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Bladder Cancer Collaborative Stage Variables and Their Data Quality, Usage, and Clinical Implications: A Review of SEER Data, 2004-2010

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Abstract

Background—Several changes were made to bladder cancer staging guidelines between the 6th and 7th editions of the American Joint Committee on Cancer (AJCC) staging manuals. Also, Collaborative Stage (CS) Data Collection System version 2 (CSv2) implemented for 2010 Surveillance, Epidemiology, and End Results (SEER) cases involved collection of three new site-specific factors (SSFs): World Health Organization/International Society of Urological Pathology Grade (SSF1), size of metastasis in regional lymph nodes (SSF2) and extranodal extension (SSF3). Our objective was to evaluate these new SSFs to assist researchers on use/interpretation, and to describe data quality issues to be addressed moving forward.

Methods—Staging trends were assessed for invasive and noninvasive bladder cancer cases from 2004-2010. Among 2010 cases, staging was compared using the AJCC 6th and 7th edition guidelines, and evaluation of completeness/quality of the SSFs was performed in relevant subgroups.

Results—Age-adjusted incidence rates and proportions of cases by stage remained steady from 2004-2010. Changes from the AJCC 6th to 7th edition caused no substantial movement between stages. SSF1 had a known value in 82% of cases, which was higher than the traditional SEER Grade/Differentiation variable. SSF2 and SSF3 were less complete, with 41% and 37% having known values, respectively, among cases with lymph node involvement (according to CS Lymph Node variable).

Conclusion—SSF1 was more complete and straightforward to interpret than the traditional Grade/Differentiation variable. SSF2 and SSF3 were less complete, may be associated with data quality issues, and should only be used among cases with known lymph node involvement.

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Keywords

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Introduction

Bladder cancer is the sixth most common cancer in the United States,¹ with an estimated 74 690 new cases to be diagnosed in 2014.² It affects primarily the elderly, with more than two-thirds of the cases diagnosed in individuals over the age of 65.³ Men are 4 times more likely to develop bladder cancer in their lifetime than women, and this male preponderance is seen across all major racial-ethnic groups.² Bladder cancer rates are twice as high in whites compared to blacks or Hispanics.² It is estimated that 15 580 deaths will occur from bladder cancer in 2014.² When comparing the annual number of new bladder cancer cases and deaths, it is important to note that the Surveillance, Epidemiology, and End Results (SEER) Program has combined Stage 0 with Stages I-IV in the reporting of incidence rates since 1985 because of the perceived difficulty in identifying the presence or absence of superficial or early invasion in pathology reports.^{4,5}

Approximately 95% of bladder cancers in the United States are urothelial (transitional) cell type. The remaining 5% include squamous, glandular, or undifferentiated cell type tumors. Tumor grade and stage are the two most important prognostic factors in bladder cancer. The grading system for bladder cancer underwent many revisions prior to the general acceptance of the 1998 World Health Organization/International Society of Urological Pathology (WHO/ISUP) grading system,⁶ which itself was revised in 2004.⁷ As part of the newly introduced Collaborative Stage (CS) Data Collection System version 2 (CSv2) for 2010 cases, SEER is reporting grade information in accordance with the 2004 WHO/ISUP grading system in a new site-specific factor (SSF), and also will continue to record grade information in the traditional grade variable that is required for all cancer sites. Because this has been a time of transition for pathologists in terms of grading systems, which could lead to inconsistencies in clinical documentation, and because this was the first time that the WHO/ISUP grade was specifically collected by SEER, an in-depth evaluation of bladder cancer grade variables was warranted.

New SEER variables related to lymph node involvement were also introduced in CSv2. Lymph node dissection is not only an integral part of the surgery for muscle-invasive bladder cancer but also provides staging information. The criteria for N staging (N refers to the involvement of nearby [regional] lymph nodes) underwent changes in the American Joint Committee on Cancer's (AJCC) AJCC Cancer Staging Manual, 7th Edition⁸ and no longer takes into account the size of the metastasis in the lymph nodes. Beginning with cases diagnosed in 2010, SEER is collecting the size of the metastasis in the regional lymph nodes in a new SSF. It has been reported that both the 6th and the more recent 7th editions of the TNM (tumor-node-metastasis) staging system have limited prognostic value among lymph node-positive cases.⁹ Other lymph nodal characteristics, such as the presence of extranodal spread, also might be of prognostic significance in bladder cancer patients.¹⁰ SEER has begun to capture extranodal extension of regional lymph nodes in another new SSF.

Objectives

The objectives of this bladder cancer report are to: 1) examine the trends of AJCC 6th edition¹¹ stage distributions for bladder cancer in the SEER combined areas from 2004 to 2010; 2) compare the staging system between the AJCC 6th and 7th editions^{8,11} by comparing stage distributions of 2010 cases and examining how the change impacted stage at diagnosis; and 3) describe the SSFs for bladder cancer introduced in the CSv2 so that data quality of these new factors can be assessed and improved moving forward.

