Comparison of Stage at Diagnosis of Cancer in Patients Who Are on Dialysis versus the General Population

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Background and Objectives: Frequent medical encounters in patients with ESRD on dialysis may allow early detection of malignancies despite low rates of cancer screening in this population. It is therefore unclear whether dialysis patients are disadvantaged in terms of cancer diagnosis. This study compared stage at diagnosis of cancer in a population-based sample of patients with ESRD versus the general population.

Design, Setting, Participants, & Measurements: The Surveillance, Epidemiology, and End Results Medicare database was used to identify patients with ESRD and incident cancers from 1992 through 1999. Modified Poisson regression models were used to predict nonlocalized stage of cancer at diagnosis in patients with ESRD versus the general population, adjusting for demographics, cancer site, region, year of diagnosis, and comorbidity. Two general population comparisons were used: Standardized Surveillance, Epidemiology, and End Results public-use data and Medicare control subjects without ESRD matched 3:1 to patients with ESRD.

Results: A total of 1629 patients with ESRD and incident cancer were identified. Overall, the likelihood of nonlocalized stage at diagnosis was not significantly different for patients with ESRD versus the standardized Surveillance, Epidemiology, and End Results general population or matched Medicare control subjects. Stratifying by cancer site, colorectal cancers were significantly more likely to be diagnosed earlier in the ESRD group, whereas prostate cancers were significantly more likely to be diagnosed at a later stage.

Conclusions: With the exception of prostate cancer, patients with ESRD are not more likely to present with later stage malignancies compared with the general population.

S
creening for cancer in patients who have ESRD and are on dialysis remains controversial (1–3). Despite some evidence supporting an increased risk for malignancy in patients who are on long-term dialysis (4), the issue of cancer is generally overshadowed by the overwhelming cardiovascular mortality (5,6). A cost-effectiveness analysis suggested that a general cancer screening program in this population would be of minimal value, adding <5 d of life saved per person under the most optimistic assumptions (7). Indeed, population-based assessments suggest that cancer screening does occur less frequently in dialysis patients versus the general population (8,9).

Some authors, however, have expressed concern over the low rates of cancer screening in the long-term dialysis population and suggest that the decision to screen may need to be individualized, with consideration given to patients with a reasonable life expectancy (2,3,8). In addition, the issue of cancer may become more relevant in dialysis patients with the progressive aging of the population (10) and trends showing improvement in cardiovascular outcomes in recent years (11).

Nevertheless, the frequent medical encounters that occur by virtue of the dialysis procedure may allow for early detection of malignancies even in the absence of formal screening for cancer. It is therefore unclear whether long-term dialysis patients are disadvantaged in terms of cancer diagnosis. To address this issue, we compared stage at diagnosis of cancer in a population-based sample of long-term dialysis patients versus the general population.

Materials and Methods

Data Sources

This study used the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database (12). The SEER program, sponsored by the National Cancer Institute, consists of a group of population-based tumor registries in selected geographic areas covering approximately 14% of the US population. Medicare is a federal program that covers health services for patients on the basis of age (≥65 yr), disability, or need for renal replacement therapy. It provides data in the form of claims submitted by providers for reimbursement that include information on diagnoses (for justification of services rendered) and the service, testing, or procedure carried out. The information in the two programs was merged using an algorithm involving a match of social security number, name, gender, and date of birth, as described else-

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where (13). The version of the SEER-Medicare database used for this study contained Medicare claims through 2001 and SEER cancer cases through 1999. Additional information on cancer in the general population was available from the SEER public-use data files (14).

Study Patients
Among patients in the SEER-Medicare database with an incident cancer from January 1, 1992, through December 31, 1999, patients with ESRD that required dialysis were identified. First, patients with ESRD as their original source of Medicare entitlement (generally those younger than 65 yr) were identified directly from the Medicare entitlement indicator code. Second, for those whose original entitlement for Medicare was not due to ESRD (generally those ≥65 yr of age), patients were identified on the basis of an outpatient Medicare claim for a dialysis procedure (any of Current Procedural Terminology, Fourth Edition [CPT-4] codes 90918 to 90925, 90935 to 90937, 90945 to 90947, 99559, 90951 to 90958, 90966 to 90985, 90988 to 90991, or 90994; or revenue center codes 80X, 82X, 83X, 84X, 85X, 86X, or 87X; or International Classification of Diseases, Ninth Revision [ICD-9] procedure codes 39.95 or 54.98) combined with a diagnosis of chronic renal failure (any of ICD-9 codes 582, 585, 586, 587, 403, 404, or 250.4). Patients whose cancer was diagnosed before their designation of ESRD or after a renal transplant (identified from ICD-9 procedure code 55.69) were excluded. Cancer sites with <100 cases were excluded.

