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SWOG

A PHASE III SURGICAL TRIAL TO EVALUATE THE BENEFIT OF A STANDARD VERSUS AN EXTENDED PELVIC LYMPHADENECTOMY PERFORMED AT TIME OF RADICAL CYSTECTOMY FOR MUSCLE INVASIVE UROTHELIAL CANCER.

NCT #01224665

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SWOG/SWOG

ALLIANCE/Alliance for Clinical Trials in Oncology

ECOG-ACRIN/ECOG-ACRIN Cancer Research Group

NCIC-CTG/NCIC Clinical Trials Group

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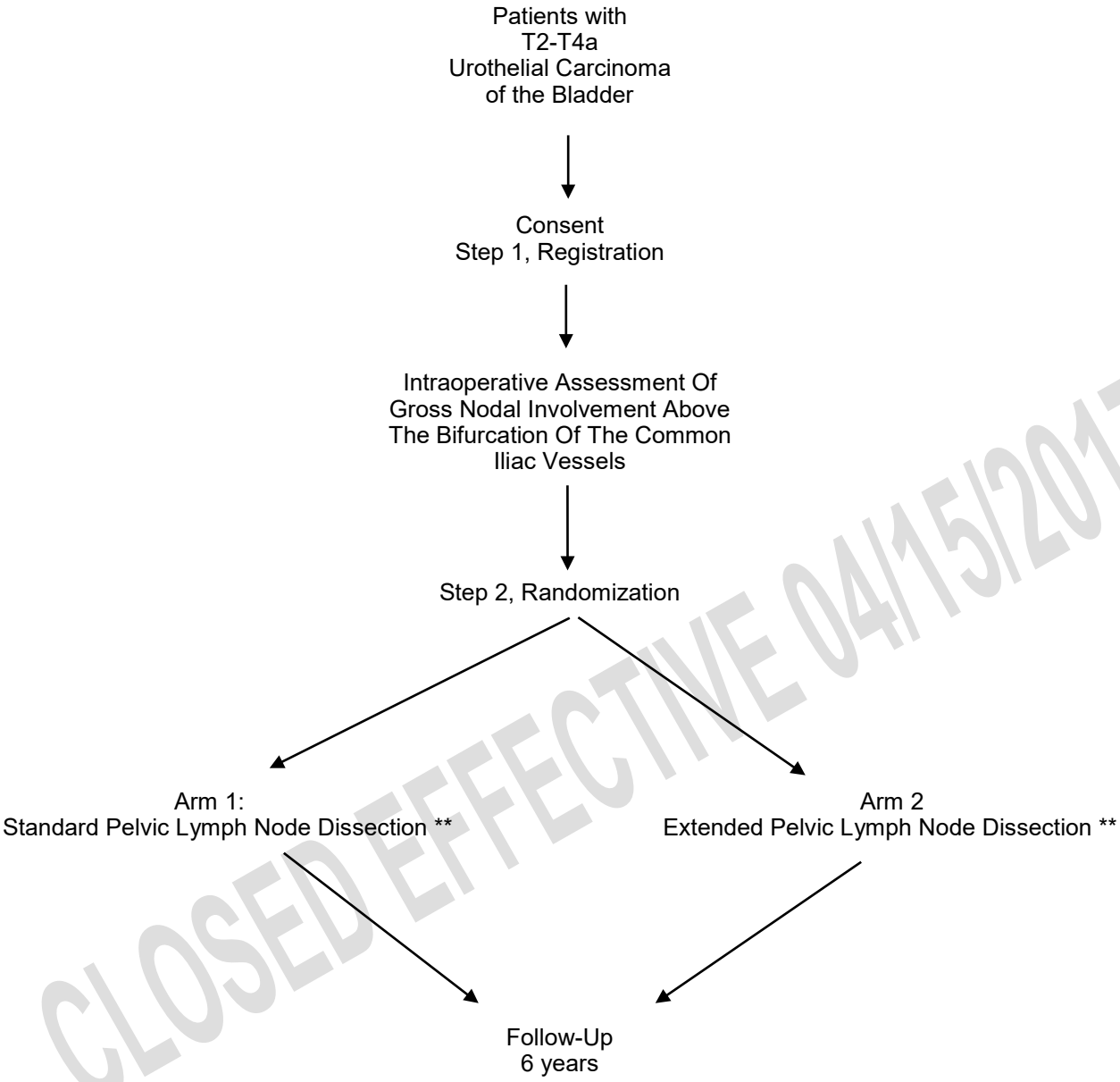
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone: 1-866-651-CTSU Fax: 215-569-0206	Please refer to the patient enrollment section for instructions on using the OPEN system.	Online Data Submission: Institutions participating through CTSU are required to submit and amend their data electronically via Online Data Submission. Access the SWOG Workbench using your CTSU User ID and password at the following url: https://crawb.crab.org/TXWB/ctsulogon.aspx Exceptions: Data items that are not available for online submission (operative and pathology reports, patient completed forms, scan reports, etc.) may be submitted by FAX at 800/892-4007. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Sites must use the current form version and adhere to the instructions and submission schedule outlined in the protocol. CTSU sites must follow procedures outlined in the protocol for Site Registration, Patient Enrollment, Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement.		
For treatment-related questions, contact the Study PI of the Coordinating Group. (Dr. Seth P. Lerner at 713/798-6841). **For eligibility or data submission questions,** contact the SWOG Data Operations Center at 206/652-2267.		
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website https://www.ctsu.org		
The CTSU Web site is located at https://www.ctsu.org		

SCHEMA

NOTE: Participation in this study is limited to pre-approved, credentialed surgeons (see S1011 protocol abstract page on http://swog.org for list of pre-approved, credentialed surgeons and Section 12.1 for credentialing process).



** For patients who did not receive neoadjuvant chemotherapy, post operative adjuvant chemotherapy for pT any, N+ or pT3-4, N0 is strongly recommended but not required and will be left up to the treating physician. We strongly encourage patient evaluation for adjuvant chemotherapy in a multidisciplinary session with the treating urologic surgeon and GU medical oncologist coordinating decision making and administration of chemotherapy.

1.0 OBJECTIVES

1.1 Primary Objective

a. To compare disease-free survival (DFS) in patients undergoing radical cystectomy for muscle-invasive urothelial carcinoma of the bladder (UCB) treated with radical cystectomy and extended pelvic lymph node dissection (PLND) compared to radical cystectomy and standard pelvic lymphadenectomy.

1.2 Secondary Objectives

a. To compare overall survival (OS) in patients randomized to extended PLND versus those randomized to standard pelvic lymphadenectomy.

b. To evaluate operative time, whether or not nerve sparing was performed, intra-operative, peri-operative and 90 day morbidity and mortality, length of hospital stay, histology (pure urothelial versus mixed), lymph node counts and lymph node density, adjuvant chemotherapy received, and local and retroperitoneal soft tissue recurrence in patients randomized to extended PLND versus those randomized to standard pelvic lymphadenectomy. Proximal extent of node dissection in those patients randomized to extended PLND will be evaluated as well.

1.3 Translational Medicine Objectives

a. To bank paraffin embedded blocks or slides of the primary tumor for future translational medicine studies including markers of epithelial and mesenchymal transition and correlate these findings with pathologic T stage and node metastasis as well as DFS and OS.

b. To determine the prognostic value of several putative markers of the pre-metastatic niche in muscle-invasive bladder cancer, including (1) extent of neutrophil infiltration, (2) phosphorylated signal transducer and activator of transcription 3 (pSTAT3) expression, (3) vascular endothelial growth factor 1 (VEGFR1) expression, and (4) macrophage infiltration.

c. To evaluate whether the prevalence of the pre-metastatic niche is different amongst patients that received neoadjuvant chemotherapy as compared to those who did not.

2.0 BACKGROUND

Despite the fact that pelvic lymphadenectomy is performed at the time of radical cystectomy for urothelial carcinoma of the bladder (UCB), there are no data from randomized clinical trials, which define an association between the extent of the lymphadenectomy and disease progression or survival. There is considerable debate regarding the degree of improvement in outcome gained with a more extensive lymphadenectomy for patients undergoing cystectomy for bladder cancer. This is exemplified by the large degree of variability in the extent of dissection and number of nodes removed by urologists. The extent of nodal dissection promoted by many academic centers involves an extended dissection with the upper limit designated by the aortic bifurcation or the inferior mesenteric artery (IMA). *(1,2,3,4,5)* The average number of lymph nodes removed at these centers is 20-30 lymph nodes. In fact, it is has been proposed that a minimum number of lymph nodes (~25) be utilized for quality assurance purposes for patients undergoing this operation. *(6)* However, in a large multi-institutional trial evaluating the role of neoadjuvant chemotherapy, 9% of patients at major academic centers had no lymph node dissection and 37% underwent a limited dissection (obturator nodes only). *(7)* Moreover, population-based data from the SEER program cancer registry demonstrates a pervasive lack of enthusiasm for an extended

lymph node dissection with 40% of patients having no lymph nodes recovered during cystectomy. *(8)* As more attention has been applied to this important quality measure in recent years there has been a modest increase in the number of nodes removed and a decrease in the percent of patients with no node dissection at all. *(9)*

Data from several retrospective series and one prospective non-randomized cohort suggest that patients undergoing an extended pelvic lymphadenectomy may derive a survival benefit compared to those undergoing a limited pelvic node dissection. *(10)* However, conclusions drawn from these studies are subject to significant biases inherent in observational studies of surgical procedures. In addition, there is no prospective data regarding the morbidity as a result of the extent of the nodal dissection. We acknowledge that there is a potential for an increase in post-operative morbidity associated with an extended node dissection (possibly related to increased operative time and/or blood loss) that could outweigh any derived benefit. This provides further support for the importance of studying this dilemma in a randomized controlled trial (RCT). In addition, the importance of a RCT to address the extent of nodal dissection in bladder cancer is reflected in the experience of our surgical colleagues in gastric and pancreas cancer.

Gastrectomy with an extended regional (D2) lymphadenectomy is the standard treatment for curable gastric cancer in Asia. However, because of a 10-30% rate of para-aortic node involvement, additional para-aortic nodal dissection (PAND) has been performed in Japan since the 1980s for patients with advanced stage disease. A landmark RCT asked the question of whether the addition of PAND to the D2 lymphadenectomy improved survival for patients with stage T2-4 tumors. *(11)* The overall incidence of surgery-related complications was 20.9% in the D2 lymphadenectomy group and 28.1% in the group assigned to D2 lymphadenectomy plus PAND ($p = 0.07$). The authors observed no significant differences in recurrence-free or overall survival rates between the two groups. *(12)*

Similarly, extended lymph node dissections for pancreatic head cancer have been conducted since the 1980s. Several retrospective trials demonstrated improved survival rates for patients undergoing extended nodal dissection. A RCT to assess the difference between a standard and extended nodal dissection was initiated but closed after an interim analysis revealed a poorer survival and increased morbidity in the extended nodal dissection group. *(13)*

An extended node dissection in patients undergoing cystectomy for bladder cancer may offer a survival benefit compared to a standard node dissection via more complete tumor eradication, improved staging and thus identifying patients who may benefit from adjuvant chemotherapy, or other theoretical mechanisms. In order to optimize the benefits of an extended node dissection through improved nodal staging, all patients with node metastasis will be strongly advised to receive peri-operative chemotherapy which is currently considered a standard of care in locally advanced urothelial bladder cancer. In addition and in accordance with standard of care, chemotherapy will be strongly recommended for patients found to have advanced pathologic stage (pT3-T4) at cystectomy. Failure to include this stipulation in the trial design could result in biased administration of adjuvant chemotherapy, influenced by which arm the patient was randomized to, and lead to non-informative results.