Data Description

Schemas for Bladder Cancer

In the CS system, the schema for bladder cancer includes the following topographies based on the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3)¹²: C67.0–C67.9. The AJCC 7th edition includes histologies of 8000-8576, 8940-8950, and 8980-8981. Different from the AJCC 7th edition, the AJCC 6th edition includes all histologies in ICD-O-3, except those listed on the Histology Exclusion Table: http://web2.facs.org/cstage0204/bladder/Bladder_ppd.html.

Analysis Cohorts

To be eligible for inclusion in the analysis of this report, cases must have histology groupings that are included in staging for *both* the AJCC 6th and 7th editions as well as the schema for bladder cancer. Cases diagnosed at autopsy or on the death certificate only were excluded from these analyses. Bladder cancer cases staged as noninvasive papillary transitional carcinoma (Ta) or urothelial carcinoma in situ (Tis) were analyzed together with invasive cases. As previously mentioned, the rationale for this approach is that the SEER Program has combined Stage 0 with Stages I-IV in reporting incidence and survival rates since 1985 because of the perceived difficulty in identifying the presence or absence of superficial or early invasion in pathology reports.^{4,5}

To examine the trends of CS-derived AJCC 6th edition stage distributions for bladder cancer (ie, objective #1), all eligible cases (including both noninvasive and invasive) diagnosed between 2004 and 2010 were selected. Because the AJCC 7th edition was first implemented in SEER for cases diagnosed in 2010, the comparison of stage distributions derived from CS in the AJCC 6th and 7th editions (ie, objective #2) was limited to bladder cancer cases diagnosed in 2010. Likewise, the assessment of CS SSFs for bladder cancer (ie, objective #3) was based on cases diagnosed in 2010, when the three SSFs were collected for the first time as part of CSv2. Analyses were further limited to appropriate subsets of cases in the evaluation of completeness and quality of SSFs. For example, only patients who had urothelial carcinoma were included in the analysis of SSF1 (WHO/ISUP Grade), and only patients who had known lymph node involvement were included in the analyses of SSF2 (Size of Metastasis in Lymph Nodes) and SSF3 (Extranodal Extension of Regional Lymph Nodes).

Key Changes in AJCC Staging Between the 6th and 7th Editions

One major change in the AJCC 7th edition impacted the T categories. Subepithelial invasion of the prostatic urethra no longer receives T4 staging status; rather it is considered T1 according to the AJCC 7th edition. Prior to the 7th edition, cancers that invaded the prostatic stroma, regardless of whether the invasion was transmural or subepithelial via the prostatic urethra, were staged as T4a.

Substantial changes also were made to the N categories for bladder cancer in the 7th edition (Table 1). Previously the N categories considered the size of the metastasis in the lymph node, but this is no longer done in the 7th edition. The size of the metastasis in the regional lymph nodes was added as a new SSF (SSF3), however. Also, common iliac nodes are now defined as regional nodes (secondary drainage region) and not as metastatic disease.

Description of T, N, and M Variables (collected for cases diagnosed in 2004+)

CS Extension (T Stage) identifies contiguous growth of the primary tumor within the bladder or its direct extension into neighboring organs. If the patient does not receive neoadjuvant systemic therapy, this information should be captured from the pathology report. If the patient does receive neoadjuvant therapy, the extension should be coded for the farthest extension identified prior to treatment (clinically). The CS Lymph Node field (N Stage) identifies the regional lymph nodes involved with the bladder cancer at the time of diagnosis. Registrars are instructed to record involved lymph nodes from the pathology report, if available, when the patient received no neoadjuvant therapy prior to surgery. If the patient did receive neoadjuvant therapy, registrars are instructed to code the farthest involved regional lymph nodes, regardless of whether the information was documented prior to surgery or following treatment. The CS Metastasis at Diagnosis variable (M Stage) identifies the distant site(s) of metastatic involvement at the time of diagnosis. Registrars are asked to assign the highest code for metastasis at diagnosis, regardless of how the determination was made (clinical versus pathological), and regardless of whether or not the patient had neoadjuvant therapy. Of note, each year since 2004, 96-97% of bladder cancer cases have had known values for the CS Extension variable. Likewise, 94-97% of bladder cancer cases have had known values for CS Lymph Nodes, and 96-98% of cases have had known values for CS Metastasis at Diagnosis each year since 2004.

SSF Descriptions

Under CS, data items related to staging, prognosis, and treatment, as well as those of clinical significance, are referred to as SSFs.

When CS version 1 (CSv1) was implemented in 2004, no SSFs were introduced for bladder cancer. With the introduction of the CSv2 schema, three new SSFs were collected by SEER registries for cases of bladder cancer diagnosed in 2010; they are summarized in Table 2.

