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Economic Burden of Renal Cell Carcinoma (RCC) and Treatment Patterns, Overall Survival and Healthcare Costs among Older Metastatic RCC Patients

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Economic Burden of Renal Cell Carcinoma (RCC) and Treatment Patterns, Overall Survival and Healthcare Costs among Older Metastatic RCC Patients

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

by

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List of Abbreviations

RCC: renal cell carcinoma

mRCC: metastatic renal cell carcinoma

CN: cytoreductive nephrectomy

OS: overall survival

DSS: disease specific survival

THC: total healthcare cost

SEER: Surveillance Epidemiology and End Results

ICD-O: International Classification of Diseases for Oncology

ICD-CM: International Classification of Diseases Clinical Modification

HCPCS: The Healthcare Common Procedure Coding System

NDC: National Drug Code

IPTW: inverse probability of treatment weight

VEGF: vascular endothelial growth factor

GLM: generalized linear model

HR: hazard ratio

OR: odds ratio

AJCC: American Joint Committee on Cancer

mTOR: mammalian target of rapamycin

TKI: tyrosine kinase inhibitor

PD-1: programmed cell death protein

VHL: Von Hippel-Lindau

FDA: Food and Drug Administration

NCCN: National Comprehensive Cancer Network

NCI: National Cancer Institute

ACS: American Cancer Society

MSKCC: Memorial Sloan Kettering Cancer Center

ECOG: Eastern Cooperative Oncology Group

HRQoL: health related quality of life

PEDSF: patient entitlement and diagnosis summary file

DME: durable medical equipment

PDE: prescription drug event

HHA: home health agency

HS: hospice care

SNF: skilled nursing facitlity

ProjPrev: Projected Prevalence

PSM: propensity score matching

HMO: health maintenance organization

FFS: fee for service

ABSTRACT

Background

Renal cell carcinoma (RCC) is the most common type of kidney cancer. Patients diagnosed with metastatic RCC (mRCC) have shorter overall survival compared to those diagnosed at earlier stages. Several targeted therapies, which cost from $7,000 - $16,000 per month have been approved since 2005 to treat mRCC. In addition, there is a growing interest in the use of cytoreductive nephrectomy (CN) with targeted therapies among mRCC patients. However, little is known regarding the economic burden of RCC and role of CN and prescribing patterns of targeted therapies among older mRCC patients.

Objectives

1) To assess the economic burden of RCC among older adults in the targeted therapy era 2) To compare the overall survival (OS) and total healthcare cost (THC) among older mRCC patients receiving CN and targeted therapy versus patients receiving targeted therapy alone 3) To describe prescribing patterns of targeted therapies and associated OS and THC among older mRCC patients.

Methods

This dissertation was conducted using the Surveillance Epidemiology and End Results (SEER) - Medicare linked data. For the first objective, the study included a prevalent cohort of RCC patients from 2013, diagnosed during 2005 - 2013 and continuously enrolled in Medicare. RCC patients were matched to non-cancer beneficiaries using propensity score matching. Generalized linear models estimated the incremental healthcare costs. Incremental total healthcare cost (THC) was multiplied by the estimated number of RCC patients on Medicare to calculate the total economic burden of RCC. For the second objective, we included patients diagnosed with

mRCC between 2007-2014 and compared overall survival (OS), and THC between patients who received CN + targeted therapy and targeted therapy alone. A propensity score based inverse probability of treatment weighting (IPTW) method was used to balance the two treatment groups. A Cox proportional hazard model assessed the risk for death and a GLM compared healthcare costs between the groups. For the third objective, patients with mRCC were defined as patients who were diagnosed at stage-IV or at earlier stages but were currently using targeted therapies. Further, we restricted our sample to patients who initiated targeted therapy. We described the frequencies of the most common first and second line targeted therapies. We also described OS and THC per month for clear-cell and non-clear cell mRCC for each therapy and line of therapy.

Results

The first study included 10,392 each of RCC and control patients. The average THC associated with RCC was $7,419. The average THC was $4,584 for patients diagnosed at stage-I, $4,727 for stage-II, $9,331 for stage-III, and $31,637 for stage-IV. The annual economic burden of RCC on Medicare was estimated to be $1.5 billion. The second study included 471 mRCC patients that received CN + targeted therapy or targeted therapy alone. The median OS from the adjusted survival curves was significantly higher ($p < 0.0001$) for CN + targeted therapy group (15 months) than the targeted therapy alone group (10 months). CN + targeted therapy group had 0.63 times the risk of death (HR = 0.63) compared to the targeted therapy alone group. The adjusted total healthcare cost per month was $17,159 for CN + targeted therapy group and $18,120 for the targeted therapy alone group ($p = 0.4389$). The third study included 915 mRCC patients with targeted therapy prescription. Among clear cell mRCC patients, sunitinib (384, 48%) and everolimus (101, 13%) were the top first and second line targeted therapies. Of 109 non-clear cell patients, sunitinib (n = 35, 32%) and temsirolimus (n = 26, 24%) were the most commonly

prescribed first line targeted therapies. Among patients who received multiple lines, VEGF-mTOR was the most commonly prescribed sequence. The median OS and median monthly THC was similar across targeted therapy sequences.

Conclusions

The economic burden of RCC varied substantially between early stage and metastatic patients. Among mRCC patients, use of CN among targeted therapy users was associated with a higher median OS and similar monthly THC over a lifetime. Sunitinib and everolimus were the most common first and second line targeted therapies among mRCC patients. The descriptive analysis suggested that OS and THC were similar across types of targeted therapy sequences.

Chapter 1: Introduction

Renal Cell Carcinoma

Epidemiology

Renal cell carcinoma (RCC) is the most common type of kidney cancer. About 9 out of 10 kidney cancers are RCC. [1, 2] Other forms of kidney cancer include transitional cell carcinomas, Wilms tumors, and renal sarcomas. RCC usually grows as a single tumor within a kidney, however, sometimes multiple tumors can be found in one or both the kidneys. A very early stage RCC is often asymptomatic but large tumors often show symptoms that include presence of blood in the urine, lower back pain on one side, mass on the side or lower back, fatigue, loss of weight, fever, and anemia. Subtypes of RCC include clear-cell RCC, which accounts for 70% of cases, Papillary (10%), Chromophobe (5%) and rare types (5%) and unclassified (10%). These subtypes play an important role in deciding treatment or in finding out if cancer might be due to inherited genetic syndrome.[1, 2]

The American Cancer Society (ACS) estimated that in the U.S, in 2017, approximately 63,700 new kidney cancer cases (39,650 in men and 23,050 in women) would be diagnosed and 14,240 people (9,240 men and 5,000 women) would die from this disease.[1] These numbers include all types of kidney and renal pelvis cancers. Overall, the lifetime risk for developing kidney cancer is about 1 in 63 (1.6%). Incidence for RCC has increased from 9 per 100,000 persons in 1990s to 15 in 2007 and leveled off in the last few years.[1, 2] The median age of RCC diagnosis is 64 years and it very uncommon among individuals aged < 45 years. Men often have a higher risk (~2 times) for RCC than women. Other risk factors for RCC include smoking, obesity, high blood pressure, African American and American Indian race, workplace exposure to substances such as cadmium,

family history, certain medicines such as diuretics, an advanced kidney disease that requires dialysis and presence of genetic conditions such as Von Hippel-Lindau (VHL) disease.[1]

Staging and Survival

Cancer staging indicates the extent of the disease and its prognosis. The most common staging system for RCC is that of the American Joint Committee on Cancer (AJCC).[1, 3] Stage-I indicates that the tumor is 7 cm across or smaller, located only in the kidney and has not spread to lymph nodes or distant organs. Stage-II indicates that the tumor is larger than 7 cm across but is still only in the kidney. There is no spread to lymph nodes or distant organs. Stage-III indicates that the tumor has spread to the major blood vessels – the renal vein and inferior vena cava, into the tissue surrounding the kidney, or to nearby lymph nodes. Stage-IV indicates that the tumor has spread outside of the kidney to the adrenal gland, to distant lymph nodes, or to other organs.

According to statistics presented by the Surveillance, Epidemiology and End Result (SEER) program, about 65% of RCC cases are diagnosed at localized stage, 16% have involvement of regional lymph nodes, 16% are diagnosed with distant metastasis and 3% have unknown stage.[2] Further, literature suggests that about 15%-40% of patients are diagnosed at the metastatic stage and among those diagnosed at early stages; over 30-33% eventually progress to metastatic stage.[4, 5] The five-year survival rate for RCC patients based on data from 2007 to 2013 was 74.1%; however, it varied by cancer stage. Survival rates were 93% for localized, 63% for regional, 38% for unknown and 12% for metastatic renal cell carcinoma (mRCC) patients.[2]

Treatment for Stages I-III [1]

Patients with localized tumor are often treated with surgery that includes partial or radical (complete) nephrectomy. Partial nephrectomy removes portions of a kidney while radical nephrectomy involves complete removal of kidney. Partial nephrectomy is often the treatment of

choice in tumors up to 7 cm in size. Surgery may involve removal of lymph nodes near the kidney, especially if they are enlarged. If cancer has grown into the nearby vein (stage-III), surgery is needed to remove a tumor from the veins. Adjuvant therapy, which, includes surgery followed by treatment with targeted therapy, chemotherapy, or radiation therapy has also been tried as another option among Stage-III patients. So far, it has not been shown to help patients live longer.[1] There are, however, ongoing clinical trials that are looking at adjuvant treatment for locally advanced RCC. Patients that cannot undergo surgery because of other serious medical problems, patients may be given local treatments such as cryotherapy, radiofrequency ablation, or arterial embolization or radiation therapy. These options, however, are often considered as less effective options than surgery. Active surveillance is another option for some people with small kidney tumors. In this approach, the tumor is watched closely (with CTs or ultrasounds) and only treated if it grows.[1]

Treatment for Stage IV / mRCC

Treatment among mRCC patients depends largely on the extent of tumor growth and overall health status; however, for the most part, it involves the use of systemic therapy with immunotherapy or targeted therapy agents.[1] Before 2005, the treatment of mRCC mainly included cytokines: high dose interleukin-2 and interferon-alpha. However, both drugs were associated with low response rate, higher toxicity and improvement of fewer than 6-12 months in the OS.[6, 7] From 2005 to 2012, the US Food and Drug Administration (FDA) approved seven targeted therapies to treat mRCC.[8-12] These therapies included vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitors (TKI) sorafenib, sunitinib, pazopanib, and axitinib; the mammalian target of rapamycin inhibitors (mTOR) everolimus and temsirolimus; and the anti-VEGF

monoclonal antibody bevacizumab. Everolimus and axitinib are approved only as second-line treatments. From 2016, cabozantinib, lenvatinib, and nivolumab were approved for mRCC. Details of these therapies are given in Table 1.

Table 1. FDA approved targeted therapies for metastatic Renal Cell Carcinoma

Drug	FDA approval	Mechanism	Line of therapy	Dosage Regimen
Sorafenib	2005	VEGF- TKI	First & Second	400 mg twice a day
Sunitinib	2006	VEGF- TKI	First & Second	50 mg once a day, 4 weeks on 2 weeks off
Temsirolimus	2007	mTOR	First & Second	25 mg IV infusion once weekly.
Everolimus	2009	mTOR	Second only	10 mg once daily.
bevacizumab + interferon-alfa	2009	Anti-VEGF	First & Second	10 mg/kg IV every 2 weeks + interferon alfa
Pazopanib	2009	VEGF-TKI	First & Second	800 mg / day
Axitinib	2011	VEGF-TKI	Second only	5-10 mg twice a day
Cabozantinib	2016	TKI with multiple pathway inhibitor	First & Second	60 mg per day
Lenvatinib	2016	VEGF-TKI	Second	18 mg per day with everolimus
Nivolumab	2016	PD -1	First and second	240 mg every 2 weeks

Sequencing of Targeted Therapies

Patients treated with first-line targeted therapy often develop resistance in 6-11 months and as a result, need subsequent lines of therapy to control disease progression.[9, 13] Several studies have assessed the appropriate sequence of targeted therapies to improve OS. Based on previous studies, the most common sequences in clinical practice included VEGF followed by mTOR and VEGF followed by VEGF.[14-16] Some patients with poor risk may receive mTOR as a first line followed by VEGF. Studies which compared OS between VEGF-VEGF and VEGF-mTOR found no

significant difference in the OS between the sequences.[17, 18] The National Comprehensive Cancer Network (NCCN) develops evidence-based guidelines to help healthcare professionals in oncology to decide appropriate treatment strategy for cancer patients. Category-1 recommendations indicate uniform consensus about the appropriateness of intervention among NCCN panel members based on a high-level of evidence; category-2A indicates uniform consensus based on a lower level of evidence; category-2B indicates some consensus based on a lower level of evidence and category-3 indicates major disagreement about the appropriateness of the intervention.[19] The NCCN guidelines during 2007-2012 included sunitinib, pazopanib, and bevacizumab/interferon with category-1 recommendation and sorafenib with category-2A recommendation for the first-line treatment. Recommendations for the second line therapy included all of the above agents and everolimus. However, axitinib and everolimus have a category-1 recommendation as second-line treatments [19-21] No recommendations were made for the use of third-line use of targeted therapies.

Role of Cytoreductive Nephrectomy (CN)

Prior to the targeted therapy era, CN was considered as a preferred treatment option among mRCC patients that were eligible for surgery. Two RCTs demonstrated that the use of CN in addition to cytokine therapies resulted in improved OS by additional 6 months.[22, 23] As a result, CN followed by interferon-alpha had level-1 evidence to treat mRCC patients. However, with the approval of targeted therapies which were more effective than cytokine therapies, the role of CN has been questioned. Some studies have found the use of CN decreased after 2005.[24, 25] However, a few retrospective studies conducted in the targeted therapy era suggested that CN may still play an important role in improving OS among mRCC patients who received targeted therapies.[26, 27]

Two prospective trials are also ongoing to understand the efficacy of CN among targeted therapy users.[28] However, their results may be limited based on their selection criteria and thereby not generalizable to all patients diagnosed with mRCC.

Economic Burden of RCC

Diagnosis and treatment of RCC can impose a significant economic burden on the healthcare system, patients, and their caregivers. Economic burden typically includes direct medical and non-medical costs and indirect cost, which include the cost associated with absenteeism, mortality, and loss of employment. About 46% of all RCC patients are on Medicare making it the largest payer for RCC patients in the U.S.[1, 29]

According to a review published in 2010, the economic burden of RCC in the U.S ranged from $600 million to $5.19 billion, with annual per-patient medical costs between $16,488 and $43,805 (2009 USD).[30] In 2006, the economic burden specifically among mRCC patients was estimated to be between $107 to $556 million (2006 USD) in the US.[31] In another study, the average annual direct medical cost among older RCC patients was $11,169; and varied from $24,694 in the initial, $6,218 in the continuous, to $26,784 in the late phase of the survival curve among RCC patients (2009 USD).[32] Further, costs among patients treated with targeted therapies were 3-5 times higher than those for patients not treated with targeted therapy. Higher late phase cost and high cost among targeted therapy users suggest that the burden among patients with mRCC may increase as patients would receive more lines of therapies during to expanding landscape of systemic therapies.

Rationale

A number of studies assessed the economic burden of RCC in the cytokine era. However, only one study was conducted during the earlier years of the targeted therapy era.[32] Further, costs among patients on Medicare Part D plans were not assessed as Part D data was not available until 2007. As a result, little is known about the economic burden of RCC in the targeted therapy era. Further, economic burden by stage at which cancer is diagnosed is not well understood. Further, no study has projected the total economic burden to the entire Medicare population. As the landscape of targeted therapies continues to evolve, patients are more likely to receive multiple lines of targeted therapies than they received in the past. This would increase healthcare cost to Medicare. On the other side, for early stage patients, use of active surveillance, advanced imaging, and minimally invasive surgical techniques may result in cost savings. As a result, it is important to understand the economic burden of RCC in the targeted therapy era.

Among mRCC patients, the role of CN was well established before targeted therapies were approved. However, few studies have assessed the effects of CN and targeted therapy on OS of mRCC patients in the targeted therapy era.[26, 27] Further, none of the studies were specifically conducted among older adults. The socioeconomic and clinical predictors of CN and/or targeted therapy use among Medicare patients and the healthcare costs associated with the use of CN and targeted therapy are not well understood among Medicare patients. Examination of OS and healthcare cost would provide real-world evidence on the use of CN and targeted therapy among older adults.

As the landscape of targeted therapies expanded from 2005 - 2012, a number of studies assessed sequencing of targeted therapies and its association with the OS. [14-16] However, none of the studies assessed prescribing patterns among older mRCC patients. Availability of several

targeted therapies, patients' and physicians' preferences, older age, frailty, drug interactions and comorbidities may complicate prescribing patterns of targeted therapies among older adults. Therefore, one of the aims of this dissertation is to describe prescribing patterns, OS and healthcare costs among mRCC patients on targeted therapies.

Specific Aims

This dissertation included three specific aims, which formed the basis for three research studies. These studies and research questions that they address are listed below.

Study 1: Economic Burden of Renal Cell Carcinoma among Older Adults in the Targeted Therapy Era.

Research Questions:

1. What is the average direct healthcare cost associated with RCC in a given year?
2. What is the total economic burden of RCC on Medicare?
3. How do the average cost and the total economic burden vary by stage at diagnosis?
4. What are the most common drivers of total healthcare cost?

Study 2: Utilization of Targeted Therapy and Cytoreductive Nephrectomy among Older Adults with Metastatic Renal Cell Carcinoma: Analysis of Survival and Healthcare Costs

Research Questions:

1. What is the prevalence of targeted therapy and cytoreductive nephrectomy use among older mRCC patients?
2. What are the sociodemographic and clinical predictors of mRCC patients receiving CN and /or targeted therapy?

3. Is there a difference in the overall survival between mRCC patients who received CN and targeted therapy versus targeted therapy alone?
4. Is there a difference in the total healthcare cost between mRCC patients who received CN and targeted therapy versus targeted therapy alone?

Study 3: Prescribing Patterns of Targeted Therapies, Overall Survival, and Total Healthcare Cost among Older Adults with Metastatic Renal Cell Carcinoma in the U.S

Research Questions:

1. What proportion of mRCC patients received two or more lines of targeted therapies?
2. What were the most common targeted therapy sequences among mRCC patients?
3. How did overall survival vary by the targeted therapy sequences?
4. How did total healthcare costs vary by the targeted therapy sequences?

