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Competing Risks of Death in Patients with Localized Renal Cell Carcinoma: A Comorbidity Based Model

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Abstract

Purpose—Multiple risks compete with cancer as the primary cause of death. These factors must be considered against the benefits of treatment. We constructed a competing causes of death model to help contextualize treatment tradeoff analyses in patients with localized RCC.

Patients and Methods—6,655 individuals 66 years old with localized RCC were identified in the linked SEER Medicare dataset (1995–2005). We used Fine and Gray's competing risks proportional hazards regressions to predict probabilities of competing mortality outcomes. Prognostic markers included race, gender, tumor size, age, and the CCI Score.

Results—After a median follow-up of 43 months, age and comorbidity score strongly correlated to patient mortality and were most predictive of non-kidney cancer deaths as measured by concordance statistics. We demonstrate that patients with localized node negative kidney cancer have low 3 (4.7%), 5 (7.5%) and 10 (11.9%) year probabilities of cancer specific death, but significantly higher overall risk of death from competing causes within 3 (10.9%), 5 (20.1%) and 10 (44.4%) years of diagnosis of RCC, depending on their comorbidity scores.

Conclusions—Informed treatment decisions regarding patients with solid tumors must integrate not only cancer-related variables, but also factors that predict for non-cancer death. Here we establish a comorbidity based predictive model, which may assist in patient counseling by allowing quantification and comparison of competing risks of death in patients 66 and older with localized RCC who choose to proceed with surgery.

Keywords

renal cell carcinoma; nomogram; survival; competing risks; comorbidities

Introduction

Oncologic treatment trade-off methods pose significant clinical challenges.¹ While quantifying uncertainty is inherently difficult, clinicians and patients perceive medical trade-

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off decisions differently than other choices.² Barriers to this process are found at many levels and hence few objective tools to quantitate medical uncertainty are used in clinical practice.³

Patients with localized kidney cancer present a unique opportunity to model competing risk outcomes for several reasons – (1) detection is often incidental⁴ (2) many patients are elderly with pre-existing comorbidities⁵ (3) robust natural history data are starting to emerge.⁶ Here we develop a competing risks model of survival for patients with kidney cancer using linked population based data. The goal was to achieve quantification and comparison of risks of death from RCC versus from other causes in patients presenting with localized disease. To our knowledge, this is among the first competing risks models, which incorporates patient comorbidity status into risk quantification, and, thus, affords a tool for providing a contextual framework to making judicious treatment trade-off decisions.

Methods

Patient Population

We included patients for whom kidney cancer was their first lifetime cancer diagnosis. We also only included patients who had Medicare part A and B coverage for one year before and one year after cancer diagnosis. Those who died less than one year after diagnosis, but had Medicare part A and B coverage until death were also included. As such, although most beneficiaries enter Medicare at age 65 years, we restricted the study sample to subjects who were aged 66 years or older at diagnosis to ensure that all patients had at least 1 year of claims data from which to derive the burden of comorbidity. Of these, 22 were excluded due to missing diagnosis dates. 7,326 had sufficient Medicare coverage for study inclusion. A further 460 patients without common histologies (clear cell, papillary, chromophobe, or non-specified adenocarcinoma), 27 with tumors greater than 20 cm, and 174 with missing covariate data were excluded. The final sample had, 6,665 individuals 66 years or older with localized, node negative RCC in the linked SEER Medicare dataset (1995–2005). Patients with clear cell, papillary, chromophobe, or adenocarcinoma histology codes identified on final pathology were included.

Quantification of Patient Comorbidity Status

Using 19 codes from the 9th version International Classification of Disease (ICD-9) classification and assigning to appropriate weights to these codes we generated the CCI for each patient at the time of localized RCC diagnosis.^{7–9} The CCI algorithm for use with Medicare claims data was the one provided by the National Cancer Institute for SEER Medicare projects.¹⁰ As everyone in the sample had a kidney cancer diagnosis, cancer diagnosis was not used to calculate the CCI score.

