Title
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Patient Function, Long-term Survival, and Use of Surgery for Kidney Cancer

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Abstract

Background: Beyond age and comorbidity, functionality can shape the long-term survival potential of cancer patients. Accordingly, we compared mortality and receipt of cancer-directed surgery according to baseline functional health among older adults with kidney cancer.

Methods: Using SEER-Medicare data from 2000–2009, we studied 28,326 elderly subjects with primary kidney cancer. Patient function was quantified using function-related indicators, claims indicative of dysfunction and disability. Adjusting for patient and cancer characteristics, we used competing risk regression to assess the relationship between function-related indicator count and cause-specific mortality and then generalized estimating equations to quantify the probability of surgery.

Results: We identified 13,619 (48.1%) adults with at least 1 function-related indicator. Higher indicator category was associated with older age, greater comorbidity, female gender, unmarried status, lower socioeconomic status, and higher cancer stage ($p<0.001$). Compared with patients with count of 0, those with count of 1 (HR 1.10, 95% CI 1.04–1.16) and ≥2 (HR 1.46, 95% CI 1.39–1.53) had higher other cause mortality. Conversely, kidney cancer mortality varied minimally with patient function. Patients with ≥2 indicators received cancer-directed surgery less often than those without disability (OR 0.61, 95% 0.56–0.66), though treatment probabilities remained high for patients with loco-regional disease and low for adults with metastatic cancer.

Conclusion: Among older adults with kidney cancer, functional health stands as a significant predictor of long-term survival. However, receipt of cancer-directed surgery appears largely determined by cancer stage. Patient functionality should be considered more heavily when deciding treatment for older adults with kidney cancer.

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Condensed Abstract:

In addition to age and comorbidity, patient function impacts the long-term survival of adults with kidney cancer. While baseline disability influences treatment use to a modest degree, receipt of surgery varies mostly with cancer stage, underscoring the need to more meaningfully consider functionality in the management of patients with cancer of the kidney.

Keywords

aged; functional status; kidney neoplasm; nephrectomy; survival

Introduction

Unlike most other malignancies, kidney cancer incidence continues to rise. Consequently, kidney cancer now stands as the 7th most common solid organ malignancy in the US, accounting for 62,700 new cases and 14,240 corresponding deaths annually.[1, 2] Beneath this overlying trend lies a seismic shift in demographics. While the majority of cases occur in young and middle-aged adults, the risk of disease peaks for adults in the 7th, 8th, and 9th decades of life.[3] When coupled with an aging population,[4] elderly adults with kidney cancer represent a burgeoning pool of cancer patients in the US.

Although curable with surgery alone, the decision for treatment can be highly involved for elderly patients with kidney cancer. Given the physiologic process of aging and the increased prevalence of comorbid conditions, the morbidity associated with surgery can be sizeable, despite recent advances in percutaneous and minimally invasive techniques.[5–8] At the same time, these patients carry substantial risk from competing causes of death, thereby limiting the potential to prolong life with cancer treatment.[9, 10] Though less often considered, at least at a population level, patient functionality—whether physical, mental, or emotional—may exacerbate the balance between providing benefit and inflicting harm. Beyond age and comorbidity, functional decline and disability befall many elderly cancer patients, leading to the use of assistive devices or manifesting in the form of other conditions including frailty, falls, fractures, and dementia. Such deficits have been associated with worsening treatment-related morbidity and toxicity.[11–15] Specific to kidney cancer, performance status has been identified as a clinically important modulator of short- and long-term survival in the setting of both localized and advanced disease.[16, 17] However, the extent to which patient function impacts the competing threats of kidney cancer and other cause mortality remains poorly understood.

Using nationally representative data, we compared kidney cancer mortality, other cause mortality, and receipt of cancer-directed surgery according to functional health, expecting higher incidence of non-kidney cancer death and lower use of surgery among adults with evidence of functional decline or disability. In doing so, we aim to provide critical insight on the role of patient function in shaping long-term survival and treatment utilization to further optimize care for the anticipated plurality of elderly Americans with kidney cancer.

