footnote 3 changed from:** If a post-neoadjuvant therapy Chest CT or CXR is conducted prior to registration, it does not need to be repeated after registration at the pre-operative assessment. **Footnote 3 changed to**: All patients must have a Chest CT or CXR prior to surgery. If a Chest CT or CXR is done prior to registration at the time of diagnosis or anytime during or after neoadjuvant therapy, then it does not need to be repeated after registration at the pre-operative assessment.
	Sec 4, pg 11-12 **Patient Registration/Randomization**	**Section has been updated with instructions for using OPEN registration system.**
	Sec 5.2.6 (old) / 5.3 (new), pg 15 **Intraoperative pathology**	**Section renumbered to 5.3.**
	Sec 5.3, pg 15 **Intraoperative Pathology**	**Added to section title:** **and Pathologic Examination of Surgical Specimen**
	Sec 5.3, pg 15	**Added new second paragraph:**

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	Intraoperative Pathology	**Pathologists should make every effort to identify at least 12 lymph nodes in the surgical specimen. Efforts to locate lymph nodes (e.g., defatting) should be included in the pathology report.**
	Sec 5.3, pg 15 **Intraoperative Pathology**	**First and second sentences of third paragraph changed from:** **The mesorectal specimen should be photographed with the laparoscope or OR camera to verify the quality of the dissection. These photographs should be retained in patient records.** **First and second sentences of third paragraph changed to:** **NOTE: The mesorectal specimen must be photographed with the laparoscope or OR camera to verify the quality of the dissection. These photographs should be retained in patient's research records.**
	All remaining subsections of Sec 5, pgs 15-18	**Sections renumbered.**
	Sec 11.5, pg 26 **Clinical Monitoring**	**ACOSOG changed to CTSU re: CDUS reporting.**
	Sec 15.1, pg 33 **Model Consent**	**Model consent moved to Section 15.1 (first appendix).**
	Sec 15.1, pg 34 **Model Consent: "What are the two types of surgery?"**	**Fourth paragraph, second sentence changed from:** In colon cancer, laparoscopic-assisted rectal resections seem... **Fourth paragraph, second sentence changed to:** In colon cancer, laparoscopic-assisted resections seem...
	Sec 15.1, pg 34 **Model Consent: "What will happen if I take part in this research study?; Before surgery..."**	**Added as new bulleted item:** A pregnancy test (if you are of childbearing potential and have not already had a pregnancy test)
	Sec 15.1, pg 34 **Model Consent: "What will happen if I take part in this research study?; Before surgery..."**	**Last bulleted item changed from:** Chest CT scan or chest x-ray (if you have not had one since you finished your chemotherapy). **Last bulleted item changed to:** Chest CT scan or chest x-ray (if you have not already had one).
	Sec 15.1, pg 35 **Model Consent: Study Chart**	**" 2 weeks before surgery " row amended as follows:** - Added to routine blood tests: including pregnancy test (if needed) - Parenthetical description for CT scan changed to: (if you have not already had one)
	Secs 15.2 thru 15.4, pgs 41-43	**Sections renumbered.**
	Sec 15.2, pg 41 **Staging Reference**	**Table updated with 2010 AJCC staging guidelines.**
	Sec 15.4 pg 43 **Cancer Trials Support Unit (CTSU) Participation Procedures**	**Section updated with new contact information and use of OPEN; subsections renumbered.**
End A3 changes		
09/01/2009	**Z6051 A2**	**ACOSOG activation**
08/13/2009	**Z6051 A2**	**CTEP approval**
Begin A2 changes:		
	Title page	Updated: Version number, version dates
	All pages	Updated: Footers, page numbering
	Pg 2	Updated: Pathology co-chair email

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	Contact Information	
	Pg 2 **Contact Information**	Added: New pathology co-chair
	Pg 3 **Participants**	CTSU contact table moved to Appendices.
	Pg 3 **Participants: Cancer Trials Support Unit (CTSU) investigators**	Added to end of first paragraph: CTSU contact and logistical information is found in the Appendices.
	Sec 1.7, pg 8 **Schema**	Updated: first box of schema diagram to include only T3N0 and T1-3N1-2 stage disease.
	Sec 2.1, pg 9 **Eligibility Criteria**	Criterion #2 changed from: T3N0M0, TanyN1-2M0 disease as determined by pre-treatment CT scans and pelvic MRI or transrectal ultrasound. Patients with T4 disease extending to circumferential margin of rectum or invading adjacent organs are not eligible. Criterion #2 changed to: T3N0M0, T1-3N1-2M0 disease as determined by pre-treatment CT scans and pelvic MRI or transrectal ultrasound. Patients with T4 disease are not eligible.