Statistical Analysis

We used cumulative incidence curves for kidney cancer-specific survival and Kaplan-Meier curves for OS. We used Fine and Gray's competing risks proportional hazards regressions to predict 5 year probabilities of competing mortality outcomes from kidney cancer death and other cause of death. In developing the nomogram, we used estimated model coefficients to

assign points to each characteristic, and predictions from the model to map cumulative point totals for each outcome to estimated probabilities. Prognostic markers included race, gender, tumor size, age, and the CCI Score.^{7, 8}

Nomogram and Calibration

Employing the Fine and Gray regression, we constructed a model for prediction of competing risks of death in our cohort of patients with localized kidney cancer.¹¹ The model is a competing risks proportional hazards regression, which accounts for the fact that a given individual can only have one competing outcome, and, as such, can only succumb to kidney cancer or to a non-kidney cancer cause. For continuous variables, we used restricted cubic splines with 3 knots at the 10%, 50%, and 90% empirical quantiles to model continuous variables,^{12, 13} except for the Charlson score in which we set the knots at the values 1, 3, and 7 since the 10% and 50% empirical quantiles were both the minimum value of zero. We included year of diagnosis in the models as a continuous variable, but did not include it in the nomogram itself. Instead, we set the outcomes to those that would be predicted with the last year of data (2005).

Accuracy of the nomogram was assessed using leave one out prediction as previously described.¹³ For each individual, we predicted five year outcomes after fitting the models using the other observations. We then averaged the Fine and Gray predictions within the deciles of the ordered predictions. Within each decile, we also estimated the unadjusted probability of death using cumulative incidence functions. We then plotted unadjusted versus model average predictions.

Results

Demographics

Demographics of the 6,665 patients in our cohort are shown in Table 1. The patient population was consistent with most demographics of localized kidney cancer, namely white (88.3%), male (54.4%), and clear cell histology (87.8%). Median age at diagnosis was 73 years (range 66–96). Median year of diagnosis was 2002 (1995–2005). Median length of follow-up until censoring or death was 43 months (range <1 to 143 months). 2,179 individuals had 5 or more years of follow-up. A total of 7% of patients in the cohort died from kidney cancer, while 21.2% died from other causes.

Fine and Gray's Competing Risks Proportional Hazards Regression Analysis

Age strongly correlated to patient mortality and was most predictive of non-kidney cancer deaths ($p < 0.001$ for joint test of age coefficients for non-kidney cancer death, $p = 0.062$ for joint test of age coefficients for kidney cancer death). Increasing tumor size was related to death from kidney cancer and inversely related to death from other causes (Figure 1) ($p = 0.04$ for size in other cause death model, $p < 0.001$ for size coefficients in kidney cancer mortality model). Risks of dying from other causes outweighed risks of dying from kidney cancer in most patients when stratified by CCI, except for those individuals without comorbidities whose renal masses exceeded 7cm in diameter (Figure 1). Racial differences had less of an impact on kidney cancer ($p = 0.93$) than non-kidney cancer death ($p < 0.001$).

Both men and black patients were more likely to die from other non-kidney cancer causes ($p<0.001$ for male effect on other cause mortality, $p=0.33$ for male effect on kidney cancer mortality). Comorbidity status greatly impacted probability of non-kidney cancer death (Figure 1 and 2). At higher level of comorbidity, in the final model CCI status also adversely affected chances of survival from kidney cancer ($p<0.001$ for CCI effect on both kidney cancer death and non-kidney cancer death outcomes).

Nomogram

Employing the Fine and Gray's competing risks proportional hazards model, we constructed a nomogram to be used in the clinical setting (Figure 3a). We employed quintile calibration as previously described.^{13, 14} Figure 3b presents the results of the model calibration. Given that all points are close to the 45 degree line, the model is well calibrated.

Discussion

Patients with localized solid tumors are at risk of death from competing causes prior to disease progression and cancer related mortality. A variety of forces often conspire to underestimate these competing risks of death, particularly in the aged and/or infirmed, while potentially overestimating patient and physician perceptions of cancer risk in the newly diagnosed.