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Chapter 2

Study 1: Economic Burden of Renal Cell Carcinoma among Older Adults in the Targeted Therapy Era

ABSTRACT

Objective

To assess the economic burden of renal cell carcinoma (RCC) among older adults on Medicare.

Methods

The study analyzed the Surveillance Epidemiology and End Result - Medicare linked data. We included a prevalent cohort of RCC patients from 2013, diagnosed during 2005 - 2013, and continuously enrolled in Medicare. RCC patients were matched to non-cancer beneficiaries using propensity score matching. Healthcare costs were calculated using a phase-based approach, which classified patients into early, continuing and late phases of care. Generalized linear models estimated average annual incremental costs. Incremental total healthcare cost (THC) was multiplied by the estimated number of RCC patients on Medicare to calculate the total economic burden of RCC.

Results

The study included 10,392 each of RCC and control patients. The average annual THC associated with RCC was $7,419 for all phases, $22,752 for initial phase, $4,860 for continuing phase and $13,232 for the late phase of care. The average THC was $4,584 for patients diagnosed at stage-I, $4,7272 for stage-II, $9,331 for stage-III, and $31,637 for stage-IV. For patients diagnosed at stages I-III, hospital cost (approximately $1,500 - $3,400) was the largest component of THC. For stage-IV patients, prescription drug cost ($11,747) was the largest component of THC. The annual economic burden of RCC on Medicare was estimated to be $1.51 billion.

Conclusions

Economic burden of RCC varied substantially between early stage and metastatic patients. This research provided a baseline that can be used to assess the economic value of emerging therapies among older RCC patients.

BACKGROUND

Renal cell carcinoma (RCC) is the most common type of kidney cancer. In 2017, approximately 63,990 new kidney cancer cases would be diagnosed and 14,440 people would die from this disease.[1] The median age of RCC diagnosis is 64 years. Medicare covers about 46% of RCC patients.[2, 3] As the number of older adults continues to increase, the burden of management of RCC on Medicare will be substantial.

Management of RCC has evolved over time. Smaller tumors (≤ 4 cm) are now typically managed with active surveillance, cryotherapy, radiofrequency ablation or partial nephrectomy. Patients with localized but larger tumors (≥ 4 cm) are treated with nephrectomy.[2, 4, 5] Significant changes in treatment patterns also occurred in the management of metastatic RCC (mRCC). Until 2005, systemic therapy for mRCC included the use of interleukin-2 and interferon-alfa.[6, 7] From 2005, targeted therapies, which cost from $5,000 – $15,000 per month, were approved to treat mRCC. These included sorafenib, sunitinib, and temsirolimus, pazopanib, everolimus, bevacizumab, and axitinib.[8-11] Recently, FDA approved cabozantinib in intermediate and poor risk patients as a first line therapy[12] and programmed death (PD)-1 targeted check-point inhibitor, nivolumab as a 2nd line therapy.[13] In addition, there is a great interest in the combination regimens such as nivolumab and ipilumimab.[14] Nevertheless, the costs of targeted therapies, along with the costs of administration and management of adverse events, may result in a significant economic burden on Medicare.

A number of studies in the past have assessed the economic burden of RCC.[3,15-19] Estimates from previous studies on the economic burden of RCC ranged from $600 million to $5.19 billion, with annual per-patient medical costs between $11,169 and $43,805 (2009 USD). However, a majority of studies were conducted during the cytokine therapy era. Only Shih et al. (2011)

assessed the economic burden of RCC at the beginning of the targeted therapy era using Medicare data from 1991 to 2005 and MarketScan claims data from 1991 to 2007.[18] The average annual direct medical cost among older RCC patients was $11,169. Further, costs among patients treated with targeted therapies were 3-5 times higher than for patients not treated with targeted therapy. Because Medicare Part D was not available in 2005, drug costs were assessed using Medicare supplemental coverage data from MarkeScan. These costs may not accurately represent the burden among all older patients on Medicare Part D plans. Additionally, a number of targeted therapies approved since 2009 were not included in this study.[18] As the landscape of targeted therapies continues to evolve, patients are more likely to receive multiple lines of targeted therapies than they received in the past.[20] This would increase healthcare cost to Medicare. On the other side, for early stage patients, use of active surveillance, advanced imaging, and minimally invasive surgical techniques may result in cost savings.

The aim of this study was to assess the economic burden of RCC among older adults from Medicare's perspective. The study also assessed healthcare costs by types of resources used and the stage at which cancer was diagnosed.

METHODS

Data Source

SEER-Medicare

The Surveillance Epidemiology and End Result (SEER) program, initiated by the National Cancer Institute (NCI), collects information on cancer statistics in an effort to reduce the cancer burden among the U.S population.[21] The information collected by this population-based cancer registry includes demographics, incident cancer diagnosis, cause of death, cancer stage, tumor

characteristics, and surgery and radiation therapy provided during the first course of treatment. As of 2016, SEER registries covered 28% of the U.S population.[22] Medicare data provides information on Part A (hospital), Part B (outpatient) and Part D (prescription drug) claims for Medicare beneficiaries. SEER-Medicare links SEER and Medicare data. In order to compare cancer patients on Medicare living in SEER regions to non-cancer patients, NCI provides a 5% random sample of Medicare beneficiaries with no cancer from SEER regions.[21]

We used 2005-2013 SEER-Medicare linked data for RCC patients and a 5% random sample of non-cancer Medicare beneficiaries for controls. The Patient Entitlement and Diagnosis Summary File (PEDSF) was used to obtain demographics and cancer diagnosis-related information. Resource use and cost-related information were obtained from Medicare Provider Analysis and Review (MEDPAR), outpatient, carrier, Part D event (PDE), home health agencies (HHA), hospice (HS) and durable medical equipment (DME) files. The MEDPAR file was used to obtain inpatient hospital and skilled nursing facility (SNF) claims. The HS file provided data on hospice care utilization. The carrier file provided information on non-institutional physician-provided services whereas the outpatient file provided information on institutional physician-provided services. The PDE file provided data related to prescription medication use (Medicare Part D). DME files provided data on the use of durable medical equipment while HHA files were used to get information on services provided in patients' homes.

Study Design and Sample Selection

The study used a prevalence-based design to quantify the economic burden of RCC in 2013. Patients diagnosed in 2013 and before (from 2005) were identified using ICD-O (v.3) code C649 and relevant histology types ('8260', '8310', '8312', '8316', '8317', '8318'). Healthcare costs were examined using 2013 claims. To be included in the study, patients needed to be alive for at

least one month in 2013. We excluded patients aged < 65 years at the time of diagnosis, diagnosed with another cancer, diagnosed on autopsy, with cancer reported by death certificate, or enrolled in health maintenance organizations (HMOs). Control group was assigned a random date of pseudo-diagnosis between January 2013 to end of December 2013. Control patients aged <65 years at the time of pseudo-diagnosis, not continuously enrolled in Medicare, or enrolled in HMOs were excluded. Figure 1 depicts the sample selection process for the RCC and control groups.

The total healthcare cost (THC) was estimated using the phase-based approach, which classifies patients into early, continuing and late phases of care.[18, 23, 24] In this study, early phase included patients diagnosed in 2013 who remained alive at the end of 2013. Patients who died in 2013 represented the late phase. Patients diagnosed before 2013 who remained alive at the end of 2013 represented the continuing phase. A pseudo date of diagnosis and Medicare date of death were used to classify control patients into initial, continuing and late phases. To reduce selection bias, RCC patients were matched in a 1:1 ratio with control patients for each phase using propensity score matching (PSM). PSM was a two-step process. In the first step, the probability of being diagnosed with RCC was calculated using multivariable logistic regression controlling for age, sex, race, SEER registry, urban-rural status and NCI Comorbidity Index score. In the second stage, patients from RCC and control groups were matched using a greedy matching technique.[25] The quality of matching was assessed by the distribution of propensity scores and comparing standardized scores for patient characteristics before and after matching. Standardized scores of <10% after matching indicated a good match.[26, 27]

Study Measures

Healthcare cost

Since this study was conducted from Medicare's perspective, only direct medical costs to Medicare were included. Out of pocket costs were not included in the cost analysis. Costs were defined as the amounts reimbursed by Medicare for each claim. Costs were calculated for each type of resource used and aggregated to obtain THC. Incremental cost, which is the difference in the average cost of RCC and matched control patients was the costs associated with RCC. Incremental costs were estimated for each phase as well as for the aggregated sample.

Other variables

These variables included patient demographics, urban/rural status, geographical region based on areas represented by SEER registry, cancer stage, histology and NCI comorbidity index. We used the American Joint Committee on Cancer (AJCC 6th edition) criteria to classify patients into stages I - IV and unknown stage.[28]

RCC prevalence/number of patients

Identifying the number of older RCC patients in the U.S was a two-step process. In the first step, we calculated the number of older RCC patients living in areas represented by SEER registries in 2015 (diagnosed before and during 2015) using SEER Stat software.[29] In the second step, the estimate based on SEER registries was used to derive the number of older RCC patients in the U.S using the Projected Prevalence (ProjPrev) Software developed by the NCI.[30]

Statistical Analysis

We compared patient characteristics between unmatched RCC and control groups using chi-square tests and t-tests as appropriate. After PSM, differences in characteristics were examined using paired t-tests and McNemar tests. Incremental costs between matched groups were calculated using generalized linear models controlling for age, sex, race, SEER registry, urban/rural status, NCI Comorbidity Score and length of the time spent in each phase of care. The

choice of distribution for GLMs was based on modified Park tests, while the appropriate links were selected based on Pearson correlation tests, Pregibon link tests, and modified Hosmer and Lemeshow tests. In cost categories with excess zeros (defined as ≥ 20%), two-part models were used. In a two-part model, the first part calculated the probability of having a positive cost. The second part calculated the expected mean cost. This mean cost was multiplied by the probability calculated in the first part to estimate the mean cost for the sample. Incremental costs were calculated between RCC and non-cancer controls for the overall sample and by cancer stage. While calculating costs by cancer stages, we compared costs for each stage to costs for non-cancer controls. Upon examination of the distribution of THC, we excluded observations with THC > $400,000 (99.9th percentile) and their matched cases or controls, which were considered as outliers. In addition, to account for the skewed distribution of cost data, we calculated confidence intervals for mean costs using a non-parametric bootstrapping method with 1000 replications.

The total economic burden of RCC among older adults was calculated by multiplying the average incremental THC with the estimated number of older RCC patients in the U.S. All costs were inflated to 2015 USD using the Consumer Price Index for medical care services and medical care commodities.[31]

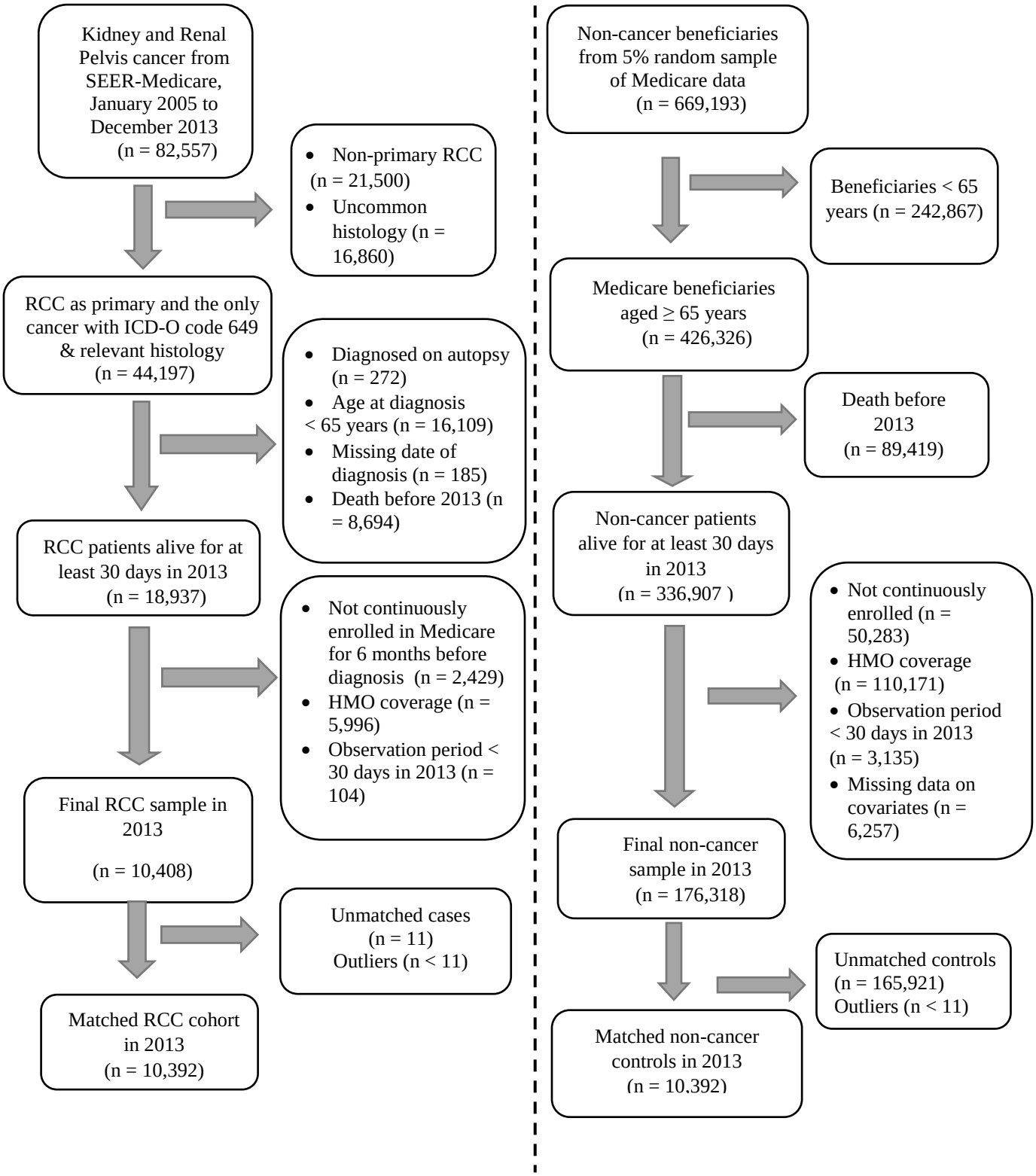
Sensitivity Analyses

First, we included observations that were considered as outliers in the base-case scenario. Second, since comorbidities may fall into the causal pathway between RCC diagnosis and healthcare costs, we excluded the NCI comorbidity score from the propensity score model and re-examined incremental costs and total economic burden. Third, we excluded covariates from the GLM model after matching RCC and control groups to calculate incremental costs. Fourth, we used GLM models using the commonly used log link and gamma distribution instead of

distributions and links, which were chosen based on the model fit tests. The stage of cancer in SEER data is determined at the first cancer diagnosis. Some of the early stage patients from 2005-2012 may have progressed to stage-IV in 2013. Therefore, we assumed that 30% of patients diagnosed with earlier stages prior to 2013 may have progressed to stage-IV in 2013.[32-34] Under this assumption, we recalculated the total economic burden among stage-IV and overall RCC patients.

All statistical analyses were conducted at an alpha level of 0.05 using SAS v.9.4 (SAS Institute Inc., Cary, NC), and STATA (version 13.0, StataCorp, College Station, TX).

Figure 2.1. Sample selection process for Renal Cell Carcinoma and non-cancer patients in this study



RESULTS

Sample Characteristics

Patient characteristics for RCC and control group patients before and after matching can be found in Table 2.1 The sample before matching included 10,408 RCC and 170,061 control patients. Before matching, large differences were observed between characteristics of RCC and control patients. The RCC group had a lower proportion of patients (16% vs 25%) aged > 80 years, a higher proportion of males (56% vs 39%), and Caucasians (87% vs 83%) and a lower proportion of patients with zero NCI comorbidity score (53% vs 70%) than control group.

The study sample after matching included 10,392 each of RCC and control patients. The magnitude of difference observed between RCC and control groups was reduced after matching. The average age was 74 years for RCC and 75 years for controls. RCC and control groups had a similar proportion of males (56% vs 59%), Caucasians (87% vs 84%) and patients with zero NCI comorbidity score (53% vs 51%). All standardized differences between matched groups, except age, were < 10%, which indicated a good match between the two groups.

Among RCC patients, 65% were diagnosed at stage-I, 8% was diagnosed at a stage-II, 15% were diagnosed at stage-III, and 7% were diagnosed at stage-IV. About 81% had a clear-cell histology.

Total Healthcare Cost per patient

The annual THC per patient was $23,489 for RCC and $16,070 for the matched control group. The incremental THC per patient was the $7,419 for all phases combined, $22,752 for the initial phase, $4,860 for the continuing phase and the $13,232 for the late phase. In each phase, the difference in cost between the RCC and control group was significant ($p < 0.05$). The THC per patient also varied by stage at which the cancer was diagnosed. Average incremental THCs for patients diagnosed at stages I and II were approximately $4,700 - $5,000; whereas the average

incremental THCs for those diagnosed at stage-III and stage-IV were $9,331 and the $31,637 respectively. The average THC for patients diagnosed at stage-IV was about 6-7 times higher than the costs for patients diagnosed at stages I and II. For patients diagnosed at stages I - III, average THCs and incremental costs were higher in the initial and late phases than in the continuing phase. However, for patients diagnosed with stage-IV (mRCC), average THCs were similar across all three phases of care while incremental THCs were higher in the initial and continuing phases than the late phase. Details of costs for RCC and control group patients by a phase of care and stage at diagnosis can be found in Table 2.2

Total Economic Burden of RCC on Medicare

Based on the SEER Stat analysis, there were 18,121 older RCC patients alive in areas covered by SEER registries in 2015. The projected count of older RCC patients in the U.S. calculated using ProjPrev was 204,256. Multiplying the incremental cost of RCC by the projected number of RCC patients resulted in the total economic burden of $1,52 billion. To calculate economic burden by stages, we first calculated the number of RCC patients at various stages of diagnosis by assuming a distribution similar to SEER data. The total economic burden was estimated to be $524 million for stage-I, $68 million for stage-II, $267 million for stage-III, $1.0 billion for stage-IV and $166 million for the unknown stage. The weighted total economic burden of RCC was found to be $2.06 billion.