SSF1—WHO/ISUP Grade—The ISUP developed a new grading system that was adopted by the WHO in 2004. This new WHO/ISUP system is based on more objective, clear-cut criteria for each classification (low grade versus high grade). It applies only to urothelial (transitional cell) carcinomas and typically is documented in pathology reports.¹³ The

WHO/ISUP system clarified that there is no need to grade Tis because all are high-grade lesions by definition. Those staged as Ta should still be graded as high or low.¹³ The WHO/ISUP grade is necessary for staging under CSv2.

SSF2—Size of Metastasis in Lymph Nodes—Although no longer considered in the N staging of bladder cancer in the AJCC 7th edition, the size of the largest metastasis in the regional lymph nodes is thought to have clinical/prognostic significance.^{10,14} Of note, with the introduction of the AJCC 7th edition, the College of American Pathologists (CAP) protocol for carcinoma of the urinary bladder no longer includes size of metastasis in regional lymph nodes.¹⁵ SEER instructs registrars to code the size of the largest metastasis (in mm) in a lymph node as documented in the pathology report, not the size of the lymph node. If the size of the metastasis is not documented, registrars are instructed to code the size of the largest involved lymph node as documented pathologically or clinically, with pathology taking priority. This factor is only relevant among bladder cancer cases that have lymph node involvement, which is indicated by CS Lymph Node values other than 00 (no involvement) or 99 (unknown involvement).

SSF3—Extranodal Extension of Regional Lymph Nodes—Extranodal extension, meaning a metastatic tumor in a regional lymph node that grows outward into the surrounding connective tissue, is also thought to have prognostic significance, as studies have demonstrated that it is associated with risk of recurrence and death among node-positive bladder cancer patients.^{10,14,16} Extranodal extension, however, is not specifically included in the current CAP protocol for carcinoma of the urinary bladder.¹⁵ Registrars are instructed to code the status of extranodal extension, whether assessed clinically or pathologically, for any involved regional lymph node(s). If nodes are involved, and the sources of information that typically would contain information about extranodal extension (ie, pathology or imaging reports) are available but contain no information regarding extranodal extension, registrars are instructed to code 010 (no extranodal extension was documented). If no pathology or imaging reports are available, however, and the only available documentation contains a reference to lymph node involvement with no mention of extranodal extension, then registrars are instructed to code 030 (nodes involved, unknown if extranodal extension). Again, this factor is only relevant among bladder cancer cases that have regional lymph node involvement, which is indicated by CS Lymph Node values other than 00 (no involvement) or 99 (no involvement).

Results

A total of 118 516 cases of bladder cancer were diagnosed from 2004 to 2010 in 18 population-based registries in the National Cancer Institute's (NCI) SEER Program. Figure 1 depicts the number of cases included in analyses for each objective.

Objective 1: Trends in AJCC 6th Edition Staging Distribution for Bladder Cancer, 2004-2010

Overall, the age-adjusted rates by stage of bladder cancer remained fairly steady between 2004 and 2010 (Figure 2). Likewise, the proportions of bladder cancer by stage also remained fairly constant during this time period (Figure 3).

Objective 2: Comparison of AJCC Stage: 6th and 7th Editions

The changes from the AJCC 6th edition to the 7th edition did not appear to cause any movement between stages among cases diagnosed in 2010 (Table 3). There was a key change related to N staging, but any lymph node involvement (N1, N2, N3) in both the 6th and 7th editions generally causes the case to be considered Stage IV; so all cases with lymph node involvement would have been in Stage IV under the AJCC 6th edition and remained there under the AJCC 7th edition. The T staging changes related to urothelial carcinoma with subepithelial prostatic stromal invasion did not appear to cause any cases to move between stages. Twenty-six cases that were previously categorized as “unknown” under the AJCC 6th edition were classified as Stages I-III under the 7th edition (agreement rate 95.9%).

Objective 3: SSFs

SSF1—WHO/ISUP Grade—Of the total 17 338 cases diagnosed with bladder cancer in 2010, 17 079 (98.5%) cases were considered to have urothelial (transitional cell) morphology and therefore were included in the analysis of SSF1. Of these cases, 13 986 (81.8%) had a known WHO/ISUP Grade; 43.2% of those with known values were classified as low grade, and 56.8% were classified as high grade (Table 4). The information was “not collected” in 1.5% of cases, and the remaining 16.7% of cases were classified as unknown. Further analyses to determine potential reasons for the “unknown”/“not collected” values (18.2% of cases) included examination by type of diagnostic confirmation; approximately 90% of cases were confirmed via positive histology. It therefore is presumed that the pathology reports for these cases with positive histologic confirmation did not contain information related to the WHO/ISUP grade.

SSF1 vs. Grade/Differentiation—SEER has continued to collect the traditional Grade/Differentiation variable, in addition to the WHO/ISUP Grade SSF. The distribution of grades by year is illustrated in Table 5. It is important to note that due to the evolving grading systems used by pathologists, there have been changes to the coding guidelines over the past several years that likely impacted the way grade was interpreted by registrars and documented in the Grade/Differentiation variable.

