The majority of patients who are diagnosed with bladder cancer initially present with noninvasive disease (1). Nevertheless, 40%–80% of patients diagnosed with superficial bladder cancers will experience a recurrence, including 10%–25% of those with potentially lethal muscle-invasive disease, within the first 3 years after diagnosis (2–4). Current guidelines from the American Urologic Association (5,6) and the National Comprehensive Cancer Network (5,6) recommend frequent cystoscopic surveillance of patients diagnosed with superficial bladder cancer. However, physicians treating patients with superficial bladder cancer vary widely in their adherence to surveillance guidelines (7). Practical and ethical considerations that preclude randomized controlled trials to establish the impact of surveillance on survival of patients with superficial bladder cancer include the high recurrence rate, the ability of cystoscopic surveillance to identify recurrence early, the demonstrated efficacy of local therapy in preventing or delaying the development of muscle-invasive disease, and the overall poor prognosis of muscle-invasive disease (7–10).

The Surveillance, Epidemiology, and End Results (SEER)–Medicare database that links individual identifiers in the SEER registry to the Medicare master enrollment files has been a valuable resource for evaluating patterns of health-care delivery to older cancer patients and their subsequent outcomes (11). In this issue of the Journal, Hollenbeck et al. (12) have used the SEER–Medicare database to identify 20713 individuals who were diagnosed with early-stage bladder cancer (ie, superficial bladder cancer or stage 0 or I including Ta, T1, Tis) between 1992 and 2002 and the health-care provider who submitted the most bladder cancer-related claims associated with each patient. The authors define “treatment intensity” for each patient in terms of the inpatient and outpatient Medicare payments associated with the early-stage bladder cancer diagnosis, including payments for radical cystectomy. Providers were then ranked according to average early-stage bladder cancer Medicare expenditures. The association of these expenditure rankings with practice patterns related to bladder cancer management and outcomes was examined. The primary outcome of interest was all-cause mortality, whereas the secondary outcomes...
included bladder cancer–specific mortality and subsequent major medical interventions, including radical cystectomy, chemotherapy, and radiation therapy. Mortality was adjusted for demographic characteristics, tumor grade, stage, number of comorbidities, and a composite measure of socioeconomic status.

The authors sought to evaluate the impact of varying practice styles during the 2-year period following the initial diagnosis on patient outcomes. Of note, the authors report that providers with the highest average bladder cancer expenditures within the first 2 years after diagnosis more frequently used endoscopic surveillance, intravesical therapy, and imaging studies along with subsequent major medical interventions. Patients treated by such providers were found to have greater bladder cancer–specific mortality but no difference in all-cause mortality compared with those treated by providers with the lowest bladder cancer expenditures.

Although the analyses presented by Hollenbeck et al. represent intriguing and thought-provoking results, retrospective population-based studies based on health-care claims such as this study must be interpreted with caution. The decision to equate Medicare bladder cancer expenditures with treatment intensity presents a number of challenges for interpreting the results. For example, including the single most expensive procedure—radical cystectomy—among the bladder cancer expenditures that the authors use to define treatment intensity appears to represent a self-fulfilling prophecy that “high treatment intensity” will be associated with major medical interventions. Providers who routinely treat higher risk cases of superficial bladder cancer are likely to perform the most cystectomies and thus may often be categorized as “high–treatment intensity” providers while their patients also experience the highest risk of bladder cancer–specific mortality. It also seems very unlikely that more aggressive treatment and surveillance would increase the risk of disease progression, as one might conclude from this study (12). Rather, an association between provider expenditure rankings and the use of more expensive surveillance and treatment procedures would appear to be an example of a cause-and-effect fallacy. This problem is perhaps most apparent when considering the substantial overlap in procedures between those included in expenditure rankings (independent variable) and those considered as processes-of-care (outcomes). Also, because major surgery, complications requiring hospitalization, and poorly controlled comorbidities disproportionately drive much of the associated costs, expenditures are not a good surrogate for appropriate surveillance and treatment.

