BLADDER CANCER SURVIVAL STUDY

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More than 71,000 new cases of bladder (urothelial) cancer were diagnosed in the United States in 2009 accounting for approximately 14,000 deaths annually. In recent decades the overall incidence of bladder cancer has appeared to be rising and this may be due to the latent effects of tobacco abuse, which is very prevalent in the Southeastern portion of the United States, and particularly in Kentucky, Tennessee, the Carolinas, and Georgia. The single most important risk factor for urothelial cancer is smoking. Other well described factors include exposure to aniline dyes used in coloring, printing, and rubber industries. A history of radiation or cyclophosphamide chemotherapy can increase the risk of developing bladder cancer.

Initial treatment of bladder tumors involves excisional biopsy in the form of a transurethral resection (TURBT). This may require more than one sitting in cases where the tumor is large or the initial sampling is found to be incomplete. The TNM staging system for bladder cancer was used (AJCC Cancer Staging Manual. 6th ed. New York, NY: Springer, Copyright 2002, 335-340). In the case of stage Ta but high-grade urothelial cancer or of stage TIS or T1, intravesical chemo/ immunotherapy are often warranted. The agents most commonly utilized for chemotherapy in the USA are Mitomycin and Doxorubicin. Bacillus Calmette-Guerin (BCG) is the most frequently used intravesical agent for immunotherapy, with the addition of Interferon in some cases to treat refractory disease. BCG is the agent of choice for intravesical therapy in patients with high-grade tumors. The majority of patients present with non-muscle invasive disease (~ 70%). The minority of patients (~25%) present with tumor invasion into the muscularis propria (T2 or T3). These patients typically require a radical cystectomy with urinary diversion and regional lymphadenectomy. Cystectomy is the surgical removal of the entire urinary bladder. An ileal conduit involves repurposing a segment of the ileum to divert urine from the ureters to the skin, where it is collected with an external bag. A neobladder, a much more complex form of urinary reconstruction after cystectomy, involves reconfiguring a segment of small and/or large intestine as a continent internal storage pouch for urine. Urethrectomy, surgical removal of the urethra, may also be required.

In males, simultaneous Urethrectomy is not routinely performed unless the tumor involves the urethra. In females, urethrectomy is typically performed concomitantly, unless a neobladder is planned. In select cases of muscle-invasive disease, a bladder-preserving approach employing

systemic chemotherapy and radiation may be therapeutic. Management of metastatic bladder cancer typically relies on systemic combination chemotherapy with any of several common regimens, most frequently Gemcitabine and Cisplatin (GC) or Methotrexate, Vinblastine, Adriamycin, and Cisplatin (MVAC). The former regimen is less toxic, but both appear to have similar efficacy in the metastatic setting.

We will report the University of Tennessee Medical Center Knoxville (UTMCK) survival data and management of patients who were diagnosed and treated with bladder cancer.

Methods:

Data of interest was extracted from the UTMCK Tumor Registry from the period of January 1993 to December 2008. This data includes stage at initial diagnosis, age at diagnosis, initial treatment, secondary treatment, the development of secondary cancers, and survival.

Results:

Bladder Cancer Incidence:

The number of new cases of bladder cancer detected at UTMCK through the Tumor Registry from 1993 – 2008 was 832 cases. The number of cases diagnosed each year is shown in Figure 1. We have seen an increase in the number of new cases diagnosed each year, with the highest number of cases in 2002, 2004, 2007 and 2008. The breakdown by sex was 597 males (71.75%) and 235 females (28.25%) shown in Figure 2. Bladder cancer is nearly three times more common in men than women. Bladder cancer is roughly two times as common among American white males as among African-American males and is roughly one and one-half times more common among white American women than among African-American woman.

Age:

The age at diagnosis is shown in Figure 3. The majority of the patients presented between the ages of 60-79, evenly divided @ 30.4% between 60-69 and 70-79 years of age. The median age for men in our study was 68 years and 70 for women. The number of patients presenting in the 80-89 age group was 15.1%. We are seeing an increasing number of octogenarians in our clinics with either gross or microscopic hematuria who are found to have urothelial cancer upon clinical work up.

Stage:

The initial stage at diagnosis is shown is Figure 4. The majority of patients were Stage T 0/I (67%) which is slightly less than the national average. The remainder (33%) presented with

Stage II, III, and IV muscle-invasive, extra-vesical, or metastatic disease. The stage was unknown in 26 (3%) of patients

The TNM staging system for bladder cancer was used (AJCC Cancer Staging Manual. 6th ed. New York, NY: Springer, Copyright 2002, 335-340).