Table 2.1 Characteristics of Renal Cell Carcinoma and non-cancer patients in this study.

Characteristics	RCC (n = 10,408) n, (%)	Non-cancer (n = 170,061) n, (%)	RCC (matched) (n = 10,392) n, (%)	Non-cancer (matched) (n = 10,392) n, (%)	Standardized difference after matching
Age (mean, SD) * +	73.8 (6.3)	75.5 (7.3)	73.8 (6.3)	74.9 (7.1)	0.1645
Age categories (year) * +					
- 65 to 69	3,225 (31.0)	43,043 (25.3)	3,216 (31.0)	2,883 (27.7)	0.0705
- 70 to 74	3,486 (33.5)	52,207 (30.7)	3,479 (33.5)	3,251 (31.3)	0.0468
- 75 to 79	2,003 (19.2)	32,763 (19.3)	2,003 (19.3)	1,995 (19.3)	0.0017
- 80 and older	1,694 (16.3)	42,048 (24.7)	1,694 (16.3)	2,263 (21.8)	0.1397
Gender (% Male) * +	5,863 (56.3)	65,978 (38.8)	5,850 (56.3)	6,162 (59.3)	0.0608
Race (%) * +					
- Caucasian	9,000 (86.5)	140,757 (82.8)	8,989 (86.5)	8,756 (84.3)	0.0629
- Black	815 (7.8)	12,063 (7.1)	812 (7.8)	1,013 (9.8)	0.0680
- Others	593 (5.7)	17,241 (10.1)	591 (5.7)	623 (6.0)	0.0127
NCI Comorbidity Index Score (mean, SD) * +	0.5 (1.0)	0.9 (1.4)	0.9 (1.3)	1.0 (1.4)	0.0582
NCI Comorbidity Index Score categories * +					
- 0	5,469 (52.6)	11,9240 (70.1)	5,468 (52.6)	5,283 (50.8)	0.0358
- 1 to 2	3,685 (35.4)	41,956 (24.7)	3,682 (35.4)	3,725 (35.8)	0.0086
- 3 or more	1,254 (12.1)	8,865 (5.2)	1,242 (11.9)	1,384 (13.3)	0.0413
Urban /Rural (%)					
- Big Metro	5,295 (50.9)	87,713 (51.6)	5,289 (50.9)	4,856 (46.7)	0.0830
- Metro	3,161 (30.4)	51,905 (30.5)	3,153 (30.4)	3,289 (31.6)	0.0280
- Urban	683 (6.6)	10,902 (6.4)	682 (6.6)	822 (7.9)	0.0520
- Less urban	1,018 (9.8)	15,834 (9.3)	1,017 (9.8)	1,172 (11.3)	0.0483
- Rural	251 (2.4)	3,707 (2.2)	251 (2.4)	253 (2.4)	0.0013
SEER region *					
- North East	2,042 (19.6)	33,885 (19.9)	2,040 (19.6)	2,076 (20.0)	0.0087
- South	2,823 (27.1)	40,345 (23.7)	2,818 (27.1)	2,743 (26.4)	0.0163
- North Central	1,246 (12.0)	19,078 (11.2)	1,245 (12.0)	1,242 (12.0)	0.0001
- West	4,297 (41.3)	76,753 (45.1)	4,289 (41.3)	4,331 (41.7)	0.0082
Phase of Care					
- Initial Phase	1,779 (17.1)	24,580 (14.5)	1,778 (17.1)	1,777 (17.1)	NA
- Continuing Phase	7,806 (75.0)	138,112 (81.2)	7,794 (75.0)	7,794 (75.0)	
- Late Phase	823 (7.9)	7,369 (4.3)	820 (7.9)	821 (7.9)	
Cancer Stage					
- Stage I	6,720 (64.6)	NA	6,710 (64.6)	NA	NA
- Stage II	784 (7.5)		782 (7.5)		
- Stage III	1554 (14.9)		1,551 (14.9)		
- Stage IV	756 (7.3)		755 (7.3)		
- Unknown	594 (5.7)		594 (5.7)		
Histology					
- Clear cell	8,455 (81.2)	NA	8,443 (81.3)	NA	NA
- Non-clear cell	1,953 (18.8)		1,949 (18.8)		

Note: NA: not applicable; * Difference was statistically significant (p <0.05) before matching; +: difference was statistically significant after matching

Table 2.2 Annual total healthcare cost associated with Renal Cell Carcinoma by disease phase and by stage at which cancer was diagnosed

Cancer stage at diagnosis	RCC (US $) (mean, 95%CI)	Matched Non-Cancer (US $) (mean, 95%CI)	Incremental Cost (US $) (mean, 95%CI)
Any Stage (n = 20,784)			
All phases	23,489 (22,805 - 24,174)	16,070 (15,507 - 16,633)	7,419 (6,553- 8,285)*
Initial	32,669 (31,109 - 34,229)	9,917 (8,911 - 10,923)	22,752 (20,875 - 24,629)*
Continuing	18,939 (18,226 - 19,652)	14,078 (13,525 - 14,631)	4,860 (3,965 - 5,756)*
Late phase	54,983 (51,790 - 58,176)	41,750 (38,737 - 44,764)	13,232 (9,015 - 17,450)*
Stage- I (n = 17,102)			
All phases	20,528 (19,749 - 21,306)	15,944 (15,385 - 16,504)	4,584 (3,652 - 5,515)*
Initial	29,073 (27,113 - 31,033)	9,942 (8,925 - 10,959)	19,131 (16,905 - 21,356)*
Continuing	17,210 (16,408 - 18,012)	14,150 (13,574 - 14,725)	3,060 (2,044 - 4,077)*
Late phase	52,314 (46,565 - 58,063)	43,006 (39,798 - 46,214)	9,307 (2,755 - 15,860)*
Stage - II (n = 11,174)			
All phases	20,671 (18,407 - 22,936)	15,944 (15,385 - 16,504)	4,727 (2,418 - 7,037)*
Initial	33,417 (26,976 - 39,859)	9,926 (8,922 - 10,930)	23,491 (17,112 - 29,870)*
Continuing	16,403 (14,107 - 18,699)	14,226 (13,660 - 14,793)	2,177 (-208 - 4,561)
Late phase	52,068 (37,575 - 66,560)	43,196 (39,847 - 46,545)	6,398 (-6,125 - 23,868)
Stage - III (n = 11,943)			
All phases	25,275 (23,524 - 27,027)	15,944 (15,385 - 16,504)	9,331 (7,505 - 11,157)*
Initial	36,489 (31,738 - 41,241)	9,879 (8,874 - 10,884)	26,610 (21,756 - 31,464)*
Continuing	20,946 (19,038 - 22,854)	14,190 (13,624 - 14,756)	6,756 (4,783 - 8,729)*
Late	57,923 (50,237 - 65,610)	42,966 (39,752 - 46,181)	14,957 (6,701 - 23,213)*
Stage- IV (n = 11,147)			
All phases	47,581 (44,217 - 50,946)	15,944 (15,385 - 16,504)	31,637 (28,220 - 35,054)*
Initial	50,805 (44,477 - 57,133)	9,862 (8,892 - 10,832)	40,943 (34,530 - 45,357)*
Continuing	46,546 (40,344 - 52,749)	14,250 (13,678 - 14,823)	32,296 (26,064 - 38,528)*
Late	62,008 (55,880 - 68,135)	41,647 (38,500 - 44,795)	20,360 (13,571 - 27,150)*
Stage- Unknown (n = 10,986)			
All phases	27,579 (24,562 - 30,597)	15,944 (15,385 - 16,504)	11,635 (8,559 - 14,712)*
Initial	35,026 (26,059 - 43,992)	10,014 (8,953 - 11,076)	25,011 (15,908 - 34,115)*
Continuing	22,971 (19,534 - 26,408)	14,258 (13,691 - 14,825)	8,713 (5,229 - 12,198)*
Late	59,415 (46,816 - 72,013)	42,398 (39,238 - 45,557)	17,017 (4,309 - 29,725)*

*** statistically significant difference (p-value < 0.05)**

Healthcare Costs by Types of Services Used

RCC patients had significantly higher costs than controls for all types of resources used except for DME and SNF. For RCC patients, costs related to hospitalizations ($2,282 per patient), hospital outpatient use ($1,497 per patient) and physician-provided services ($ 1,544 per patient) were the top three drivers of THC.

Among stage-I RCC patients, the cost associated with hospital use, outpatient services, physician-provided services, prescription drugs and hospice care services were significantly (p-value <0.05) higher than control group patients. Costs associated with hospital use, outpatient services and physician provided care were the top three drivers of THC. A similar pattern was observed for stage-II and stage-III patients. However, THC incurred among patients with stage III were ~ 2 times the costs for stages I and II. For stages, I - III, costs associated with hospice care, DME, SNF and home health services did not differ significantly from controls. Patients diagnosed at stage-IV (mRCC) exhibited a different distribution of cost drivers compared to patients diagnosed at earlier stages. For patients diagnosed at stage-IV, incremental costs were ~ 9 times higher than patients from stages I and II and ~ 4 times higher than stage-III patients. For mRCC patients, prescription drug cost ($11,747) was the largest component of THC. Unlike patients from earlier stages, stage-IV patients had significantly ($p<0.05$) higher home health and hospice care costs than control group patients. Details regarding costs by types of resources used and cancer stages are described in Table 2.3

Table 2.3 Healthcare cost by types of resources used and cancer stage at diagnosis

	RCC (mean, 95%CI)	Matched Non-Cancer (mean, 95%CI)	Incremental Cost (mean, 95%CI)
Any Stage (n = 20,784)			
Total	23,489 (23,141 - 24,511)	16,070 (15,178 - 16,289)	7,419 (6,553 - 8,285)*
Hospital	4,830 (4,564 - 5,095)	2,548 (2,320 - 2,776)	2,282 (1,929 - 2,634)*
ED	4,709 (4,455 - 4,964)	3,899 (3,648 - 4,150)	811 (461 - 1,161)*
Skilled nursing facility	1,503 (1,372 - 1,634)	1,405 (1,278 - 1,532)	98 (-80 - 276)
Outpatient services	3,053 (2,902 - 3,204)	1,556 (1,469 - 1,644)	1,497 (1,327 - 1,666)*
Physician services	4,419 (4,288 - 4,551)	2,875 (2,801 - 2,976)	1,544 (1,385 - 1,704)*
Prescription drugs	3,817 (3,538 - 4,097)	2,169 (2,067 - 2,272)	1,648 (1,352 - 1,944)*
DME	232 (215 - 250)	247 (225 - 268)	-14 (-38 - 10)
Hospice care	723 (627 - 818)	551 (469 - 634)	172 (51 - 292)*
Home health	818 (771 - 866)	691 (645 - 737)	127 (63 - 192)*
Stage - I (n = 17,102)			
Total	20,528 (19,749 - 21,306)	15,944 (15,385 - 16,504)	4,584 (3,652 - 5,515)*
Hospital	4,417 (4,096 - 4,738)	2,543 (2,316 - 2,770)	1,917 (1,532 - 2,301)*
ED	4,204 (3,892 - 4,516)	3,855 (3,607 - 4,103)	350 (-33 - 732)
Skilled nursing facility	1,356 (1,202 - 1,510)	1,411 (1,284 - 1,538)	-55 (-251 - 142)
Outpatient services	2,710 (2,535 - 2,885)	1,561 (1,473 - 1,649)	1,149 (955 - 1,343)*
Physician services	3,987 (3,849 - 4,125)	2,873 (2,786 - 2,961)	1,114 (949 - 1,278)*
Prescription drugs	2,458 (2,299 - 2,617)	2,279 (2,160 - 2,398)	179 (-19 - 377)
DME	223 (205 - 242)	246 (225 - 268)	-23 (-49 - 3)
Hospice care	393 (309 - 477)	580 (493 - 667)	-187 (-304, -69)*
Home health	746 (690 - 803)	695 (648 - 741)	52 (-20 - 123)
Stage- II (n = 11,174)			
Total	20,671 (18,407 - 22,936)	15,944 (15,385 - 16,504)	4,727 (2,418 - 7,037)*
Hospital	4,128 (3,313 - 4,943)	2,543(2,316 - 2,770)	1,585 (747 - 2,424)*
ED	4,390 (3,304 - 5,478)	3,855 (3,607 - 4,103)	536 (-573 - 1,646)
Skilled nursing facility	1,267 (827 - 1,707)	1,411 (1,284 - 1,538)	-144 (-600 - 313)
Outpatient services	2,394 (1,950 - 2,838)	1,561 (1,473 - 1,649)	833 (381 - 1,825)*
Physician services	3,830 (3,409 - 4,252)	2,873 (2,786 - 2,961)	957 (492 - 1,360)*
Prescription drugs	3,522 (2,456 - 4,588)	2,279 (2,160 - 2,398)	1,243 (183 - 2,304)
DME	256 (167 - 343)	246 (225 - 268)	9 (-81 - 99)
Hospice care	701 (350 - 1052)	580 (493 - 667)	121 (-238 - 480)
Home health	763 (602 - 8923)	695 (648 - 741)	68 (-98 - 234)
Stage- III (n = 11,943)			
Total	25,275 (23,524 - 27,027)	15,944 (15,385 - 16,504)	9,331 (7,505 - 11,157)*
Hospital	5,896 (5,141 - 6,652)	2,543 (2,316 - 2,770)	3,353 (2,564 - 4,142)*
ED	4,733 (4,099 - 5,364)	3,855 (3,607 - 4,103)	878 (183 - 1,574)*
Skilled nursing facility	1,323 (1,036 - 1,610)	1,411 (1,284 - 1,538)	-88 (-405 - 229)
Outpatient services	3,387 (2,991 - 3,784)	1,561 (1,473 - 1,649)	1,826 (1,424 - 2,228)*
Physician services	4,982 (4,568 - 5,396)	2,873 (2,786 - 2,961)	2,109 (1,686 - 2,532)*
Prescription drugs	4,330 (3,503 - 5,158)	2,279 (2,160 - 2,398)	2,052 (1,218 - 2,886)*
DME	213 (176 - 249)	246 (225 - 268)	-34 (-73 - 5)
Hospice care	821 (552 - 1,089)	580 (493 - 667)	241 (-38 - 519)
Home health	909 (782 - 1,036)	695 (648 - 741)	215 (80 - 349)*

*** Statistically significant differences, p < 0.05**

Table 2.3 (continued)

	RCC (mean, 95%CI)	Matched Non-Cancer (mean, 95%CI)	Incremental Cost (mean, 95%CI)
Stage- IV (n = 11,147)			
Total	47,581 (44,217 - 50,946)	15,944 (15,385 - 16,504)	31,637 (28,220 - 35,054)*
Hospital	5,574 (4,586 - 6,562)	2,543 (2,316 - 2,770)	3,031 (2,009 - 4,053)*
ED	7,532 (6,490 - 8,574)	3,855 (3,607 - 4,103)	3,677 (2,591 - 4,764)*
Skilled nursing facility	2,266 (1,689 - 2,842)	1,411 (1,284 - 1,538)	855 (274 - 1,435)*
Outpatient services	6,685 (5,840 - 7,530)	1,561 (1,473 - 1,649)	5,124 (4,280 - 5,968)*
Physician services	8,061 (7,306 - 8,816)	2,873 (2,786 - 2,961)	5,188 (4,422 - 5,953)*
Prescription drugs	14,026 (11,530 - 16,522)	2,279 (2,160 - 2,398)	11,747 (9,258 - 14,237)*
DME	279 (200 - 357)	246 (225 - 268)	32 (-46 - 111)
Hospice care	2,457 (1,877 - 3,036)	580 (493 - 667)	1,877 (1,298 - 2,455)*
Home health	1,374 (990 - 1,387)	695 (648 - 741)	680 (448 - 912)*
Stage-Unknown (n = 10,986)			
Total	27,579 (24,562 - 30,597)	15,944 (15,385 - 16,504)	11,635 (8,559 - 14,712)*
Hospital	4,259 (3,172 - 5,347)	2,543(2,316 - 2,770)	1,716 (598 - 2,835)*
ED	6,323 (5,237 - 7,409)	3,855 (3,607 - 4,103)	2,468 (1,352 - 3,585)*
Skilled nursing facility	2,614 (1,936 - 3,291)	1,411 (1,284 - 1,538)	1,203 (514 - 1,892)*
Outpatient services	3,002 (2,470 - 3,534)	1,561 (1,473 - 1,649)	1,441 (903 - 1,979)*
Physician services	4,506 (4,046 - 4,967)	2,873 (2,786 - 2,961)	1,633 (1,165 - 1,984)*
Prescription drugs	3,865 (2,573 - 5,157)	2,279 (2,160 - 2,398)	1,586 (278 - 2,895)*
DME	301 (217 - 384)	246 (225 - 268)	54 (-32 - 140)
Hospice care	1,337 (834 - 1,839)	580 (493 - 667)	757 (251 - 1,262)*
Home health	849 (661 - 1,037)	695 (648 - 741)	155 (-41 - 350)

*** Statistically significant difference, p < 0.05**

Sensitivity Analyses

The average THC changed by only a small magnitude (less than 1 to 2%) in the unadjusted analysis and after including outliers. When NCI-comorbidity score was excluded from the propensity score model, the incremental cost per person increased by 45% from $7,419 to $10,770. The total economic burden on Medicare increased from $1.5 billion to $1.8 billion. The THC for mRCC increased by 10%. The use of log link and gamma distribution in a GLM resulted in a 4% increase in the average THC and total economic burden on Medicare. Under the assumption that about 30% of patients diagnosed before 2013 at earlier stages progressed to a metastatic stage, the estimated economic burden of RCC was $3.3 billion and among metastatic patients was $2.5 billion. Details regarding sensitivity analyses are described in Table 2.4

Table 2.4 Results from sensitivity analyses

	Incremental cost per patient (US $)				Total economic burden (US $)			
	Any stage	**Change from base case**	**Stage-IV**	**Change from base case**	**Any stage**	**Change from base case**	**Stage-IV**	**Change from base case**
Base case	**7,419**	**NA**	**31,637**	**NA**	**1.51 billion**	**NA**	**1.03 billion**	**NA**
Including potential outliers	7,330	-1.20%	31,458	-0.6%	1.50 billion	-1.20%	1.03 billion	-0.6%
Excluding NCI comorbidity index score from matching	10,770	+ 45.17%	34,880	+10.25%	2.20 billion	+ 45%	1.14 billion	+10.25%
Excluding covariates from the regression after matching	7,274	-1.95%	31,013	-1.97%	1.49 billion	-1.95%	1.01 billion	-1.97%
GLM with log link and Gamma distribution	7,739	+4.31%	31,235	-1.27%	1.58 billion	+4.31%	1.02 billion	-1.27%
Assume that 30% from earlier stages and diagnosed before 2013 may have reached to advanced stage in 2013 **	7,419	NA	31,637	NA	3.34 billion	+120.39%	2.53 billion	+145.14%

NA: not applicable, ** average costs were considered same as main analysis but the number of RCC patients varied.