There were no specific SEER guidelines for coding Grade/Differentiation for bladder tumors diagnosed prior to 2004. For the diagnosis years of 2004 to 2009, instructions specified that the WHO/ISUP grade was not to be used to code the Grade/Differentiation field. In other words, if the only grade provided in the pathology report was specifically noted to be a “WHO Grade,” then registrars were instructed to code “not determined, not stated, or not applicable” for the Grade/Differentiation variable. The guidelines, however, provided the

conversion table shown in Table 6. No distinction was made regarding noninvasive versus invasive cases.

As described previously, the WHO/ISUP grading system was introduced in 2004; some pathologists may have started to adopt this system shortly thereafter. It is possible that “low grade” and “high grade” began to be reported without the words “WHO Grade,” and subsequently were coded in the Grade/Differentiation field, despite the fact that the SEER coding instructions stated not to use the WHO/ISUP grade to code that particular field.

More recent guidelines for 2010 cases may at least partially explain the dramatic increase in the proportion coded as 9 (not determined, not stated, or not applicable) from 2009 to 2010, as displayed in Table 7. The new addition to the coding guidelines for Grade/Differentiation in 2010 cases stated:

“Code grade 9 (unknown) for non-invasive urothelial (transitional) tumors. The grading of urothelial tumors is based on the WHO Classification, which is a three grade system. The 3 grade levels describe levels of neoplasia rather than differentiation, although the term grade is used for both. WHO Grade III or WHO High Grade is equivalent to non-invasive carcinoma or carcinoma in situ (for flat lesions). Path reports often omit the words “WHO Grade,” shortening the descriptor to just plain “grade.” When you see the words “Grade III” or “high grade,” do not code in the grade field.”

Figure 4 provides the distribution of the Grade/Differentiation variable for Ta/Tis bladder cancer cases from 2004 to 2010 and displays the impact that may have been associated with these new coding guidelines. From 2004 to 2009, the Ta/Tis cases were predominantly coded as “intermediate” grade. In 2010, however, there was a major shift to “unknown/not determined, not stated, or not applicable.”

The coding instructions for the Grade/Differentiation variable may explain some discrepancies between WHO/ISUP Grade and Grade/Differentiation for 2010 cases, particularly among the “unknown” cases. Table 7, in which column percentages sum to 100%, illustrates that 60.4% of WHO/ISUP low-grade cases were classified as well differentiated or intermediate grade, 1.5% as poorly differentiated or undifferentiated, and 38.1% were unknown; 2.5% of the WHO/ISUP high-grade cases were classified as well differentiated or intermediate grade, 80.0% as poorly differentiated or undifferentiated, and 17.5% were unknown; 19.6% of cases classified as WHO/ISUP = “not collected” and 57.3% of cases classified as WHO/ISUP = “unknown” had known Grade/Differentiation values.

SSF2—Size of Metastasis in Lymph Nodes—Table 8 displays the trends in the Collaborative Stage Lymph Node (CS LN) variable from 2004 to 2010 under the AJCC 6th edition, which as previously mentioned, was based on the size of the metastasis in the lymph nodes, as well as on the number of nodes (single vs. multiple). Table 8 also displays the values of SSF2 that have been collapsed into categories of <2 cm, 2-5 cm, and >5 cm to make them more comparable to the N Staging categories of the AJCC 6th edition. It appears that a substantial portion of cases considered N2 under the AJCC 6th edition met that criteria due to multiple node involvement rather than size—because there were only 18 cases with

lymph node metastases of 2 to 5 cm according to SSF2, which only considers size and does not consider whether single vs. multiple nodes were involved. The number of cases with unknown size according to SSF2 is much larger than the number of cases categorized as NX according to the AJCC 6th edition.

Of the total 17 338 cases diagnosed with bladder cancer in 2010, the CS LN variable indicated that 16 067 (92.7%) of cases were considered to have no lymph node involvement, 584 (3.4%) were considered to have unknown lymph node involvement, and 687 (4.0%) were considered to have lymph node involvement. Cases with no or unknown lymph node status (CS LN = 00 or 99) were excluded from the analysis of SSF2, as illustrated in Table 4. Among those with lymph node involvement according to the CS LN variable, 284 (41.3%) had known values for size of metastasis coded, either as exact sizes (in mm) or in size ranges. In addition, 391 (56.9%) had an unknown value, and 12 (1.7%) were coded as not having any regional lymph nodes involved, despite the fact that the CS LN variable indicated lymph node involvement.