	Sec 3, pg 10 **Study Calendar**	Deleted from Prior to tx/reg column: Chest CT or CXR
	Sec 3, pg 10 **Study Calendar**	Added in Pre-op column: Chest CT or CXR, with footnote 3 reference.
	Sec 3, pg 10 **Study Calendar: Footnotes**	* footnote changed from: Pre-registration tests and evaluations will be conducted within 42 days prior to neoadjuvant therapy at the time of diagnosis. Consent will be signed after neoadjuvant therapy. * footnote changed to: Pre-registration tests and evaluations will be conducted prior to neoadjuvant therapy at the time of diagnosis. Consent will be signed after neoadjuvant therapy is completed and prior to registration.
	Sec 3, pg 10 **Study Calendar: Footnotes**	** footnote changed from: Patients will be registered/randomized within 6 weeks after completion of neoadjuvant therapy. Surgery will be scheduled to occur within 4-8 weeks after completion of neoadjuvant therapy. ** footnote changed to: Patients may be registered/randomized anytime after completion of neoadjuvant therapy, but surgery must occur within 4-12 weeks (28-84 days) after completion of neoadjuvant therapy.
	Sec 3, pg 10 **Study Calendar: Footnotes**	Deleted from end of first sentence of # footnote: or until relapse
	Sec 3, pg 10 **Study Calendar: Footnotes**	Added new footnote: [3] If a post-neoadjuvant therapy Chest CT or CXR is conducted prior to registration, it does not need to be repeated after registration at the pre-operative assessment.
	Sec 4.3, pg 11 **Registration/Randomization Procedures**	First paragraph changed from: Patients will be registered and randomized within 6 weeks after completion of neoadjuvant therapy. First paragraph changed to: Patients may be registered/randomized anytime after completion of neoadjuvant therapy, but surgery must occur within 4-12 weeks (28-84 days) after completion of neoadjuvant therapy.

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	Sec 5.1, pg 12 **Neoadjuvant Chemoradiation Therapy**	Deleted from end of first paragraph: The therapy will be completed within 6 weeks prior to registration/randomization.
	Sec 5.1, pg 12 **Neoadjuvant Chemoradiation Therapy**	Second paragraph changed from: Surgery will be scheduled to occur within 4-8 weeks after the completion of neoadjuvant therapy. Second paragraph changed to: Patients may be registered/randomized anytime after completion of neoadjuvant therapy, but surgery must occur within 4-12 weeks (28-84 days) after completion of neoadjuvant therapy.
	Sec 5.2.3, pg 13 **Operative technique**	Deleted from end of second paragraph: Hybrid operations which complete a portion of the operation laparoscopically but convert to open for the distal rectal dissection shall be considered open procedures.
	Sec 5.2.3, pg 13 **Operative technique**	Deleted from end of third paragraph: The ―hybrid‖ procedure uses laparoscopic techniques to mobilize the left colon but open, blunt and sharp techniques to remove the rectum. This is essentially the definition of conversion to an open operation and will therefore require analysis in the open group.
	Sec 5.4.2, pg 17 **Stoma Quality of Life Scale (SQOLS)**	Added new third paragraph: Ostomy education may be provided to patients pre-operatively. Formal ostomy teaching by a Wound Ostomy Continence Nurse (WOCN) will be documented on the Registration form as well as any other education provided to the patient. WOC Nurses are Registered Nurses who hold a baccalaureate degree or higher and complete a formal, accredited WOC full scope or specialty education program.
	Sec 6.1, pg 17 **Follow-up of Patients with Disease Relapse**	Second sentence changed from: Patients will be followed for survival every 6 months until 5 years. Second sentence changed to: Patients will be followed for survival as required by the Study Calendar until 5 years.