DISCUSSION

This study assessed the economic burden of RCC from Medicare's perspective. We used the most recent SEER-Medicare data to reflect the economic burden in the later part of the targeted therapy era (2009-2013). This was also the first study among older adults, in this era, to assess drivers of healthcare costs for patients diagnosed at different stages. The average THC associated with RCC was $7,419 while the total economic burden was estimated to be $1.52 billion. Due to a higher prevalence of patients diagnosed at stage-I, costs associated with stage-I were the largest component of the total economic burden. However, in terms of average THC, patients diagnosed at stage-IV had the highest costs compared with patients diagnosed at earlier stages.

The average THC estimate from our study was similar, although slightly lower than the estimate of $11,169 from a study by Shih et al. Some methodological differences may explain slightly lower costs in our study. Shih et al. used frequency matching to match RCC and control patients on patient demographics; while we used propensity scores calculated using patient demographics and NCI comorbidity index. In a sensitivity analysis, matching only on demographics resulted in a similar cost estimate ($10,770) than the estimate from Shih et al.[18]

The total economic burden of RCC (estimated at $1.5 - $3 billion) in our study was lower than the economic burden of RCC projected by Mariotto et al ($4 - $6 billion) in the cytokine era.[17] Several reasons could explain the differences. First, we included only the most common histologies of RCC, while Mariotto et al estimated costs for all forms of kidney cancers. Second, we used PSM where propensity scores were based on demographics and NCI comorbidity index as opposed to matching only on age and gender. Third, several changes occurred in the management of RCC over the last decade. While approval of several targeted therapies may have resulted in an increase

in THC for stage-IV patients, uptake of less invasive surgical procedures and active surveillance among early stage patients could have resulted in lower healthcare costs.

The pattern of THC by phases of care was similar to previous studies. THC was highest in the initial phase during which patients undergo screening, receive aggressive cancer-related treatment and require monitoring and treatment of adverse events and complications. THC was lowest in the continuing phase, a phase where patients often have a remission and require minimal follow-up care. THC in the late phase was higher than the continuing phase but lower than the initial phase of care. [18, 23] Other Studies published using a phase of care approach have found that THC was highest in the late phase of care. A different pattern of THC for the late phase of care in our study could be due matching on comorbidities and/or differences in the operational definition of the phase of care. Because stage-IV patients have a shorter survival compared to patients diagnosed at earlier stages, their costs were similar across all three phases.

In our study, the costs among mRCC patients were about 9 times higher than patients diagnosed at stages- I and II. In addition, the average cost for stage-IV patients was approximately $28,000 more than the average cost for early stage patients. In contrast, during the cytokine era, Hollenbeak et al. found that 1-year cost among patients with distant metastasis was $4,482 higher (2 times higher) than costs among patients with localized disease[3] and Lang et al. estimated that the average cost for metastatic patients ($26,573) was lower than the average cost for localized disease ($36,968), which was surprising considering the aggressive treatment given among patients with the metastatic stage.[16] Our findings suggest that although the life expectancy among mRCC patients increased in the targeted therapy era, it also resulted in higher costs for stage-IV patients. For patients diagnosed at stages-I to III, hospital cost was the largest component (~ 40%) of THC. Higher costs related to hospital use may indicate the use of partial or complete

nephrectomy, laparoscopic surgery and local therapies such as radiofrequency ablation which are primarily used to treat early stage, localized tumor and require hospitalization. Services provided by physicians and other healthcare professionals in hospitals and noninstitutional physician offices were the next largest components (5% each) of THC for these patients. Smaller or non-significant differences in the costs for the use of ED, DME, prescription drugs, hospice care, and home health services suggested that patients diagnosed at stages I and II may use these services no more often than matched non-cancer patients. THC among stage-III patients was about two times higher than costs for stages-I and II, which could be due to an advanced form of the disease and relatively aggressive form of treatment. In contrast to patients diagnosed at stage-I and II, prescription drug costs among those diagnosed at stage-III was significantly higher than control patients. This could be due to the use of systemic therapy in patients with recurrent disease or adjuvant use after nephrectomy. For stage-IV patients, prescription drug costs accounted for 36% of THC, which suggest the use of high-cost targeted therapies and medications given to control complications arising at the site of metastasis (eg. bisphosphonates for bone metastases). In addition to prescription drugs, costs associated with ED use were substantially high among mRCC patients and accounted for 12% of THC. Costs associated with hospice care and skilled nursing home facility use were much higher for mRCC patients than patients with earlier stages, which suggests the extensive use of nursing and palliative care among stage-IV patients.

This study has several limitations. We used PSM to reduce selection bias and make RCC and control groups similar in patient characteristics. However, we could not match on factors that were not observed in the SEER-Medicare data such as performance status. Second, while projecting the total economic burden to the entire Medicare population of age $\geq$ 65 years, we assumed that patients on managed care plans have the same costs as patients from fee-for service

(FFS) plans. While it was necessary to exclude patients from managed care plans due to unavailability of their Part A and Part B claims in the SEER-Medicare data, average costs among managed care patients may differ from patients on FFS plans. This may result in under or over-estimation of the total economic burden. Due to unavailability of the data after 2013, the study did not include newer targeted therapies such as cabozantinib, approved in 2016. The SEER data measures cancer stage only at the time of first cancer diagnosis. Hence, the prevalence of RCC by stage was calculated based on the initial staging information, which may not be the most recent staging information. According to the literature about 30-33% of patients diagnosed at earlier stages eventually progress to the metastatic stage.[32, 33] It is, therefore, possible that we underestimated prevalence and total economic burden of mRCC. Lastly, the use of administrative claims and registry data are subject to miscoding errors.

Despite these limitations, our study provided important information on the economic burden of RCC and drivers of the THC for patients diagnosed at various stages. Several targeted and immunotherapies have been approved recently to treat mRCC. In addition, targeted therapies are currently being studied among locally advanced (stage-III) patients as adjuvant therapies. This study may provide a baseline that can be used to evaluate the value of emerging therapies among older RCC patients.

Appendix for study 1

Appendix 2.1 Characteristics of Renal Cell Carcinoma and non-cancer patients before and after propensity score matching - all phases combined

Characteristic	RCC (n = 10,408)	Non-cancer (n = 170,061)	Standardized differences before matching	RCC (matched) (n = 10,397)	Non-cancer (matched) (n = 10,397)	Standardized differences after (1:1) matching
Age at diagnosis	73.8 (6.3)	75.5 (7.3)	0.2872	73.8 (6.3)	74.9 (7.1)	0.1645
Age categories (year) * +						
- 65 to 69	31.0	25.3	0.1264	31.0	27.7	**0.0705**
- 70 to 75	33.5	30.7	0.0599	33.5	31.3	**0.0468**
- 76 to 80	19.2	19.3	0.0005	19.3	19.3	0.0017
- > than 80	16.3	24.7	0.2104	16.3	21.8	**0.1397**
Gender (% Male)	56.3	38.8	0.3567	56.3	59.3	**0.0608**
Race (%)						
- Caucasian	86.5	82.8	0.1028	86.5	84.3	**0.0629**
- Black	7.8	7.1	0.0281	7.8	9.8	0.0680
- Others	5.7	10.1	0.1650	5.7	6.0	**0.0127**
CCI (mean)	0.5 (1.0)	0.9 (1.4)	0.3654	0.9 (1.3)	1.0 (1.4)	**0.0582**
Urban /Rural (%)						
- Big Metro	50.9	51.6	0.0141	50.9	46.7	0.0830
- Metro	30.4	30.5	0.0033	30.4	31.6	0.0280
- Urban	6.6	6.4	0.0061	6.6	7.9	0.0520
- Less urban	9.8	9.3	0.0160	9.8	11.3	0.0483
- Rural	2.4	2.2	0.0155	2.4	2.4	**0.0013**
Registry (%)						
- S. Francisco	3.1	3.8	0.0408	3.1	1.9	0.0755
- Connecticut	5.6	5.7	0.0025	5.6	5.7	0.0029
- Detroit	5.5	5.5	0.0031	5.5	5.7	0.0058
- Hawaii	1.2	1.3	0.0114	1.2	1.6	0.0358
- Iowa	6.4	5.7	0.0286	6.4	6.3	**0.0067**
- N Mexico	2.7	2.8	0.0114	2.7	3.8	0.0663
- Seattle	5.3	5.4	0.0038	5.3	4.5	0.0393
- Utah	1.9	2.2	0.0186	1.9	1.8	**0.0100**
- Atlanta	2.6	2.8	0.0097	2.6	1.3	0.0941
- San Jose	2.3	2.6	0.0193	2.3	3.4	0.0641
- Los Angeles	6.3	7.5	0.0436	6.3	6.0	**0.0132**
- Greater Cali	18.5	19.5	0.0264	18.5	18.7	**0.0054**
- Kentucky	8.2	6.7	0.0572	8.2	7.3	**0.0367**
- Louisiana	7.7	5.8	0.0755	7.7	10.5	0.0990
- New Jersey	14	14.3	0.0071	14.0	14.3	0.0080
- Georgia	8.6	8.4	0.0058	8.6	7.3	0.0469

NOTE: Values in bold indicate reduction in standardized differences

Appendix -2.2 Characteristics of Renal Cell Carcinoma and non-cancer patients before and after propensity score matching - initial phase

Characteristic	RCC (N = 10,408)	Non-cancer (N = 170,061)	Standardized differences before matching	RCC (matched) (N = 1,777)	Non-cancer (matched) (N = 1,777)	Standardized differences after (1:1) matching
Age at diagnosis	73.8 (6.6)	75.9 (7.9)	0.2872	73.8 (6.6)	74.2 (7.1)	**0.0530**
Age categories						
- 65 to 69	31.3	25.5	0.1283	31.3	30.7	**0.0121**
- 70 to 75	32.8	29.8	0.0651	32.8	34.4	**0.0333**
- 76 to 80	19.1	17.4	0.0424	19.1	16.1	0.0768
- > than 80	16.9	16.9	0.2536	16.9	18.8	**0.0499**
Gender (Male %)	62.0	40.6	0.4378	62.0	62.0	**0.0608**
Race (%)						
- Caucasian	85.4	81.2	0.1141	85.4	84.5	**0.0267**
- Black	8.8	7.8	0.0369	8.8	10.1	0.0461
- Others	5.8	11.0	0.0190	5.8	5.4	**0.0171**
CCI	1.1 (1.5)	0.6 (1.2)	0.3654	1.1 (1.5)	1.2 (1.6)	**0.0233**
Urban /Rural (%)						
- Big Metro	50.4	51.7	0.0246	50.4	50.8	**0.0067**
- Metro	31.0	31.0	0.0005	31.0	31.0	0.0012
- Urban	6.3	6.2	0.0190	6.7	6.6	**0.0023**
- Less urban	9.0	9.0	0.0255	9.7	9.2	**0.0173**
- Rural	2.1	2.1	0.0002	2.1	2.4	0.0188
Registry (%)						
- S. Francisco	3.6	3.9	0.0143	3.6	3.8	**0.0119**
- Connecticut	4.3	5.3	0.0430	4.3	4.3	**0.0000**
- Detroit	5.7	5.5	0.0123	5.7	5.8	**0.0024**
- Hawaii	1.2	1.3	0.0124	1.2	1.1	**0.0107**
- Iowa	6.0	5.6	0.0135	6.0	5.2	0.0318
- N Mexico	2.9	2.9	0.0013	2.9	2.8	0.0034
- Seattle	5.2	5.5	0.0125	5.2	4.8	0.0206
- Utah	2.2	2.1	0.0053	2.2	2.1	**0.0038**
- Atlanta	2.0	3.0	0.0658	2.0	1.6	**0.0253**
- San Jose	3.0	2.7	0.0152	3.0	3.1	**0.0065**
- Los Angeles	5.9	7.6	0.0717	5.9	5.9	**0.0023**
- Greater Cali	18.8	20.0	0.0306	18.8	19.1	**0.0086**
- Kentucky	8.7	6.7	0.0751	8.7	9.3	**0.0215**
- Louisiana	7.8	5.6	0.0880	7.8	7.6	**0.0063**
- New Jersey	14.3	13.7	0.0182	14.3	16.30	0.0546
- Georgia	8.5	8.6	0.0036	8.5	7.0	0.0547

NOTE: Values in bold indicate reduction in standardized differences

Appendix 2.3 Characteristics of Renal Cell Carcinoma and non-cancer patients before and after propensity score matching – continuing phase

Characteristic	RCC (N = 10,408)	Non-cancer (N = 170,061)	Standardized differences before matching	RCC (matched) (N = 7,794)	Non-cancer (matched) (N = 7,794)	Standardized differences after (1:1) matching
Age at diagnosis	73.4 (6.1)	75.1 (7.0)	0.2573	73.4 (6.1)	74.8 (7.0)	**0.2128**
Age categories						
- 65 to 69	32.2	26.2	0.1316	32.2	30.7	**0.0927**
- 70 to 75	34.4	31.7	0.0584	34.4	34.4	0.0714
- 76 to 80	18.9	19.6	0.0168	18.9	19.6	0.0166
- > than 80	14.5	22.6	0.2083	14.5	21.5	**0.1814**
Gender (male %)	55.0	38.5	0.4379	55.0	58.9	**0.0608**
Race (%)						
- Caucasian	86.5	83.0	0.1142	86.5	83.5	**0.0267**
- Black	7.6	7.0	0.0368	7.6	10.0	0.0461
- Others	5.9	10.0	0.1904	5.9	6.5	**0.0171**
CCI	0.8 (1.3)	0.5 (0.9)	0.3475	0.8 (1.2)	0.9 (1.3)	**0.0820**
Urban /Rural (%)						
- Big Metro	51.4	51.7	0.0246	51.4	45.7	**0.0067**
- Metro	30.3	30.4	0.0005	30.3	32.1	0.0012
- Urban	6.4	6.4	0.0190	6.4	8.2	**0.0022**
- Less urban	9.4	9.3	0.0254	9.4	11.7	**0.0172**
- Rural	2.4	2.2	0.0002	2.4	2.3	0.0188
Registry (%)						
- S. Francisco	3.0	3.8	0.0143	3.0	1.5	**0.0118**
- Connecticut	6.1	5.7	0.0430	6.1	6.2	**0.0000**
- Detroit	5.6	5.4	0.0122	5.6	5.6	**0.0024**
- Hawaii	1.2	1.3	0.0123	1.2	1.8	**0.0106**
- Iowa	6.3	5.7	0.0135	6.3	6.5	0.0318
- N Mexico	2.6	2.8	0.0013	2.6	4.3	0.0034
- Seattle	5.4	5.4	0.0124	5.4	4.3	0.0206
- Utah	1.7	2.2	0.0052	1.7	1.5	**0.0038**
- Atlanta	2.7	2.7	0.0658	2.7	1.1	**0.0253**
- San Jose	2.3	2.6	0.0152	2.3	3.7	**0.0065**
- Los Angeles	6.3	7.4	0.0717	6.3	6.0	**0.0024**
- Greater Cali	18.2	19.5	0.0305	18.2	18.5	**0.0086**
- Kentucky	8.1	6.7	0.0751	8.1	6.4	**0.0216**
- Louisiana	7.6	5.8	0.0879	7.6	11.4	**0.0063**
- New Jersey	14.2	14.4	0.0181	14.2	14.0	0.0546
- Georgia	8.7	8.4	0.0035	8.7	7.4	0.0546

NOTE: Values in bold indicate reduction in standardized differences

Appendix 2.4 Characteristics of Renal Cell Carcinoma and non-cancer patients before and after propensity score matching – late phase