SSF3—Extranodal Extension of Regional Lymph Nodes—Similar to the analysis of SSF2, those with no or unknown lymph node involvement (CS LN = 00 or 99) were excluded from the analysis of SSF3, leaving 687 cases considered to have lymph node involvement. Among those with lymph node involvement according to the CS LN variable, 187 (27.2%) did not have extranodal extension present, 67 (9.8%) did have extranodal extension present, and 288 (41.9%) had unknown extranodal extension (Table 4). There were 91 (13.3%) with a value of “unknown” (regional lymph nodes not stated/regional lymph nodes cannot be assessed/not documented in patient record), and 54 (7.9%) were coded as *not* having lymph node involvement, despite the fact that the CS LN variable indicated that lymph nodes were involved. Therefore, among the cases with known lymph node involvement according to the CS LN variable, the percentage of known values (ie, extranodal extension present or not present) for SSF3 was only 37.0%.

Discussion

Overall, our analyses demonstrated that there was little change in the age-adjusted rates of bladder cancer by stage under the AJCC 6th edition from 2004 to 2010, and the distribution of bladder cancers by stage remained stable during this time period. In addition, the changes to bladder cancer staging implemented in the AJCC 7th edition caused very little change among 2010 cases in the classification of stage compared to the AJCC 6th edition.

Our analyses of the three new CSv2 SSFs for bladder cancer yielded some interesting findings that should be considered by researchers who plan to use these factors in future studies. The differences between SSF1 (WHO/ISUP grade) and the traditional SEER Grade/Differentiation variable suggest that the WHO/ISUP grade is the more reliable way to assess grade among 2010 cases. The WHO/ISUP Grade SSF had a known value in 81.8% of urothelial (transitional cell) morphology cases in 2010, and a value corresponding to “not collected” or “unknown” in 18.2% of cases. SEER Grade/Differentiation was coded “unknown” in 30% of 2010 cases, and it appears that changes in coding instructions for registrars may have caused a major shift in the classification of Ta and Tis cases.

Importantly, the traditional Grade/Differentiation variable will begin to officially incorporate the WHO/ISUP grade according to recent coding guidelines for 2012 and 2013 cases. These guidelines specify that grades for Ta cases are to be collected, and that “low grade” should be coded as “well differentiated” (code = 1), and “high grade” should be coded as “poorly differentiated” (code = 3). For invasive cases, registrars are still instructed to code “low grade” cases as “intermediate” (code = 2) and “high grade” cases as “undifferentiated” (code = 4). This will likely cause a shift away from the “unknown” category for a number of Ta cases, but still potentially leaves room for confusion among registrars. Such confusion may result from the fact that the Grade/Differentiation variable is based on a 4-level grading system used to capture what used to be a 3-level grading system—but that now essentially is a 2-level grading system, as pathologists adopt the WHO/ISUP 2004 grading system. As an example, the 4-level Grade/Differentiation variable includes “intermediate” grade, with a code equal to 2. Table 6, however, illustrates that when the pathologist records the grade to be “2/3,” the registrar is to record it as an intermediate grade with a code equal to 3. Under the WHO/ISUP 2-grade system (ie, “low” versus “high”), instructions indicate that “low grade” should be coded as Grade/Differentiation equal to 2, which is the code for “intermediate.” Thus, the term “intermediate” seems fairly ambiguous, depending on which grading system is being used and coded.

Given that diffusion of the 2004 WHO/ISUP grading system into regular practice was likely highly variable among pathologists in varying stages of their careers and practicing in different settings and geographic areas—and given the evolving coding guidelines and interpretations of how to document Grade/Differentiation—it does not appear possible to create a clean transition from Grade/Differentiation to the new WHO/ISUP grade SSF to allow for examination of the WHO/ISUP grade (based on the 2004 system) both before and after 2010. If the research question and time period of interest allow, use of the new WHO/ISUP SSF in 2010 cases is likely a more straightforward approach to assessing grade, as it appears to be reasonably complete and may improve as use of the WHO/ISUP grade continues to diffuse into the pathology community.

Similar to bladder cancer grading systems, the staging criteria related to metastases in the lymph nodes has undergone substantial recent changes that likely have impacted consistency in clinical documentation. Our analyses showed that attempting to examine size of metastasis in the regional lymph nodes both before and after 2010 is likely to be very problematic. In an effort to create comparable categories of size using the CS LN variable prior to 2010 cases and using the new SSF2 that captures size of the largest metastasis in the lymph nodes in cases diagnosed in 2010 and after, it appears that many of those classified as N2 prior to 2010 were likely done so due to multiple nodes rather than having a single node 2 to 5 cm in size. Furthermore, SSF2 is missing in more than half of the cases with known lymph node involvement. As previously mentioned, the size of the metastasis in the lymph node is no longer required for N staging, and is no longer an element that is included in the CAP Protocol, so the completeness of this particular factor may further deteriorate in future years. If researchers are interested in examining this variable, it is recommended that they do so for those with a CS LN value that indicates lymph node involvement. Of note, a small number of cases (N = 12) had an SSF2 value indicating no lymph node involvement, despite the fact that the CS LN value suggested otherwise. In addition, a small number of cases (N =

18) had a CS LN value suggesting no or unknown lymph node involvement, but a size was recorded in SSF2. As the CS LN variable has a much longer history and a consistently high rate of completeness, it is recommended that SSF2 only be examined for those cases with a CS LN value other than 00 (no involvement) or 99 (unknown involvement). It also is important for researchers to consider that SSF2 may contain the size of the metastasis in the lymph node, or the size of the lymph node itself when size of metastasis is not documented, and there is no indicator of which was ultimately recorded.