Study Variables
Demographics such as age at diagnosis, gender, race, marital status, date of cancer diagnosis, and geographic region of residence were available from the SEER-Medicare data files. In addition, the SEER cancer files provided information on the site of cancer and the stage at diagnosis. Cancer staging for this study was based on the SEER “historic” staging system, which is divided as in situ, localized (confined to organ), regional (extension beyond organ), or distant (invasion of adjacent organs or distant metastases) spread (15). For the purposes of analysis, the staging variable was dichotomized as localized (in situ or localized) versus nonlocalized (regional or distant). This cutoff was chosen for clinical relevance because for most malignancies, localized tumors are potentially curable. However, choosing the stage cutoff as nondistant (in situ, localized, or regional) versus distant did not alter the study conclusions. For lymphomas, “localized” stage equated to nodal disease confined to one side of the diaphragm, whereas “nonlocalized” stage equated to disease involving both sides of the diaphragm or extranodal spread. For prostate cancer, the SEER staging system combines localized and regional cases into one stage, so it was analyzed separately as nondistant versus distant spread. Socioeconomic status in the form of income was not available at the individual level, so a surrogate value was used based on percentage of residents living below the poverty level in the census tract of residence. Comorbidity was assessed using a modified form of the Charlson comorbidity index developed for use with Medicare claims (16,17). The public-use SEER data contained information on age, gender, race, cancer site, stage, geographic region, and year of diagnosis.

Statistical Analyses
The observed rates of patients who had ESRD and received a diagnosis at a nonlocalized stage were calculated for each cancer site. Comparisons were made with the general population in two ways. First, standardized rates of stage at diagnosis in the general population were estimated by applying the appropriate cancer site-, age-, gender-, race-, year-, and region-specific rates from public-use SEER data to the numbers of patients with ESRD within the appropriate strata. These data were entered into a modified Poisson regression model (which allows for valid estimation of relative risks [RR]) (18) with the dependent variable being nonlocalized stage at diagnosis. RR with 95% confidence intervals (CI) for nonlocalized stage at diagnosis for patients with ESRD versus general population were calculated overall and for each cancer site.

The second general population comparison involved use of patients without ESRD in the SEER-Medicare database as a reference group. This approach was therefore limited to older patients but had the advantage of eliminating the influence of health insurance coverage (because all patients were Medicare eligible) and allowing adjustment of other potential confounders that influence stage at diagnosis, such as marital status, socioeconomic status, and comorbidity. For evaluation of comorbidity (from claims in the 12 mo preceding diagnosis of cancer), these analyses were limited to patients who were ≥66 yr of age, enrolled in Medicare part A and B, and not a member of a health maintenance organization for the 12 mo before cancer diagnosis. Three patients without ESRD were selected by matching at cancer site, age at diagnosis (±5 yr), gender, race, and year of diagnosis for each patient with ESRD. Patients without ESRD were selected randomly when more than three were identified, whereas all were selected when three or fewer matching patients were identified (for 98.5% of patients with ESRD, three or more control subjects were identified). The modified Poisson regression approach was again used to build a model predicting stage at diagnosis of cancer by ESRD status.

Analyses were performed with the software package SAS 9.1 (SAS Institute, Cary, NC). All tests of statistical significance were two-sided, with P < 0.05 being considered statistically significant. The study protocol was approved by the local institutional review board at the University of Texas Medical Branch at Galveston.

Results
A total of 1629 patients with ESRD and incident cancer were identified in the SEER-Medicare database from 1992 through 1999. Table 1 presents their demographic characteristics and distribution of cancer sites. The overall age of the group at diagnosis was 67.4 yr, with roughly two thirds of patients aged ≥65 yr. For patients who were aged ≥65 yr, the most common cancer sites were the major solid-organ malignancies: Lung, colorectal, prostate, and breast. In contrast, in younger patients, renal cell cancers were especially frequent, with kidney being the second most common cancer site after lung.