A poll of centers of excellence suggest that a 10-12% improvement in 3-year DFS (65-67%) for patients in extended lymphadenectomy would be meaningful and establish extended node dissection as the standard of care in this patient population

Since the introduction of MVAC chemotherapy in the 1980s, little progress has been made in improving survival for patients with advanced bladder cancer. Despite a significant improvement in overall survival with administration of peri-operative chemotherapy, the mortality rate for patients undergoing radical cystectomy for UCB approaches 50%. A properly performed lymph node dissection may provide a significant improvement in survival for these patients. Currently the boundaries of a pelvic node dissection for patients undergoing radical cystectomy for UCB are not clear and the urologic community has failed to define a standard template. The literature is replete with various proposed definitions. Defining, a standard nodal dissection for this disease is

critical because the extent of lymph node dissections are increasingly being compromised due to the increasing performance demands placed on the surgeon and the widespread utilization of robotic laparoscopy for this operation. Performing an extended lymph node dissection takes additional time, especially with a robotic laparoscopic approach. Retrospective data and expert opinion are a poor substitute for level I evidence as demonstrated by the findings of RCTs of extended versus standard LND in other solid organ malignancies.

Early reports of radical cystectomy for UCB stressed the high rate of local recurrence that was related, in part, to limited or no dissection of the regional lymph nodes. A greater understanding of the pathways by which UCB progressed, locally and regionally, suggested that a more radical resection might have therapeutic benefit. *(14)* Jewett hypothesized that 25% to 30% of recurrences in pelvic lymph nodes were due to inadequate lymphadenectomy. In patients undergoing radical cystectomy for UCB the involvement of regional lymph nodes varies from 14% to 40%, thus it is important to define the extent of lymphadenectomy. *(15,16,17)* Published outcomes following attempts at controlling the regional lymphatics for bladder cancer date back to 1932 when the routine inclusion of a pelvic lymph node dissection at the time of radical cystectomy was initiated. *(18)*

Controversy regarding the role of lymphadenectomy and the extent of the dissection necessary to obtain maximal tumor control has persisted to the present. Some surgeons recommend that the proximal limit of resection be the level of the bifurcation of the common iliac vessels, since patients with nodal disease superior to this point are thought to be incurable by radical cystectomy. *(19)* In contrast, others advocate an extended lymph node dissection beyond this point, citing non-randomized data as supportive of a more extensive dissection for improved staging and therapeutic efficacy. *(20,21,22)*

Several institutional studies have reported improved outcome in patients undergoing an extended lymph node dissection, as defined by the number of lymph nodes identified pathologically. In a study of 447 patients Leissner et al. found a 20% improvement in overall 5- year survival (85% of patients, with organ-confined UCB and greater than or equal to 16 lymph nodes resected survived 5 years compared to 65% of patients with less than or equal to 15 lymph nodes resected). Control of local disease also was superior in patients having a more extensive, compared to a limited nodal resection (17% recurrence compared to 27% recurrence). *(23)*

At Memorial Sloan-Kettering Cancer Center (MSKCC) the recent experience with radical cystectomy was reviewed to determine the relationship between the extent of lymphadenectomy and staging, disease control and prognosis. *(24,25,26)* A total of 322 patients with UCB treated by radical cystectomy were reviewed; 258 patients demonstrated no evidence of node involvement while 64 patients had regionally involved lymph nodes. Overall 5-year survival was improved in patients with a greater number of lymph nodes examined regardless of the status of the nodes. For the node-negative group 5-year survivals of 80%, 60%, and 20% were observed for patients with greater than 8, 4 to 7, and 0 to 3 nodes respectively examined following radical cystectomy. For patients with positive node disease, a 50% versus a 20% 5-year survival was seen if greater than versus less than 11 nodes were examined. Koppie and colleagues evaluated over 1,000 consecutive patients from 11 different surgeons with different extents of dissection. They observed that the probability of survival continued to rise with increasing numbers of lymph nodes removed up to a threshold of 23 nodes. *(27)*

Poulsen et al. reported their group's experience with 194 patients treated by either limited or extended lymph node dissection at the time of radical cystectomy. *(28)* These investigators found a significantly greater number of nodes were removed with the extended dissection (mean 25, range 9 to 67) compared to the limited dissection (mean 14, range 5 to 30). The extended dissection identified a larger percentage of patients with nodal metastases (improved staging). For patients where the primary UCB was confined to the bladder wall, positive nodes were identified in patients having the extended (12.5%) compared to the limited (8.9%) resection. The potential contribution of the extended, compared to limited, dissection to improved cancer control was suggested by a recurrence-free survival at 5 years for the subgroups with tumors confined to the bladder wall (tumor stage pT2b or less) (85% versus 64%, $p < 0.02$) and without evidence of

lymph node metastasis (stage pT3a or less, pN0) (90 % versus 71%, p < 0.02). Similarly, local recurrence rates (2% versus 7%) and distant metastatic risk (10% versus 21%) was improved in patients undergoing an extended dissection compared to a limited dissection. These data were corroborated in a recent update of this series which highlighted the fact that one-third of patients had nodal metastasis proximal to the anatomical limits of a node dissection limited to the true pelvis only. *(29)* In summary these data provide compelling evidence that an extended node dissection may provide a survival benefit for patients undergoing radical cystectomy for UCB. Nevertheless, the inherent aforementioned biases and lack of a control arm limits the conclusions drawn from these studies.

A review of the contemporary cystectomy literature which includes a mix of standard and extended node dissection suggests that a reasonable estimate of disease-free and overall survival associated with standard node dissection for patients with muscle invasive bladder cancer (≥ T2) is 55% at 3 years and 55% at 5 years (Table 1 and 2) respectively.

Table 1. Percentage 5 year *disease-free survival (DFS)* by pathologic stage after radical cystectomy with and without pelvic lymph node metastasis: selected series reporting DFS (2000-2009)

Selected Series	No. of PTS	≤P1	P2a	P2	P2b	P3a	P3	P3b	P4a,b	N neg	N pos	All pts
Dalbagni, et al (2001)	300	Not reported										
Stein, et al (2001)	1054	80-88		81		68		47	44	78	35	68
Madersbacher, et al (2003)	507	76		74			52		36	---	33	62
Hautmann, et al (2006)	788	90		72			43		28	75	21	66
Shariat, et al (2006)	888	81		72			44		28	80	35	58
Ghoneim, et al (2008)	2720	82	75		53		40		29	62	27	56
Manoharan, et al (2009)	432	81		70			44		16	72	29	64
Volkmer, et al (2009)	1270	Not reported										62

Table 2. Percentage 5 year *overall survival (OS)* by pathologic stage after radical cystectomy with and without pelvic lymph node metastasis: selected series reporting OS (2000-2009)

Selected Series	No. of PTS	≤P1	P2a	P2	P2b	P3a	P3	P3b	P4a,b	N neg	N pos	All pts
Dalbagni, et al (2001)	300	64	63	59	58	23	26	28	27			45
Stein, et al (2001)	1054	74		72		58		38	33	69	31	66
Madersbacher, et al (2003)	507	63		63		*NS*			32	---	26	59
Hautmann, et al (2006)	788	Not reported										58
Shariat, et al (2006)	888	Not reported										
Ghoneim, et al (2008)	2720	Not reported										
Manoharan, et al (2009)	432	79		60			43		17	69	22	59

Accrual capability: The Study Chairs have consulted extensively with the major centers of excellence with respect to the overall management of bladder cancer and specifically radical cystectomy as well as surgeons experienced with extended pelvic and iliac lymphadenectomy. Prior to protocol development, the Study Chairs conducted a survey in order to understand practice patterns and willingness and ability to randomize. Commitments were obtained from each of the centers and surgeons surveyed to randomize eligible patients (see table below). The Study Chairs polled 15 urologists practicing at 7 high-volume centers regarding their interest in participation in this trial. Each center agreed to participate in the study and reported that their anticipated yearly enrollment in this trial would be up to 340-370 patients annually.

Site	Surgeons	# patients potentially eligible/year
Baylor College of Medicine	Amiel, Lerner	40
MD Anderson Cancer Center	Dinney, Grossman, Kamat	80
Memorial Sloan-Kettering Cancer Center	Bochner, Dalbagni	50
Oregon Health and Science University	Koppie	20-30
University of Southern California	Skinner, Daneshmand	50-70
University of Texas Southwestern	Lotan, Raj, Sagalowsky	50
Washington University School of Medicine	Kibel, Grubb	50
Total	15 surgeons	340-370 year

The size of the eligible population is estimated as 340-370 annually from these centers alone before expanding the trial to additional sites. We anticipate a high acceptance to the trial by patients based on experience with similar trial designs in gastric and esophageal cancers. These are data provided by the surgeons at these sites and represent a high-side estimate of annual accrual. There is an obvious large pool of patients for accrual and commitments from each of these centers to accrue. In order to achieve an accrual rate of 13 patients/month when each of these sites has IRB approval we would require approximately one half of the estimated accrual capability from these sites only. Since this survey, we have obtained commitments from BC Cancer Agency (Peter Black), Cleveland Clinic (Andrew Stephenson), Rochester (Edward Messing), and University of Texas Health Science Center San Antonio (Robert Svatek and Dipen Parekh). These are high volume SWOG sites. ALLIANCE formally reviewed and unanimously approved the trial. This will facilitate participation from MSKCC and adds vanguard sites at University of Chicago (Gary Steinberg and Norm Smith), Ohio State (Kamal Pohar), and UCSF (Max Meng). ECOG-ACRIN has also agreed to participate and sites expressing interest include Vanderbilt (Peter Clark, Mike Cookson, Sam Chang) and UT Southwestern. If we achieve the accrual required to meet the vanguard feasibility portion of the trial, then the trial would be expanded to other interested centers in SWOG, ALLIANCE and ECOG-ACRIN that meet the credentialing requirements.

Inclusion of Women and Minorities:

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below. Both men and women of all races and ethnic groups are eligible for this study.

Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	10	43	53
Not Hispanic or Latino	116	451	567
Total Ethnic	126	494	620
Racial Category			

Ethnic Category	Females	Males	Total
American Indian or Alaskan Native	0	2	2
Asian	2	9	11
Black or African American	14	36	50
Native Hawaiian or other Pacific Islander	0	0	0
White	110	447	557
Racial Category: Total of all Subjects	126	494	620

3.0 DRUG INFORMATION

There is no drug information for this study.