Table 1: Classification Criteria for Bladder Cancer by Stage:

Stage 0 Ta or Tis, N0, M0, (Non-invasive papillary carcinoma or Ca in situ)

Stage 1 T1, N0, M0 (invades sub epithelial connective tissue)

Stage 2 T2 a & b, N0, M0 (invades muscle)

Stage 3 Ta & b, N0, M0 (microscopically, macroscopically: extravesical mass or tumor invades prostate, uterus, vagina)

Stage 4 T4b, N0, M0 (tumor invades pelvic wall, abdominal wall) or any T with N1, 2, or 3 and M0 or M1 (metastasis in a single lymph node or distant metastasis)

Treatment:

The initial treatment for all patients to establish the diagnosis was surgery in 83%, usually consisting of a transurethral resection of the tumor with muscle included in the resection or biopsy to establish the stage. A small number of patients were treated with surgery and biologic response modifiers (i.e. BCG immunotherapy). BCG is usually given intravesically after a diagnosis of TIS or high grade T1 tumors to decrease recurrence and/or progression to T2 disease. An additional small number of patients were treated with surgery and intravesical chemotherapy (Mitomycin C or Adriamycin). These agents were used before BCG became the standard of care. Seventeen patients who presented with higher stage disease (T3, T4) were treated with chemo radiation and surgery. These are shown in Figure 5.

For those patients who were diagnosed as T0 (Ta,TIS) 373 patients, transurethral resection (TUR) was the only treatment in 354 (94.9%). Five patients were treated with partial cystectomy, 2 with total simple cystectomy, and seven (5 TIS) with radical cystectomy. The patients treated with partial cystectomy had isolated, well-defined lesions with a 2 cm negative margin and no evidence of TIS. Those patients treated with total simple or radical cystectomy had diffuse disease in the bladder that was not amenable to local/transurethral therapy.

For those patients who were diagnosed as stage T1, transurethral resection (TUR) was the only treatment in 78%, followed by TUR and BCG in 17%, and TUR and intravesical chemotherapy in 4% (Figure 6). Radical cystectomy with urinary diversion or partial cystectomy was the sole treatment in the majority of T2 patients (81%). An additional 13% received chemotherapy and or radiation therapy post-operatively (Figure 7). Patients with T3 disease were treated with radical cystectomy with urinary diversion or partial cystectomy only in 80%. The other 20% of T3 patients were treated with adjuvant chemotherapy and or radiation (Figure 8). The treatment of patients with T4 disease was more varied: some patients were treated with TUR

only followed by chemotherapy and/or radiation and depending on the response, then were treated with radical cystectomy and urinary diversion or partial cystectomy. Some were treated with radical cystectomy and urinary diversion followed by chemotherapy and/or radiation. Six percent of patients were not treated due to advanced disease and or poor medical condition (Figure 9). Partial cystectomy was only used in 5.5% of surgically treated patients with T2, T3, and T4 disease.

Patients with T1 Grade 3 disease represent a group of patients who have a high rate of progression to T2 disease. Treatment recommendations include an induction course of BCG or Mitomycin C followed by maintenance therapy or radical cystectomy with urinary diversion as initial therapy in select patients. In our series, 66 patients had T1 Grade 3 disease: 18 (27%) recurred locally and were treated with radical cystectomy, 1 (1%) recurred in the pelvis and 3 (4.5%) had distant metastases.

Secondary Cancer Diagnoses

A secondary primary cancer was diagnosed in 31.7% of the patients (264/832). The Tumor Registry had the secondary sties documented on 196 cases yielding 233 secondary sites (some patients had more than 2 primary sites). Prostate cancer was the most common followed by kidney cancer (Figure 10).

Bladder Cancer Survival by Stage

The overall bladder cancer survival by stage at UTMCK is shown in Figure 11. Our data is compared to National Cancer Data Bank from 1344 programs stage for stage in Figure 12 (a-e). There is no significant difference in Stages 0, 1, and 4. Our survival data is better for Stages 2 and 3. The reason for this remains speculative.

Discussion

Bladder cancer is a lethal disease whose primary cause is tobacco use. The use of tobacco is very prevalent in the southeastern United States. The number of newly diagnosed cases in both sexes has been steadily increasing over the past decade. The observed increase in incidence could be due to more assiduous diagnostic workup of individuals who present with hematuria and irritative voiding symptoms. Development of guidelines for workup of microhematuria and for improved physician and patient education has also probably contributed to observed increases in detection rates. We have presented data from a 15 year period at the University of Tennessee Medical Center Knoxville. Our data is consistent with data presented in the urologic literature in regards to presentation, age at diagnosis, stage at diagnosis, and treatment at each stage of the disease. Overall, survival of patients with bladder cancer has been steadily improving over the past four decades. While much of this gain could be the result of improvements in treating low-grade/stage disease and TIS, it appears that age-adjusted death rates have declined even in patients with invasive disease. This is shown in comparing our data with that of 1344 national cancer programs (Figure 13).

Suggested Reading

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