	Sec 7.3, pg 18 **Pathologic Evaluation of the Resected Specimen**	Bulleted list changed from: The specimen, pinned by the surgeon in the operating room for orientation, will be inked by the pathologist for margin determination, and fixed in 10% formalin. The size of the residual tumor or ulcer corresponding to the tumor site will be measured. Dissection of the fixed specimen will consist of serial slicing of the rectal wall through the tumor and surrounding mesorectal fat in a plane perpendicular to the mucosa. The quality of the mesorectal excision will be categorized as 1) complete, 2) nearly complete, or 3) incomplete, according to Dutch Colorectal Cancer Group methods[43]. A careful search will be conducted for any potential lymph nodes in the fragment of fat contained in the specimen. Sections will be obtained at 5 mm intervals, embedded in paraffin, cut in 5 *u*m sections, and stained with H&E. The deepest level of invasion in the rectal wall or mesorectal tissue will be determined and the distance measured from the overlying inked surface to the tumor. Any lymph nodes will be cut in half longitudinally; the half of the node not used for diagnostic purposes will be fixed in formalin and embedded in paraffin. Findings will be reported per the recommendations of the Association of Directors of Anatomic and Surgical Pathology [Pathology 1996]. Bulleted list changed to:

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		The quality of the mesorectal excision will be categorized as 1) complete, 2) nearly complete, or 3) incomplete, according to Dutch Colorectal Cancer Group methods[43]. It is imperativethat this determination be made before the specimen has been inked or sectioned. The specimen will be inked by the pathologist for margin determination, and fixed in 10% formalin. It may be necessary to open the specimen at the time of surgery for intra-operative margin assessment, tumor banking, or other considerations. In those instances where the specimen must be opened, it is imperative that assessment of the mesorectal excision and inking of radial margins occurs prior to opening of the specimen. Prior opening of the specimen should not fundamentally alter the pathologic evaluation. The size of the residual tumor or ulcer corresponding to the tumor site will be measured. Dissection of the fixed specimen will consist of serial slicing of the rectal wall through the tumor and surrounding mesorectal fat in a plane perpendicular to the mucosa. The deepest level of invasion in the rectal wall or mesorectal tissue will be determined and the distance measured from the overlying inked radial margin to the tumor. Sections will be obtained at 5 mm intervals, embedded in paraffin, cut in 5 *u*m sections, and stained with H&E. Although not strictly required, in cases where only a mucosal scar or ulcer is noted, we would strongly recommend submission of the entire scar/ulcer to evaluate for microscopic residual tumor. A careful search will be conducted for any potential lymph nodes in the fragment of fat contained in the specimen. Any lymph nodes identified should be submitted in their entirety.
	Sec 8.3, pg 21 **Expected Adverse Events**	Updated: section number
	Sec 15.3, pg 35 **Cancer Trials Support Unit (CTSU) Participation Procedures**	Added: CTSU contacts table
	Sec 15.3.3 (new), pg 36 **Data Submission**	Added: section number
	Sec 15.3.4 (new), pg 37 **Other Protocol Requirements**	Updated: section number
	Sec 15.4, pg 39 **Model Consent: "Before surgery..."**	Added third bulleted item: Chest CT scan or chest x-ray (if you have not had one since you finished your chemotherapy).
	Sec 15.4, pg 40 **Model Consent: Study Chart**	Ad d ed to −2 wee ks b efo re su rger y‖: Have chest CT scan or chest x-ray (if you have not had one since you finished your chemotherapy).
	Sec 15.4, pg 44 **Model Consent: "Will my medical information be kept private?"**	Added to entities with access to patient records: The Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials
End A2 changes		
03/04/2009	**Z6051 A1**	**ACOSOG activation**
02/26/2009	**Z6051 A1**	**CTEP approval**

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Begin A1 changes:		
	Title page	Updated: Version number, version dates
	All pages	Updated: Footers, page numbering
	Contact Information, pg 2	Added: Research Coordinator for Study Chair, Patient Advocate
	Contact Information, pg 2	Updated: CTSU Contact, Disease Site Coordinator
	Participants, pg 3	Added: **CALGB members** CALGB Co-Chair: Martin Weiser, MD New York, NY Phone: (212) 639-6698 Fax: (212) 794-3198 Email: weiser1@mskcc.org
	Sec 1.7, pg 8 **Schema**	Updated first box in schema diagram to include N2.
	Sec 2.1, pg 9 **Eligibility Criteria**	#1 changed from: ...(<12cm from the anal verge)... #1 changed to: ...(≤12cm from the anal verge)...
	Sec 2.1, pg 9	#2 updated to include N2.
	Sec 2.1, pg 9	#4 changed from: Age >18 years #4 changed to: Age ≥18 years
	Sec 2.1, pg 9	#5 changed from: ECOG (Zubrod) Performance Status < 2. #5 changed to: ECOG (Zubrod) Performance Status ≤ 2.
	Sec 2.1, pg 9	#6 changed from: Body Mass Index (BMI) <34. #6 changed to: Body Mass Index (BMI) ≤34.
	Sec 2.1, pg 9	#9 changed from: ... must be amenorrheic for > 12 months... #9 changed to: ...must be amenorrheic for ≥ 12 months...
	Sec 3, pg 10 **Study Calendar**	Added at 1-2 weeks: H&P, vitals, ECOG PS.