Materials and Methods

Data Source and Cohort Identification

Using linked SEER-Medicare data from the National Cancer Institute, we identified subjects aged greater than 65 years diagnosed with primary, non-urothelial kidney cancer from 2000 through 2009. SEER is a population-based cancer registry that maintains data regarding incidence, treatment, and mortality representative of the US population.[18] The Medicare program provides primary health insurance for 97% of the US population aged 65 or older.[19] Successful linkage with Medicare claims is achieved for over 90% of covered patients whose cancer information are tracked by SEER.[19]

We identified a preliminary cohort of 30,158 subjects after excluding those without continuous enrollment from 12 months prior to 6 months following surgery (or death) and those enrolled in a Medicare managed care plan, as follow-up may be incomplete. Next, we restricted our sample to patients with complete cancer staging information (n=28,458). We then excluded those with hospice care in the year prior to diagnosis (n=46) and/or bilateral disease (n=86) to create an analytic cohort of 28,326 subjects.

Primary Measure of Patient Function

For our measure of functionality, we examined Medicare claims in the 12 months preceding cancer diagnosis and applied function-related indicators as described by Chrischilles et al.[20] These indicators are derived from claims indicative of reduced functional status (e.g., mobility-assist device, falls, fractures, home oxygen, pressure ulcers) or overall dysfunction and/or disability (e.g., dementia, depression, malnutrition, respiratory failure, sepsis). These types of claims have demonstrated strong relationships with patient-reported performance status as measured by the Eastern Cooperative Oncology Group scale, short-term mortality, and long-term survival, all independent of comorbidity.[20, 21] For the purpose of this study, we created a three-tier categorical variable with indicator count equal to 0, 1, and ≥2.

Additional Patient Covariates

From SEER-Medicare, we extracted patient demographics including age, gender, marital status, race, and year of diagnosis. We utilized census-tract level estimates of high school education and median income divided into equally-sized tertiles as measures of socioeconomic status and further identified the rural/urban residential status. Comorbidity was assigned using the Klabunde modification of the Charlson Comorbidity index based on inpatient and outpatient claims submitted during the 12 months prior to kidney cancer diagnosis.[22] We also classified tumor stage (i.e., AJCC stages I–IV) based on cancer information contained within SEER, which is drawn from both clinical and pathologic data sources.

Outcome Measures relating to Survival and Surgical Treatment

For survival, we measured the interval from the date of diagnosis to the date of death or until December 31, 2010 as reported by SEER. For each patient, we classified the vital status as expired from kidney cancer, expired from other causes, or alive according to the included cause of death variable.

Next, we applied a validated, claims-based algorithm to determine the receipt of cancer-directed surgery for each subject based on inpatient hospital and physician claims using International Classification of Diseases, 9th revision, Clinical Modification (ICD-9) and Current Procedural Terminology (CPT) codes.[23] Given recent practice trends, this algorithm has been further broadened to capture those treated with ablative therapies. As part of a planned sensitivity analysis, we also identified treatment according to the SEER treatment variables.

Statistical Analysis

First, we compared patient and cancer-specific characteristics according to function-related indicator category using chi-square testing. We then assessed the risks of kidney cancer and other cause mortality according to our measure of patient function using competing risks regression models as described by Fine and Gray.[24] These models adjust for age and comorbidity as well as race, gender, marital status, receipt of surgery, socioeconomic status, cancer stage, and selected interaction terms. In addition to our primary model, we fitted secondary models for each specific cancer stage. Our failure event was defined as other cause mortality; the competing risk was kidney cancer mortality. As described previously, we elected to use a competing risks model rather than a Cox proportional hazards model because the latter treats competing events as censored observations, and its cause-specific hazard function does not have a direct interpretation in terms of survival probability. Results are reported as sub-hazard ratios (HR) with 95% confidence intervals (CIs) and risk-adjusted cumulative mortality incidences over time.

Next, we evaluated the likelihood of surgical treatment according to function-related indicator category. To do so, we used generalized estimating equations to account for regional-level clustering at the level of SEER-designated health service areas. These models adjust for patient characteristics, cancer stage, and year of treatment. From these models, we calculated predicted probabilities for surgery—for the overall cohort and again by cancer stage—and obtained 95% confidence intervals using bootstrapping with replacement for 1000 replications.

To confirm the robustness of our findings, we performed several sensitivity analyses. First, to verify that functional health acts independent of comorbidity,[25] we examined subgroups according to Charlson Comorbidity score. We also constructed models that tested the function-related indicators collectively in place of our primary summary measure. Second, as the decision to treat is typically based on clinical not pathological stage, we fitted models using tumor size. Third, we examined models using treatment as defined by SEER to ensure that our findings are not attributable to coding misclassification.