4.0 STAGING CRITERIA (AJCC SEVENTH EDITION, 2010)

Primary Tumor (T)

T2 Tumor invades muscularis propria

pT2a Tumor invades superficial muscularis propria (inner half)
pT2b Tumor invades deep muscularis propria (outer half)

T3 Tumor invades perivesical tissue

pT3a Microscopically
pT3b Macroscopically (extravesical mass)

T4 Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall

T4a Tumor invades prostatic stroma, uterus, vagina
T4b Tumor invades pelvic wall, abdominal wall

Regional Lymph Nodes (N)

Regional lymph nodes include both primary and secondary drainage regions. All other nodes above the aortic bifurcation are considered distant lymph nodes.

NX Lymph nodes cannot be assessed
N0 No lymph node metastasis
N1 Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)
N2 Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node metastasis)
N3 LYMPH NODE METASTASIS TO THE COMMON ILIAC LYMPH NODE

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the **S1011** Prestudy Form and submit to the Data

Operations Center in Seattle (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 28, 56 or 70 falls on a weekend or holiday, the limit may be extended to the next working day.**

Step 1 (Registration)

5.1 Disease-related Criteria (Step 1)

a. Patients must have histologically-proven (T2, T3, or T4a) urothelial carcinoma of the bladder (UCB) that requires primary radical cystectomy for definitive treatment. Patients must not have clinical stage consistent with a low-risk of node metastasis (CIS only, T1). Patients with a T4b (fixed lesion) are not eligible for this study.

NOTE: Patients with predominant urothelial carcinoma with elements of adenocarcinoma, squamous cell carcinoma, micropapillary or minor components of other rare phenotypes are eligible. Patients with predominantly small cell, squamous cell, or adenocarcinoma histologies are not eligible. Patients with other non-urothelial cancers are not eligible (e.g., sarcoma, lymphoepithelial, nested variant).

Clinical stage is based on all of the following: TURBT(s) that determined the need for cystectomy, bimanual exam and cross sectional imaging.

b. There must be plans for the cystectomy and lymph node dissection (LND) to be performed within 28 calendar days following registration. Laparoscopic surgery is not allowed.

c. Surgery must be planned to be performed by a pre-approved, study-specific credentialed surgeon (see Section 12.1 for credentialing process). The registering physician MUST be the pre-approved, credentialed surgeon intended to perform the assigned procedure.

d. Patients must not have undergone a prior partial cystectomy for invasive bladder cancer. Patients must not have received any prior pelvic surgery that would obviate a complete extended lymphadenectomy (e.g. aorto-femoral/iliac bypass) or for whom the surgeon feels that their ability to perform a standard or extended pelvic node dissection would be compromised.

5.2 Prior Therapy Criteria

a. Prior neoadjuvant chemotherapy for this cancer is permitted however patients must have completed treatment within 70 days prior to cystectomy and recovered from all associated toxicities at the time of registration.

b. Patients must not have received any prior pelvic irradiation.

c. Patients must have no evidence of visceral or nodal metastatic disease proximal to the common iliac bifurcation on 2 view chest x-ray or CT of the chest and abdominal-pelvic imaging with computerized tomography or MRI of the abdomen and pelvis. Chest x-ray or CT of the chest and CT or MRI of the abdomen and pelvis must be obtained within 56 days prior to registration. PET/CT may be used as an alternative to CT or MRI or to resolve possible areas of metastases seen on cross sectional imaging.

5.3 Clinical/Laboratory Criteria

a. Patients must have bilirubin, SGOT, SGPT and alkaline phosphatase values within the institutional upper limit of normal (ULN). These laboratory values must be obtained within 28 days prior to registration. Patients with levels of one or more of these enzymes greater than IULN may still be enrolled if metastatic disease is excluded with appropriate imaging which may include dedicated liver imaging, bone scan, PET, CT, MRI, or biopsy when appropriate.

b. Patients must have a complete physical examination and medical history within 28 days prior to registration.

c. ***Choose one of the following 2 o*** Patients must have a Zubrod performance status (see Section 10.5) of 0, 1, or 2 and in the registering physician's opinion be medically suitable to undergo cystectomy.***ptions:***

d. Women must not be pregnant or nursing at the time of radical cystectomy since the surgery and prolonged general anesthesia would place the fetus at considerable risk for demise. The prolonged recovery and debility of the patient would severely limit the patients' ability to nurse and care for an infant.

Women of reproductive potential must agree to use an effective contraceptive method at the time of radical cystectomy, throughout the surgical recovery period, and during post-operative neoadjuvant chemotherapy (if clinically indicated). A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, she is responsible for beginning contraceptive measures.

e. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for 5 years.

5.4 Specimen Submission Criteria

a. Patients must be offered the opportunity to participate in specimen banking for future use to include the translational medicine studies outlined in Section 15.0.

5.5 Regulatory Criteria

a. Patients or their legally authorized representative must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

b. As part of the OPEN registration process (see Section 13.4 for OPEN access instructions), the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

Step 2 (Randomization)

Patients must meet all of the criteria in Step 1 above and be registered to the study in order to be eligible for Step 2 (Randomization). Randomization will occur at the time of surgery following complete intra-abdominal and pelvic exploration ruling out visceral metastatic disease and gross nodal disease in the extended template (common iliac, pre-sciatic [fossa of Marseilles], pre-sacral, para-aortic, pre-aortic, pre-caval, para-caval) nodes.

5.6 Disease-related Criteria (Step 2)

a. Patients must not have intra-operative evidence of pelvic lymph node involvement (confirmed by frozen section) at or above the bifurcation of the common iliac vessels in any of the extended template. **Rationale**: Failure to excise lymph nodes with known cancer involvement would be a substantial deviation from standard of care or may be a cause for abandoning the operation in favor of systemic chemotherapy.

b. Patients must not have intra-operative evidence of T4b disease.

6.0 STRATIFICATION FACTORS

Patients will be randomized using a dynamic balancing algorithm *(30)* with stratification based on:

a. Neoadjuvant chemotherapy: Cisplatin based, vs. Carboplatin based, vs. Other, vs. none.

b. Clinical stage T2 vs. T3 or T4a. NOTE: Clinical stage is based on all of the following: TURBT(s) that determined the need for cystectomy, bimanual exam and cross sectional imaging.

c. Zubrod performance status: 0-1 vs. 2.

7.0 TREATMENT PLAN

For surgical-related questions, please contact Dr. Seth P. Lerner at 713/798-6841, Dr. Robert Svatek at 210/602-3116, or Dr. Theresa Koppie at 503/346-1500. For chemotherapy-related questions, please contact Dr. Ajjai Alva at 734/936-0091.

7.1 Timing of Randomization

Randomization will be done at the time of surgery after the exploration in order to eliminate any bias in interpretation of the findings of the intra-operative exploration and to minimize drop-outs due to a positive finding of metastatic disease outside the standard node dissection template. After surgical exploration of the abdomen and pelvis and the absence of visceral metastatic and gross positive nodes in any of the extended template fields, surgery will then proceed according to randomization assignment.

7.2 Treatment

a. Standard Pelvic Lymph Node Dissection

All potential lymph node bearing tissue to include a complete dissection of the external and internal iliac and obturator lymph nodes. All potential node bearing tissue should be removed within the following boundaries: laterally the genitofemoral nerve; distally Cooper's ligament to include the lymph node of Cloquet; proximally the common iliac (CI) bifurcation; medially the bladder to

include the tissue medial to the hypogastric artery; and posteriorly the floor of the obturator fossa with circumferential mobilization of the external iliac artery and vein unless contraindicated due to extensive atherosclerotic vascular disease.

b. Extended Pelvic Lymph Node Dissection

This includes the standard pelvic lymph node dissection described in Section 7.2a plus bilateral common iliac nodes to include the node bearing tissue in the pre-sciatic region (fossa of Marseilles), pre-sacral nodes including the node bearing tissue anterior to the left common iliac vein and medial to the common iliac arteries up to the bifurcation of the aorta. The node dissection may be extended proximal to the aortic bifurcation up to the inferior mesenteric artery (IMA) to include the distal paracaval, pre-caval, pre-aortic and paraortic lymph nodes according to surgeon preference.

7.3 Adherence to Recommendations for Adjuvant Chemotherapy

For patients who did not receive neoadjuvant chemotherapy, post operative adjuvant chemotherapy for pT any, N+ or pT3-4, N0 is strongly recommended but not required and will be left up to the treating physician. The Study Chairs will review the records of all patients enrolled to assess adherence to this recommendation. Non-compliance with this recommendation will be addressed by inquiry with the site physicians and coordinators.

7.4 Submission of Lymph Nodes

At a minimum the standard pelvic lymph node dissection will be submitted to the institutional pathologist for routine histology in two separate packets labeled left and right pelvic. The extended pelvic lymph node will be submitted in a minimum of 3 packets labeled left and right common iliac (including the tissue dissected from the fossa or Marseilles - also referred to as pre-sciatic) and pre-sacral. If the nodes are dissected from the bifurcation of the aorta proximally then these will be submitted as a separate packet(s). All of these regions may be submitted in smaller packets (e.g. external iliac, obturator, internal iliac) at the surgeons preference. The **S1011** Intra-Op Surgical Assessment Form describing the node packet submission to pathology must be completed and submitted to the Data Operations Center in Seattle per Section 14.4b.

7.5 Criteria for Removal from Protocol Treatment

a. Intra-operative complication requiring immediate completion or termination of surgery such as myocardial infarction or serious vascular injury.

b. When the patient is off protocol treatment and **S1011** Surgeon's 90-Day Assessment Form Standard Versus Extended LND has been submitted.

c. The patient may withdraw from the study at any time for any reason.

7.6 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the study forms.

7.7 Follow-Up Period

All patients will be followed for recurrence and survival for a maximum of 6 years after Step 2, Randomization or until death (whichever occurs first).

8.0 DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 Dose Modifications

There are no dosage modifications for this study.

8.3 Dose Modifications Contacts

For surgical-related questions, please contact Dr. Seth P. Lerner at 713/798-6841, Dr. Robert Svatek at 210/602-3116, or Dr. Theresa Koppie at 503/346-1500. For chemotherapy-related questions, please contact Dr. Ajjai Alva at 734/936-0091.