SSF3 (extranodal extension) also has a high rate of unknown values, but it may be less problematic in this circumstance because registrars may be capturing all of the times when extranodal extension is present and documented, and most of the “unknowns” may reflect when the lymph nodes were not examined or when there was no extranodal extension so none was documented in the pathology report. There does not yet appear to be overwhelming consensus on the prognostic importance of extranodal extension, as multiple studies have yielded conflicting results. This new SEER variable may provide another avenue for researching the prevalence and importance of extranodal extension among bladder cancer patients with regional lymph node involvement. Extranodal extension is not included in the current CAP protocol for carcinoma of the urinary bladder, however, so there certainly is a possibility that the extranodal extension SSF is not always complete.¹⁵ Nonetheless, it also is possible that when present, extranodal extension is consistently documented by pathologists. Similar to SSF2, it is recommended that SSF3 be evaluated only among those with known lymph node involvement according to the CS LN field. Fifty-four cases were listed as having no lymph node involvement despite the CS LN field having indicated that there was involvement, and 38 cases were listed as having an SSF3 value of 10, 20, or 30 (all of which indicate that lymph nodes were involved), despite the CS LN field having indicated no or unknown involvement of lymph nodes. Although these discrepant numbers are relatively small, they may suggest a data quality issue that is best addressed by relying on the more established CS LN variable to evaluate lymph node involvement.

In summary, there appear to be some inconsistencies in the new bladder cancer SSFs that reflect a transitional period in the grading and staging of bladder cancer. The new WHO/ISUP SSF introduced in 2010 cases represents the most straightforward approach to assessing grade going forward, and it should continue to improve over time as use of the WHO/ISUP grading system diffuses more widely into the pathology community. SSFs 2 and 3 should be interpreted with caution and used only when the more established, high quality CS LN variable indicates lymph node involvement.

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Figure 1.

This flowchart describes the number of cases included in analyses for each objective.

Figure 2.

This graph shows age-adjusted bladder cancer rates by stage, AJCC Cancer Staging Manual, 6th Edition, 2004-2010 (per 100 000 population). Note: Rates are per 100 000 and are age-adjusted to the 2000 US standard population (19 age groups). Data source for all figures: NCI's SEER Program's SEER-18 geographic areas (SEER-18, includes: San Francisco [SF]-Oakland standard metropolitan statistical area [SMSA], Connecticut, Detroit [Metropolitan], Hawaii, Iowa, New Mexico, Seattle [Puget Sound], Utah, Atlanta [Metropolitan], San Jose-Monterey [SJM], Los Angeles, Alaska Natives, Rural Georgia, California excluding SF/SJM/Los Angeles, Kentucky, Louisiana, New Jersey, Greater Georgia). 0a refers to Stage 0 tumors classified as noninvasive papillary transitional carcinoma, and 0is refers to Stage 0 tumors classified as urothelial carcinoma in situ.

Figure 3.

This graph illustrates bladder cancer distribution by stage, AJCC 6th edition: comparison of 2004 and 2010 cases, SEER-18. 0a refers to Stage 0 tumors classified as noninvasive papillary transitional carcinoma, and 0is refers to Stage 0 tumors classified as urothelial carcinoma in situ.

Figure 4. Distribution (%) of the Grade/Differentiation variable for Ta/Tis bladder cancer cases from 2004 to 2010, SEER-18. Ta refers to noninvasive papillary transitional carcinoma, and Tis refers to urothelial carcinoma in situ.

Table 1
Comparison of N^a Staging in the AJCC 6th and 7th Editions

N	AJCC 6th Edition	AJCC 7th Edition
N1	Single lymph node, 2 cm or less	Single positive node in primary drainage regions
N2	Single lymph node more than 2 cm but less than 5 cm or multiple lymph nodes but none more than 5 cm	Multiple positive nodes in primary drainage regions
N3	One or more lymph nodes greater than 5 cm	Common iliac node involvement

Abbreviations: AJCC, American Joint Committee on Cancer; cm, centimeters.

^aN refers to the involvement of nearby (regional) lymph nodes.