All statistical testing was 2-sided, completed using computerized software (STATA version 14.1, College Station, TX), and carried out at the 5% significance level. This study was approved by the Institutional Review Board at the University of California, Los Angeles.

Results

Of 28,326 patients with kidney cancer identified during the study period, nearly half had one or more function-related indicator—8,012 (28.3%) had one positive indicator and 5,607 (19.8%) had 2 or more. As reported in Table 1, higher function-related indicator category was associated with older age, female gender, unmarried status, lower socioeconomic position, comorbidity burden, and more advanced cancer ($p<0.001$). Statistically significant relationships with race/ethnicity ($p=0.001$) and year of diagnosis ($p=0.041$) were also observed.

Adjusting for patient characteristic including preexisting comorbidity, receipt of surgery, and cancer stage, we found that patients with 1 function-related indicator (HR 1.10, 95% CI 1.04–1.16) and those with ≥2 (HR 1.46, 95% CI 1.39–1.53) had higher risk of other cause mortality compared with those without any positive indicator. The association between functionality and kidney cancer mortality was less clear. For instance, compared with patients without a single indicator, those with 1 (HR 1.08, 95% CI 1.02–1.13) had a slightly higher risk of kidney cancer mortality while those with ≥2 (HR 1.03, 95% CI 0.96–1.11) did not. As illustrated in Figure 1, risk-adjusted 5-year incidence of other cause mortality was 22%, 24%, and 30% versus kidney cancer mortality of 16%, 17%, and 16% for patients with function-related counts of 0, 1, and ≥2, respectively. Risk-adjusted 10-year incidence of other cause mortality was 38%, 41%, and 50% while the incidence of kidney cancer mortality was 19%, 20%, and 19% according to function-related indicator category. Figure 2 depicts the risk-adjusted incidences of death further stratified by cancer stage.

In terms of treatment, patients with ≥2 function-related indicators (OR 0.61, 95% CI 0.56–0.66) received surgery less often than those with no positive indicator after adjusting for patient characteristics, cancer stage, and year of diagnosis. In contrast, there appeared to be no difference in use of surgery between patients with function-related indicator counts of 0 and 1 (OR 1.03, 95% CI 0.95–0.11). Model-adjusted predicted probabilities of surgery according to function-related indicator category stratified by cancer stage are illustrated in Figure 3. As depicted, the described relationship between surgery and our functional health measure remained consistent across each specific cancer stage though absolute usage appeared far lower for patients with stage IV kidney cancer.

Our findings did not differ substantively when stratifying our analysis by Charlson Comorbidity score. Furthermore, most function-related indicators significantly predicted other cause mortality and surgical utilization (Supplementary Table 1). Our findings also remained consistent when using tumor size instead of or in combination with cancer stage. When using the SEER treatment variable, we found that both patients with 1 (OR 0.86, 95% CI 0.79–0.93) and ≥2 function-related indicators (OR 0.49, 95% CI 0.45–0.54) received treatment less often than their peers with no function-related indicators.

Discussion

In the current era, surgery remains a first-line treatment for patients with kidney cancer. Given both disease-related and general population trends, however, the decision to extirpate or ablate may grow increasingly complex, as patients and providers weigh the potential harms of surgery with the opportunity for benefit as well as need for resource use and cost. Accordingly, more careful attention has been given to a patient's underlying health status, particularly with respect to age and comorbidity.[9, 10] Our findings indicate that patient functionality can have further bearing on other cause mortality and may also influence, at least to some degree, the use of cancer-directed surgery for older adults diagnosed with kidney cancer.

Over the past two decades, functional status—physical, mental, and emotional—has emerged as a vital determinant of cancer survivorship. For several types of cancer, functional decline has been linked to poor tolerance of systemic therapy as well as reduced overall survival.[26–28] While a similar observation between performance status and survival has been made in kidney cancer,[29] our findings suggest that this relationship may be driven more so by competing health concerns given the similar risk of kidney cancer mortality irrespective of functionality. Indeed, functional decline independently predicts survival in the general community and may serve as a harbinger for other geriatric conditions such as frailty, dementia, and depression.[25, 30] Though not examined in this current study, deficits in function and performance status have also been associated with a more morbid and burdensome surgical course, particularly for older cancer patients.[11, 14, 15] By extension then, for patients with significant dysfunction or disability, the oncologic benefit from kidney cancer surgery must be sufficiently high for treatment to be worthwhile.