8.4 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the Operations Office, Study Chair, the NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

		Hospitalization		Year 1				Year 2				Year 3				Year 4	Year 5	Year 6
REQUIRED STUDIES	PRE STUDY	Day of Surgery	Day of Discharge	Mo 3	Mo 6	Mo 9	Mo 12	Mo 15	Mo 18	Mo 21	Mo 24	Mo 27	Mo 30	Mo 33	Mo 36	Mo 48	Mo 60	Mo 72
PHYSICAL																		
History and Physical Exam	X [a]			X	X	X	X		X		X		X		X	X	X	X
Height, Weight and Performance Status	X																	
Hospitalization assessment [b]			X															
Adverse Event/Morbidity assessment [c]			X	X														
LABORATORY																		
Bilirubin	X			X	X	X	X		X		X		X		X	X	X	X
SGOT and SGPT	X			X	X	X	X		X		X		X		X	X	X	X
Alkaline Phosphatase [d]	X			X	X	X	X		X		X		X		X	X	X	X
STAGING																		
TURBT	X																	
Bimanual Exam	X																	
X-RAYS AND SCANS																		
CT or MRI of abdomen and pelvis	X				X		X		X		X		X		X	X	X	X
2 view Chest X-ray or CT of the Chest	X			X	X	X	X		X		X		X		X	X	X	X
Bone Scan, PET/CT or other imaging directed at potential visceral or node metastatic sites	X [d]																	
SPECIMEN SUBMISSION																		
Two Paraffin Embedded Blocks or 10 unstained slides from Primary Tumor		X [e]																
8 unstained, formalin-fixed paraffin embedded (FFPE) sections from the left-pelvic and right-pelvic lymph nodes		X [e]																

Calendar continued on next page. Click here for footnotes.

TREATMENT (see Section 7.0 for details)																		
Surgical assessment of nodal dissection [f]		X																
Standard or Extended Pelvic Lymph Node Dissection		X																
Submission of Materials for Surgical Review [g]		X																
Adjuvant chemotherapy [h]				X														

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.

a Physical exam and medical history must be completed within 28 days prior to registration (see Section 5.3b).
b See **S1011** Surgeons Post-Op Data Form (see protocol abstract page, www.swog.org).
c Morbidity data **collected** on both **S1011** Surgeon's Post-Op Data Form Standard Versus Extended LND and **S1011** Surgeon's 90-Day Assessment Form Standard Versus Extended IND (see protocol abstract page, www.swog.org).
d Bone scan required if patient has an elevated alkaline phosphatase or bone pain.
e For patients who consent to specimen banking, specimens must be collected after completion of the final pathologic evaluation.
f See **S1011** Intra-Op Surgical Assessment Form (see protocol abstract page, www.swog.org).
g See Section 12.2
h For patients who did not receive neoadjuvant chemotherapy, post operative adjuvant chemotherapy for pTany, N+ or pT3-4, N0 is strongly recommended, but not required and will be left up to the treating physician.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Measurability of lesions

a. **Measurable disease**: Measurable disease is defined differently for lymph nodes compared with other disease and will be addressed in a separate section below.

1. Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 2.0 cm by chest x-ray, by ≥ 1.0 cm with CT or MRI scans, or ≥ 1.0 cm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters (or millimeters).

   The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

2. Malignant lymph nodes are to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in **SHORT AXIS** (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

b. **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with ≥ 1.0 cm to < 1.5 cm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered non-measurable as are previously radiated lesions that have not progressed.

c. **Notes on measurability**

1. For CT and MRIs, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should by performed with breath-hold scanning techniques, if possible.

2. PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT.

3. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

1. Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition simple cysts.

4. If a target lesion becomes very small some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default measurement of 0.5 cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0cm should be recorded.

10.2 Recurrence

Criteria for recurrence will include measurable disease on cross-sectional imaging or plane radiography targeting lung, liver and bone as most common sites for recurrence. Bone scintigraphy may be used according to Good Medical Practice. Local pelvic recurrence may be determined by cross-sectional imaging and/or DRE (and confirmed by biopsy if indicated). PET/CT may be used to confirm suspicious abnormalities on other imaging modalities.

10.3 Disease-Free Survival

From date of randomization to date of first documentation of relapse/recurrence or death due to any cause. Patients last known to be alive without report of relapse/recurrence are censored at date of last contact.

10.4 Overall Survival

Measured from date of randomization to date of death from any cause. Patients known to be alive are censored at date of last contact.

10.5 Performance Status

Patients will be graded according to the Zubrod Performance Status Scale.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

11.0 STATISTICAL CONSIDERATIONS

11.1 Accrual Goal

We anticipate that 113 eligible patients will be randomized per year to this study on a group-wide basis. We will also assume that 10 percent of enrolled patients will be found to be clinically or pathologically ineligible and hence, not randomized so our Step 1 sample size will be inflated to account for this. Based on an extensive review of the contemporary literature (see Section 2.0, Table 1), we estimate that 3-year disease free survival (DFS) for patients at increased risk for pelvic and iliac node metastasis undergoing a standard pelvic lymphadenectomy is 55%. A poll of centers of excellence suggest that a 10-12% improvement in 3-year DFS (65-67%) for patients in extended lymphadenectomy would be meaningful and establish extended node dissection as the standard of care in this patient population. Assuming exponential survival, 5 years of patient accrual, 3 additional years of follow-up and a sample size of 564 eligible patients (282 per arm), the study has 85% power to detect a 28% reduction in the hazard rate of progression or death with extended lymph node dissection compared to limited

dissection (hazard ratio 0.72). This corresponds to an improvement in 3-year DFS from 55% to 65% or alternatively median DFS would be extended from 3.5 to 4.8 years if the DFS distributions are exponential. We will use a one sided stratified log rank test with α = 0.025, and the analysis will be intent-to-treat.

Assuming an ineligibility rate of 10%, total accrual (eligible + ineligible patients) to the initial step is expected to be 620 patients.

As a secondary endpoint, overall survival is also of great interest. If extended lymph node dissection is found to be statistically significantly better than standard lymph node dissection with respect to DFS, then an analysis of the survival endpoint will follow. We will allow for three more years of follow-up after the primary analysis has been conducted to assess potential survival differences. If we assume that the standard arm has 5-year survival of 55% then we will have 83% statistical power to detect a hazard ratio of 0.72 (55% vs. 65% survival at 5 years) using a one-sided stratified logrank test with alpha=0.025.

11.2 Analysis of Primary Endpoint

The trial will first open to selected sites with high volume cystectomy practices (more than 30 per year). Each surgeon will be credentialed for enrolling in this vanguard lead-in based on review of case logs, operative and pathology reports as well as photographic documentation of competence in performing a pelvic and iliac lymphadenectomy including standard pelvic plus bilateral common iliac and pre-sacral nodes. Rationale: to monitor quality control – a) ability to consistently perform extended node dissection and completeness of the standard dissection; b) make necessary modifications to protocol if needed; c) to monitor effects of neoadjuvant chemotherapy and consistency of adjuvant chemotherapy; d) to monitor any morbidity attributable to extended node dissection.

A first feasibility analysis would be conducted after the first 15 patients have been randomized. This analysis will address the feasibility and measurement quality of the video and/or photographic documentation of the nodal dissections at each institution by surgeon. The Study Chairs anticipate that the intra-operative photography will be of sufficient quality to credibly demonstrate the expected completeness of the node dissection. The video and/or photographs will be analyzed for compliance with the stated boundaries of the nodal dissection and feed-back will be given to each center based on this feasibility analysis. Operative and pathology reports will be analyzed for consistency with the photographic documentation.

The second feasibility analysis would be conducted 1 year after all vanguard sites have IRB approval of this study at which time it is expected that approximately 100 patients will have been enrolled. If the planned accrual rate of 100 patients is not met, consideration will be given to closing the study due to lack of feasibility. However, this is just a guideline and there may be extenuating circumstances related to, for example, delays in IRB approval that might also be considered. If the study does reach this initial accrual goal, it would be opened up more broadly to other qualifying centers.

If this trial continues past the two feasibility assessments, three formal interim analyses are planned to evaluate the efficacy of extended lymph node dissection. The first will be conducted after 25% of the expected events (relapse or death without relapse) have been reported on the control arm. The second after 50% of the events have occurred on the control arm, and the third when 75% of the expected events have occurred on the control arm. See the table for number of events and expected time when events will occur. The interim analyses will be conducted based on the number of events in the standard LND arm and not the estimated calendar time. Estimated number of events in the experimental arm are provided for descriptive purposes only. At each interim analysis, evidence suggesting early termination of the trial and a conclusion that the extended lymph node dissection is no better than standard dissection would be if the alternative hypothesis of a 28% improvement in DFS with the experimental arm is

rejected at the 0.005 level, using an extension of the logrank test that allows for testing a relative risk not equal to 1. In addition, the null hypothesis of no difference in DFS will be tested at the one-sided level of 0.005. If the decision is to continue the study for the full specified period, we estimate the final analysis will occur approximately three years after completion of accrual. The final DFS analysis will be conducted when 184 events have been observed on the standard LND arm, using a one-sided stratified logrank test with a significance level of 0.022 to account for multiple interim testing.

If the DFS analysis is statistically significant, the survival analysis will follow approximately two years later when 166 deaths have occurred on the control arm. The stratified logrank test will be performed at the one-sided 0.025 level.

Interim Analysis	Anticipated Analysis Time Relative to Study Activation	Percent of Expected Information On Control Arm	# of Events in the Control Arm (Standard LND)	Anticipated # of Events on Experimental Arm (Extended LND) (assuming the alternative hypothesis)
1	38 months	25%	46	34
2	56 months	50%	92	70
3	73 months	75%	139	108

With 282 eligible patients randomized to each arm, estimates of morbidity and toxicity frequencies can be estimated to within ± 6% (95% confidence interval).

In addition to formally testing DFS at the interim analyses, the DSMC will also consider the secondary endpoints of morbidity (intra-operative and up to 90 days post-operatively) and survival.

11.3 Analysis of Surgical Endpoints

Surgical endpoints in patients randomized to extended PLND versus standard PLND will also be of interest, including operative time, whether or not nerve sparing was performed, morbidity and mortality (intra-operative, peri-operative, and at 90 days), length of hospital stay, underlying histology (pure urothelial versus mixed), lymph node counts and lymph node density, and whether adjuvant chemotherapy was received. These will be analyzed using generalized linear models, with confidence intervals and tests based on robust standard errors. Adjustments will be made for multiple comparisons. In patients randomized to the extended PLND arm, the proximal extent of node dissection will be analyzed in an exploratory manner. Also, the two arms will be compared for differences in time to local recurrence, and the time to retroperitoneal soft tissue recurrence using a log-rank test.

11.4 Analysis of Translational Medicine Endpoints

Aim: To identify the relationship between expression of markers of epithelial mesenchymal transition in the primary bladder tumor with local tumor stage, the burden of lymph node metastases, and the likelihood of disease recurrence among patients undergoing cystectomy for muscle invasive bladder cancer.

Tumor marker expression will be measured as a function of proportion of cells staining and intensity of staining (IHC studies) and/or relative level of mRNA expression (compared to internal controls). Associations between marker expression and nodal status (positive vs negative, low disease burden versus high disease burden), and neoadjuvant chemotherapy will be tested using chi square test. Kaplan Meier estimates of survival and DFS based on marker expression will be performed and corresponding survival and DFS curves will be compared using log rank testing. Cox proportional hazards regression analysis will be performed to estimate hazard ratios for progression free survival. Those analysis will be repeated, stratified by whether patients received

neoadjuvant and adjuvant chemotherapy. Where associations look different by strata, formal tests of interaction will be performed in order to assess markers associated with chemoresistance.