Table 2
CSv2 SSFs for Bladder Cancer

SSF	Codes/Descriptions
SSF1: WHO/ISUP Grade	010: Low-grade urothelial (transitional cell) carcinoma 020: High-grade urothelial (transitional cell) carcinoma 888/987/988: Not applicable 998: No pathologic examination of primary site 999: Unknown WHO/ISUP grade/Not documented in patient record
SSF2: Size of Metastasis in Lymph Nodes	000: No regional lymph nodes involved 001-979: 1-979 millimeter (mm) (Exact size of lymph node metastasis to nearest mm) 980: 980 mm or larger 988: Not applicable 990: Microscopic focus or foci only and no size of focus given 991: Described as "less than 1 centimeter (cm)" 992: Described as "less than 2 cm" or "greater than 1 cm" or "between 1 cm and 2 cm" 993: Described as "less than 3 cm" or "greater than 2 cm" or "between 2 cm and 3 cm" 994: Described as "less than 4 cm" or "greater than 3 cm" or "between 3 cm and 4 cm" 995: Described as "less than 5 cm" or "greater than 4 cm" or "between 4 cm and 5 cm" 996: Described as "less than 6 cm" or "greater than 5 cm" or "between 5cm and 6 cm" 997: Described as "more than 6 cm" 999: Regional lymph node(s) involved, size not stated/Unknown if regional lymph node(s) involved/Not documented in patient record
SSF 3: Extranodal Extension of Regional Lymph Nodes	000: No regional lymph nodes involved 010: Extranodal extension not present/Regional nodes described as mobile 020: Extranodal extension present/Regional nodes described as fixed or matted 030: Regional nodes involved, unknown if extranodal extension 888/988: Not applicable 999: Unknown; regional lymph nodes not stated/Regional lymph nodes cannot be assessed/Not documented in patient record.

Abbreviations: cm, centimeter; CSv2, Collaborative Stage Version 2; SSFs, site-specific factors; ISUP, International Society of Urological Pathology; mm, millimeter; WHO, World Health Organization.

Table 3
Stage Classification of 2010 Cases by AJCC 6th Edition Compared to AJCC 7th Edition

AJCC 7									
AJCC 6	0a ^a	0is ^b	I	II	III	IV	Unknown	TOTAL	
0a	8073	0	0	0	0	0	0	8073	
0is	0	870	0	0	0	0	0	870	
I	0	0	3828	0	0	0	0	3828	
II	0	0	0	2000	0	0	0	2000	
III	0	0	0	0	695	0	0	695	
IV	0	0	0	0	0	1226	0	1226	
Unknown	0	0	4	18	4	0	620	646	
TOTAL	8073	870	3832	2018	699	1226	620	17 338	

Abbreviation: AJCC, American Joint Committee on Cancer.

^a0a refers to Stage 0 tumors classified as noninvasive papillary transitional carcinoma.

^b0is refers to Stage 0 tumors classified as urothelial carcinoma in situ.

Table 4
Values for SSFs Among 2010 Cases^a

	Code	Total Cases	Percent of Total Cases
SSF 1: WHO/ISUP Grade^b			
Low-grade urothelial (transitional cell) carcinoma	10	6037	35.3%
High-grade urothelial (transitional cell) carcinoma	20	7949	46.5%
Not collected	998	248	1.5%
Unknown	999	2845	16.7%
TOTAL		17 079	100.0%
SSF2: Size of Metastases in Regional Lymph Nodes^c			
No regional lymph nodes involved	000	12	1.7%
Exact size coded (1-979 mm, 980+) or range given	1-979, 980 990-997	284	41.3%
Unknown	999	391	56.9%
TOTAL		687	100.0%
SSF3: Extranodal Extension^c			
No regional lymph nodes involved	00	54	7.9%
Extranodal extension not present Regional nodes described as mobile	10	187	27.2%
Extranodal extension present Regional nodes described as fixed or matted	20	67	9.8%
Regional nodes involved, unknown if extranodal extension	30	288	41.9%
Unknown; regional lymph nodes not stated Regional lymph nodes cannot be assessed Not documented in patient record	999	91	13.3%
TOTAL		687	100.0%

Abbreviations: CS, Collaborative Staging; ISUP, International Society of Urological Pathology; mm, millimeters; SSFs, site-specific factors; WHO, World Health Organization.

^a Includes both noninvasive and invasive cases.

^b Cases that were not considered urothelial (transitional cell) were excluded.

^c Cases with CS Lymph Node values of no involvement (00) or unknown involvement (99) were excluded.

