High Morbidity and Mortality Found for High-Risk, Non–Muscle-Invasive Bladder Cancer

Nearly 75% of patients with high-risk, non–muscle-invasive bladder cancer recur, progress, or die within 10 years of their diagnosis, according to a recent study published in Cancer (published online ahead of print June 4, 2013. doi: 10.1002/cncr.28147).

In this article, Karim Chamie, MD, MSHS, assistant professor in the department of urology at the University of California at Los Angeles and colleagues note that the bladder cancer-related mortality rate has dropped only 5% in the last 15 years, a slower decline than for most other solid tumors. They hypothesized that quality of care may be at least part of the problem and noted that suboptimal care (eg, not following guidelines) has been documented in patients with advanced and early bladder cancer.

A previous claims-based study of 4545 cases of high-grade, non–muscle-invasive bladder cancer found that only one patient received all the follow-up surveillance and treatments recommended in national guidelines, including those from the American Urological Association and the National Comprehensive Cancer Network (Cancer. 2011;117:5392-5401). Using data from the same study, researchers found that patients who received at least one-half of the recommendations had a statistically significant survival advantage (Cancer. 2012;118:1412-1421). The objective of the current study was to better elucidate the natural history of high-grade, non–muscle-invasive bladder cancer in terms of recurrence, progression, and cancer-related mortality.

**Study Results**

Dr. Chamie and his colleagues used the Surveillance, Epidemiology, and End Results (SEER)-Medicare Database to identify patients with bladder cancer who were diagnosed from 1992 to 2002. They identified 7420 patients aged at least 66 years with an incident diagnosis of nonmetastatic, high-grade, urothelial, non–muscle-invasive cancer. Within the study period, 981 patients (13%) died of bladder cancer, 2449 (33%) progressed to muscle-invasive disease, and 2897 (39%) had a non–muscle-invasive recurrence.

The 2-year, 5-year, and 10-year recurrence rates were 61%, 69%, and 74%, respectively; the corresponding progression rates were 13%, 23%, and 33%, respectively; and the bladder cancer-specific mortality rates were 6.5%, 10%, and 12%, respectively.

A competing-risks regression analysis was used to characterize the incidence of recurrence, progression, and bladder cancer-related mortality. This was done because competing causes of death may have precluded some patients from developing disease recurrence. The competing event was non–bladder cancer-related mortality, and was adjusted for age, sex, race, marital status, zip code-level income and education, comorbidity, tumor grade, and disease stage. These estimates were reported as subhazard ratios. The authors believe that this statistical model was appropriate because their recurrence and progression rates overall are in line with several previous single-institution series.

Using the multivariate competing-risks regression analysis, T1 disease was associated with a higher risk of recurrence (hazard ratio, 1.22; 95% confidence interval, 1.15-1.3) than Ta disease. The patients with T1 disease had a 7% higher absolute risk of recurrence at each time interval. Socioeconomic status, Tis disease, and higher-grade cancer were not found to be predictors of recurrence.

The group of subjects aged 70 years or older had a significantly lower hazard of progression than the younger patients. Also, those aged 80 years and older had a lower incidence of progression than their younger counterparts, but a higher absolute incidence of dying of bladder cancer than patients aged younger than 70 years. Women had a higher hazard of disease progression than men, and African Americans had a higher hazard of progression than whites.

“These findings are in line with previous findings,” says Douglas Scherr, MD, associate attending urologist at New York-Presbyterian Hospital, and professor of urology at...
Weill Medical College of Cornell University, both in New York City. “This is precisely why bladder cancer is such an expensive cancer to care for over the course of a lifetime since lifelong surveillance is necessary and recurrence is more the norm than the exception,” adds Dr. Scherr, who was not involved with the study.

**Clinical Implications**

Dr. Chamie and his colleagues note that their study is not the first to report on the progression and recurrence of non–muscle-invasive bladder cancer, but is the first to study it from a population standpoint. The main finding is that nearly 75% of patients with high-grade, non–muscle-invasive bladder cancer will develop disease recurrence within 10 years. Some 41% recurred with non–muscle-invasive disease, and 33% recurred with muscle-invasive bladder cancer. Among the group that develops disease progression, 40% die of bladder cancer, the researchers found.

“Patients with high-grade, non–muscle-invasive bladder cancer should be treated like they have high-grade bladder cancer and not just non–muscle-invasive bladder cancer,” says Dr. Chamie. “Many clinicians still falsely perceive [high-grade] non–muscle-invasive disease as indolent. The rate of compliance with guideline recommendations for patients with bladder cancer is suboptimal,” he adds. “This may be due to clinicians not being cognizant of the recurrence, progression, and mortality rate for bladder cancer. Most studies have been single-institution series, and thus are subject to referral bias. Our hope is that our manuscript has shed further light on how morbid high-risk bladder cancer can be,” he notes. Dr. Scherr agrees that poor compliance with bladder cancer guidelines is a pervasive problem, noting that “bladder cancer management requires stringent and often arduous compliance, and unfortunately, is not often adhered to.”

A second major finding was that women and African Americans had a higher risk of progression and death from bladder cancer and that advancing age was associated with higher bladder cancer-specific mortality. The authors note this could be due to lower responses to the treatments; less aggressive treatment by the provider; or potential patient-level problems, such as simply the ability to get to the doctor for frequent visits.

Dr. Chamie believes the biggest challenge will be to overcome patient-, provider-, and systems-based barriers to compliant care. “On a patient level, no amount of publications and guidelines is going to modify the adoption of weekly intravesical Bacillus Calmette-Guérin (BCG) therapy if an elderly patient doesn’t have the appropriate social support,” Dr. Chamie notes. “On a provider level, in the absence of an electronic medical record system that keeps track of hundreds of patients nested within a provider’s practice, it is easy to see how a patient can have a delay in care,” he adds. “On a system level, there are not only chemotherapy shortages, but also a BCG shortage. Most large institutions have many vendors to choose from, but community practices, where the bulk of patients with bladder cancer are cared for, may not have that luxury.”

Limitations of the current study include the fact that it is an observational study and variables not included in the analysis may affect outcomes, and that claims-based data, rather than pathology stage-based data, were used to define disease progression. However, when using the SEER-Medicare Database, claims data must be used. Despite any limitations, this study highlights the significant morbidity of high-grade bladder cancer. When progression to invasion occurs, the death rate from bladder cancer is high.

“Data-driven, guideline-based management is critical,” Dr. Scherr says. “The definition of treatment failure to intravesical agents also needs to be understood, particularly with T1 disease, and early radical cystectomy can often be lifesaving. If adherence to these principles cannot be accomplished, then referral to a center with a robust experience and a team approach should be considered,” he adds.

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