If we assume that 70% of patients will have adequate tissue samples available based on prior SWOG experience with surgical trials, then we will have 396 samples (198 per arm). The following table provides estimate of the minimally detectable hazard ratio for disease-free survival for those with the tissue marker of interest vs. those without. These calculations assume 5 years of accrual, 3 additional years of follow-up, median DFS of 3-year in those with the marker, a two-sided alpha=0.05 and 80% statistical power. Similar survival hazard ratios can be detected with two additional years of follow-up. These calculations also assume there is no interaction between the marker of interest and the randomized treatment assignment (type of lymph node dissection).

	Prevalence of Tissue Marker		
	10%	20%	30%
DFS Hazard Ratio for Those with versus Those without the Marker of Interest	1.82	1.57	1.50

In some cases, there may be a combination of markers that have a multiplicative effect on the risk of relapse or death. In addition to assessing multivariate proportional hazards regression models, we will also develop classification and regression trees to assess these potential multiplicative effects among the markers.

Although statistical power is lower, we also would like to evaluate whether some tissue markers are predictive of DFS and survival in those who receive neoadjuvant chemotherapy compared to those who did not. In other words, we will evaluate the marker by chemotherapy interaction, at least in a preliminary fashion. If we assume the following distribution of a tissue marker and neoadjuvant chemotherapy:

	Prior Exposure to Neoadjuvant chemotherapy			
Tissue Marker Status (30% prev.)	Yes		No	
Absent	35%	HR = .48	35%	HR = 1.0
Present	15%		15%	

(and assume 55% 3-year DFS for those without the marker) and we specify a two-sided alpha=0.05 then there will be 80% statistical power to detect a difference in DFS hazard ratios of 1.0 for the tissue marker absence vs. presence in those without neoadjuvant chemotherapy versus a HR = 0.48 for the tissue marker absence vs. presence in those with prior chemotherapy, suggesting a predictive tissue marker for chemotherapy resistance.

This analysis assumes that type of nodal surgery does not have an impact, and the randomized groups are pooled together.

11.5 Data and Safety Monitoring Committee Oversight

A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of SWOG, three SWOG members, three non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every six months from the SWOG Statistical Center, and will meet at the Group's bi-

annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study.

12.0 DISCIPLINE REVIEW

12.1 Surgeon Credentialing

Each surgeon must be pre-approved and credentialed to participate in this study. Credentialing will be performed by the Study Chairs and will include:

a. Completion of accredited urologic residency training (for all participating surgeons);

b. Cumulative number of radical cystectomies over past 3 years ≥ 50;

c. Number of radical cystectomies performed at your hospital(s) (not necessarily by one surgeon) > 30/year;

d. De-identified operative and pathology reports from five recent radical cystectomies;

e. Representative intra-operative photos (or edited video) demonstrating complete extended pelvic and iliac lymphadenectomy. Minimum photos required are right and left pelvic and extended LND if this was performed showing right and left CI, pre-sacral and proximal limit of dissection.

A completed **S1011** Surgeon Credentialing Checklist (available on the **S1011** protocol abstract page on http://swog.org) plus operative reports, pathology reports, and photo documentation must be submitted electronically to the SWOG Genitourinary Protocol Coordinator at S1011Credentialing@swog.org for distribution to the Study Chairs. Within two weeks of submission of all credentialing information, the SWOG Operations Office or Study Chair will notify the surgeon when approved for participation. No registration will be accepted until the surgeon is credentialed. Credentialing may be subject to review at time of audit. See also Section 14.0 for on-study data submission requirements.

12.2 Surgery Review

a. All surgeries performed as part of this study will undergo a central surgical review. The goal of this review is to verify that the lymph node dissection was done according to the assigned randomization and the criteria specified in Section 7.0 of the protocol.

b. The following are required to be submitted within 14 days of surgery to the SWOG Data Operations Center in Seattle (see Section 14.4b):

1. **S1011** Intra-Op Surgical Assessment Form Standard versus Extended LND;

2. Digital image(s) of intra-operative photo(s) showing extent of node dissection;

3. Copy of the operative report(s);

4. Copy of corresponding pathology report(s).

The **S1011** Urology Study Chairs will review all these data within 7 days of receipt and interact with the surgeons at each site to provide feedback in order to ensure the consistency of the extent of node dissection in the two arms.

Independent oversight will be provided by the SWOG Surgery Quality Committee who will review these data at least annually and make recommendations for improvement in monitoring and data collection as needed.

13.0 REGISTRATION GUIDELINES

NOTE: Participation in this study is limited to pre-approved, credentialed surgeons. The SWOG Operations Office or Study Chair will notify each surgeon when approved for participation. The registering physician must be the pre-approved, credentialed surgeon intended to perform the assigned procedure.

13.1 Registration Timing

Patients must be registered prior to surgery (no more than 28 calendar days prior to planned surgery).

13.2 Investigator/Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Web site (enter credentials at https://www.ctsu.org; then click on the Register tab) or by calling the PMB at 301/496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each investigator or group of investigators at a clinic site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

Requirements for site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

13.3 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

Oncology Patient Enrollment Network (OPEN) will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Cooperative Group Credit

f. Credit Investigator

g. Patient Initials

h. Patient's Date of Birth

i. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

j. Country of Residence

k. ZIP Code

l. Gender (select one):
- Female Gender
- Male Gender

m. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

n. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self-Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

o. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White Unknown

13.4 Registration Procedures

a. All site staff will use OPEN to enroll patients to this study. OPEN is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed

at https://open.ctsu.org, from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

b. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should refer to Section 5.0 to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).
- The study site is listed as "approved" in the CTSU RSS.

c. 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' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the SWOG or CTSU roster:

1. If you are a SWOG member, to perform registrations on SWOG protocols you must have an equivalent 'Registrar' role on the SWOG roster. Role assignments are handled through SWOG.

2. If you are not a SWOG member, to perform registrations on SWOG protocols you must have the role of Registrar 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' web site. This will allow them to assign staff the "Registrar" role.

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

d. Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

13.5 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see below for details.

14.3 Data Submission Procedures

Institutions must submit on-study data electronically via the Web by using the SWOG CRA Workbench and follow-up data through the Medidata Rave® clinical data management system.

a. To access the CRA Workbench **for on-study data**, go to the SWOG Web site (http://swog.org) and logon to the Members Area. After you have logged on, click on the *CRA Workbench* link to access the home page for CRA Workbench website. Next, click on the *Pre-Rave Data Submission* link and follow the instructions.

To submit data via the web the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,

2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed, and

3. You have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam/index.jsp)

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For other difficulties with the CRA Workbench, please email technicalquestion@crab.org.

b. To submit **follow-up data**, access to the trial in Medidata Rave® is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, you must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam/index.jsp) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

All users at sites that were approved for registrations in RSS will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and

can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU help Desk at 888/823-5923 or by e-mail at ctsucontact@westat.com.

You may also access Rave® via the SWOG CRA Workbench on the SWOG website (www.swog.org) by clicking the link for Rave Data Submission.

c. If you need to submit data that are not available for online data submission, the only alternative is via facsimile. Should the need for this occur, institutions may submit data via facsimile to 800/892-4007 or 206/342-1680 locally. Please do not use a cover sheet for faxed data. Please make sure that each page of all faxed data include the SWOG patient number, study ID and patient initials

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF STEP 1, REGISTRATION:

Submit the following:

S1011 Prestudy Form

Operative Report from TURBT

Pathology Report from TURBT

Radiology reports from cross-sectional imaging performed to determine the pre-REG clinical T stage, e.g. CT, MRI, or PET/CT.

b. WITHIN 14 DAYS OF SURGERY, FOR ALL PATIENTS RECEIVING ON-STUDY SURGERY:

Submit copies of the following:

S1011 Intra-Op Surgical Assessment Form Standard Versus Extended LND

Intra-Op Photos
(Note: The Photo Upload Form is located in the data submission section of the SWOG CRA Workbench in the **S1011** Reg 2 folder under the 'Follow Up' tab. Photos should be obtained after the randomization and surgical assessment).

Operative Report from cystectomy

Pathology Report from cystectomy

c. IF PATIENT CONSENTED, WITHIN 28 DAYS OF RANDOMIZATION:

Submit specimens as outlined in Section 15.0.

d. IF PATIENT NOT ELIGIBLE OR NOT CONTINUING TO STEP 2 RANDOMIZATION, WITHIN 14 DAYS AFTER GOING OFF STUDY:

S1011 Pre-Randomization Off Study Form

S1011 Intra-Op Surgical Assessment Form Standard Versus Extended LND
(Note: No Intra-Op photos are required for patients not going on to Step 2, Randomization)

e. WITHIN 7 DAYS FROM HOSPITAL DISCHARGE:

S1011 Surgeon's Post-Op Data Form Standard Versus Extended LND

S1011 Adverse Event Form

f. WITHIN 90 DAYS POST-SURGERY

S1011 Surgeon's 90-Day Assessment Form Standard Versus Extended LND

S1011 Adverse Event Form

g. AFTER SURGERY, EVERY THREE MONTHS FOR YEAR ONE; EVERY SIX MONTHS FOR YEARS TWO AND THREE; AND ANNUALLY UNTIL SIX YEARS AFTER RANDOMIZATION OR UNTIL DEATH:

Submit copies of the **S1011** Follow Up Form
(via the Medidata Rave® clinical data management system)

h. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death **and a final S1011** Follow Up Form.
(via the Medidata Rave® clinical data management system)

15.0 SPECIAL INSTRUCTIONS

Specimens for banking and translational medicine studies (submitted to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201) are optional for the patient.

Sites must seek additional patient consent for the future use of paraffin embedded tissue (or slides). If patient consents, specimens must be submitted as described below. Specimens will be banked for future use including exploration of the role of epithelial-to-mesenchymal transition in bladder cancer metastasis (see Appendix 18.2 for a description of methods). The translational medicine studies will be performed once funding is obtained.

15.1 Specimen Submission Timepoints

With patient's consent, specimens must be submitted at the following times (see Section 9.0):

Within 28 days of randomization, submit:

a. Two paraffin embedded blocks (preferred) or 10 unstained slides from the primary tumor (allowed, if the primary tumor blocks will not be released) AND a copy of the pathology report

b. Eight unstained, 4-micrometer (μm), formalin-fixed, paraffin-embedded (FFPE) sections from the "left pelvic" and "right pelvic" lymph node packets

15.2 Specimen Submission Instructions

Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp) or via the link on the **S1011** protocol abstract page on the SWOG website (www.swog.org).

15.3 Specimen Collection Kits

Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe

expedited adverse event reporting for this protocol. See also Appendix 18.1 for general and background information about expedited reporting.

b. Reporting methods

This study requires that expedited adverse event reporting use the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS web-based application located at http://ctep.cancer.gov.

c. When to report an event in an expedited manner

When the adverse event requires expedited reporting per Table 16.1 below, submit the report within 10 calendar days of learning of the event.

d. Other recipients of adverse event reports

The Operations Office will forward reports and documentation to the appropriate regulatory agencies as required.