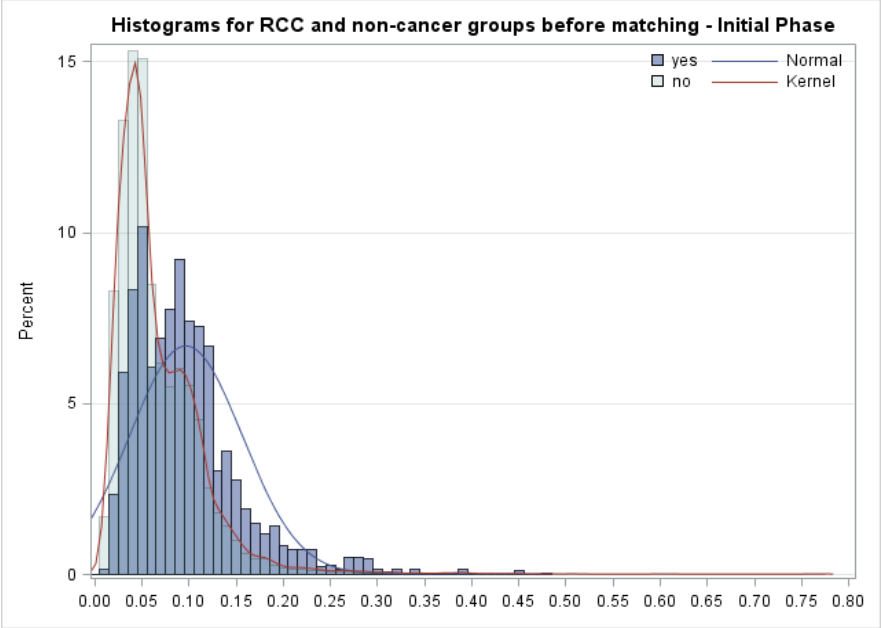
Characteristic	RCC (N = 10,408)	Non-cancer (N = 170,061)	Standardized differences before matching	RCC (matched) (N = 821)	Non-cancer (matched) (N = 821)	Standardized differences after (1:1) matching
Age at diagnosis	76.9 (7.4)	81.6 (7.9)	0.6184	76.9 (7.4)	76.9 (7.4)	**0.0048**
Age categories						
- 65 to 69 (%)	19.1	7.9	0.3308	32.2	30.7	**0.0216**
- 70 to 75 (%)	26.5	16.0	0.2582	34.4	34.4	0.0137
- 76 to 80 (%)	22.6	19.2	0.0840	18.9	19.6	0.0176
- > than 80 (%)	31.8	56.9	0.5208	14.5	21.5	**0.0157**
Gender (male %)	57.0	38.8	0.3712	56.9	57.3	**0.0607**
Race (%)						
- Caucasian	88.3	84.7	0.1064	88.3	91.0	**0.0880**
- Black	7.7	7.1	0.0224	7.7	6.6	0.0426
- Others	4.0	8.2	0.1765	4.0	2.4	**0.0897**
CCI	1.4 (1.7)	1.1 (1.5)	0.1933	1.4 (1.7)	1.3 (1.7)	**0.0377**
Urban /Rural (%)						
- Big Metro	47.1	49.9	0.0546	47.1	48.2	**0.0219**
- Metro	29.3	31.4	0.0458	29.2	28.4	**0.0188**
- Urban	7.5	6.8	0.0301	7.6	8.2	**0.0226**
- Less urban	13.2	9.8	0.1086	13.3	11.7	**0.0479**
- Rural	2.8	2.2	0.0382	2.8	3.5	0.0417
Registry (%)						
- S. Francisco	2.6	3.3	0.0427	2.6	1.7	0.0590
- Connecticut	3.8	5.6	0.0858	3.8	3.5	**0.0129**
- Detroit	4.5	7.1	0.1104	4.5	6.6	**0.0906**
- Hawaii	1.1	1.1	0.0031	1.1	1.5	0.0325
- Iowa	8.3	6.2	0.0779	8.3	6.5	**0.0699**
- N Mexico	2.6	2.8	0.0151	2.6	1.7	0.0590
- Seattle	4.9	5.1	0.0098	4.9	5.1	0.0112
- Utah	2.8	2.2	0.0363	2.8	4.0	0.0671
- Atlanta	2.9	2.8	0.0056	2.9	2.9	**0.0000**
- San Jose	1.3	2.1	0.0561	1.3	1.3	**0.0000**
- Los Angeles	8.0	6.8	0.0482	8.0	6.2	0.0666
- Greater Cali	20.1	18.4	0.0523	20.3	19.5	**0.0214**
- Kentucky	9.0	7.2	0.0644	9.0	10.7	**0.0572**
- Louisiana	7.8	6.4	0.0523	7.8	8.2	**0.0134**
- New Jersey	11.9	14.2	0.0679	11.9	13.3	**0.0403**
- Georgia	8.3	8.8	0.0180	8.3	7.3	0.0363

NOTE: Values in bold indicate reduction in standardized differences

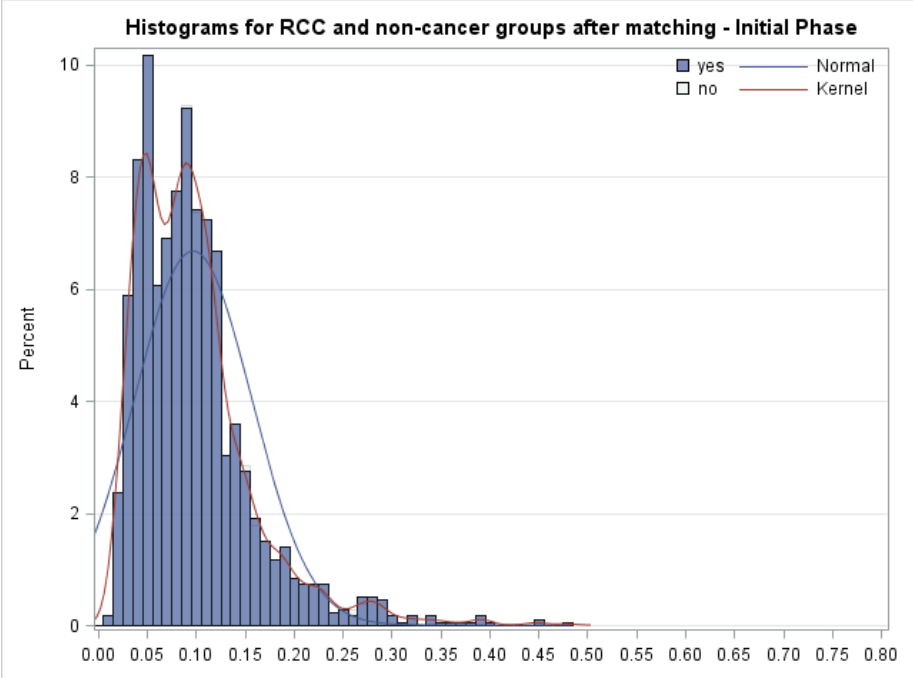
Appendix 2.5 Distribution of propensity scores before and after matching by phases

A. Initial Phase

Before Match:

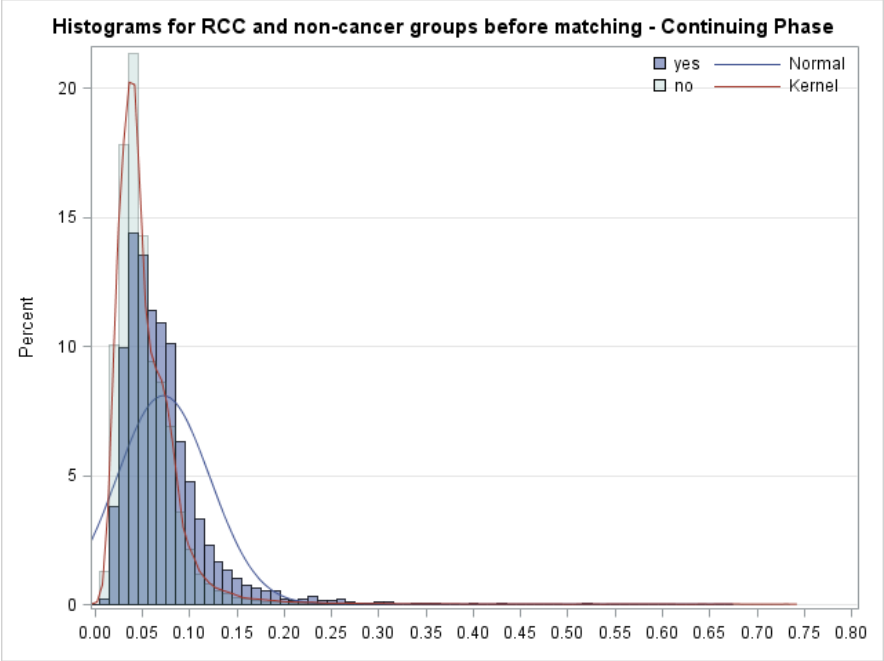


After Match:

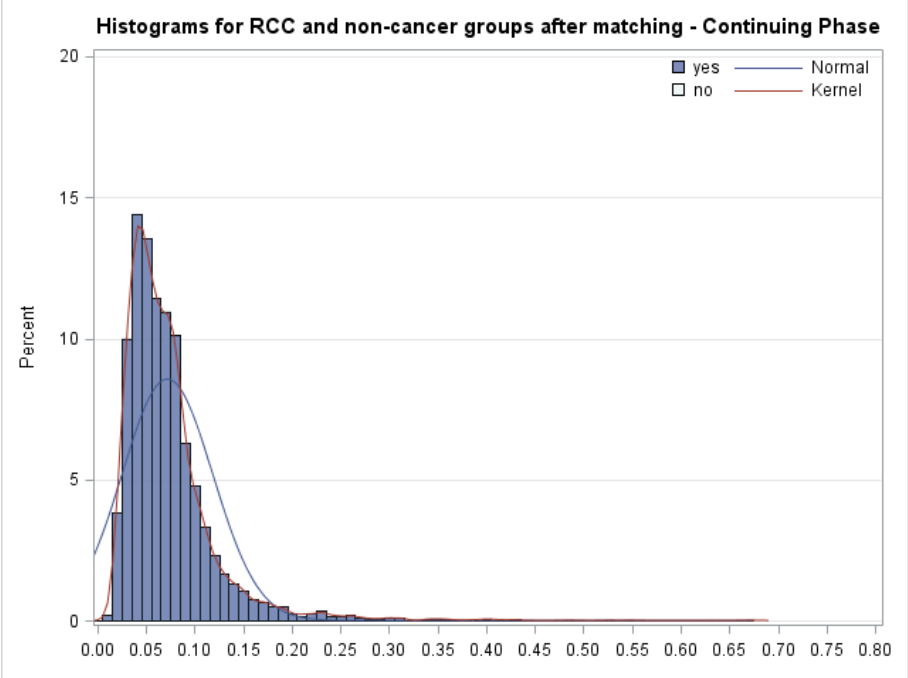


B. Continuing Phase

Before Match:

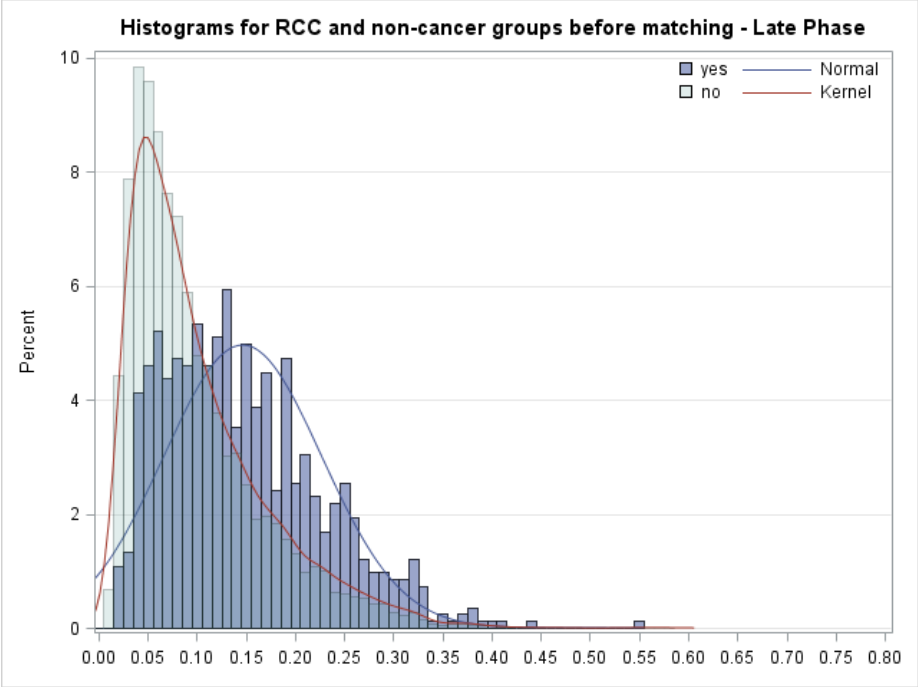


After Match:

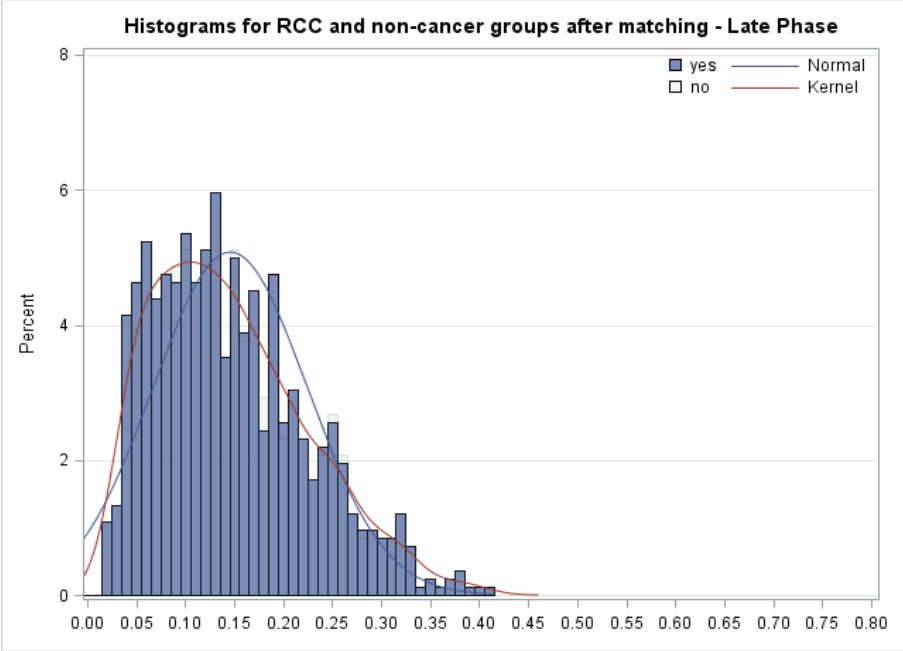


C. Late Phase

Before Match



After Match



Appendix 2.6. Medical Consumer Price Index values for 2013 and 2015

Cost category	Category used from CPI report	CPI in 2013	CPI in 2015	Multiplication factor
Hospital and ED	Inpatient hospital	259.724	303.260	**1.168**
Outpatient	Outpatient hospital	601.670	672.374	**1.118**
Carrier	Professional services	349.468	371.546	**1.063**
SNF	Nursing home and adult day services	194.472	213.676	**1.099**
Prescription drugs	Prescription drugs	442.580	502.510	**1.135**
DME	Durable medical equipment (medical supplies and equipment)	101.022	99.272	**0.983**
Home health	Home health	115.117	120.550	**1.047**
Hospice care	No specific category (use medical care which is average of all services)	425.134	463.675	**1.091**

Source: Consumer Price Index for all Urban Consumers (CPI-U): U.S. city average, detailed expenditure categories 2013 (January 2014 report) and 2015 (December 2015 report)

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Chapter 3

Study 2: Utilization of Targeted Therapy and Cytoreductive Nephrectomy among Older Adults with Metastatic Renal Cell Carcinoma: Analysis of Survival and Healthcare Costs

ABSTRACT

Objectives

Since 2005, targeted therapies have become a standard of care for metastatic renal cell carcinoma (mRCC). However, previous studies suggest that 25%-40% of mRCC patients do not receive targeted therapies. Furthermore, due to availability of several targeted therapies, there is uncertainty about the role of cytoreductive nephrectomy (CN) in the treatment of mRCC. The specific aims of this study were 1) to examine the prevalence and predictors of targeted therapy and CN use among older mRCC patients 2) to compare the survival and 3) to compare healthcare costs among older patients who received targeted therapy alone versus CN + targeted therapy.

Methods

This study analyzed the 2007-2014 Surveillance Epidemiology and End Result (SEER)-Medicare database. Patients newly diagnosed with primary mRCC at the age of 65 or more, who also had continuous enrollment in Medicare Parts A, B and Prescription Drug Plans (PartD) were included. First, we assessed the predictors of receiving either CN or targeted therapy (any active treatment). A multivariable logistic regression assessed the odds for receiving active treatment versus no active treatment. Second, we assessed predictors of receiving a CN + targeted therapy. A multinomial logistic regression assessed the odds for receiving CN + targeted therapy and CN alone versus targeted therapy alone. Third, we compared overall survival (OS), disease-specific survival (DSS) and total healthcare costs (THC) between targeted therapy alone and CN + targeted

therapy groups. A propensity score based inverse probability of treatment weighting (IPTW) method was used to balance the two treatment groups. A Cox proportional hazard model assessed the risk for death and a generalized linear model compared the healthcare costs between the groups. All costs were inflated to 2016 U.S Dollars.

Results

Of 1,263 mRCC patients 672 (53%) received active treatment. Patients diagnosed at age > 80 years, with NCI comorbidity index scores ≥ 3, and with unknown tumor grade and metastases to liver or brain were less likely to receive active treatment. Patients who were married, diagnosed from 2010-2013 and with higher tumor involvement were more likely to receive active treatment. Of patients receiving active treatment, 360 (54%) received targeted therapy alone, 201 (30%) received CN + targeted therapy, and 111 (17%) received CN alone. Patients who had higher lymph node involvement, metastasis to bone or liver, lived in North Central or West regions were significantly less likely to receive CN + targeted therapy compared to targeted therapy alone. Living in urban areas, higher tumor involvement, and poorly differentiated tumor grade increased the odds for receiving CN + targeted therapy compared to targeted therapy alone. The median OS from the adjusted survival curves was significantly higher ($p < 0.0001$) for CN + targeted therapy group (15 months) than the targeted therapy alone group (10 months). CN + targeted therapy group had 0.63 times the risk of death (HR = 0.63) compared to the targeted therapy alone group. The adjusted total healthcare cost per month was $17,159 for CN + targeted therapy group and $18,120 for the targeted therapy alone group ($p = 0.4389$). Sensitivity analysis suggested that total healthcare cost tended to be higher for the targeted therapy alone group.

Conclusions

About one-half of older mRCC patients on Medicare did not receive either CN or targeted therapy. One-third of patients receiving targeted therapy also underwent CN. Use of CN among targeted therapy users was associated with a higher median overall survival and disease-specific survival and similar monthly total healthcare cost over a lifetime. Among clinically appropriate mRCC patients, CN could play an important role in the targeted therapy era.

BACKGROUND

Renal cell carcinoma (RCC) is the most common type of kidney cancer. About 9 out of 10 kidney cancers are RCC. The American Cancer Society (ACS) estimated that in 2017, approximately 63,990 new kidney cancer cases would be diagnosed and 14,440 people would die from this disease.[1] The median age of RCC diagnosis is 64 years and men are at two times higher risk than women to be diagnosed with RCC. About 15%-40% of RCC patients are diagnosed at the metastatic stage and over 30% of those diagnosed at early stages eventually progress to the metastatic stage.[2, 3]

Before 2005 (cytokine era), systemic therapies for mRCC included cytokine therapy with high dose interleukin-2 and interferon-alpha. However, both drugs were associated with low tumor response rate, high toxicity, and improvement of less than 6 to12 months in overall survival (OS).[4, 5] Since 2005, the US Food and Drug Administration (FDA) approved several targeted therapies to treat mRCC. These have demonstrated a significant improvement in survival outcomes compared to cytokine therapies.[6-10] These therapies included the tyrosine kinase inhibitors (TKI) sorafenib, sunitinib, pazopanib, axitinib, and cabozantinib; the mammalian target of rapamycin inhibitors (mTORi) everolimus and temsirolimus; the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab and programmed death (PD)-1 check-point inhibitor, nivolumab.