The analyses of competing risks to date have largely focused on later stages of the cancer patient's clinical trajectory, when tradeoffs and interactions between treatment toxicities for advanced staged disease are weighed against existing ailments. Lee et al performed a systematic review assessing the impact of comorbidities on chemotherapy use and outcomes in solid tumors, noting that the majority of studies reported decreased chemotherapy administration and inferior survival independent of treatment in patients with comorbidities. The authors repeatedly emphasize that existing data are limited in scope and quality.¹⁵ Lughezzani et al performed a population based competing risks analysis using SEER data in patients undergoing radical cystectomy for bladder cancer noting at 5 years after radical cystectomy 9–27% of patients died from other causes.¹⁶ Kiely et al used a “Best case, Worst Case” pooled analysis making use of simple multiples of an OS curve's median to estimate typical (half to double the median), best case (triple the median) and worst case (one quarter of the median) scenarios for survival in metastatic breast cancer; although, they did not factor comorbidities into their analysis.¹⁷

Few competing risks models have been developed for localized solid tumors given 1) the biologic heterogeneity of many low stage solid cancers, 2) their long latency period from diagnosis to death in treated individuals and 3) sparse natural history data for nearly all solid tumors in untreated patients. One exception is localized prostate cancer.^{18–20}

As natural history data have been published for untreated localized renal tumors, limited but pertinent competing risk data have begun to emerge.⁶ Several recent reports have highlighted the discrepancy between kidney cancer specific risk of death and competing risk from comorbidities, predominantly in treated patients. Data from a phase III EORTC trial comparing radical versus partial nephrectomy for localized tumors ≤ 5 cm revealed that, of

117 deaths over a median follow up period of 9.3 years, 10.3% were a result of RCC compared to 89.7% from other causes.²¹ In an institutional series of 537 patient >75 years of age with renal masses <7cm, Lane et al. reported that over a median follow up period of 3.9 years, the most common cause of death was cardiovascular (29%) compared to cancer progression (4%).²² Additional studies have attempted to quantitate competing risks of death in patients with RCC.²³ These investigators found that patients with the smallest tumors had the lowest cancer specific mortality, and that competing cause mortality increased with age (28% 5 year competing cause mortality rate in patients > 70 years). The authors recommended re-evaluation of initial management strategies in select patients with small renal tumors.²³

Until recently no tools existed for a physician to quantitate the probability of a patient dying from RCC and compare this to the chances of succumbing to other causes. Indeed, assessing competing risks of death should be a major consideration in treatment planning, but has largely remained qualitatively relegated to clinical “gestalt.” Yet, physicians have great difficulty providing accurate estimates of patients’ life expectancy after an initial cancer diagnosis.²⁴ A lack of objective tradeoff tools and guidance information is frequently cited as one reason for a physician’s reluctance to estimate competing risks.²⁵ Our initial analysis was among the earliest attempts to quantitate competing risks¹⁴ and has been externally validated²⁶, but criticized for failing to incorporate comorbidity data.⁵ Indeed, because the prevalence of both cancer and non-cancer comorbidities rise with age, integration of comorbidities into a competing risks predictive model is essential.^{5, 27, 28, 29} Therefore one of the strengths of the current model is its ability to quantitate competing risk accounting for comorbidities. For instance, an 80 year old African American male with a history of a myocardial infarction, moderate renal insufficiency (CCI of 3), and a 4 cm renal mass is expected to have a 5-year mortality of 5% from RCC versus 48% from non-kidney cancer causes. Meanwhile, a 75 year old Caucasian female with no significant comorbidities (CCI of 0) and a 7 cm renal mass is predicted to have a 5-year mortality of 13% from RCC and 7.5% from other causes. Currently in the absence of such a model, stratification of risk is largely qualitative. Indeed, we believe predictive models such as this can serve to objectify every-day treatment decisions and may help decrease overtreatment of the elderly and/or infirmed.