In this context, our study also suggests that patient functionality has begun to seep into the collective decision-making process for patients with kidney cancer. Across the spectrum of disease, patients in poor functional health received treatment less often than those with no or limited evidence of functional decline. These findings are consistent with previous studies that found performance status to be a key consideration in the use of surveillance for small kidney tumors and of cytoreductive nephrectomy for patients with metastatic cancer.[17, 31, 32] Even so, our findings indicate that receipt of surgery is driven far more by cancer stage. In the case of stage I kidney cancer, over 75% of patients in poor functional health received cancer-directed surgery despite a six-fold higher risk of death from causes other than kidney cancer. Conversely, relatively few patients—including those without a single indicator of disability—undergo cytoreductive nephrectomy, despite evidence demonstrating a clinical benefit and acceptable tolerability.[33, 34] So while receipt of surgery does vary with patient function, there appears to be areas of both over-treatment and under-treatment in kidney cancer care.

These results should be considered in the context of several limitations. First, the relationship between functional health and our study endpoints could result from residual confounding related to comorbidity. However, our applied measure has been shown to be independent of conventional comorbidity indices,[20] and we noted similar findings when stratifying our analysis by comorbidity subgroups. Furthermore, the observed relationships between individual indicators and our selected endpoints show consistency in directionality, supporting the robustness of our measure for patient function. Second, our findings may be subject to the staging procedure used by SEER. However, we noted no difference when using tumor size rather than stage in our models. Third, patients treated for presumed cancer but found to have benign disease may be excluded from SEER, thereby influencing our results.[35] This would likely bias our findings toward the null though and would be less applicable to patients with stage II – IV disease. Forth, the omission of tumor complexity could also bias our findings as they relate to kidney cancer mortality and receipt of surgery. Though important clinically, tumor complexity would likely have greater bearing on surgical approach. Additionally, our findings do not change when adjusting for size, a contributor to complexity, in addition to cancer stage. Fifth, our assessment of surgery depends on the accuracy of our surgical assignment. For this reason, we used a validated algorithm based on Medicare claims and noted similar results when using surgery as defined by SEER.[23] Sixth, given the predominance of surgery in kidney cancer treatment, we did not assess the relationship between functionality and receipt of medical therapies (i.e., immunotherapy and targeted therapy). It is worth noting that studies in other disease sites have demonstrated a similar relationship between patient function and receipt of chemotherapy.[36] Finally, while findings arising from Medicare data may not be generalizable to younger patients, functional health is considered to be more pressing in the older population studied herein.

These considerations notwithstanding, our findings have important implications for the management of kidney cancer, particularly at the bookends of the disease. For patients presenting with stage I kidney cancer, both age and comorbidity are built into existing management guidelines, though these patients are often overtreated.[37, 38] Since functional health also appears to be an important modulator of long-term outcomes, consideration of these aspects of health may help further fine-tune treatment selection given the multitude of management options now available. At the other extreme, there may be additional opportunity to pursue cytoreductive nephrectomy in patients without any identifiable disability.

To move forward on these fronts, oncologic providers could give greater weight to ECOG or Karnofsky performance status scales when assessing patients with kidney cancer. In addition to these tools, comprehensive geriatric assessments may bring greater clarity to a patient's physical, mental, and emotional function. In fact, as many as 40% of patients with good performance status (i.e., ECOG 0–1) have a deficit in their Activities of Daily Living or Instrumental Activities of Daily Living, mental status, emotional state, or energy level.[11] Conversely, high functioning treatment candidates can also emerge who would otherwise be overlooked due to age.[11–13] Through this activity, patient preferences, risk tolerance, and values may also be better appreciated during the decision-making process. In either scenario, kidney cancer care may be improved by a more conscious and purposeful assessment of patient function and its subsequent application to treatment selection.