Currently, cytoreductive nephrectomy (CN) is considered standard prior to systemic therapy in appropriate patients with mRCC. The combined use of CN and cytokine therapy (referred as CN + targeted therapy henceforth) was well established in the cytokine era. Prospective studies conducted during the cytokine era found that mRCC patients who underwent CN followed by cytokine therapy had 6 months of higher median survival compared to patients

that received cytokine therapy alone. [11-13] However, some studies reported that with the approval of targeted therapies since 2005, utilization of CN among mRCC patients has decreased.[14, 15] This could be due to lack of randomized controlled trials demonstrating the efficacy of the CN + targeted therapy. However, retrospective studies published in the last 4-5 years suggested that CN + targeted therapy resulted in a significantly higher OS compared to patients on targeted therapy alone.[16-18] Nevertheless, the appropriate sequence of therapy remains to be determined.

Several studies have been conducted among patients who initiated targeted therapies. However, little is known about the prevalence and predictors of targeted therapy used alone or in combination with CN among older patients that have reached the metastatic stage at the time of incident RCC diagnosis. Previous studies conducted among younger populations suggested that about 25-40% of mRCC patients did not receive targeted therapy.[19, 20] This percentage could be much higher among older adults due to the presence of comorbid conditions and frailty. These factors could also affect survival outcomes among older patients. Further, none of the studies compared healthcare cost between patients receiving targeted therapy alone versus CN + targeted therapy. Medicare is the single largest payer for RCC patients, covering about 46% of all RCC patients.[1, 21] Targeted therapies cost from US $6,000 to $15,000 per month.[22] In addition, CN and post-surgical care may increase the overall healthcare cost among patients that received CN + targeted therapy. However, patients undergoing CN may incur lower healthcare cost due to having a several month gaps in targeted therapy treatment after surgery.

The first aim of this study was to examine the prevalence and predictors of targeted therapy and CN use among older adults with mRCC. The study also described characteristics of patients that used CN alone, targeted therapy alone and patients that did not receive either CN or targeted therapy (referred to as any active treatment henceforth). The second aim of the study was to

compare OS and disease-specific survival (DSS) among patients that received targeted therapy alone versus CN + targeted therapy. The study hypothesized that patients that used CN + targeted therapy compared to targeted therapy alone would have longer OS and DSS. The third aim of the study was to compare healthcare cost between patients that received targeted therapy alone versus CN + targeted therapy. We hypothesized that patients that received CN + targeted therapy would incur higher healthcare cost than targeted therapy alone.

METHODS

Data Source[23]

SEER-Medicare

The Surveillance Epidemiology and End Result (SEER) program, initiated by the National Cancer Institute (NCI), collects information on cancer statistics in an effort to reduce the cancer burden among the U.S population.[23] The information collected by this population-based cancer registry includes demographics, incident cancer diagnosis, cause of death, cancer stage, tumor characteristics, and surgery and radiation therapy provided during the first course of treatment. As of 2017, SEER registries covered 28% of the U.S population.[24] Medicare data provides information on hospital (Part A), outpatient (Part B) and prescription drug (Part D) claims for Medicare beneficiaries. SEER-Medicare links SEER and Medicare data and is an excellent source to conduct population-based health services research on cancer patients in the U.S.

We used 2007-2014 SEER-Medicare data. The Patient Entitlement and Diagnosis Summary File was used to obtain demographics and cancer diagnosis-related information. Resource use and cost-related information were obtained from Medicare Provider Analysis and Review (MEDPAR), outpatient, carrier, Part D event (PDE), home health agencies (HHA), hospice (HS) and durable medical equipment (DME) files. The MEDPAR file was used to obtain

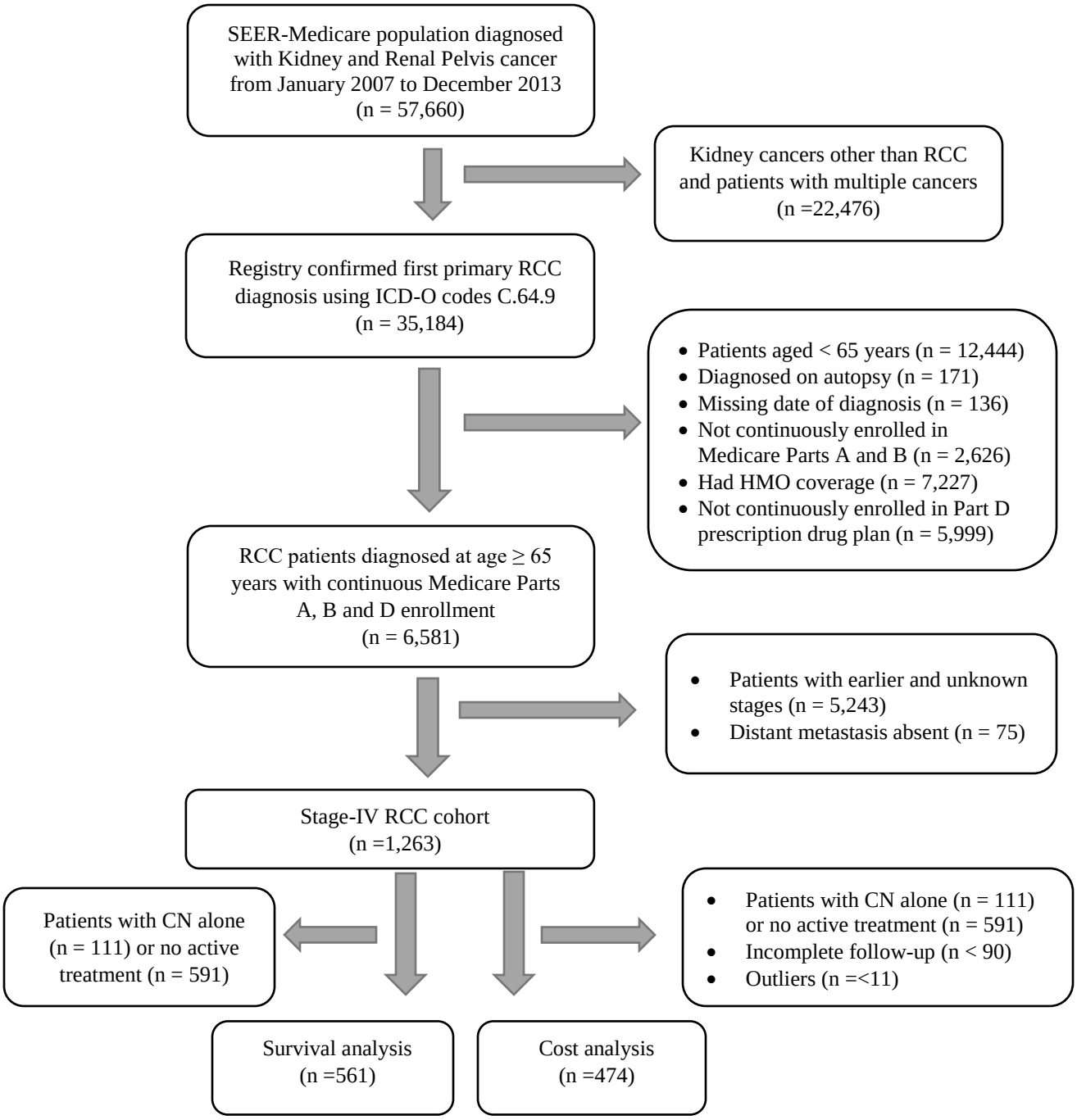
inpatient hospital and skilled nursing facility (SNF) claims. The HS file provided data on hospice care utilization. The carrier file provided information on non-institutional physician-provided services whereas the outpatient file provided information on institutional physician-provided services. The PDE file provided data related to prescription medication use (Medicare Part D). DME files provided data on the use of durable medical equipment while HHA files were used to get information on services provided in patients' homes.

Study Design and Sample Selection

This was a retrospective cohort study. The study first identified patients with diagnosis of RCC using the International Classification of Diseases for Oncology, 3rd edition code C649 and relevant histology types ('8260', '8310', '8312', '8316', '8317', '8318'). The criteria developed by the American Joint Committee on Cancer (AJCC) - 6th edition, was used to identify Stage-IV patients. Further, we limited our sample to stage-IV patients with confirmed distant metastasis (M1 status). We excluded patients aged < 65 years, diagnosed with another cancer at the time of RCC diagnosis, diagnosed on autopsy, with cancer reported by death certificate, or enrolled in health maintenance organization (HMO) plans. Figure 1 depicts the sample selection process in detail. Baseline characteristics were identified from the year prior to mRCC diagnosis.

For OS we followed patients from diagnosis until death or until the end of December 2015. For DSS, the study period ended on December 31, 2014 because information on RCC-specific death was only available until the end of 2014. For cost comparisons, we assessed lifetime cost defined as costs incurred from the first use of CN or targeted therapy (index date) until death. Approximately 86% of the sample had a complete follow-up. We excluded patients that did not have a complete follow-up from the cost analysis.

Figure 3.1 Sample selection process for this study.



Study Measures

The study first compared predictors of any active treatment (CN or targeted therapy) versus no active treatment. Then, among patients that received active treatment, we assessed predictors of CN alone and CN + targeted therapy compared to targeted therapy alone as a reference group. Comparisons for survival and costs were conducted between targeted therapy alone and CN + targeted therapy groups. Patients that received CN alone or did not receive active treatment were excluded from the survival and cost comparisons.

Targeted therapy / Cytoreductive Nephrectomy

Oral targeted therapies were identified using generic names and National Drug Codes (NDCs) from Medicare Part D while injectable-targeted therapies were identified using healthcare procedural codes (HCPC) from Medicare Part B data. Information related to partial or radical nephrectomy was obtained from a combination of SEER registry codes, the Current Procedural Terminology (CPT) codes from outpatient and carrier files, and ICD9- CM procedure codes from inpatient hospital files. The date of first targeted therapy or CN use after mRCC diagnosis was considered as the index date. The codes used to identify targeted therapies and CN can be found in the Appendix.

Overall survival /disease-specific survival

The study defined overall survival as the time in months from the date of diagnosis until the date of death or until the end of 2015. Both OS and DSS were calculated. Cause of death information from registry data (PEDSF file) was used to identify RCC specific death to calculate DSS. Patients that were alive beyond the end of December 2014 were censored.

Healthcare costs

Costs were the amounts reimbursed by Medicare for each claim related to health services utilized by mRCC patients from index date until death. Costs were reported as monthly costs. Total healthcare cost was further categorized into prescription drug cost and medical cost.

Other variables

These variables included patient's sociodemographics, tumor characteristics, site of metastasis, histology, claims-based performance status and NCI comorbidity index score. Information on these variables was obtained in the year prior to mRCC diagnosis.

Statistical Analysis

The study first compared characteristics across treatment modalities using Chi-square test for categorical variables and ANOVA for continuous variables. Multivariable (binary) logistic regression assessed predictors of active treatment. Among patients who received active treatment, multinomial logistic regression was used to assess predictors of CN + targeted therapy and CN alone compared to targeted therapy alone. The Andersen Behavior Model (ABM) was used to guide the selection of variables (see Figure 2). As per the ABM, factors associated with choice of treatment can be characterized into 'predisposing' (e.g. age, sex, race), 'enabling' (e.g., education and income measured at the zip code level), and 'need' (e.g. tumor characteristics, histology, NCI comorbidity score) factors.[25, 26]

A Kaplan Meier curve and log-rank test compared the unadjusted median OS and DSS for targeted therapy alone versus CN + targeted therapy groups. To reduce selection bias, we calculated propensity score-based inverse probability of treatment weights (IPTW). In the first step, we calculated the propensity (probability) of a patient receiving CN + targeted therapy versus targeted therapy alone. In the second step, individuals were weighted by the inverse probability of receiving the treatment that they actually received. To reduce the bias resulting from extreme

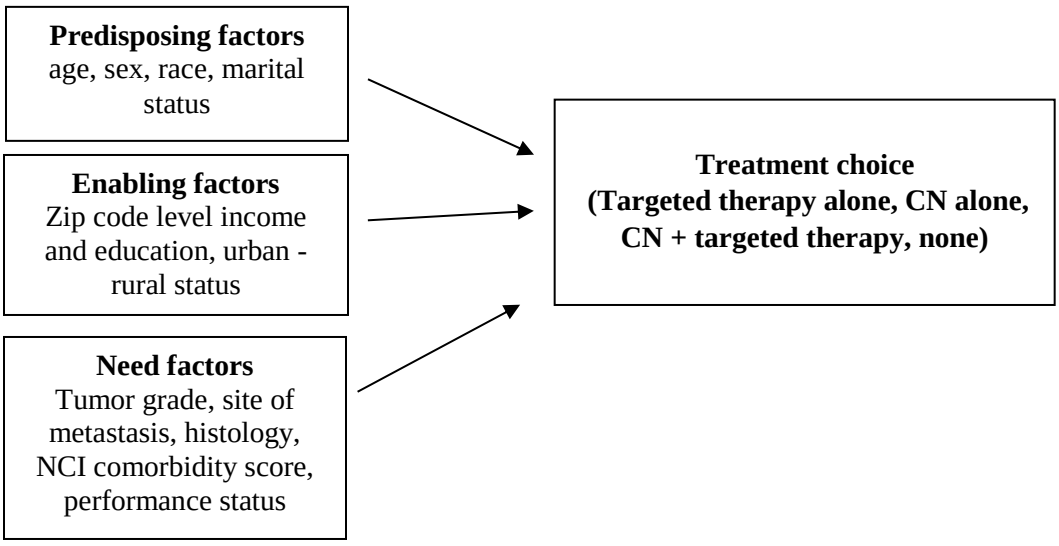
weights or propensity scores, stabilized weights were calculated using a technique described by Robins et al (2000) and Austin et al. (2009).[27, 28] Stabilized weights were then used in a Cox proportional hazard model to calculate the risk of death between the two groups. Survival probabilities from the Cox proportional hazard model were used to describe adjusted survival curves and median survival for both the groups.

Similar to survival outcomes, costs were compared using stabilized IPTWs. Due to the skewed nature of cost data, generalized linear models (GLMs) with log link and gamma distribution was chosen based on results from Modified Park tests, Pearson correlation tests, Pregibon link tests, and modified Hosmer and Lemeshow tests. All costs were inflated to 2016 USD using the Consumer Price Index for medical care services and medical care commodities.[29] All statistical analyses were conducted at an alpha level of 0.05 using SAS v.9.4 (SAS Institute Inc., Cary, NC), and STATA (version 13.0, StataCorp, College Station, TX).

Additional Analyses

Some mRCC patients may receive delayed treatment or may not require immediate treatment with CN or targeted therapy after being diagnosed with mRCC. This may affect the comparison of OS and DSS in the study because survival was measured from the date of diagnosis and not from the date of treatment initiation. To understand the effect of the definition of the follow-up period, we measured survival as the time from treatment initiation until death or until the end of the study period. In addition, we used multivariable regression methods instead of propensity score-based IPTW to compare survival outcomes and healthcare costs between patients who received targeted therapy alone and CN + targeted therapy.

Figure 3.2 Conceptual framework adapted from the Anderson Behavioral Model to predict the choice of treatment.



RESULTS

Prevalence of Treatment Modalities

The final study sample included 1,263 patients. Of these, 360 (29%) patients received targeted therapy alone, 201 (16%) received CN+ targeted therapy, 111 (9%) patients received CN alone and 591 (47%) patients did not receive CN or targeted therapy. Characteristics of patients across treatment modalities are presented in Table 3.1

Predictors of receiving CN or targeted therapy versus none

Multivariable binary logistic regression analysis found that patients who were aged > 80 years at the time of diagnosis, had NCI comorbidity score of 3 or more, had unknown tumor grade, had liver or brain metastasis, and used home health service before diagnosis were significantly ($p < 0.05$) less likely to receive CN or targeted therapy. Patients who were married, were diagnosed between 2010-2013, and had higher tumor involvement and a higher number of ED visits before diagnosis were significantly ($p < 0.05$) more likely to receive CN or targeted therapy. Gender, race, SEER region, urban/rural status, tumor size, the extent of lymph node involvement, lung or bone metastasis, baseline physician visits or DME use were not significant predictors of receiving CN or/targeted therapy (Table 3.2).