Table 2 presents data based on modified Poisson regression models comparing the likelihood of a nonlocalized stage of cancer at diagnosis in the ESRD group with standardized general population data from SEER. RR  1 suggest a later stage at diagnosis in patients with ESRD, whereas ratios < 1 suggest an earlier stage at diagnosis. Overall, there was no significant difference in stage at diagnosis for patients with ESRD versus the general population when all cancer sites were examined simultaneously. When the analysis was stratified by individual cancer sites, colorectal cancers were significantly more likely to be diagnosed at an earlier stage in patients with ESRD, whereas prostate cancers were significantly more likely to be diagnosed at a later stage compared with the general population. This pattern was similar when the analyses were divided into patients who were younger than 65 and those who were ≥65, although none of the results achieved statistical significance. In the younger age group, there was a trend toward earlier stage at diagnosis in the ESRD group for kidney cancers (RR 0.64; 95% CI 0.38 to 1.06; P = 0.08). No substantial differences were noted when the analyses were stratified by race or gender (data not shown).

Table 3 presents data based on modified Poisson regression
models comparing likelihood of a nonlocalized stage of cancer at diagnosis in the ESRD group with matched Medicare control subjects without ESRD, adjusted for comorbidity, income, and marital status. This analysis was limited to Medicare-eligible patients who were aged ≥66 yr. Similar to the analysis presented in Table 2, there was no significant difference in stage between the ESRD and non-ESRD groups when all cancer sites were analyzed together. Colorectal cancers were again significantly more likely to be diagnosed earlier in the ESRD group, whereas prostate cancers were significantly more likely to be diagnosed at a later stage. Compared with the analysis of patients who were aged ≥65 yr in Table 2, the RR for lymphoma and lung, kidney, and breast cancers increased, but only kidney cancers were diagnosed at a significantly later stage in the ESRD group (RR 1.36; 95% CI 1.00 to 1.85; P = 0.048).

On the basis of the consistent finding of significant differences in stage at diagnosis for prostate and colorectal cancers, additional analyses were performed to examine whether differences between the ESRD and non-ESRD groups existed in frequency of medical workup relevant to these malignancies. Medicare claims were searched to determine the rates of prostate-specific antigen (PSA) testing (any of CPT-4 codes 84152 to 84154 and Healthcare Common Procedure Coding System code G0103) and lower gastrointestinal endoscopy (any of ICD-9 procedure codes 45.23 and 45.24; CPT-4 codes 45330, 45355, and 45378; and Healthcare Common Procedure Coding System codes G0104 and G0105) in the prostate cancer and colorectal cancer groups, respectively, during the period 12 to 24 mo before diagnosis. This period was chosen to avoid simply identifying the tests that actually led to the diagnosis of the cancer. PSA testing was significantly less likely (odds ratio 0.59; 95% CI 0.36 to 0.96), whereas lower endoscopy (colonoscopy or flexible sigmoidoscopy) was more likely (odds ratio 3.65; 95% CI 1.21 to 11.03) in the ESRD versus the non-ESRD group.

### Discussion

This is the first study, to our knowledge, that systematically compares stage at diagnosis of cancer in patients with ESRD versus the general population. Despite low rates of cancer screening in patients who have ESRD and are on dialysis, this study suggests that, with some exceptions, they are not more likely to receive a diagnosis of a later stage of cancer in comparison with the general population. This may occur because of a number of distinct qualities of the ESRD population. First,
virtually all patients with ESRD qualify for health insurance through Medicare. Health insurance availability is an important predictor of cancer stage at diagnosis (19). In our study, this is supported by the fact that patients with ESRD were generally less advantaged in terms of stage at diagnosis (i.e., RR for nonlocalized stage were higher) when the comparison group included only Medicare-eligible patients, versus the public SEER data (which also include patients without health insurance). Second, contact with medical care is frequent by virtue of the dialysis procedure. The typical hemodialysis patient may be seen as much as once a week by a physician. A higher frequency of outpatient physician visits for routine care has been associated with earlier stage at diagnosis for breast cancer (20). Third, a related point is that medical workup for a number of health issues is frequent in patients with ESRD, perhaps increasing the possibility of incidental, early-stage cancer diagnoses. This may be of particular relevance for malignancies for which no screening modality exists. For example, the high incidence of thyroid malignancies in patients with ESRD has been attributed in part to the frequent workup of parathyroid disorders (21). Finally, some dialysis patients may receive intensive screening activities as part of a workup before