Conclusion

Among older adults with kidney cancer, patient function significantly influences the risk of death from causes other than kidney cancer. Patients in poor functional health receive cancer-directed surgery less often than their better functioning counterparts across the spectrum of disease. However, treatment remains largely determined by cancer stage with high usage for localized disease and low usage for metastatic cancer. Greater consideration of functionality during decision-making may serve as an avenue for improvement in the quality of care delivery for kidney cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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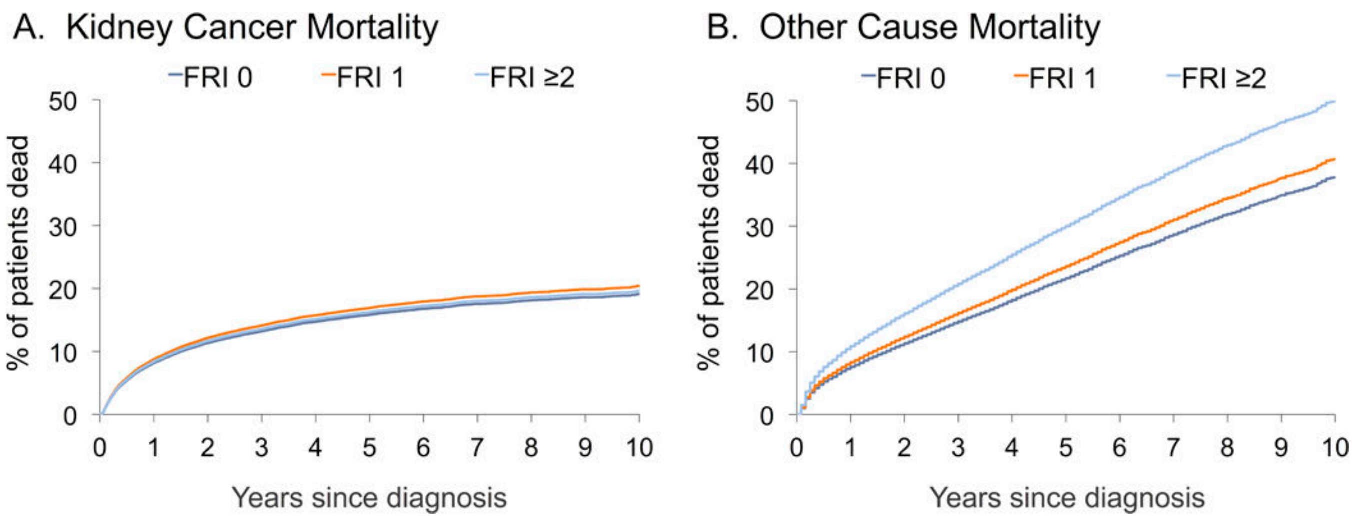

Figure 1:
Cumulative incidence of kidney cancer mortality (A) and other cause mortality (B) according to patient function as measured by function-related indicator category. Estimates are based on competing risk regression adjusting for patient characteristics, tumor stage, and receipt of surgery.

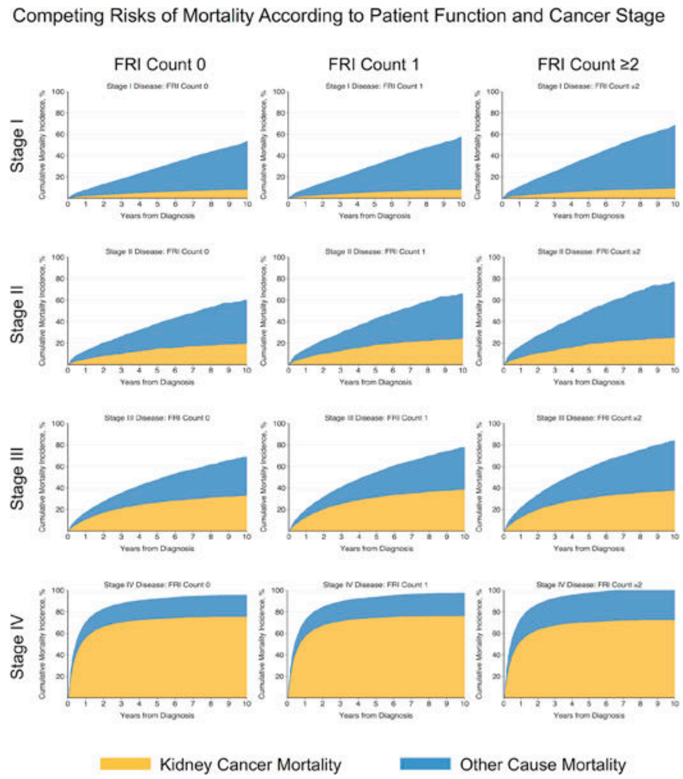

Figure 2:

Cumulative incidence of kidney cancer (yellow) and other cause (blue) mortality according to patient function and cancer stage. Functionality measured using function-related indicators. Estimates are based on competing risk regression adjusting for patient characteristics and receipt of surgery.