The greatest challenge faced by investigators in analyses of population studies involves the impact of confounding factors that are associated with both the potential causal influence and the outcome of interest. When confounding factors are unrecognized or unmeasured and not adjusted for in the analysis, a true association may be obscured or a false association may be created, which may ultimately bias the conclusions of the study. Retrospective analyses of administrative or claims data frequently create a situation where potential confounding factors related to the outcomes of interest are not available for adjustment. For example, if patients with unfavorable clinicopathological measures are more frequently seen by high-volume providers, such as those at academic centers, failure to adjust for all such features may obscure an otherwise favorable impact of such referral on surgical outcomes (13–18). Adjustment for stage and tumor grade does not entirely capture prognostic differences among patients with superficial bladder cancer (5,19). In addition to tumor stage and grade, prognostic factors that may be associated with referral of more complicated patients with a poor prognosis to providers at major treatment centers include multicentricity, tumor size, recurrent disease and multiple superficial recurrences within a short period of time, incomplete resection, and association with carcinoma in situ (CIS) (5,19). The absence of data regarding CIS in conjunction with Ta or T1 disease in the study by Hollenbeck et al. is particularly problematic because this condition is most frequently associated with the need for intravesical therapy. As such, the presence of CIS is a factor that not only drives increased resource utilization but is also linked with poor outcome, an increased risk of developing muscle-invasive disease, and the need for more intensive treatments. The absence of information on CIS in those with Ta or T1 disease could potentially explain the lack of an association between high–treatment intensity providers and better outcome.

Although Hollenbeck et al. allude to the problem of confounding in their study, their evaluation of the association between provider treatment intensity and survival in SEER–Medicare populations during different time periods provides little assurance of complete adjustment for unmeasured confounding. Because practice and referral patterns are likely to persist over time, any confounding due to the selective referral of higher risk patients to specific providers and institutions will also persist. Therefore, it remains unresolved whether the lack of an association between provider bladder cancer expenditures and survival reflects a true lack of impact of the procedures used by these practitioners or is a result of the inability to fully adjust for differences in prognosis. The latter possibility appears to be more likely as it has been demonstrated that patients with better prognostic subtypes of noninvasive bladder cancer are also likely to undergo lower intensity surveillance and lower rates of cystectomies (7). Alternatively, there is evidence from randomized controlled trials demonstrating efficacy for intravesical therapy and from multiple studies confirming reduced procedure-related mortality in high-volume settings (5,13–16). Thus, it remains possible or even likely that if the more aggressive and more expensive measures had not been used, bladder cancer–specific and overall survival of patients who received “high intensity treatment” by their providers might have been even worse than that observed by Hollenbeck et al. (12). The apparent increase in bladder cancer–specific mortality also raises the question as to whether high-risk patients with superficial bladder cancer would benefit from more aggressive intervention such as early cystectomy. Although these questions cannot be answered from the data reported by Hollenbeck et al., they should be addressed in future prospective randomized controlled trials.

So which is it? Are variations in provider treatment and surveillance intensity primarily inherent to the practice style of the practitioner and not the presenting clinical situation, or does variation in practitioner behavior reflect a more detailed understanding of the clinical situation and patient risk than can be extrapolated from the retrospective registry claims data provided by the SEER–Medicare database? The apparent association between provider treatment intensity defined as greater average bladder cancer expenditures and worse bladder cancer–specific but not overall survival is more likely the result of confounding by unavailable prognostic factors than the
result of adverse events resulting from the procedures themselves. Further clinical studies are needed to determine whether any of the treatment or surveillance procedures represent unnecessary processes of care that can be safely eliminated or are valuable management approaches for patients at greater risk for recurrence and death from invasive bladder cancer. Current clinical practice guidelines on the management of superficial bladder cancer should be followed until more compelling data emerge that confirm that less aggressive treatment and surveillance strategies are safe and effective (5,6).

References