Table 5

Grade/Differentiation by Year, 2004-2010

Grade	Year	2004	2005	2006	2007	2008	2009	2010
Well Differentiated (Code = 1)		2478 (14.8%)	2449 (14.7)	2276 (13.7%)	2175 (12.8%)	2059 (12.1%)	1785 (10.4)	1542 (8.9%)
Intermediate (Code = 2)		5207 (31.1%)	4896 (29.4)	4753 (28.7%)	4659 (27.3%)	4534 (26.6%)	4417 (25.8)	3134 (18.1)
Poorly Differentiated (Code = 3)		4331 (25.9%)	3951 (23.7)	3731 (22.5%)	3514 (20.6%)	3383 (19.8%)	2893 (16.9)	2758 (15.9)
Undifferentiated (Code = 4)		2964 (17.7%)	3478 (20.9)	3955 (23.9%)	4391 (25.8%)	4647 (27.3%)	5084 (29.7)	4719 (27.2)
Not determined, not stated, or not applicable (Code = 9)		1758 (10.5%)	1869 (11.2)	1856 (11.2%)	2316 (13.6%)	2432 (14.3%)	2937 (17.6)	5185 (29.9)
Total Cases		16 738 (100%)	16 643 (100%)	16 571 (100%)	17 055 (100%)	17 055 (100%)	17 116 (100%)	17 338 (100%)

Table 6
Grade Conversion Table Provided to SEER Registrars Since 2004

Term Used in Pathology Report	Grade/Differentiation	Code
1/3, 1/2	Low Grade	2
2/3	Intermediate Grade	3
3/3, 2/2	High Grade	4

Abbreviation: SEER, Surveillance, Epidemiology, and End Results Program.

Table 7
Grade Classifications by WHO/ISUP Grade (SSF1) and Traditional Grade/Differentiation Variable, 2010 (columns total to 100%)

Grade/Differentiation	WHO/ISUP Grade (SSF1)					Total Cases ^a
	Low (code = 10)	High (code = 20)	Not Collected (code = 998)	Unknown (code = 999)		
Well Differentiated (Code = 1)	1297 (21.5%)	17 (0.2%)	8 (3.2%)	208 (7.3%)		1530
Intermediate (Code = 2)	2348 (38.9%)	185 (2.3%)	15 (6.0%)	530 (18.6%)		3078
Poorly Differentiated (Code = 3)	68 (1.1%)	2072 (26.1%)	14 (5.6%)	535 (18.8%)		2689
Undifferentiated (Code = 4)	26 (0.4%)	4285 (53.9%)	12 (4.8%)	358 (12.6%)		4681
Unknown (Code = 9)	2298 (38.1%)	1390 (17.5%)	199 (80.2%)	1214 (42.7%)		5101
Total	6037 (100%)	7949 (100%)	248 (100%)	2845 (100%)		17079

Abbreviations: ISUP, International Society of Urological Pathology; SSF, site-specific factor; WHO, World Health Organization.

^a Only cases with urothelial (transitional cell) morphology were included.

Table 8
Comparison of CS LN Involvement From 2004-2010 to SSF2: Size of Metastasis in Regional Lymph Nodes^a in 2010

CS LN	AJCC 6th Edition						AJCC 7th Edition	
	2004	2005	2006	2007	2008	2009	2010 ^a	SSF2 ^b
N0: No known regional lymph node involvement	15215 (90.9)	15195 (91.3)	15155 (91.5)	15618 (91.6)	15688 (92.0)	15821 (92.4)	16092 (92.8%)	No lymph nodes involved Code: 000 15 766 (90.9%)
N1: Single node, <2 cm	362 (2.2%)	388 (2.3%)	419 (2.5%)	408 (2.4%)	429 (2.5%)	397 (2.3%)	253 (1.5%)	<2 cm Codes: 001-200, 990-992 280 (1.6%)
N2: Single node, 2-5 cm, or Multiple nodes	158 (0.9%)	162 (1.0%)	200 (1.2%)	239 (1.4%)	223 (1.3%)	224 (1.3%)	400 (2.3%)	2-5 cm Codes: 201-500, 993-995 18 (0.1%)
N3: One or more nodes, >5 cm	10 (0.1%)	19 (0.1%)	16 (0.1%)	19 (0.1%)	12 (0.1%)	19 (0.1%)	8 (0.1%)	>5 cm 501-980, 996-997 4 (0.0%)
NX: Unknown regional lymph node involvement	993 (5.9%)	879 (5.3%)	781 (4.7%)	771 (4.5%)	703 (4.1%)	655 (3.8%)	585 (3.4%)	Unknown 999 1270 ^c (7.3%)
TOTAL	16738 (100%)	16643 (100%)	16571 (100%)	17055 (100%)	17055 (100%)	17116 (100%)	17338 (100%)	17 338 (100%)

Abbreviations: AJCC, American Joint Committee on Cancer; cm, centimeter; CS, Collaborative Staging; LN, lymph nodes; SSF, site-specific factor.

^aThe AJCC 6th edition was applied to 2010 cases for the purposes of this analysis. In Surveillance, Epidemiology, and End Results (SEER) Program public release files, 2010 cases are staged according to the AJCC 7th edition.

^bSSF2 is based on the size of the largest metastasis in the Regional Lymph Nodes.

^cThis includes 12 cases that were coded as SSF2 = 00 (no lymph node involvement), despite having a CS LN code that indicated involvement.