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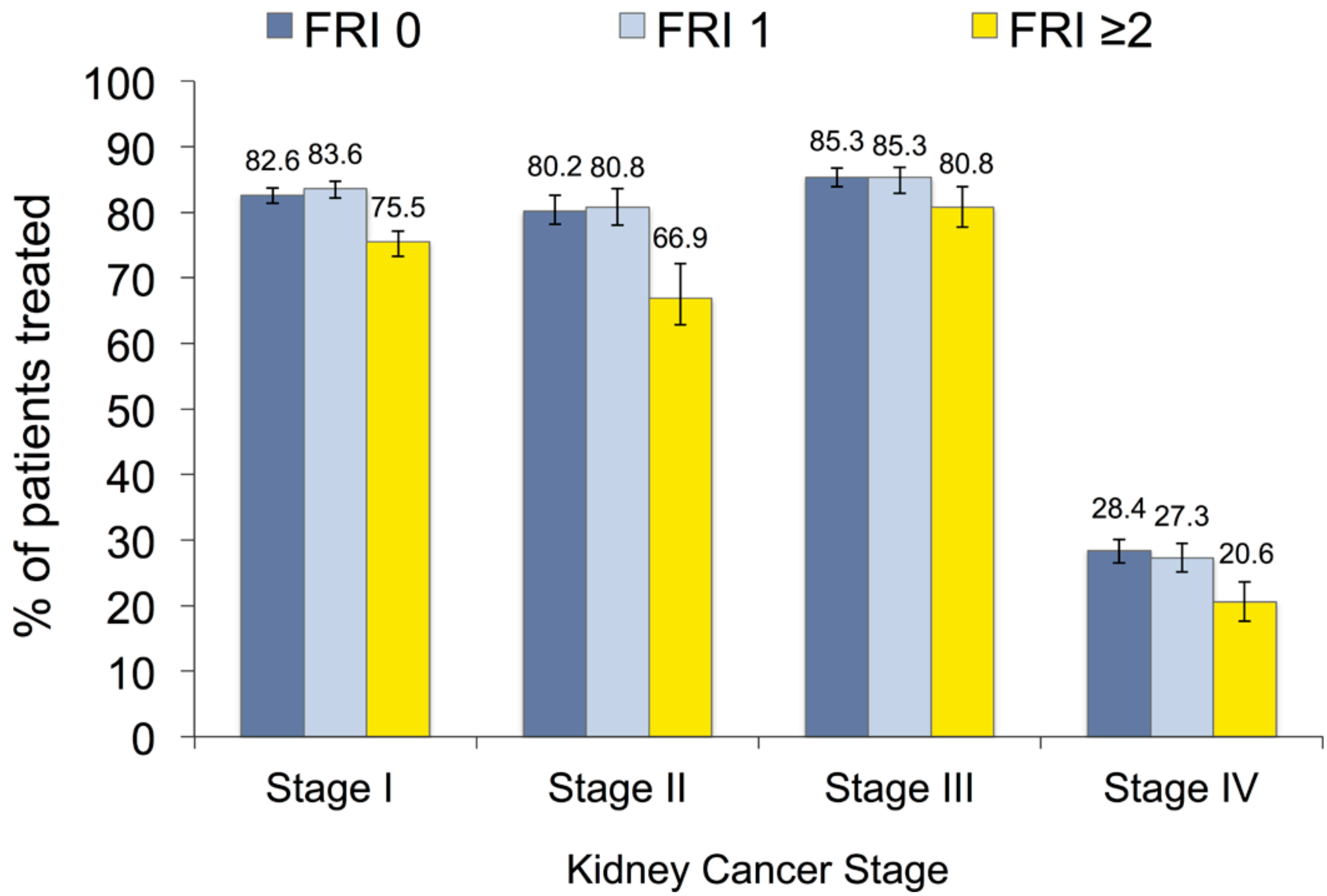

Figure 3:
Predicted probability of surgical treatment for kidney cancer according to patient function and cancer stage. Functionality measured using function-related indicators. Estimates are derived from generalized estimating equations, adjusted for patient characteristics and year of diagnosis. 95% confidence intervals obtained using bootstrapping with replacement for 1000 replications.