Table 2. Likelihood of nonlocalized stage of cancer at diagnosis in the ESRD versus standardized general population

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Overall Group</th>
<th>Patients Aged &lt;65 Yr</th>
<th>Patients Aged ≥65 Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ESRD (%)</td>
<td>General Population (%)</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>All</td>
<td>45.5</td>
<td>50.0</td>
<td>0.90 (0.81 to 1.01)</td>
</tr>
<tr>
<td>Breast</td>
<td>32.5</td>
<td>28.8</td>
<td>1.13 (0.82 to 1.54)</td>
</tr>
<tr>
<td>Bladder</td>
<td>28.8</td>
<td>23.8</td>
<td>1.21 (0.72 to 2.03)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>40.9</td>
<td>52.6</td>
<td>0.78 (0.62 to 0.98)</td>
</tr>
<tr>
<td>Kidney</td>
<td>33.6</td>
<td>40.4</td>
<td>0.83 (0.58 to 1.18)</td>
</tr>
<tr>
<td>Lung</td>
<td>62.9</td>
<td>71.4</td>
<td>0.88 (0.74 to 1.04)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>61.7</td>
<td>58.0</td>
<td>1.06 (0.75 to 1.52)</td>
</tr>
<tr>
<td>Prostatee</td>
<td>12.6</td>
<td>6.7</td>
<td>1.87 (1.05 to 3.33)</td>
</tr>
</tbody>
</table>

CI, confidence interval; RR, relative risk.

Table 3. Likelihood of a nonlocalized stage of cancer at diagnosis in the ESRD versus matched non-ESRD Medicare population

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Overall Group</th>
<th>Non-ESRD (%)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>45.9 (728)</td>
<td>49.6</td>
<td>0.97 (0.89 to 1.07)</td>
</tr>
<tr>
<td>Breast</td>
<td>30.7 (140)</td>
<td>24.1</td>
<td>1.35 (0.99 to 1.82)</td>
</tr>
<tr>
<td>Bladder</td>
<td>25.7 (70)</td>
<td>26.4</td>
<td>1.02 (0.64 to 1.63)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>39.0 (195)</td>
<td>50.9</td>
<td>0.81 (0.66 to 0.98)</td>
</tr>
<tr>
<td>Kidney</td>
<td>55.8 (52)</td>
<td>42.2</td>
<td>1.36 (1.00 to 1.85)</td>
</tr>
<tr>
<td>Lung</td>
<td>62.1 (240)</td>
<td>70.6</td>
<td>0.92 (0.82 to 1.04)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>61.3 (31)</td>
<td>58.1</td>
<td>1.09 (0.78 to 1.51)</td>
</tr>
<tr>
<td>Prostatee</td>
<td>13.7 (139)</td>
<td>6.5</td>
<td>2.36 (1.35 to 4.13)</td>
</tr>
</tbody>
</table>

CI, confidence interval; RR, relative risk.

CI, confidence interval; RR, relative risk.

aLimited to patients aged ≥66 yr, enrolled in Medicare part A and B, and not a member of a health maintenance organization for the 12 mo before cancer diagnosis.

b Patients who had cancer in the SEER-Medicare database and did not meet criteria for ESRD status. Three were selected randomly for each patient with ESRD by matching at cancer site, age at diagnosis (±5 yr), gender, race, year, and region strata from the ESRD group.

c From a modified Poisson regression model predicting nonlocalized stage at diagnosis, with independent variables including ESRD status, age at diagnosis, race, gender, SEER geographic region of residence, year of diagnosis, and cancer site.

d From a modified Poisson regression model similar to the overall group but limited to patients aged <65 yr at diagnosis.

e From a modified Poisson regression model similar to the overall group but limited to patients aged ≥65 yr at diagnosis.

f Excluding prostate cancer.

g Outcome is likelihood of distant stage at diagnosis.
renal transplantation. However, because no information on wait-listing for transplant was available, this issue could not be examined directly as part of this study.