Adverse events determined to be reportable must also be reported according to local policy and procedures to the Institutional Review Board responsible for oversight of the patient.

e. Expedited reporting for surgery-only protocols

Reporting requirements for surgical treatment are provided in Table 16.1. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Program at the SWOG Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1. Expedited reporting requirements for adverse events experienced by patients who have received surgery on this study.

ATTRIBUTION	Grade 4		Grade 5[a]	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			**CTEP-AERS**	**CTEP-AERS**
Possible, Probable, Definite	**CTEP-AERS**		**CTEP-AERS**	**CTEP-AERS**

CTEP-AERS: Indicates an expedited report is to be submitted using the NCI CTEP-AERS within 10 working days of learning of the event.

a This includes all deaths within 30 days of the surgical procedure, regardless of attribution. Any death that occurs more than 30 days after the surgical procedure and is attributed (possibly, probably, or definitely) to the surgery and is not due to cancer recurrence must be reported according to the instructions above.

b Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent by fax to 210-614-0006.

17.0 BIBLIOGRAPHY

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18.0 APPENDIX

18.1 Determination of Expedited Adverse Event Reporting Requirements

18.2 Translational Medicine Background and Methods

18.1 Determination of Expedited Adverse Event Reporting Requirements

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. Expedited adverse event reporting principles and general guidelines follow; specific guidelines for expedited adverse event reporting on this protocol are found in Section 16.0.

All serious adverse events must also be reported to the local Institutional Review Board (IRB). Documentation of this reporting should be maintained for possible inspection during quality assurance audits.

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Submission (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.
When a study includes both investigational and commercial agents, the following rules apply.

- *Concurrent administration*: When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.
- *Sequential administration*: When a study includes an investigational agent(s) and a commercial agent(s) on the same study arm, but the commercial agent(s) is given for a period of time prior to starting the investigational agent(s), expedited reporting of adverse events that occur prior to starting the investigational agent(s) would follow the guidelines for commercial agents. Once therapy with the investigational agent(s) is initiated, all expedited reporting of adverse events should follow the investigational guidelines.

Steps to determine if an adverse event is to be reported in an expedited manner

Step 1: *Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE).* The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov)**.** Additionally, if assistance is needed, the NCI has an Index to the CTCAE that provides help for classifying and locating terms. All appropriate treatment locations should have access to a copy of the CTCAE.

Step 2: *Grade the event using the NCI CTCAE version specified.*

Step 3: *Determine whether the adverse event is related to the protocol therapy (investigational or commercial).* Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: *Determine the prior experience of the adverse event. Expected* events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered *unexpected,* for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in

- the current NCI Agent-Specific Adverse Event List (for treatments using agents provided under an NCI-held IND);
- the drug package insert (for treatments with commercial agents only);
- Section 3.0 of this protocol.

Step 5: *Review Table 16.1 in the protocol to determine if there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring.*

Step 6: *Determine if the protocol treatment given prior to the adverse event included an investigational agent(s), a commercial agent(s), or a combination of investigational and commercial agents.*

NOTE: If the patient received at least one dose of investigational agent, follow the guidelines in Table 16.1.

NOTE: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the agent(s) must be reported according to the instructions in Table 16.1.

18.2 Translational Medicine Background and Methods

a. Translational Medicine: Exploring role of epithelial-to-mesenchymal transition in bladder cancer metastasis.

1. Background

Despite the clinical importance of metastasis, much remains to be learned about the biology of the metastatic process. The development and progression of cancer is a multistep process. The classical view of metastasis is that during tumor progression, cancer cells acquire multiple alterations that render them increasingly competent to establish metastatic lesions in specific organs. *([1])*

Epithelial-to-mesenchymal transition (EMT) is a developmental program that plays critical roles in wound healing and solid tumor metastasis. *(2)* The process is characterized by loss of adhesion and cell polarity accompanied by cellular invasion and migration. At the molecular level, EMT is associated with loss of expression of E-cadherin, adherens junction, and cell polarity genes coupled with increased expression of matrix metalloproteases and vimentin, as well as elevated expression of transcriptional repressors of E-cadherin, such as Twist, Zeb-1, Zeb-2, Snail, and Slug. Members of the miR200 family of micro RNAs also play central roles in maintaining the "epithelial" phenotype by directly binding to the transcripts encoding Zeb-1 and Zeb-2, therapy suppressing their translation and promoting their degradation. *([3],[4])* The TGFB/bone morphogenic protein (BMP) cytokines and other paracrine drivers of the EMT phenotype act in part by downregulating expression of the miR200 family and promoting expression of E-cadherin's repressors. *(5)*

It has recently been demonstrated that Twist, a repressor of CDH1, may promote tumor metastasis by silencing Ecadherin expression and inducing EMT. *(6)* Twist expression has been associated with higher stage and grade for patients with bladder cancer. Moreover, twist expression and loss of E Cadherin in the primary bladder tumors have been shown to be independent predictors of disease specific survival for patients with bladder cancer. *(7)* It has also been suggested that Twist regulates apoptosis through p53 dependent and independent pathways, resulting in chemoresistance to cisplatin and microtubule agents such as taxanes, which are frequently used in the treatment of advanced bladder cancer. *(8)*

The p63 proteins were originally cloned due to their homology to p53. However, p63 does not appear to function as a classical tumor suppressor, since it is rarely genetically inactivated in epithelial malignancies. Recent work suggests that urothelial cancer stem cells retain expression of several of the molecular markers that are expressed by the normal basal urothelial cells, including p63. Nonetheless, other studies have concluded that p63 is downregulated in muscle-invasive tumors, suggesting that it might in fact function as a tumor suppressor to inhibit invasion and metastasis. *(9)*

Activation of the AKT signaling pathway gives cancer cells a proliferative and survival advantage. Dysregulation of the AKT pathway is a frequent event in cancer and can occur as the result of several mechanisms, but is most commonly due to the inactivation of PTEN via deletion and/or mutation, or mutation of PIK3CA, the catalytic subunit of the PI3K protein

complex. Recent studies have shown that both PIK3CA mutations and PTEN deletions are frequent events in bladder cancer, with 25% of tumors having PIK3CA mutations, predominantly in the helical domain, and 12% having loss of heterozygosity at the PTEN locus. *(10)* Furthermore, at the expression level, 49% of tumors studied showed significant down-regulation of PTEN. *(11)* Importantly, it has been demonstrated in various settings that AKT has a role in EMT, and that this mechanism may be mediated by the activity of MMP. *(12,13,14,15)*

Another key regulatory checkpoint dysregulated in bladder cancer is the RB/p16 axis, which normally controls transit through the G1-S transition. Alterations in both the RB or p16INK4A tumor suppressor genes are common events in bladder cancer, occurring as mutations and deletions. *(16)* Interestingly, recent studies have found a linkage between RB depletion and EMT through deregulation of E-cadherin, suggesting that loss of RB not only affects proliferation, but can also aid in the transition to a metastatic phenotype through EMT. *(17)*

It has been demonstrated that loss of E-cadherin expression accompanied by increased expression of matrix metallprotease-9 (MMP-9) was associated with a poor outcome in patients with muscle-invasive urothelial cancer. *(18)* More recently, two other groups linked EMT to poor outcome in patients. *(19,20)* In addition, in other solid tumors EMT is associated with "stemness" and drug resistance. *(21,22)*

The goal of this correlative study is to explore the role of epithelial mesenchymal transition in the process of metastases and disease progression for patients undergoing radical cystectomy for bladder cancer.

2. Specific hypotheses:

Hypothesis: Epithelial mesenchymal transition drives lymph node metastasis and systemic circulation of tumor cells in patients with muscle invasive bladder cancer.

Aim a: To identify the relationship between expression of markers of epithelial-mesenchymal transition in the primary bladder tumor with local tumor stage, the burden of lymph node metastases, and the likelihood of disease progression among patients undergoing cystectomy for muscle invasive bladder cancer.

Aim b: To correlate the expression of markers of epithelial-mesenchymal transition in primary bladder tumors.

3. Methods and specimen collection

Sample collection:
After the patient has consented to the **S1011** trial, radical cystectomy with lymph node dissection will be performed in a carefully controlled fashion per study protocol. Bladder and nodal specimens will be fixed in formalin and paraffin embedded according to a study prescribed protocol. Two paraffin embedded blocks representative of the primary tumor will be sent to the SWOG biorepository, where tissues will be used for tissue microarrays and allocated for RNA extraction. (See Section 15.0)

Immunohistochemistry protocol:
The following well-characterized antibodies and corresponding final working concentrations will be used for this study: E-Cadherin , mAb, Zymed,Cat# 13-1700, 1:1000, Twist, rabbit poly Ab, Santa Cruz

Biotechnology, clone H81, dilution 1:50; EGFR , mAb, Zymed 28-005, dilution 1:10; Ki67 (MIB-1), mAb, DAKO, M7240, dilution 1:2000; P53 (AB-2), mAb, calbiochem, #0P09L, dilution 1:500; P63(4A4), mAb, Santa Cruz, # sc-8431 , dilution 1:500; pAKT(ser 473), rabbit poly, cell Signaling, # 3787L, dilution 1:50; PTEN mAb, Cascade, ABM-2052, dilution 1:75; RB, mAb, QED, #3101-31-7, dilution 1:1000.

An avidin-biotin peroxidase method will be used for immunohistochemical staining. Briefly, 6-µm whole-mount sections will be deparaffinized in xylene and rehydrated in graded alcohol. Endogenous peroxidase will be blocked by immersing slides in 0.1% PBS/H2O2 for 15 min. For antigen retrieval, slides will be exposed to heating in a microwave oven and 0.01 mol/L citric acid (pH 6) for 15 min. After cooling to room temperature, appropriate blocking sera will be applied for 30-min incubation followed by 4°C overnight incubation with primary antibodies. After extensive washing, adequate secondary antibodies (biotinylated horse anti-mouse or goat anti-rabbit, 1:500) will be applied for 30-min incubation followed by avidin-biotin complex for an additional 30 min. Diaminobenzidine will be used as the final chromogen, and then the slides will be counterstained with hematoxylin, dehydrated, and mounted.

For each molecular marker, expression will be recorded as the percentage of tumor cells with positive immunostaining as well as the intensity of staining on a scale of 0-2, where 0=no or weak staining, 1=moderate staining, and 2=strong staining.

