Evaluation of the accuracy of ultrasound in monitoring the size and growth of small renal masses

IRB Protocol
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A. Study Purpose and Rationale

Bladder cancer is the most common malignancy of the urinary system, with an estimated 74,000 new cases and 15,000 deaths in the United States in 2012. It is the fourth leading cause of cancer death in males (from highest to lower risk of cancer death: lung, prostate, colon, bladder). It is also the most expensive malignancy in the United States, with an estimated cost of greater than $4 billion per year. Ninety percent of cases in the US are urothelial cell carcinoma (UCC), with squamous cell carcinoma, small cell carcinoma, and adenocarcinoma comprising the remainder of cases.

At presentation, 75% of bladder UCC are low grade and stage Ta (noninvasive papillary) or T1 (tumor invades subepithelial connective tissue, but not muscularis propia).

Approximately 75-85% of all patients with bladder cancer are initially diagnosed with "non-muscle-invasive disease," which includes stages Ta, TIS or T1. The presence of muscle invasion is an important clinical distinction, as patients with muscle invasive bladder cancer have < 50% 5-year overall survival rate, even with aggressive treatment.

Cystoscopy with biopsy is a primary tool in determining the histologic grade and depth of invasion of a bladder tumor. Bimanual exam and imaging studies are also important in determining local extent or invasion of disease, as well as pelvic lymph node involvement. Radical cystectomy is the standard of care for patients with muscle invasive disease, but it is a highly morbid operation, and has a much lower overall survival rate in patients who are found to have node-positive disease at time of cystectomy.

Among patients with muscle invasive bladder UCC, 60% have muscle invasive tumors at initial presentation, while 40% have progressed from noninvasive tumors. The three main indications for intravesical therapy are:

1) Eradication of TIS with or without associated papillary tumor.
2) Eradition of residual papillary tumor after incomplete resection.
3) To reduce recurrence and progression in completely resected tumors.

The most important objective in treating non-muscle invasive bladder cancer is to prevent progression to muscle invasive disease. Standard recommended use of intravesical chemotherapy involves one dose within 24 hours (ideally within 6 hours) of transurethral

resection of bladder tumor (TURBT) in the absence of bladder perforation. Conversely, BCG should never be given intravesically within 2 weeks of TURBT, and instead, it is usually admisnistered beginning 3-4 weeks after TURBT.

In comparing intravesical chemotherapy and BCG, studies have found that intravesical chemotherapy (mitomycin, thitepa, doxorubicin) reduces tumor recurrence after transurethral resection (mean reduction in recurrence = 14%), but studies have not been able to show that it has an influence on the time to progression to muscle invasive disease. On the other hand, BCG reduces recurrence resection (mean reduction in recurrence = 43%) and significantly reduces the risk of progression after transurethral resection. Maintenance BCG improves long-term results, while maintenance chemotherapy offers no advantage. Therefore, intravesical BCG therapy is the most effective regimen for non-muscle invasive bladder cancer and is the standard of care after transurethral resection of high-risk non-muscle invasive bladder cancer.

However, some patients with non-muscle invasive bladder cancer experience tumor recurrence after BCG therapy. Risk factors for recurrence include: multiple or diffuse bladder tumors, recurrence less than 1 year from resection, incomplete tumor resection, and large bladder tumor (especially >3 cm), higher tumor stage, higher tumor grade, concurrent presence of CIS, tumor aneuploidy, visible bladder tumor within 6 months after treatment.

There is not set protocol for BCG therapy and duration of therapy is instructed to be individualized to each patient, but the general principals are to:

1) Administer BCG intravesically once a week for 6 weeks, then re-evaluate the bladder 6 weeks after therapy is finished (urine cytology, cystoscopy, and +/-repeat biopsy).
2) If T1, high grade Ta, or CIS recurs after the initial 6 weeks of BCG, physicians and patients may consider another 6 week course of BCG vs. radical cystectomy
3) If BCG eradicates bladder UCC, consider maintenance BCG therapy.

It has been found that two 6 week courses of BCG have a higher response rate than one 6 week course, and this is often the route many physicians take with their patients.

It is important to note that delaying radical cystectomy more than 12 weeks (from the time of muscle invasion is diagnosed) decreases disease specific survival and overall survival.

Until recently, there has been no standard classification for BCG failure. Recurrence (one of the descriptors of "BCG failure") of carcinoma in situ is a stage that is better-studied after BCG therapy. About 80% of CIS will recur after TURBT, but only 30% will recur after BCG therapy. Bladder recurrence of Ta cancer after TURBT alone is 50%, most within one year. Bladder recurrence of T1 stage cancer after TURBT alone is more than 70%. More studies on recurrence after BCG and TURBT in patients with Ta and T1 are needed.

In 2005, Nieder and colleagues met at the international consensus panel to discuss the management of nonmuscle invasive tumors. One of the many things discussed by this group was the definition of BCG failure, where the term was broken down into four main categories:

BCG-refractory disease is the term used to describe when there is failure to achieve a disease-free status by 6 months after initial BCG therapy with either maintenance or retreatment at 3 months because of either persistent or rapidly recurrent disease. It also includes any progression in stage, grade or disease extent by 3 months after first cycle of BCG. *BCG-resistant disease* is when there is recurrence or persistence of disease at 3 months after the induction cycle. It is of lesser degree, stage or grade and is no longer present at 6 months from BCG retreatment with or without TUR. Disease improves then resolves with further BCG. *BCG-relapsing* disease is when there is recurrence of disease after achieving a disease-free status by 6 months. In short, disease resolves after BCG then returns. Relapse is further identified by time of recurrence as early (within 12 months), intermediate (12-24 months) or late (>24 months).