Table 3.1 Characteristics of mRCC patients by treatment group in study 2

Characteristic	Targeted therapy alone (n = 360) n, %	CN alone (n = 111) n, %	CN + targeted therapy (n= 201) n, %	None (n = 591) n, %
Age at diagnosis (years) +				
- 65-69	93 (26)	30 (27)	77 (38)	93 (16)
- 70-75	121 (34)	34 (31)	69 (34)	122 (21)
- 76-80	89 (25)	34 (31)	44 (22)	130 (22)
- More than 80	57 (16)	13 (12)	11 (6)	246 (42)
Sex +				
- Male	209 (58)	60 (54)	127 (63)	294 (50)
- Female	151 (42)	51 (46)	74 (37)	297 (50)
Race/Ethnicity +				
- White	304 (84)	>95 (>89)	178 (89)	500 (85)
- Black /others	56 (16)	<11 (<10)	23 (11)	91 (15)
Marital status +				
- Married	186 (52)	65 (59)	130 (65)	229 (39)
- Single/Divorced/Separated	174 (48)	46 (41)	71 (35)	362 (61)
Zip code- college educated +				
- 0 to 15%	105 (29)	30 (27)	42 (21)	189 (32)
- 16-20%	66 (18)	23 (21)	28 (14)	100 (17)
- 21-30%	75 (21)	27 (24)	46 (23)	131 (22)
- 31% and above	114 (32)	31 (28)	85 (42)	171 (29)
Zip code level median household income (USD) +				
- < 40k	90 (25)	20 (18)	34 (17)	157 (26)
- 40k - 50 k	85 (24)	30 (27)	38 (19)	147 (25)
- 51k - 70k	98 (27)	35 (32)	65 (32)	160 (27)
- > 70 k	87 (24)	26 (23)	64 (32)	127 (22)
Urban/Rural Status				
- Big Metro	62 (17)	18 (16)	19 (10)	87 (15)
- Metro /Urban	158 (44)	51 (46)	104 (52)	282 (48)
- Less urban / Rural	140 (39)	42 (38)	78 (39)	222 (38)
SEER region				
- Northeast	55 (15)	24 (22)	38 (19)	101 (17)
- South	94 (26)	28 (25)	60 (30)	167 (28)
- North Central	47 (13)	16 (14)	20 (10)	85 (14)
- West	164 (46)	43 (39)	83 (41)	238 (40)
Year of diagnosis +				
- 2007 to 2009	125 (35)	47 (42)	64 (40)	272 (46)
- 2010 to 2013	235 (65)	64 (58)	100 (60)	319 (54)
NCI comorbidity index score +				
- 0	136 (38)	55 (50)	89 (45)	196 (33)
- 1	106 (29)	26 (23)	67 (33)	138 (23)
- 2	43 (12)	18 (16)	22 (11)	86 (15)
- 3 or more	75 (21)	12 (11)	23 (11)	171 (29)

+ Statistically significant differences based on chi-square test / ANOVA, $p < 0.05$

Table 3.1 Continued

Characteristic	Targeted therapy alone (n = 360) n, %	CN alone (n = 111) n, %	CN + targeted therapy (n = 201) n, %	None (n = 591) n, %
NCI comorbidity index score [+] (mean, standard deviation)	1.3 (1.5)	0.9 (1.2)	1.0 (1.2)	1.8 (2.0)
Tumor size [+]				
- Unknown / < 5 cm	66 (23)	21 (19)	22 (12)	129 (29)
- 5 to 7.9 cm	88 (31)	34 (30)	56 (29)	149 (33)
- ≥ 8 cm	134 (47)	55 (50)	114 (59)	173 (38)
Tumor grade [+]				
- Well/ moderate	42 (11)	23 (21)	44 (21)	21 (4)
- Poor / undifferentiated	25 (7)	66 (60)	111 (59)	42 (7)
- Unknown	293 (82)	22 (20)	46 (20)	528 (89)
Tumor extent (T) - TNM [+]				
- T0 / T1/ unknown	186 (52)	23 (21)	31 (15)	363 (61)
- T2	59 (16)	14 (13)	32 (16)	78 (13)
- T3	79 (22)	61 (55)	122 (61)	97 (16)
- T4	36 (10)	13 (12)	16 (8)	53 (9)
Lymph Node (N) - TNM [+]				
- N0 /NX	250 (69)	88 (79)	153 (76)	458 (77)
- N1 /N2	110 (31)	23 (21)	48 (24)	133 (23)
Histology				
- Clear cell	333 (93)	94 (85)	174 (87)	547 (93)
- Non-clear cell	27 (7)	17 (15)	27 (13)	44 (7)
Site of metastasis				
- Bone (yes)	177 (49)	26 (23)	57 (28)	253 (43)
- Lung (yes)	204 (57)	54 (49)	113 (56)	319 (54)
- Liver (yes)	74 (21)	22 (16)	18 (10)	145 (25)
- Brain (yes)	51 (14)	13 (12)	17 (9)	96 (16)
Performance status indicators				
Average number of services (mean, standard deviation)				
- ED visits [+]	4.0 (3.3)	4.0 (3.7)	4.2 (3.7)	2.9 (2.7)
- hospital days[+]	0.5 (1.8)	1.7 (9.2)	0.7 (2.4)	1.6 (6.4)
- SNF days[+]	1.0 (8.5)	2.5 (16.5)	0 (0)	4.2 (17.0)
- physician claims [+]	31.0 (24.9)	29.9 (25.4)	30.4 (25.3)	36.2 (35.3)
- home health claims[+]	0.2 (0.7)	0.1 (0.5)	0.0 (0.3)	0.4 (1.0)
DME use (%) [+]	140 (39)	39 (35)	59 (29)	249 (42)
Assisting devices (%) [+]	76 (21)	14 (13)	20 (10)	130 (22)

+ Statistically significant differences based on chi-square test / ANOVA, $p < 0.05$

TNM: A staging system based on the extent of the tumor (T), the extent of spread to the lymph nodes (N), and the presence of metastasis (M).

Table 3.2 Multivariable logistic regression assessing predictors of CN or targeted therapy (any treatment) versus no treatment among mRCC patients.

Characteristic	Odds Ratio (CN/ targeted therapy vs None)	95% CI	p-value
Age at diagnosis (years)			
- 65-69	Reference		
- 70-75	0.98	0.66 - 1.46	<0.0001
- 76-80	0.78	0.52 - 1.18	
- More than 80	**0.25**	**0.16 - 0.38**	
Sex			
- Female	Reference		0.8079
- Male	1.04	0.77 - 1.41	
Race/Ethnicity			
- Black /others	Reference		
- White	0.96	0.64 - 1.43	0.8211
Marital status			
- Single/Divorced/Separated	Reference		
- Married	**1.80**	**1.33 - 2.42**	**0.0001**
Zip code- college educated			
- 0 to 15%	Reference		
- 16-20%	**1.61**	**1.02 - 2.51**	**0.0390**
- 21-30%	1.57	0.99 - 2.47	0.0532
- 31% and above	1.48	0.88 - 2.49	0.1385
Zip code level median household income (USD)			
- < 40k	Reference		
- 40k - 50 k	0.78	0.50 - 1.21	0.2611
- 51k - 70k	0.88	0.55 - 1.41	0.5938
- > 70 k	1.01	0.56 - 1.84	0.9645
Urban/Rural Status			
- Less urban / Rural	Reference		
- Metro /Urban	0.81	0.49 - 1.33	0.3974
- Big Metro	0.80	0.50 - 1.27	0.3377
SEER region			
- Northeast	Reference		
- South	1.00	0.62 - 1.64	0.9720
- North Central	0.74	0.43 - 1.29	0.2852
- West	1.00	0.67 - 1.51	0.9728
Year of diagnosis [+]			
- 2007 to 2009	Reference		
- 2010 to 2013	**1.66**	**1.24 - 2.24**	**0.0008**
NCI comorbidity index score [+]			
- 0	Reference		
- 1	1.11	0.77 - 1.61	0.5666
- 2	1.30	0.50 - 1.24	0.2971
- 3 or more	**0.55**	**0.34 - 0.88**	**0.0124**

Note: p-value < 0.05 indicates statistically significant association

Table 3.2 (continued)

Characteristic	Odds Ratio (CN / targeted therapy vs None)	95% CI	p-value
Tumor size			
- Unknown / < 5 cm	Reference		
- 5 to 7.9 cm	1.12	0.77 - 1.61	0.5619
- ≥ 8 cm	1.30	0.86 - 1.96	0.2078
Tumor grade			
- Well/ moderate	Reference		
- Poor / undifferentiated	0.66	0.34 - 1.28	0.2134
- Unknown	**0.15**	**0.08 - 0.26**	**<0.0001**
Tumor extent (T) - TNM [+]			
- T0 / T1/ unknown	Reference		
- T2	1.37	0.84 - 2.21	0.2043
- T3	**2.30**	**1.55 - 3.40**	**<0.0001**
- T4	1.56	0.93 - 2.62	0.0928
Lymph Node (N) - TNM			
- N0 /NX	Reference		
- N1 /N2	0.95	0.68 - 1.31	0.7464
Histology			
- Non-clear cell	Reference		
- Clear cell	1.06	0.64 - 1.73	0.8288
Bone metastasis			
- Absent	Reference		
- Present	1.00	0.75 - 1.36	0.9641
Lung metastasis			
- Absent	Reference		
- Present	0.76	0.57 - 1.02	0.0673
Liver metastasis			
- Absent	Reference		
- Present	**0.59**	**0.42 - 0.83**	**0.0023**
Brain metastasis			
- Absent	Reference		
- Present	**0.48**	**0.32 - 0.72**	**0.0004**
Performance status indicators			
Average number of services			
- ED visits	**1.24**	**1.17 - 1.31**	**<0.0001**
- hospital days	**0.97**	**0.94 - 0.99**	**0.0273**
- SNF days	0.99	0.98 - 1.00	0.2474
- physician claims	1.00	0.99 - 1.01	0.1889
- home health claims	**0.75**	**0.60 - 0.93**	**0.0102**
DME use (Yes vs No)	0.96	0.65 - 1.42	0.8436
Assisting devices (Yes vs No)	1.10	0.70 - 1.73	0.6881

Note: p-value < 0.05 indicates statistically significant association
TNM: A staging system based on the extent of the tumor (T), the extent of spread to the lymph nodes (N), and the presence of metastasis (M).

Predictors of receiving CN+ targeted therapy versus targeted therapy alone.

Multinomial logistic regression analysis found that patients who were > 80 years old at the time of diagnosis, lived in North Central or West regions, had higher lymph node involvement, had bone or liver metastasis, had unknown tumor grade were significantly ($p < 0.05$) less likely to receive CN + targeted therapy compared to targeted therapy alone. Patients who lived in urban areas, had higher extent of tumor involvement, had poorly differentiated tumor grade, had a higher number of ED visits before cancer diagnosis were significantly ($p < 0.05$) more likely to receive CN+ targeted therapy versus targeted therapy alone.

Predictors of receiving CN alone versus targeted therapy alone.

Multinomial logistic regression analysis found that patients who had NCI comorbidity score of 3 or more, lived in South, North Central or West regions, had higher lymph node involvement, had bone or lung metastasis, had unknown tumor grade were significantly ($p < 0.05$) less likely to receive CN alone compared to targeted therapy alone. Patients who had greater extent of tumor involvement, poorly differentiated tumor grade, and more hospital stays before cancer diagnosis were significantly ($p < 0.05$) more likely to receive CN alone compared to targeted therapy alone. (Table 3.2)

Table 3.3 Multinomial logistic regression assessing predictors of CN + targeted therapy and CN alone versus targeted therapy alone among older mRCC patients.

Characteristic	CN alone (N = 111) vs targeted therapy alone (N = 360)		CN + targeted therapy (N = 201) vs targeted therapy alone (n = 360)	
	Odds Ratio	**95% CI**	**Odds Ratio**	**95% CI**
Age at diagnosis (years)				
- 65-69	Reference		Reference	
- 70-75	0.94	0.45 - 1.96	0.73	0.40 - 1.35
- 76-80	1.24	0.57 - 2.68	0.60	0.31 - 1.17
- More than 80	0.74	0.27 - 2.02	**0.24**	**0.09 - 0.61**
Sex				
- Female	Reference		Reference	
- Male	0.92	0.49 - 1.74	1.26	0.72 - 2.21
Race/Ethnicity				
- Black /others	Reference		Reference	
- White	1.89	0.74 - 4.80	1.39	0.64 - 3.04
Marital status				
- Single/Divorced/Separated	Reference		Reference	
- Married	1.12	0.59 - 2.11	1.31	0.76 - 2.27
Zip code- college educated				
- 0 to 15%	Reference		Reference	
- 16-20%	0.81	0.33 - 1.98	0.95	0.41 - 2.17
- 21-30%	1.06	0.43 - 2.65	1.53	0.67 - 3.49
- 31% and above	0.48	0.16 - 1.42	1.53	0.60 - 3.87
Zip code level median household income (USD)				
- < 40k	Reference		Reference	
- 40k - 50 k	1.51	0.59 - 3.85	0.88	0.39 - 2.02
- 51k - 70k	1.81	0.66 - 4.92	1.13	0.47 - 2.70
- > 70 k	1.49	0.41 - 5.47	0.71	0.24 - 2.12
Urban/Rural Status				
- Less urban / Rural	Reference		Reference	
- Metro /Urban	1.41	0.53 - 3.76	**3.62**	**1.45 - 9.06**
- Big Metro	0.99	0.40 - 2.41	1.94	0.84 - 4.48
SEER region				
- Northeast	Reference		Reference	
- South	**0.37**	**0.14 - 0.98**	0.98	0.43 - 2.24
- North Central	**0.19**	**0.06 - 0.61**	**0.30**	**0.10 - 0.86**
- West	**0.24**	**0.10 - 0.54**	**0.41**	**0.21 - 0.84**
Year of diagnosis				
- 2007 to 2009	Reference		Reference	
- 2010 to 2013	1.31	0.70 - 2.42	1.29	0.75 - 2.21
NCI comorbidity index score				
- 0	Reference		Reference	
- 1	0.54	0.26 - 1.14	0.99	0.54 - 1.83
- 2	1.10	0.45 - 2.70	0.74	0.32 - 1.71
- 3 or more	**0.20**	**0.07- 0.61**	0.40	0.16 - 1.00

Notes: Values in bold indicate a statistically significant association

Table 3.3 (continued)

Characteristic	CN alone (N = 111) vs targeted therapy alone (N = 360)		CN + targeted therapy (N = 201) vs targeted therapy alone (360)	
	Odds Ratio	**95% CI**	**Odds Ratio**	**95% CI**
Tumor size				
- Unknown / < 5 cm	Reference		Reference	
- 5 to 7.9 cm	1.42	0.62 - 3.19	1.35	0.66 - 2.76
- ≥ 8 cm	1.28	0.54 - 3.02	1.42	0.67 - 2.99
Tumor grade				
- Well/ moderate	Reference		Reference	
- Poor / undifferentiated	**6.36**	**2.71 - 14.88**	**4.63**	**2.15 - 9.98**
- Unknown	**0.16**	**0.07 - 0.35**	**0.16**	**0.08 - 0.30**
Tumor extent (T) - TNM				
- T0 / T1/ unknown	Reference		Reference	
- T2	2.13	0.78 - 5.81	2.13	0.92 - 4.91
- T3	**5.56**	**2.46 - 12.57**	**6.17**	**3.06 - 12.43**
- T4	2.48	0.82 - 7.55	1.72	0.61 - 4.82
Lymph Node (N) - TNM				
- N0 /NX	Reference		Reference	
- N1 /N2	**0.17**	**0.08 - 0.36**	**0.26**	**0.14 - 0.49**
Histology				
- Non-clear cell	Reference		Reference	
- Clear cell	2.58	0.98 - 6.74	2.21	0.93 - 5.27
Bone metastasis				
- Absent	Reference		Reference	
- Present	**0.30**	**0.16 - 0.56**	**0.45**	**0.26 - 0.78**
Lung metastasis				
- Absent	Reference		Reference	
- Present	**0.49**	**0.27 - 0.90**	0.77	0.46 - 1.31
Liver metastasis				
- Absent	Reference		Reference	
- Present	0.93	0.45 - 1.95	**0.48**	**0.24 - 0.95**
Brain metastasis				
- Absent	Reference		Reference	
- Present	0.97	0.39 - 2.42	0.52	0.23 - 1.21
Performance status indicators*				
Average number of services				
- ED visits	1.08	0.98 - 1.17	**1.10**	**1.02 - 1.19**
- hospital days	**1.14**	**1.01 - 1.28**	1.07	0.95 - 1.20
- physician claims	1.00	0.98 - 1.01	1.00	0.99 - 1.02
- home health claims	1.37	0.85 - 2.20	0.43	0.17 - 1.10
DME use (Yes vs No)	1.27	0.57 - 2.84	0.84	0.41 - 1.72
Assisting devices (Yes vs No)	0.72	0.26 - 1.97	0.70	0.28 - 1.77

Notes: Values in bold indicate statistically significant association; * SNF use was excluded due to small sample size
TNM: A staging system based on the extent of the tumor (T), the extent of spread to the lymph nodes (N), and the presence of metastasis (M).

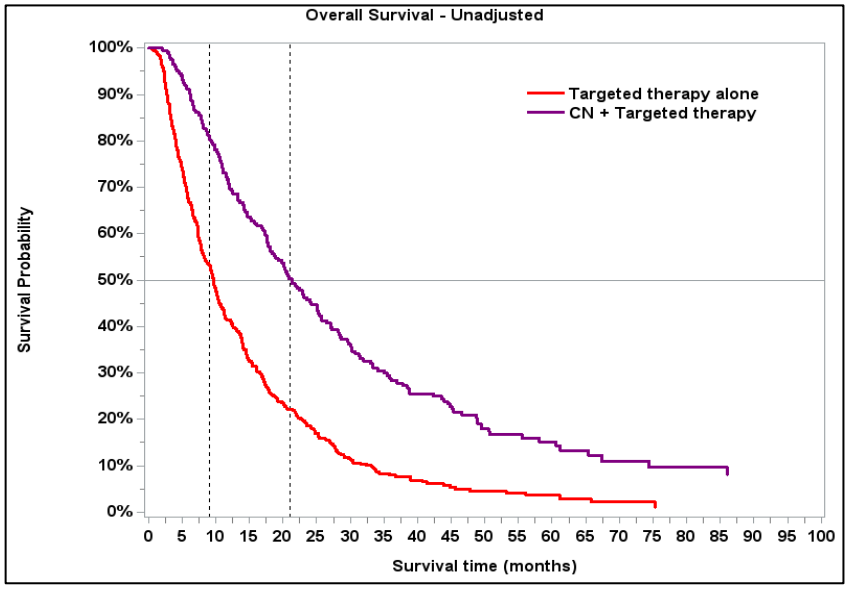
Overall Survival and Disease-Specific Survival between CN + Targeted therapy versus Targeted therapy Alone.