The scoring system utilized will be unique to each marker, as staining patterns and their significance differ for each antibody. When possible, a composite score will be used for IHC of the proposed EMT markers, so that intensity of staining and proportion of staining can be examined concurrently. In other instances, tissue expression will be scored by the proportion of cells stained. In both cases, analysis will be performed with the scores as categorical variables. For example, in our recent publication, staining for E-cadherin was categorized as 0 (negative or less than 10% moderate to strong membranous staining in tumor cells), 1 (≥10%, but less than 50% moderate to strong membranous staining), or 2 (≥50% moderate to strong membranous staining), whereas Zeb-1 was categorized as positive (nuclear staining in ≥10% of tumor cells) or negative (no nuclear staining or nuclear staining in <10% of tumor cells). The following system is commonly used to score EGFR expression in bladder tissues: zero (undetectable staining or membrane staining in less than 10% of the tumor cells), +1 (faint, incomplete membrane staining in more than 10% of the tumor cells), +2 (weak to moderate, complete membrane staining in more than 10% of the tumor cells), and +3 (strong, complete membrane staining in more than 10% of the tumor cells). EGFR protein expression is then classified as negative (scores 0 and 1) or positive (scores 2 and 3).

Real-time Reverse Transcriptase PCR analysis:
RNA isolation: Total RNA from paraffin embedded tissue samples will be isolated using RecoverAllTM Total Nucleic Acid Isolation kit for FFPE Tissues (Ambion, Inc) according to the manufacturer protocol. RNA purity and integrity will be measured by NanoDrop ND-1000 (Thermo Scientific, Wilmington, DE) and Agilent Bioanalyzer (Agilent Technology, Santa Clara, CA). EMT markers (E-cadherin, ZEB1, ZEB2, Vimentin, MMP2, MMP9 and p63) will be analyzed by real-time PCR.

Real-time PCR technology (ABI PRISM 7500; Applied Biosystems, Foster City, CA) will be used in conjunction with Assays-on-Demand (Applied Biosystems). The comparative CT method (1) will be used to determine relative gene expression levels for each target gene. The cyclophilin A gene will be used as a internal control to normalize for the amount of amplifiable RNA in each reaction. The PCR mixture consisting of Taqman Master Mix (without uracil-N-glycosylase), MultiScribe reverse transcriptase, RNase inhibitors, and 20 ng (this amount is depends on the Standard Curve generated using each set of primers) of total RNA will be prepared in a final volume of 25 ul. Thermal cycling will be initiated with reverse transcription at 48°C for 30 min and the Taq Gold activation step at 95°C for 10 min. The thermal profile for the PCR will be 95°C for 15 s and 60°C for 1 min. Data will be obtained during 40 cycles of amplification. We will use primers/probe sets (Assays-on-Demand) which are designed to amplify a shorter amplicon from Applied Biosystems to increase the sensitivity of PCR reaction since the integrity of RNA from paraffin embedded tissues will be lower relative to RNA obtained from fresh frozen tissues. E-cadherin; Hs00170423_m1, ZEB1; Hs00232783_m1, ZEB2; Hs00207691_m1, Vimentin; Hs00185584_m1, MMP2; Hs00234422_m1, MMP9; Hs00957562_m1 and Cyclophylin A; Hs99999904_m1. Primers and fluorescent probes for p63 isoforms will be designed by Primer Express 3.0 (Applied Biosystems).

For miRNA analysis, total RNA will be reverse transcribed using the miRNA-specific TaqMan miRNA Reverse Transcription kits for hsa-miR-200a, hsa-miR-200b, miR-200c, and miR-429 following the manufacturer protocol (Applied Biosystems, Inc.). miRNA expression will be quantified using commercially available TaqMan miRNA assays (Applied Biosystems, Inc.). Expression will be normalized using TaqMan miRNA endogenous control assay RNU24. Real-time PCR will be carried out on an Applied Biosystems ABI PRISM 7500 using TaqMan Universal PCR Master Mix, No AmpErase UNG (Applied Biosystems, Inc.).

b. Translational Medicine: Exploring the pre-metastatic niche in muscle-invasive bladder cancer

1. Background

The 'seed-and-soil' hypothesis was proposed by Paget in 1889, and suggests that the biological characteristics of certain tissues may foster invasion and growth of metastases. *(23)* Identification of these susceptible areas, termed pre-metastatic niches, has numerous possible clinical applications. For instance, patients with more abundant niches may have increased metastatic potential – niche prevalence could therefore serve as a personalized supplement to current prognostic models. *(24)*

In bladder cancer, we have generated preliminary data suggesting that the pre-metastatic niche may be marked by neutrophils (i.e., $CD15^+$ cells). Specifically, we have assessed benign nodal tissue derived from 20 patients with muscle-invasive bladder cancer. Through an IRB-approved protocol (COH IRB 11210), benign lymph node tissue collected at the time of cystectomy from a cohort of 20 patients was obtained. These patients had (1) a pathologically verified diagnosis of muscle invasive disease prior to cystectomy, (2) pT2a-T4N0 disease determined at the time of cystectomy, (3) no radiographic evidence of metastasis prior to cystectomy, and (4) available paraffin-embedded sections

encompassing both primary tumor and benign lymph nodes. From these patients, 4 μm sections of benign lymph node tissue were stained with monoclonal antibodies directed at VEGFR1 (ImClone Systems) and CD15 (a human neutrophil marker; Abcam). Stained sections for pSTAT3 (Santa Cruz Biotechnology) were performed, since recent data suggest the potential role of phosphorylated Signal transducer and activator of transcription 3 (pSTAT3) in mediating neutrophil recruitment to pre-metastatic sites. *(25)* Co-localization of VEGFR1 and $CD68^+$ macrophages was observed, and sections were stained with a monoclonal antibody directed at CD68 (Signet). Image Pro Plus software was used to count positive cells and an average count across the 8-100x fields was used for statistical analyses. The median age of this cohort was 70 (range, 40-86), and the cohort included a relatively balanced number of patients with clinical stage 2 and 3 disease (11 patients and 9 patients, respectively). Only 1 patient had received neoadjuvant chemotherapy in this cohort, and 2 patients had received adjuvant treatment (all 3 patients received cisplatin/gemcitabine as their cytotoxic regimen).

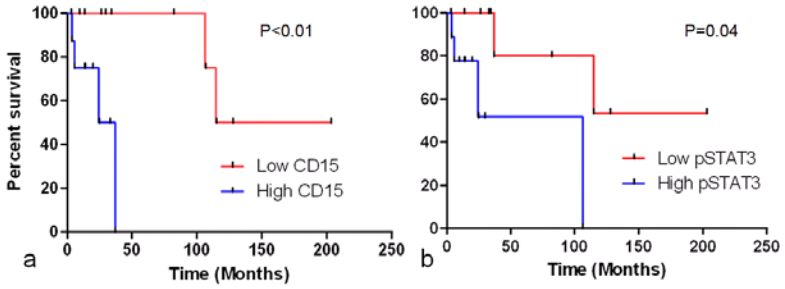

Figure 1. Increased neutrophil infiltration and STAT3 activation in the benign lymph nodes of muscle invasive bladder cancer is associated with lessened overall survival. In a cohort of 20 patients with muscle-invasive bladder cancer, survival was compared in cohorts divided by (a) $CD15^+$ cell (i.e., neutrophil) count or (b) $pSTAT3^+$ cell count above or below the mean within the overall cohort.

A wide spectrum of positive staining was seen for each of the assessed biomarkers. Analyses of overall survival were conducted using the Kaplan-Meier method (with the log-rank test) based on subgroups characterized by high (above the mean) or low (below the mean) biomarker expression. There was a significant extension of overall survival amongst patients with a decreased degree of neutrophilic infiltration (P<0.01; Figure 1). Also, lower levels of pSTAT3 were associated with improved overall survival (P=0.04; Figure 1). In contrast, no difference in outcome was observed based on VEGFR1 or CD68 expression above or below median values (P=0.60 and P=0.28, respectively). Also, no difference in survival was observed when segregating patients by clinical stage (P=0.73).

2. Statistical Plan

The primary endpoint of the clinical study is to determine whether use of radical cystectomy with extended lymphadenectomy yields an improvement in DFS as compared to radical cystectomy with standard lymphadenectomy. The study uses a historical estimate of 55% 3-year DFS in association with standard lymphadenectomy, and suggests that a 10-12% improvement (i.e., to 65-67%) would be meaningful and

establish extended lymphadenectomy as a stand of care. With these estimates in mind, assuming exponential survival, 5 years of patient accrual, 3 additional years of follow-up and a sample size of 564 eligible patients (282 per arm), the study has 85% power to detect a 28% reduction in the hazard rate of progression or death with extended lymphadenectomy (hazard ratio, 0.72). Assuming an ineligibility rate of 10%, total accrual is estimated to be approximately 620 patients.

Several correlative studies have been built into the original protocol. The statistical considerations for the current study are slightly different, as we plan to incorporate a testing and validation cohort. We expect that 395 patients will have usable lymph node samples as specified in the protocol (assuming that tissue is available for 70% of study participants). The testing cohort will be comprised of the first half of these patients, or approximately 200 patients, and the results from the second 200 patients will be used for validating the results. On a case by case basis, some patients who are found to be ineligible for the clinical trial due to reasons other than pathology may be used for these analyses.

The underlying hypothesis for the correlative studies associated with this aim is that biomarker expression levels (i.e., (CD15, pSTAT3, VEGFR1 and CD68 cell counts in the benign nodal tissue) may predict clinical outcome (i.e., DFS). For each biomarker, recursive partitioning will be used to determine the cutoff value of average cell count that maximally distinguishes DFS within the training cohort. These cutoffs will be examined in the validation cohort.

Table 1 provides an estimate of the minimally detectable hazard ratio for DFS for those with an elevated biomarker expression level (i.e., high CD15 expression) relative those with a low biomarker expression level. These effect sizes apply equally to the training and validation subsets since the sample size will be the same for both. The designation of “high” and “low” biomarker expression levels will be based on the cutoffs designated in the training cohort. These calculations assume 5 years of accrual, 3 additional years of follow-up, median 3-year DFS of 50% in those with “high” biomarker expression, a two-sided alpha of 0.05, and 80% statistical power. These calculations further assume that there is no interaction between the marker of interest and the randomized treatment assignment (type of lymph node dissection). Because all currently enrolling patients are being offered participation in the banking of their lymph node tissue, there will be no loss of sample size for this recently activated trial.

	Prevalence of “High” Biomarker Expression Level				
	10%	20%	30%	40%	50%
DFS HR	2.40	1.93	1.80	1.74	1.73

Table 1. Minimally detectable hazard ratio (HR) for DFS for those with “high” biomarker expression versus those with “low” biomarker expression. Assuming 80% statistical power, 2-sided alpha of 0.05, and 200 patients in the training set (same power for the 200 patients in the validation set).

In some cases, there may be a combination of biomarkers that have a multiplicative effect on the risk of relapse. Classification and regression trees to assess the potential multiplicative effect amongst markers and form prognostic groups based on these algorithms will be explored. Prognostic models using traditional clinical factors such as clinical stage,

pathologic stage, age, receipt of neoadjuvant chemotherapy and performance status to predict disease-free survival will be developed in the training set and the area under the curve (AUC) will be calculated in the validation set. (43) Then, the model that also incorporates markers of the pre-metastatic niche (identified in the training set) will also be added to the model and the AUC will again be estimated. A comparison of the traditional AUC to the niche AUC will be made to evaluate whether these biomarker expression factors contribute to the DFS prognosis in this patient population.