A striking finding of this study was that patients with ESRD were approximately twice as likely to present with a distant and therefore incurable stage at diagnosis of prostate cancer. This may be in part due to lower use of PSA screening in the ESRD population, demonstrated both in this study and in previous work (8,9). In addition, the absence of urinary output may hinder early diagnosis on the basis of urinary tract symptoms (22). Despite the poor outcome in distant disease, it is still unclear whether PSA screening reduces mortality in the general population (23). One of the main problems with PSA screening is the frequent detection of early-stage disease of no clinical significance as a result of the competing risk for death from other causes (24). This issue is of particular relevance given the substantial morbidity and mortality in the dialysis population. It may therefore be prudent to limit consideration of PSA screening to dialysis patients with a life expectancy of at least 10 yr and ensure an adequate discussion of the risks, benefits, and uncertainties (25).

The finding that patients with ESRD received a diagnosis of earlier stage colorectal cancers may relate to more frequent gastrointestinal workup in this population. This is supported by additional analyses demonstrating that patients with ESRD were more likely to receive colonoscopy or flexible sigmoidoscopy in the 12 to 24 mo before diagnosis of cancer. A number of factors may have contributed to this finding. Anemia is extremely common in dialysis patients and may have prompted workup for sources of gastrointestinal blood loss (26). Uremic platelet dysfunction combined with anticoagulation given during hemodialysis results in a bleeding diathesis that may bring gastrointestinal lesions to attention earlier (27). For instance, dialysis patients are more likely to have positive stool guaiac tests than nonuremic control subjects (28). Finally, diagnostic evaluations for gastrointestinal diseases that are especially common in dialysis patients, such as angiodysplasia or constipation, may lead to incidental identification of malignant lesions (29).

A number of studies have reported differences in the incidence of various cancers between the dialysis and general populations (4,30,31). Although these differences may relate to the true risks of malignancy in the setting of dialysis or uremia, they could also result from differences in surveillance for cancers. For example, if the later stage of prostate cancer in dialysis patients noted in our study were due to reduced surveillance, then a lower incidence of prostate cancer would be expected. Examining this issue, we did find that the incidence of prostate cancer was significantly lower (standardized incidence ratio 0.47; 95% CI 0.43 to 0.53) in the dialysis versus the general population, consistent with previously published findings (4,30). Similarly, if the earlier stage of colorectal cancer in dialysis patients noted in our study were due to increased surveillance, then a higher incidence of colorectal cancer would be expected. However, we did not find a significant difference in incidence of colorectal cancer (standardized incidence ratio of 0.96; 95% CI 0.84 to 1.09), although other, larger studies have noted a modest increase in the dialysis population (4,30).

This study has important limitations. It was limited by power as a result of the relatively small sample sizes. The CI for several of the individual cancer sites were therefore too wide to allow any meaningful conclusions or stratified analyses. Nevertheless, this study carries the advantage that it is population based and therefore likely to be representative of actual practice. Also, because of limitations of sample size and a Medicare claims–based approach, not all potentially relevant variables (e.g., digital rectal examinations, routine physical examinations) were available or could be entered into the models. However, the models were adjusted for a select number of variables that previously were shown to be strongly predictive of cancer stage at diagnosis, such as marital and socioeconomic status. Another limitation has to do with potential biases related to the staging process in the tumor registries. Because information from operative reports are incorporated into determination of staging, patients who undergo surgery for their cancers are more likely to be reported as having later stage tumors as a result of detection of disease extension not evident by clinical or radiologic assessments (15). This could have biased the results toward earlier stages at diagnosis reported for patients with ESRD if they systematically underwent surgery for their cancers less often. However, with the exception of prostate cancer, surgery is generally considered standard of care for most localized, solid-organ malignancies (32). When we examined the SEER data, rates of surgery for localized breast, kidney, and colorectal cancers were >90% for both the ESRD and standardized general populations. Rates of surgery for localized lung cancers were lower in patients with ESRD at 43 versus 62% in the standardized general population, likely explained by a greater number of comorbidities in the ESRD group (33). However, the adjustment for comorbidity in the analyses performed in Table 3 would have mitigated the difference in rates of surgery and its impact on assessment of stage at diagnosis.

Conclusions

This study demonstrates that, with the notable exception of prostate cancer, patients with ESRD are not more likely to present with later stage malignancies despite generally lower rates of screening compared with the general population. This may occur as a result of the higher frequency of physician visits or more intensive medical workups in patients who are on dialysis.

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Disclosures

None.
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