	Sec 3, pg 10	Added at 1-2 weeks: Adverse event assessment.
	Sec 3, pg 10	Added: Separate rows for MBFQ (bowel function) and SQOLS (stoma function).
	Sec 3, pg 10	Added at pre-op: MBFQ and SQOLS.
	Sec 3, pg 10	Deleted at 1-2 weeks, 4-6 weeks, 3 mos: MBFQ and SQOLS.
	Sec 3, pg 10	Added to SQOLS at 12 mos: Footnote 2 reference.
	Sec 3, pg 10	** footnote changed from: Patients will be registered/randomized within 4 weeks after completion of neoadjuvant therapy at the time of surgery scheduling. Surgery will be scheduled for 4-8 weeks after completion of neoadjuvant therapy. ** footnote changed to: Patients will be registered/randomized within 6 weeks after completion of neoadjuvant therapy. Surgery will be scheduled to occur within 4-8 weeks after completion of neoadjuvant therapy.
	Sec 3, pg 10	*** footnote changed from: Pre-operative evaluation will occur within 2 weeks prior to surgery. *** footnote changed to: Pre-operative evaluation will occur after registration and within 2 weeks prior to surgery.

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	Sec 3, pg 10	Added to footnotes: [2] The 12-month SQOLS is required only for patients with a permanent stoma.
	Sec 4.2, pg 11 **Registration Requirements**	Added new second paragraph: **NOTE: To ensure proper stratification, the registering physician MUST be the surgeon intended to perform the assigned procedure.**
	Sec 4.3, pg 11 **Registration/Randomization Procedures**	First sentence changed from: Patients will be registered and randomized within 4 weeks after completion of neoadjuvant therapy. First sentence changed to: Patients will be registered and randomized within 6 weeks after completion of neoadjuvant therapy.
	Sec 5.1, pg 12 **Neoadjuvant Chemoradiation Therapy**	First paragraph changed from: Patients eligible for this trial will have completed 5FU-based neoadjuvant chemotherapy/radiation therapy per the institution's individual policy. Capecitabine may be substituted for 5FU as the investigator's discretion. The therapy will be completed within 4 weeks prior to registration/randomization. First paragraph changed to: Patients eligible for this trial will have completed 5FU-based neoadjuvant chemotherapy/radiation therapy per the institution's standard of care or IRB-approved clinical trial. Capecitabine may be substituted for 5FU as the investigator's discretion. The therapy will be completed within 6 weeks prior to registration/randomization.
	Sec 5.1, pg 12	Second paragraph changed from: Surgery will be scheduled for 4-8 weeks after the completion of neoadjuvant therapy. Second paragraph changed to: Surgery will be scheduled to occur within 4-8 weeks after the completion of neoadjuvant therapy.
	Sec 5.2.3, pg 13 **Operative technique**	Added to first paragraph: **NOTE: To ensure proper stratification, the registering physician MUST be the surgeon intended to perform the assigned procedure.**
	Sec 5.2.3, pg 13	Added new fourth paragraph: Robotic procedures used to perform the pelvic dissection will be considered laparoscopic or laparoscopic assisted procedures. The non-pelvic portion of the procedure must be performed by one of the accepted laparoscopic methods (hand assisted, assisted or pure laparoscopic). The surgeons performing robotic procedures must be credentialed for laparoscopic colon, laparoscopic rectal, and robotic rectal procedures as described in Surgeon Skill Verification (Section 12). Patients who fail robotic dissection of the rectum and are switched to a laparoscopy (laparoscopic-assisted or hand-assisted) approach will still be followed in the laparoscopic group. Patients who require conversion to an open operation (greater than 10 cm incision) will be considered as converted laparoscopic.
	Sec 5.2.3, pg 14	Changed last bulleted item from: **Laparoscopic procedures will be videotaped beginning at pelvic dissection and submitted for random audit. See Section 13.0, Performance Monitoring.** Changed last bulleted item to: **Laparoscopic procedures will be videotaped beginning at pelvic dissection. Random audit of selected videotapes and photos of the mesorectum will be conducted by the study team. See Section 13.0, Performance Monitoring.**
	Sec 5.2.6, pg 14 **Intraoperative pathology**	Added to end of paragraph: **These photographs should be retained in patient records. Random audit of selected pathology documentation will be conducted by the study team. See Section 7.4, Pathology Review Committee.**
	Sec 5.2.7, pg 14	Changed from:

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	Documentation	Operative procedures and findings will be documented in the institutional operative and pathology reports and on required data forms. **Laparoscopic procedures will be videotaped beginning at pelvic dissection and submitted for random audit. See Section 13.0, Performance Monitoring.** Changed to: Operative procedures and findings will be documented in the institutional operative and pathology reports and on required data forms. **Laparoscopic procedures will be videotaped beginning at pelvic dissection. Random audit of selected videotapes and photos of the mesorectum will be conducted by the study team. See Section 13.0, Performance Monitoring.**
	Sec 5.4, pg 16 **Quality of Life**	Added new last paragraph: NOTE: QOL questionnaires for all patients should be completed as required in the Study Calendar, regardless of surgical outcome and/or conversion to open laparotomy. Questionnaires may be completed at any time during the day in the clinic, or they may be taken home by the patient for completion and then returned.