Another strength of our analysis is the use of Fine and Gray’s competing risks proportional hazards regressions. Fine and Gray’s model is a multivariable time to event model, which accounts for the fact that individuals can only have one of the competing events. Fine and Gray’s model also accounts for censoring among those who do not have an event during follow-up. Fine and Gray’s model is a model of the cumulative incidence function, which describes the probability of having an outcome by a particular time point. A key difference between estimators of the cumulative incidence function compared to the Kaplan-Meier estimator is the mechanism by which individuals who have competing events are accounted. In Kaplan-Meier survival curve estimation, censoring of competing causes of death is considered non-informative, where those who die from one cause will never be able to die from another. Estimation of the cumulative incidence function does not make such non-informative assumptions.

The current model, nevertheless, has a number of limitations. It uses data from a Medicare population pool, which is 66 and older, potentially limiting its use in younger patients. In addition, the comorbidity status as quantified by CCI is based on claims data^{7, 30} that may not accurately capture a clinician's bedside impressions of comorbidities. Furthermore, the model's reliance on the SEER's cause-of-death item, which is based on death certificate reporting, is far from perfect. Albeit, death certificate validity is felt to be relatively robust in patients with malignancy.²³ Importantly, this model yields probabilities of death from competing causes if treatment for a renal mass is pursued and the pathology is known. As such, the model is not applicable to patients with enhancing renal mass who harbor benign pathology and those with RCC who are not surgical candidates. Notably, application of this model to patients who choose AS should be done with caution. Although the cumulative natural history data of localized renal masses under AS for over 2.5 years reveal a risk of metastases of 2.1%,⁶ a prolonged natural history of untreated localized RCC cannot be assured. Nevertheless, national guidelines for the management of Stage I renal tumors in the elderly or infirmed include a role for AS, qualitatively recognizing the importance of competing risks. Thus, when applying the model in the pre-operative setting, one has to be cognizant that the prediction estimates are biased toward patients who are acceptable surgical candidates, and the impact of treatment and its effect on the model's predictions must be contextualized during clinical decision-making. In fact, the model strictly predicts risks of dying from kidney cancer and allows comparison to risks of death from other causes if a patient chooses to proceed with surgery. Although ideally a clinician would be able to provide the patient with the same information if the patient were to forego surgery, such data were not available in our cohort. Despite these limitations, we believe information afforded by our nomogram, especially if externally validated, is relevant, since it can help frame clinical discussions. Overall, in the absence of long term prospective natural history registry studies in RCC, we believe our model, while early, represents an important starting point for development of higher fidelity, robust predictive tools that can someday be used in routine clinical practice.

In summary, here we develop a competing risks of death model in patients 66 and older with localized renal cancer accounting for comorbidities. This tool is an important step toward the goal of comparing treatment choices, toxicities, outcomes and tradeoffs as we move from "how and when" to treat toward "why and if" we should.

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Figure 1.

Predicted competing risks of mortality by tumor size and comorbidity status. Red color indicates probability of kidney cancer death, while blue demonstrates chances of death from other causes.

Cause-Specific Mortality by Charlson Score

Figure 2.

Predicted probability of (A) cause-specific cumulative incidence of death and (B) overall survival, stratified by comorbidity status (Potential grouping of comorbidities: 0, 1/2, >2). In 2A, the top three lines represent deaths due to non-kidney cancer deaths, the bottom three represent deaths due to kidney cancer.

Figure 3.

(A) Nomogram evaluating 5-year competing risks of death in patients with localized renal cell carcinoma based on age, sex, race, tumor size, and comorbidity status. (B) Calibration after grouping individuals by decile of regression predicted 5-year probabilities.

Table 1

Patient characteristics

	n	%
Total	6,665	100
Race		
White	5,884	88.3
Black	545	8.2
Other	236	3.5
Gender		
Male	3,631	54.5
Female	3,034	45.5
Age at Diagnosis		
66–74	3,752	56.3%
75–84	2,612	39.2%
85–96	301	4.5%
Tumor Size		
<4 cm	2,966	56.3%
4–7 cm	2,679	40.2%
>7 cm	1,020	15.3%
Histology		
Clear cell	5,851	87.8%
Papillary	516	7.7%
Chromophobe	265	4.0%
Not-specified	33	0.5%
Charlson Comorbidity Index		
0	3,727	55.9
1 or 2	2,371	35.6
3 or greater	567	8.5