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Informed Consent Model for S1011

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

This model informed consent form has been reviewed by the DCTD/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document that are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the SWOG Operations Office for approval before a patient may be registered to this study.

Please particularly note that the questions related to banking of specimens for future study are in bolded type and may not be changed in any way without prior approval from the SWOG Operations Office.

Readability Statistics:	
Flesch Reading Ease	64.3 (targeted above 55)
Flesch-Kincaid Grade Level	8.3 (targeted below 8.5)

- Instructions and examples for informed consent authors are in *[italics]*.
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- The term "study doctor" has been used throughout the model because the local investigator for a cancer treatment trial is a physician. If this model is used for a trial in which the local investigator is not a physician, another appropriate term should be used instead of "study doctor".
- The dates of protocol updates in the header and in the text of the consent is for reference to this model only and should not be included in the informed consent form given to the prospective research participant.
- The local informed consent must state which parties may inspect the research records. This includes the NCI, the drug manufacturer for investigational studies, any companies or grantors that are providing study support (these will be listed in the protocol's model informed consent form) and SWOG.

  "SWOG" must be listed as one of the parties that may inspect the research records in all protocol consent forms for which patient registration is being credited to SWOG. This includes consent forms for studies where all patients are registered directly through the SWOG Data Operations Office, all intergroup studies for which the registration is being credited to SWOG (whether the registration is through the SWOG Data Operations Office or directly through the other group), as well as

consent forms for studies where patients are registered via CTSU and the registration is credited to SWOG.

- When changes to the protocol require revision of the informed consent document, the IRB should have a system that identifies the revised consent document, in order to preclude continued use of the older version and to identify file copies. An appropriate method to identify the current version of the consent is for the IRB to stamp the final copy of the consent document with the approval date. The stamped consent document is then photocopied for use. Other systems of identifying the current version of the consent such as adding a version or approval date are allowed as long as it is possible to determine during an audit that the patient signed the most current version of the consent form.

*NOTES FOR LOCAL INVESTIGATORS:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This model for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is titled: "Taking Part in Cancer Treatment Research Studies". This pamphlet may be ordered on the NCI Web site at *https://cissecure.nci.nih.gov/ncipubs* or call 1-800-4- CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for authors and investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

S1011, "A Phase III Surgical Trial to Evaluate the Benefit of a Standard versus an Extended Pelvic Lymphadenectomy Performed at Time of Radical Cystectomy for Muscle Invasive Urothelial 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 bladder cancer that is confined to the bladder but invades into the deep portion of the bladder and requires bladder removal with removal of the lymph nodes in your pelvis.

Why is this study being done?

The purpose of this study is to compare the effects, good and/or bad, of performing a standard lymph node removal versus an extended lymph node removal. The extended lymph node surgery removes additional lymph nodes that are farther away from the bladder than those removed during standard lymph node surgery. Lymph nodes are present throughout the body and function normally to fight infection. They may also trap cancer cells that spread from a tumor. This is also referred to as metastasis. It is important remove the lymph nodes near the bladder to determine if they contain bladder cancer cells that have spread beyond the bladder. While extended lymph node removal is done commonly at some centers it is still considered experimental since we do not know if the additional surgery improves outcome.

How many people will take part in the study?

About 620 people will take part in this study.

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

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- History and physical examination

- Blood tests to evaluate your blood counts, kidney function, liver function, and blood clotting time
- Chest X-ray or CT scan of the chest
- CT scan or MRI of the abdomen and pelvis
- Bone scan if your study doctor thinks its necessary
- A biopsy of your bladder tumor
- A manual exam of your bladder

During the study …

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures during follow-up as outlined below. They are part of regular cancer care.

- Blood tests to evaluate your blood counts, kidney function, and liver function
- Chest x-ray or CT scan of the chest
- CT scan or MRI of the abdomen and pelvis

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. This will happen after your surgery has started, so you will not know which kind of surgery you have received until after your surgery. Neither you nor your study 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 undergo standard lymph node removal at the same time that your bladder is removed.

If you are in Group 2 (often called "Arm B") you will undergo an extended lymph node removal surgery at the same time that your bladder is removed.

During the surgery, your surgeon will take photos or video demonstrating the extent of the surgery. The doctors coordinating this study will be reviewing the photo(s) and video to verify you received the surgery you were randomized to. When you are finished with the surgery, your study doctor will provide standard cancer care for your stage of cancer. Your study doctor may recommend chemotherapy given through the veins if cancer is found in your lymph nodes or if the tumor has spread into the fat surrounding the bladder or into adjacent organs and if you did not receive chemotherapy before surgery. Some patients may have received chemotherapy before surgery and may receive additional chemotherapy after surgery, depending on the stage of their disease and after discussion with their study doctor. After surgery, you will undergo routine follow-up testing including CT scans or MRIs of your abdomen and pelvis, chest x-rays, and blood tests of the liver, kidney and blood to look for cancer recurrence which are part of standard cancer care. These tests will be performed every three months for the first year after your surgery, every six months for the second and third years, and then once a year until six years after your surgery. As part of the study, you will be followed for 6 years after the surgery.

How long will I be in the study?

After you are finished undergoing the surgery, the study doctor will ask you to visit the office for follow-up exams as noted above for 6 years to make sure the cancer has not returned.

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.

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 study doctor. Another reason to tell your study 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 stop you from taking part in 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 have already been informed of the risks associated with your bladder surgery and signed a separate surgical consent. The following are the risks of participating in this 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. There is also 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 the surgery include those which are:

Likely

- **Longer operation time if randomized to extended lymph node removal which has a low likelihood of increased risk or side effects**

Less Likely

- **Small increase in chance of requiring a blood transfusion**

Rare but serious

- **Blood clots in your legs**
- **Accumulation of lymphatic fluid in your pelvis**
- **Both are risks of the procedure in general and could potentially be slightly higher with a more extensive node dissection**

Reproductive risks: You should not become pregnant while on this study. *(sentence deleted 3/29/13)* **It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.**

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 study doctors hope the extended lymph node surgery will be more useful against cancer compared to the standard lymph node surgery, there is no proof of this yet. We do know that the information from this study will help study doctors learn more about extended lymph node dissection as a treatment for cancer. This information could help future cancer patients.

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

Your other choices may include:

- **Getting treatment or care 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:

- Local Institutional Review Board (IRB)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- SWOG

A description of this study will be available on http://www.clinicaltrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results of the study. You can search this web site any time.

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

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 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 study 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 will not pay 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.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study. We will tell you about important 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 _____ *[name(s)]* at _____ *[telephone number]*.

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 _____ *(telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). *[*Only applies to sites using the CIRB.]*

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

You can say "yes" or "no" to the following studies. Please mark your choice for each study.

1. Future Contact

   Occasionally, researchers working with SWOG may have another research idea that relates to people on a SWOG study. In some cases, to carry out the new research, we would need to contact participants in a particular study. You can agree or not agree to future contact.

   I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study.

Yes **No**

Consent Form for Use of Specimens for Research

About Using Specimens for Research

You are going to have surgery to remove your bladder and the lymph nodes in your pelvis.

If you agree, samples of your tumor tissue and/or lymph nodes will be sent to an outside lab to study the biology of your cancer. The tumor tissue and lymph node samples will be taken at the time of your surgery. *(3/29/13)* (You will not need to have another biopsy or surgery for this purpose.)

We would like to keep some of the specimens that are left over for future research. If you agree, these specimens will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How Are Specimens Used for Research" to learn more about specimen research.

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 left over 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 kept for 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.

In the future, people who do research may need to know more about your health. While SWOG may give them 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.

Sometimes specimens are used for genetic research (about diseases that are passed on in families). Even if your specimens are used for this kind of research, the results will not be put in your health records.

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.

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
The greatest 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 specimens may be kept for use in research to learn about, prevent, treat or cure cancer.**

   Yes No

2. **My specimens may be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).**

   Yes No

3. **Someone may contact me in the future to ask me to allow other uses of my specimens.**

   Yes No

If you decide to withdraw your specimens from a SWOG Specimen Repository in the future, a written withdrawal of consent should be submitted through your study doctor to the SWOG Operations Office. Please designate in the written withdrawal whether you would prefer to have the specimens destroyed or returned to the study doctor.

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 this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages 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.

Participant _____

Date _____

Specimen Consent Supplemental Sheets

How are Specimens Used for Research?

Where do specimens come from?

A specimen may be from a blood sample or from bone marrow, skin, toenails or other body materials. People who are trained to handle specimens and protect donors' rights make sure that the highest standards of quality control are followed by SWOG. Your doctor does not work for SWOG, but has agreed to help collect specimens from many patients. Many doctors across the country are helping in the same way.

Why do people do research with specimens?

Research with specimens can help to find out more about what causes cancer, how to prevent it, how to treat it, and how to cure it. Research using specimens can also answer other health questions. Some of these include finding the causes of diabetes and heart disease, or finding genetic links to Alzheimer's.

What type of research will be done with my specimen?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. Some research looks at diseases that are passed on in families (called genetic research). Research done with your specimen may look for genetic causes and signs of disease.

How do researchers get the specimen?

Researchers from universities, hospitals, and other health organizations conduct research using specimens. They contact SWOG and request samples for their studies. SWOG reviews the way that these studies will be done, and decides if any of the samples can be used. SWOG gets the specimen and information about you from your hospital, and sends the specimen samples and some information about you to the researcher. SWOG will not send your name, address, phone number, social security number or any other identifying information to the researcher.

Will I find out the results of the research using my specimen?

You will not receive the results of research done with your specimen. This is because research can take a long time and must use specimen samples from many people before results are known. Results from research using your specimen may not be ready for many years and will not affect your care right now, but they may be helpful to people like you in the future.

Why do you need information from my health records?

In order to do research with your specimen, researchers may need to know some things about you. (For example: Are you male or female? What is your race or ethnic group? How old are you? Have you ever smoked?) This helps researchers answer questions about diseases. The information that will be given to the researcher may include your age, sex, race, diagnosis, treatments and family history. This information is collected by your hospital from your health record and sent to SWOG. If more information is needed, SWOG will send it to the researcher.

Will my name be attached to the records that are given to the researcher?

No. Your name, address, phone number and anything else that could identify you will be removed before they go the researcher. The researcher will not know who you are.

How could the records be used in ways that might be harmful to me?

Sometimes, health records have been used against patients and their families. For example, insurance companies may deny a patient insurance or employers may not hire someone with a certain illness (such as AIDS or cancer). The results of genetic research may not apply only to you, but to your family members too. For disease caused by gene changes, the information in one person's health record could be used against family members.

How am I protected?

SWOG is in charge of making sure that information about you is kept private. SWOG will take careful steps to prevent misuse of records. Your name, address, phone number and any other identifying information will be taken off anything associated with your specimen before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. Also, people outside the research process will not have access to results about any one person which will help to protect your privacy.

What if I have more questions?

If you have any questions, please talk to your doctor or nurse, or call our research review board at (Insert IRB's Phone Number).