BCG-intolerant disease is when disease recurs after a less-than-adequate course of therapy is applied because a serious adverse event or symptomatic intolerance that mandates discontinuation of further BCG.

Shirakawa and colleagues in 2012 performed a study that uses Nieder and colleague's classification to divide patients with non-muscle invasive bladder cancer who had undergone induction BCG therapy that had resulted in failure into 4 major BCG-failure groups. This group aimed to investigate whether the defined classification system could successfully identify patients with a higher malignant potential. Multivariate analysis showed that pathologic grade G3 at BCG failure and BCG-refractory group were independent predictors of stage progression. The 10-year progression free survival rates were 53% in BCG-refractory group, 91% in BCG-relapsing group.

This study shows how the term "BCG failure" involves heterogenous characteristics and behavior with respect to stage progression and disease-specific survival.

BCG-refractory patient are at higher risk for subsequent stage progression and disease-specific death. A recurrent pattern after induction BCG therapy according to Nieder's classification had an association with subsequent clinical course and one can identify patients who had a markedly worse outcome after initial induction BCG therapy.

There are numerous critiques of this paper. This study was performed in a retrospective manner and included a small number of patients. Some patients had undergone TURBT and intravesical chemo one or more times before initial BCG therapy. In addition, there were disparities in treatments before and after BCG failure, which may have introduced bias into the results. Most of the patients had undergone additional of intravesical agents. Moreover, this study included patients with low grade bladder cancer. Including this population can undermine the true effect of BCG, as low-grade patients have lower risk of progression to begin with.

Because there is no standard classification system for BCG failure, previous studies have noted inconsistent rates of stage progression after BCG therapy. Examples of such inconsistencies include: some studies classifying patients as having BCG failure after a single induction course of BCG, while others used failure after two courses as their definition. To add, patients with persistent disease and patients with recurrent disease after an initial response have been combined in some studies. A few reports combined all patients who could not complete the BCG therapy because of toxicity. Meanwhile, in the most general sense, any recurrence of disease after BCG therapy can be referred to as "BCG failure.". Most studies do not indicate the disease-free interval after the last BCG induction. These inconsistencies have led to comparisons of outcome in a very heterogeneous population, and this has resulted in confusion regarding treatment decisions in patients classified as having BCG failure.

I propose to further study if Nieder's definitive classification of BCG failure could estimate the different malignant potentials for subsequent stage progression and disease-specific survival. Specifically, I will investigate the differences in clinical features, and subsequent stage progression and disease-specific survival among patients with BCG failure, specifically patients in "BCG-refractory" and "BCG-relapsing" groups. I hypothesize that at the 5% level of significance (alpha), 10 year stage progression-free survival rate analysis between BCG-Refractory vs. BCG-Relapsing groups is 53.2% vs. 91.1%

Definitions: starting point will be defined as the date of BCG failure (date of recurrence, or persistence at 6 months), and end point will be defined as date of stage progression.

B. Study Design

The study design is retrospectively review data from within Caisis Cancer Database, of patients with NMIBC bladder cancer treated with TURBT + BCG over the past 22 years at Columbia University (over 170 patients). We will use Nieder's definitions of BCG Failure categories to divide patients into their corresponding groups.

The primary outcomes will be stage-free progression rate and disease-specific survival rate for BCG-refractory and BCG-relapsing groups, which has been estimated by Shirakawa and colleagues as 53.2% and. 91.1%, respectively.

Sample Size and Power

At Alpha = 0.05 and power = 0.90, 32 patients are needed in each sample. This is considering:

- Group 1 (refractory) proportion of progress-free survival rate in 10 years = .532
- Group 2 (relapsing) proportion of progress-free survival rate in 10 years = .911

C. Study Procedures:

This retrospective analysis will include:

Patients who underwent treatment with induction BCG therapy scheduled for weekly administration for 6 week at a full dose of induction BCG therapy in 40 mL of saline with retention in the bladder for 1-2 hours. (standard) After 6 weeks, repeat transurethral resection will have documented first rumor response – if any tumor left, induction therapy repeated. Patients will have been assessed at follow-up using urine cytology and cystoscopy at 3 month intervals during the initial 2 years, every 6 months for the next 3 years, and yearly thereafter. IV urography, ultrasonography, CT, PET/CT will have been used to evaluate distant metastasis and mets to the upper urinary tract every year for at least 5 years

Stage Progression will be confirmed as histological muscle invasion or distant metastases.

We will exclude patients with CIS, low grade Ta and T1. Including this population can undermine the true effect of BCG, as low-grade patients have lower risk of progression to begin with. Exclude patients who had undergone TURBT and intravesical chemotherapy one of more times before the initial TURBT+BCG therapy

We will use Nieder et al definitions of BCG Failure to divide patients into their corresponding groups: BCG refractory, BCG relapsing, BCG resistance and BCG intolerant; and we will focus on the BCG refractory and BCG relapsing populations for further analysis.

We will use the Kaplan-Meier Method to construct the stage progression-free and disease-specific survival rate curves, and they will be compared using the log-rank test. We will use the Chi-squared tes tot compare the proportions between BCG refractory and BCG resistance. We will use the Cox proportional hazards model to perform univariate and multivariate analyses of data to determine risk factors for subsequent recurrence or progression, with stepwise forward selection. Variables will include age, sex, concurrent CIS status/pathological grade/stage/tumor multiplicity at time of initial induction BCG therapy and BCG failure.

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