TITLE: BLADDER CANCER PATIENT DATABASE WITH TISSUE AND SPECIMEN PROCUREMENT.

1. Study purpose, goals, and significance:

The first goal of this study is to create a comprehensive, prospective database of patients undergoing surgical treatment for bladder cancer. The database would include pre-operative characteristics (age,clinical stage,etc), peri-operative parameters (treatment choosen, blood loss, operative time, complications,etc), pathologic data (tumor type,grade,stage), and post-operative follow up with an emphasis disease progression and survival. The second goal of the study is to create a tissue, urine, and serum bank of bladder cancer patients. This tissue/urine/serum bank will be used to potentially evaluate molecular markers, genetic alterations, and adverse histiologic characteristics. The specimens will remained linked to the patient database to allow eventual correlation between the biologic nature of the cancer cells and patient outcome. As new molecular markers are identified, maintaining a tissue/urine/serum bank will serve as an invaluble resource as it will provide a large, diverse sample of bladder cancer patients to further evaluate these markers. The significance of the entire study is that by careful correlation between biologic parameters and clinical outcomes the ability to identify patients who are at a greater risk for an adverse outcome is improved. The ability to store bladder cancer patient specimens will allow future molecular analysis to further define cancer cell biology, which may in turn contribute to the development of prognostic markers as well as novel treatments for bladder cancer.

2. Bankgrond and related research:

Bladder cancer is the fourth most common cancer in men and the eighth most common cancer in women in the United States. In 2004, there were over 60,000 new cases of bladder cancer diagnosed with over 12,000 deaths reported from the disease. A majority of these cases were superficial tumors, but 20-40% did present or will progress to muscle invasive bladder cancer.(6) In 2001, Stein et. al. published the largest series of surgically treated bladder cancer patients.(1) This publication, from the University of Southern California, reported on 1,054 patients who underwent radical cystectomy. At USC they had constructed a comprehensive database to follow these patients. Through the effort of these researchers, they were able to define survival data, prognostic variables, and time to recurrence for bladder cancer patients. This research has provided important prognostic information for both clinicians and patients. The USC group has also utilized the use of histological characteristics. In 2005, Quek et. al. reported on the prognostic significance of lymphovascular invasion in bladder cancer specimens.(2) The use of molecular techniques to elucidate cancer biology and to further develop prognostic subgroups has been applied to bladder cancer research. Olumi et. al. discovered that allelic loss of 17p, the location of the p53 gene, will predispose patients to high grade transitional cell carcinoma of the bladder.(3) The involvement of p53 in the pathogenesis was further supported by Sidransky et. al. when they reported a mutation rate in p53 of 61% of bladder cancer specimens.(4) Several research efforts have identified potential targets on a molecular level. The transmembrane glycoprotein EGF-R has an altered distribution with malignant tissue as well as normal tissue of bladder cancer patients.(5) The level of thrombospondin-1, an extracellular matrix glycoprotein which inhibits angiogenesis, was found to significantly associated with tumor and overall survival in bladder cancer patients.(5)

3. Accrual Population and Target

Given this is a prospective database it is difficult to anticipate the number of patients who will be enrolled. It is likely we could enroll 40-60 patients per year. Our hope is to continue recruitment of patients for several years with a goal of 200 patients.

4. Recruitment Methods:

The participants will be patients who are seen at the Loyola University Medical Center Department of Urology for the treatment of bladder cancer. There will be no active recruitment

5. Inclusion/Exclusion Criteria:
The study is open to all patients who will be undergoing radical cystectomy at LUMC. There are no exclusion criteria in regards to age, gender, or ethnicity.

6. Inclusion of Special Classes or Vulnerable Subjects:
Elderly patients who will undergo cystectomy, but who are not competent will be included if their legally authorized guardian consents for them.

7. Study Procedures:
i. All patients seen with a diagnosis of bladder cancer require a metastatic evaluation. This will include a CT scan of the abdomen, chest x-ray, blood count, liver function tests, and in some cases a bone scan. A significant number of these patients require a cardiac evaluation prior to surgery, this requires referral to a medical internist. The patient will need definitive surgery for the cancer. The treatment recommendations will be made according to the current standard of care. The patients choose the treatment option best for them and this does not effect the study. These patients will receive standard post-operative care (ICU,antibiotics,blood transfusions,nasogastric suction,etc) as needed. All bladder cancer patients require follow-up. This will be carried out by the attending physcians preferred schedule and will not be effected if the patient is enrolled in the study. In addition to being seen in the clinic the patients will receive periodic x-rays,CT scans, and lab tests as part of their follow-up.
ii. The only program that is added to the patients who enroll in the study will the storage of bladder tissue and collection of a urine and blood sample. The tissue collection will be performed by the LUMC pathology department after appropriate evaluation. The specimens will be stored by the LUMC Dept of Pathology until utilized in subsequent studies. The urine sample will be taken from the routine urine that is obtained in the urology clinic during a patient visit. The blood sample will be obtained when the patient gives blood for routine pre-operative labs at LUMC. For patients who have their pre-operative labs obtained outside of LUMC the sample will obained the day of surgery from a rountinely placed arterial or central line. Thus patients will not need to undergo any additional blood draws to accomodate the study.