	Sec 5.4.4, pg 17 **Linear Analogue Self Assessment (LASA)**	Second paragraph changed from: This instrument is available in other languages upon request. Second paragraph changed to: This instrument is available in English only. It may be administered to non-English speaking patients via an interpreter.
	Sec 6, pg 17 **Follow-up**	First sentence changed from: Patients will be followed...an additional 3 years or until relapse, as required,... First sentence changed to: Patients will be followed...an additional 3 years, as required,...
	Sec 6, pg 17	Second paragraph, first sentence changed from: Postoperative contact will include...and 24 months after discharge. Second paragraph, first sentence changed to: Postoperative contact will include...and 24 months after surgery.
	Sec 8.4, pg 20 **Expected Adverse Events**	Reformatted section.
	Sec 11.2.1, pg 25 **Submission of IRB Approval (new section)**	Added new section: **11.2.1 Submission of IRB Approval** IRB approval documentation must be submitted to CTSU for entry into the Regulatory Support System (RSS). This information is downloaded from RSS directly to ACOSOG and is required prior to enrollment of the first patient. Submission instructions are available on the RSS page of www.ctsu.org.
	Sec 12, pg 26 **Surgeon Skill Verification**	Added new second paragraph: NOTE: For surgeons conducting laparoscopic surgery using robotics, credentialing in the use of robotics also is required.
	Sec 12.2, pg 26 **Laparoscopic Rectal Credentialing**	Last sentence changed from: ...will be reviewed by two designated investigators... Last sentence changed to: ...will be reviewed by designated investigators...
	Sec 12.2.1, pg 26 **Robotics Credentialing (new section)**	Added: 12.2.1 Robotics Credentialing Surgeons will be credentialed for robotic laparoscopic rectal surgery, having performed at least 10 pelvic dissections using robotics and 10 laparoscopic, laparoscopically-assisted or hand-assisted operations. Surgeons will provide operative reports and pathology reports for the 10 robotic cases and 10 laparoscopic rectal cases and unedited videotapes of both their robotic and laparoscopic rectal technique. All videotapes

		submitted for this trial will be reviewed by designated investigators and approved for oncologic technique and practice.
	Sec 12.3, pg 26 **Submission Information (ACOSOG and Non-ACOSOG Investigators)**	First sentence changed from: Complete operative reports, pathology reports, and video documentation must be submitted to: First sentence changed to: A completed Surgeon Skill Verification Checklist (available on the Z6051 page of www.acosog.org), plus complete operative reports, pathology reports, and video documentation must be submitted to:
	Sec 13.2, pg 27 **Monitoring of Surgical Performance**	First sentence changed from: Video audit of laparoscopic procedures will take place throughout the trial, with random assessment of submitted videos after accrual of the first 50 and 100 patients. First sentence changed to: Video audit of laparoscopic procedures will take place for the first 100 patients randomized to the laparoscopic arm, with random audit of procedural videos after accrual of the first 50 and 100 patients.
	Sec 15.4, pg 39 **Model ICF, "After surgery..."**	Added: If you receive a laparoscopic-assisted rectal resection, the procedure will be videotaped and may be selected for central review by study personnel. This is for quality control purposes. If the videotape is submitted for review, only your study number will appear on the recording. No other identifying information will be included. If the videotape is not selected for review, then it will be destroyed.
	Sec 15.4, pg 42 **Model ICF, "Are there benefits to taking part in the study?"**	Third sentence changed from: We do know that laparoscopic-assisted rectal resection for colon cancer seems as safe and effective as open laparotomy rectal resection, and that laparoscopic-assisted rectal resection seems to shorten recovery times in resections for colon cancer. Third sentence changed to: We do know that laparoscopic-assisted resection for colon cancer seems as safe and effective as open laparotomy resection, and that laparoscopic-assisted resection seems to shorten recovery times in resections for colon cancer.
End A1 changes		
08/15/2008	**Z6051 A0**	**ACOSOG Initial Activation**
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