Table 1:

Patient characteristics according to function-related indicator count[^]

	Indicator Count 0 (N=14,707)	Indicator Count 1 (N=8,012)	Indicator Count ≥2 (N=5,607)	P-value
Age (years)				
65–69	3,154 (21.5)	1,455 (18.2)	855 (15.3)	<0.001
70–74	4,319 (29.4)	2,111 (26.4)	1,164 (20.8)	
75–79	3,604 (24.5)	2,040 (25.5)	1,361 (24.3)	
80–84	2,305 (15.7)	1,405 (17.5)	1,147 (20.5)	
85+	1,325 (9.0)	1,001 (12.5)	1,080 (19.3)	
Female	5,421 (36.9)	3,462 (43.2)	2,796 (49.9)	<0.001
Race/Ethnicity				
White	11,930 (81.1)	6,594 (82.3)	4,487 (80.0)	0.001
Black	1,335 (9.1)	674 (8.4)	589 (10.5)	
Hispanic/Latino	869 (5.9)	449 (5.6)	347 (6.2)	
Asian	444 (3.0)	229 (2.9)	131 (2.3)	
Other	129 (0.9)	66 (0.8)	53 (1.0)	
Married	9,170 (62.4)	4,593 (57.3)	2,689 (48.0)	<0.001
Rural Status	1,717 (11.7)	908 (11.3)	666 (11.9)	0.592
Income[*]				
Bottom tertile	4,685 (31.9)	2,607 (32.6)	2,139 (38.2)	<0.001
Middle tertile	4,961 (33.8)	2,649 (33.1)	1,823(32.6)	
Top tertile	5,045 (34.3)	2,749 (34.3)	1,639 (29.3)	
Education[*]				
Bottom tertile	4,782 (32.6)	2,622 (32.8)	2,030 (36.2)	<0.001
Middle tertile	4,895 (33.3)	2,671 (33.4)	1,868 (33.4)	
Top tertile	5,016 (34.1)	2,712 (33.9)	1,703 (30.4)	
Charlson Comorbidity Score				
0	9,413 (64.0)	3,970 (49.6)	1,518 (27.1)	<0.001
1	3,406 (23.2)	2,205 (27.5)	1,484 (26.5)	
2	1,041 (7.1)	895 (11.2)	962 (17.2)	
3+	847 (5.8)	942 (11.8)	1,643 (29.3)	
Tumor Stage[†]				
Stage I	8,166 (55.5)	4,501 (56.2)	3,168 (56.5)	<0.001
Stage II	1,295 (8.8)	621 (7.8)	430 (7.7)	
Stage III	2,569 (17.5)	1,282 (16.0)	810 (14.5)	
Stage IV	2,677 (18.2)	1,608 (20.1)	1,199 (21.4)	

	Indicator Count 0 (N=14,707)	Indicator Count 1 (N=8,012)	Indicator Count ≥2 (N=5,607)	P-value
Year of Diagnosis				
2000	1,178 (8.0)	646 (8.1)	412 (7.4)	0.041
2001	1,356 (9.2)	684 (8.5)	424 (7.6)	
2002	1,332 (9.1)	703 (8.8)	517 (9.2)	
2003	1,446 (9.8)	749 (9.4)	586 (10.5)	
2004	1,479 (10.1)	862 (10.8)	568 (10.1)	
2005	1,609 (10.9)	855 (10.7)	623 (11.1)	
2006	1,564 (10.6)	880 (11.0)	614 (11.0)	
2007	1,638 (11.1)	881 (11.0)	601 (10.7)	
2008	1,567 (10.7)	871 (10.9)	631 (11.3)	
2009	1,538 (10.5)	881 (11.0)	631 (11.3)	

^Column percentages may not add up to 100% due to rounding.

*Income and education data missing for 29 and 27 patients, respectively.

†Based on the American Joint Committee on Cancer Staging Manual, 10th edition.