8. Process of Informed Consent:
The attending physicians of the Department of Urology will explain the project to the patient undergoing radical cystectomy. The consent will be obtained by the attending physician during the pre-operative visit.
For those patients whose clinical information is entered in the database and this information used for retrospective chart review purposes only, the need for informed consent will be waived.

9. Data Storage and Confidentiality:
All data will be stored in a excel spreadsheet that will be maintained by the PI. All patients enrolled in the study will be assigned an unique database number (UDN). The database will only connect medical information to the UDN. The database will not contain patient names, birthdates, medical record numbers, or other identifying information. All pathologic specimens will be given a pathology specimen number (PSN) designated by the Department of Pathology. All urine and blood samples will be identified by the UDN. A second excel spreadsheet will be created that will reference the UDN and PSN to the patient name and medical record number. This second spreadsheet will be kept locked in the PI's office and only the PI will have access to it. Besides the PI, a departmental research nurses and urology residents will have access to the raw data to assist in maintaining and analysis of the data. No identifying patient information, UDN, or PSN will ever be included in research presentations or publications. At the conclusion of the study the spreadsheet containing the patients name, medical record number, UDN, and PSN will be destroyed.

10. Potential Risks:
The risks associated with participation in this project are minimal and include the possibility of invasion of privacy and loss of confidentiality. Although every measure will be undertaken to

ensure the confidentiality and privacy of the patients who participate in this study, extraction of data from hospital charts or pathology reports for research purposes, as well as obtaining information for follow-up, may be regarded by some as an invasion of privacy. Database managers, and others associated with maintaining the database, will have access to patient identifying information, thus the chance of a lapse in confidentiality is greater, than if no database were maintained

11. Potential Benefits:
This database and tissue/urine/serum bank will hopefully provide a powerful research tool that will help identify clinical, histologic, and molecular characteristics which will allow clinicians to more effectively treat patients with bladder cancer. There will be minimal to no immediate benefits for participants. It is possibe this project could contribute to development of a novel treatments that could be applied to a participant who developed recurrent cancer years after their initial treatment. There exists great potential benefit for the field of urology and society as a whole. By defining characteristics of aggressive cancers, these patients can be identified and new treatment stategies can be developed that may improve survival (early surgery, neo-adjuvant chemotherapy, extended lymph dissection, etc.). The tissue/urine/serum bank will provide large heterogeneous supply of tumor cells that can be studied. These future studies will potenially provide the foundation to the identification of novel treatment targets for bladder cancer.

12. Risk/Benefit Relationship:
The risks to the participants are minimal. They do not undergo any additional evaluation or intervention than a bladder cancer patient who is not enrolled in the study. There does exist a database that could potentially be source of a violation of confidentiality. Although with the previously outlined steps to prevent this, it is unlikely it will occur. The potential to discover additional prognostic markers and more effective treatment regimens for bladder cancer outweighs these small risks

13. Finacial Considerations:
There is no additional charge to the patient for the additional blood draw or the storage of their tissue, urine, or blood.

14. Potential Future Projects:
The following are potential projects that could arise from this project. These are areas that are of current intrest to the LUMC Department of Urology researchers.

1. Evaluation of GRP78 in the role of bladder cancer prognosis and response to neoadjuvant chemotherapy. Glucose-regulated proteins (GRP) are stress response proteins that appear to have anti-apoptotic properties that may play a role in resistence to systemic therapies.(7) The role of GRP78 in bladder cancer is an exciting area as progress has aleardy been made in regard to its involvement in prostate cancer.(8) These studies would evaluate tumor cell concentration of this protein.

2. Evaluation of heparin binding epidermal growth factor-like growth factor (HB-EGF) as marker for bladder cancer. The concentration of this protein in bladder cancer cells has already been shown to have some prognostic significance for progression.(9) At LUMC, a pilot study has demonstrated promise for HB-EGF as a urine marker for bladder cancer.(10) Futures studies would seek to expand the urine studies and include evaluation of serum.

3. Evaluation of c-Met as a urine/serum marker for transitional cell carcinoma of the bladder. c-Met is the transmembrane hepatocyte growth factor (HGF) receptor tyrosine kinase. Upregulation HGF and c-Met have been implicated in a number of human malignancies.(11) The studies would evaluate the concentration of shed c-Met in urine and serum and correlate those levels to bladder cancer progression and recurrence.

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