Unadjusted Kaplan Meier analysis found that the median OS for CN+ targeted therapy group was significantly higher than for the targeted therapy alone group (21 months vs 10 months, p <0.0001). Similarly, CN + targeted therapy group had significantly higher DSS than the targeted therapy alone group (20 months vs 10 months, p <0.0001). Kaplan Meier curves for the OS and DSS are displayed in Figure 3.2

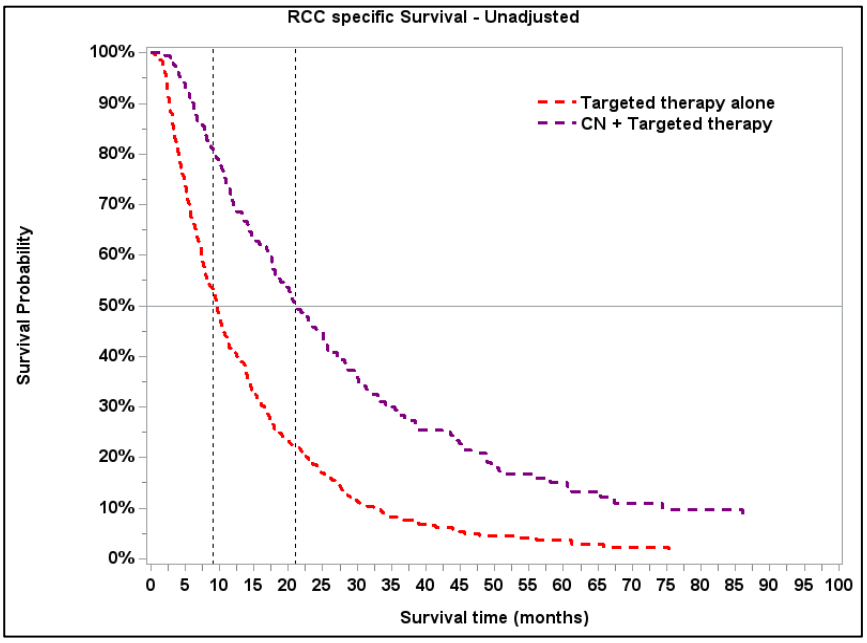
A Cox proportional hazard model after IPTW found that compared to patients that received targeted therapy alone, CN+ targeted therapy group had 0.59 times lower risk for death (HR = 0.59, 95% CI: 0.56 - 0.62; p <0.0001) due to any reason (OS). Similarly, CN + targeted therapy group had 0.63 times lower risk for RCC-related death (DSS) (HR = 0.63, 95%CI: 0.60 - 0.67; p <0.0001) compared to CN + targeted therapy group. Additionally, we used survival probabilities from the Cox proportional model to describe adjusted survival curves for OS and DSS (Figure 3). Adjusted survival curves indicated that the median OS and DSS were 5 months higher for CN+ targeted therapy group (15 months) compared to targeted therapy alone (10 months).

Figure 3.3 Kaplan Meier Survival curves comparing overall survival and disease-specific survival between CN+ targeted therapy and targeted therapy alone groups.

a. Overall survival



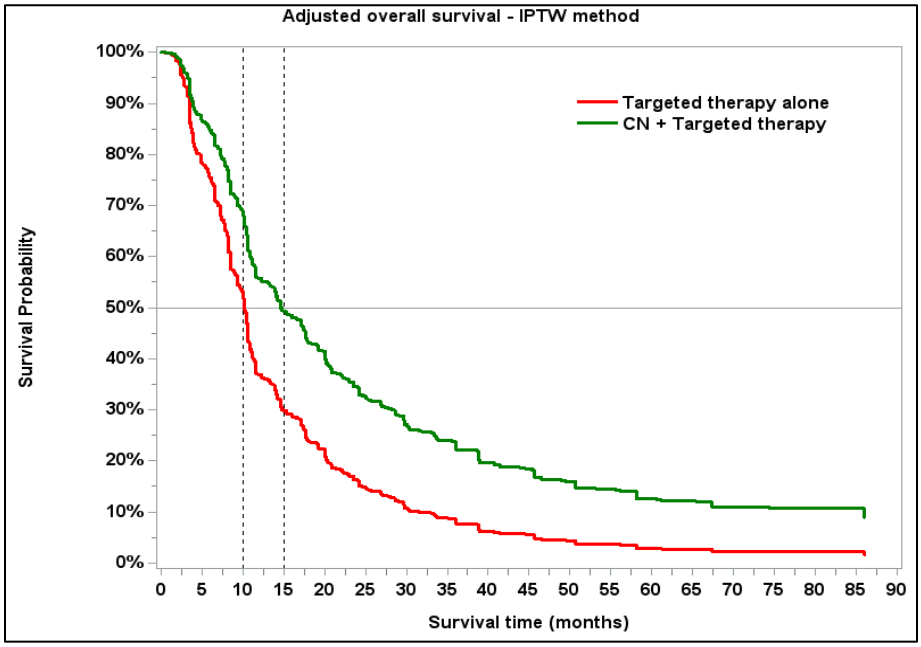
b. Disease specific survival



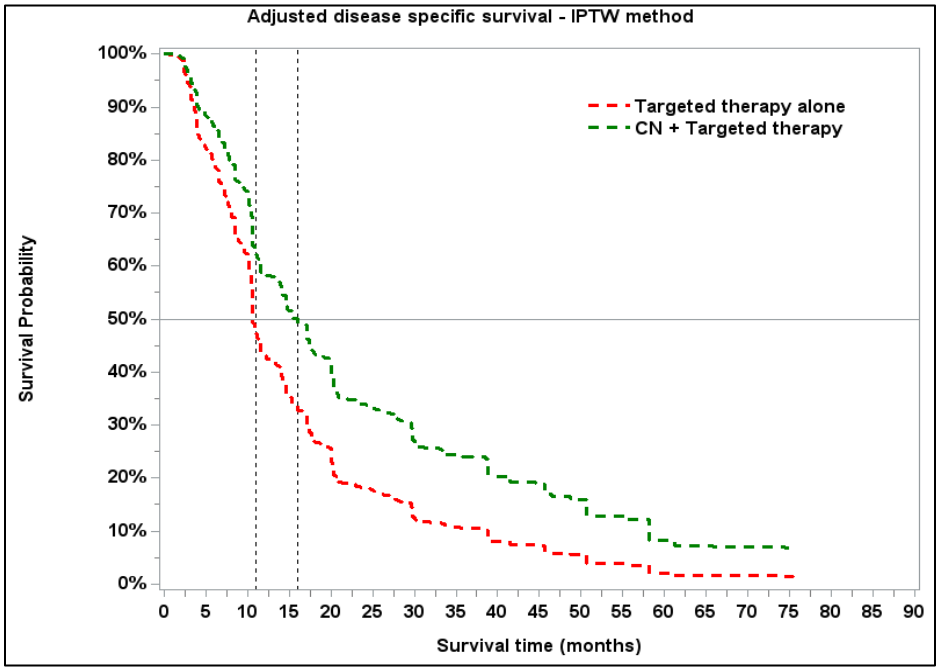
NOTE: Statistically significant difference for OS and DSS; p-value < .0001

Figure 3.4 Adjusted overall survival and disease-specific survival between CN + targeted therapy and targeted therapy alone groups.

a) Overall survival



b) Disease-specific survival



NOTE: Statistically significant difference for OS and DSS; p-value <0.0001

Healthcare Cost between CN + Targeted therapy vs Targeted therapy Alone.

Unadjusted average (monthly) total healthcare cost, medical cost and prescription drug cost are described in Table 3.4 There was no statistically significant difference in the total healthcare cost and medical cost between CN + targeted therapy and targeted therapy alone groups. However, prescription drug costs were significantly higher ($p<0.05$) for the targeted therapy alone group ($5,701) compared to CN + targeted therapy group ($2,692).

Generalized linear models using the log link and gamma distribution (after propensity score based IPTW) indicated that the total healthcare cost was similar ($p = 0.4389$) for the targeted therapy alone group ($ 18,120) compared to CN + targeted therapy group ($ 17,159). The medical cost was significantly higher for CN + targeted therapy group ($ 14,197) compared to targeted therapy alone group ($ 10,607); whereas prescription drug cost ($ 7,573) was significantly higher for the targeted therapy alone group compared to CN + targeted therapy group ($ 2,962).

Table 3.4 Unadjusted comparison of total healthcare costs, medical costs and prescription drug costs between CN+ targeted therapy and Targeted therapy alone groups.

	CN + targeted therapy (n = 154)		Targeted therapy alone (n = 326)	
Monthly Costs	**Mean (US $)**	**Median (US $)**	**Mean (US $)**	**Median (US $)**
Total healthcare costs	14,005	11,551	17,012	12,596
Medical costs	10,925	7,784	11,310	7,737
Prescription drug costs	3,081	2,692	5,701	* 4,751

* Significantly higher cost ($p <0.05$) based on Wilcoxon Mann Whitney test

Table 3.5. Generalized linear model (including IPTWs) assessing total healthcare costs, medical costs and prescription drug costs between CN+ targeted therapy and targeted therapy alone groups.

Average costs per month	CN + targeted therapy (n = 154) Mean (95%CI)	Targeted therapy alone (n = 326) Mean (95%CI)	p-value
Total healthcare costs	17,159 (15,294 - 19,252)	18,120 (16,791 - 19,554)	0.4389
Medical costs	14,197 (12,385 - 16,275)	10,607 (9,689 - 11,612)	0.0005
Prescription drug costs	2,962 (2,482 - 3,535)	7,573 (6,735 - 8,516)	<0.0001

Note: Covariates were included in the propensity score model to calculate IPTWs. The generalized linear model was run after IPTW to get cost estimates.

Additional Analysis

First, we assessed sociodemographic and clinical predictors of targeted therapy use among mRCC patients. Details about the predictors of targeted therapy use are described in Appendix 3.7 Patients that were younger at the time of diagnosis, married, and diagnosed in the late targeted therapy era had higher odds for receiving targeted therapies. As the NCI comorbidity score increased the odds for patients receiving targeted therapy decreased. Further, presence of liver or brain metastasis, and poor or unknown tumor grade decreased the odds for receiving targeted therapies. Odds for receiving targeted therapies also decreased with an increase in the average number of hospital stays and home health visits. Second, we assessed the overall survival between mRCC patients who received targeted therapies and patients who did not. These results can be found in Appendix 3.8. Adjusted survival curves suggested that median OS was 9 months for targeted therapy users and 4 months for patients that did not receive targeted therapies. A Cox proportional hazard model (after IPTW) found that patients who received targeted therapies had 0.57 times risk of death compared to patients who did not receive targeted therapy (HR = 0.57, 95%CI: 0.51 - 0.64, $p < 0.0001$).

Third, for the survival analysis that compared CN + targeted therapy and targeted therapy alone groups, we considered survival as the time from treatment initiation (either CN or targeted therapy) to death or end of 2014. The adjusted OS and DSS curves and hazard ratios were similar to our main analysis where survival was measured as a time from diagnosis. Fourth, instead of propensity scoring, we used multivariable Cox proportional hazard models. In the model assessing OS, patients from CN + targeted therapy had 0.37 (95% CI: 0.28 - 0.49) times lower risk of death compared to targeted therapy alone controlling for all other covariates. The risk of death for CN + targeted therapy was much lower in the regression model as compared to propensity score-based method, which suggested that our findings based on propensity score-based IPTW method were more conservative than the regression approach. Fifth, similar to survival outcomes, for the cost analysis, we conducted multivariable regression analysis instead of propensity score-based IPTW. Costs from the multivariable GLM indicated higher total healthcare cost for the targeted therapy alone group, most of which, was driven by higher prescription drug costs as medical costs were similar between the groups.

Discussion

This study analyzed SEER-Medicare data to compare survival and healthcare costs among mRCC patients diagnosed at age 65 and older, who received CN and targeted therapy versus targeted therapy alone. We also assessed the prevalence and predictors of targeted therapy and/or CN use in this population. Among newly diagnosed mRCC patients, only 44% received targeted therapy and 25% received CN. About 47% did not receive either targeted therapy or CN, which are considered as primary treatments for mRCC. Patients who received CN and targeted therapy had higher OS and DSS compared to patients who received targeted therapy alone. Average

monthly total healthcare costs were similar for patients who received CN and targeted therapy versus targeted therapy alone.

The prevalence of targeted therapy recipients in our study (44%) was much lower than an estimate of 60-70% reported by studies conducted among younger populations.[19, 20] Similarly, the prevalence of any active treatment (53%) in our study was also much lower than the prevalence (70%) reported in previous studies. However, it was higher than the estimate from a study conducted among older Medicare patients in the cytokine era, in which only 30% patients received either CN or cytokine therapy.[30] Additionally, patients diagnosed in the later part of targeted therapy era (2010-2013) were more likely to receive active treatment. This suggested that a higher number of older mRCC patients received active treatment in the targeted therapy era, probably because more targeted therapies became available. This trend was consistent with the findings from Banegas et al.[19] Patients aged ≥ 80 years at the time of diagnosis and who were single/ unmarried/ divorced were less likely to receive CN or targeted therapy. These findings were consistent with previous studies.[19, 30]. However, in contrast to Saigal et al.[30] we did not find any racial/ethnic disparity in our study. Clinical factors - unknown tumor grade, NCI comorbidity index score of ≥ 3, presence of liver/ brain metastasis, hospital stays and home health service use in the year prior to diagnosis were associated with not receiving active treatment. This suggested that patients who had higher comorbidities or poor health status at the time of diagnosis were not good candidates to receive active treatment; possibly because the risks associated with active treatment might outweigh their benefits.

Among patients that received active treatment, we assessed predictors of receiving CN + targeted therapy compared to patients that received targeted therapy alone. Results from the multivariable model indicated that patients with advanced age at the time of cancer diagnosis,

comorbidities, metastases to liver/ bone/ brain, and higher lymph node involvement were less likely to receive CN + targeted therapy compared to targeted therapy alone. Poor/undifferentiated tumor grade or T3 stage was associated with higher odds to receive CN. These findings were consistent with findings from Hanna et al.[17] In addition, we observed a geographical discrepancy in the use of CN such that patients from rural areas (compared to urban) or living in North Central and West regions (compared to Northeast region) were less likely to receive CN with or without targeted therapy. Future studies could further investigate reasons for geographical disparity for CN use among mRCC patients.

Findings from the adjusted survival analysis suggested that the use of CN among targeted therapy users was associated with six additional months of median OS. Unadjusted Kaplan Meier analysis suggested an additional OS of 10 months. Results from a Cox proportional hazard model after IPTW suggested that patients who used both CN and targeted therapy had a lower risk of death compared to patients receiving targeted therapy alone. The results from the propensity score based IPTW model were more conservative than the multivariable regression model but had the same directionality. Our findings were consistent with the findings from previous retrospective studies.[16, 17] Heng et al. analyzed IMDC database and found that the risk of death for targeted therapy users who received CN was significantly lower (HR = 0.60, 95% CI: 0.52 - 0.69) than patients who received targeted therapy alone.[16] Similarly, Hanna et al, using the National Cancer Data Base (NCDB), found that patients who received both CN and targeted therapy had a lower risk of death (HR = 0.49, 95%CI: 0.46 to 0.52) compared to patients on targeted therapy alone.[17]

Findings from our and other retrospective studies, however, were not consistent with a recently published prospective RCT (CARMENA).[31] This non-inferiority RCT compared survival outcomes among patients receiving CN followed by sunitinib versus sunitinib alone. The study

found that the sunitinib alone group had a higher OS (18.4 months) than patients who received CN and sunitinib (13.9 months). The HR of 0.89 (95%CI: 0.71- 1.10) was non-significant suggesting that sunitinib alone was not considered inferior to patients who received CN + sunitinib. No significant differences were observed for other outcomes such as progression free survival. This is the only prospective study that has assessed the role of CN among mRCC patients in the targeted therapy era.

As prospective studies have better internal validity and minimal selection bias, they are often considered as the gold standard and provide a higher level of evidence than retrospective studies. As a result, use of CN among mRCC patients may be questioned in the near future. Conflicting findings from the CARMENA study compared to retrospective studies may generate uncertainty in decision-making, as the risk associated with CN may not outweigh survival benefits among mRCC patients.

It is important to highlight key differences between CARMENA study and our study. The CARMENA study included patients that were good candidates for CN and sunitinib and excluded patients who had brain metastasis, cardiovascular comorbidities or poor performance status. The median age was 62 years. In contrast, in our study, the median age was 73 years. We did not exclude patients based on metastasis, comorbidities or performance status. Further, although the CARMENA study was randomized there were differences between treatment groups for the extent of tumor (T) and lymph node (N) involvement. These differences may affect survival outcomes between the treatment groups. In our study, we controlled for these differences using the IPTW method. CARMENA study controlled for prognostic risk calculated using MSKCC criteria. Although our study did not control for prognostic risk, other retrospective studies whose findings were similar to ours did control for baseline risk of prognosis.

As a prospective RCT, the CARMENA study certainly had higher internal validity than retrospective studies but the stricter inclusion/exclusion criteria may affect the generalizability of study findings. A pragmatic trial that has less strict inclusion/exclusion criteria, conducted in the U.S, which enrolls older mRCC patients from the real world clinical practice setting, may provide a middle ground between RCTs and observational studies. It may also address the issue of conflicting findings and provide evidence on the effectiveness of CN in the targeted therapy era.

No study to our knowledge has compared healthcare costs between mRCC patients who received CN+ targeted therapy versus targeted therapy alone. Results from our cost analysis suggested that patients receiving CN + targeted therapy had similar total healthcare costs to patients receiving targeted therapy alone. However, they had higher medical costs and lower prescription costs compared to patients who received targeted therapy alone. Higher medical costs could be due to the additional cost of CN and morbidity and post-surgical complications associated with CN.[32] Lower prescription drug costs for this group could be due to delayed initiation of targeted therapy after CN. The average time to receive targeted therapy after CN in our study was 6 months (median was 2.5 months). Although results from our cost analyses were not consistently robust, all suggested that use of CN did not result in higher total healthcare cost; costs were either similar or lower than the targeted therapy alone group.

The results of the study should be interpreted in light of several limitations. First, although we used a propensity score based IPTW method to reduce selection bias, we could not control for performance status of patients, prognosis, patient and physician preferences or lifestyle factors, all of which may affect treatment choice and survival outcomes. SEER-Medicare data does not provide information on performance as measured by the Karnofsky Performance Scale or the Eastern Cooperative Oncology Group scale.[33] However, to reduce the effect of this limitation, we

measured claims-based performance status from Medicare claims data as suggested by Salloum et al.[34] SEER-Medicare also does not provide information on lab values for hemoglobin, calcium, neutrophils, and platelets, which are used to assess prognosis using criteria developed by Heng et al.[35] and the Memorial Sloan-Kettering Cancer Center.[36] However, we controlled for tumor characteristics such as tumor grade, site of metastasis, histology, the extent of lymph node involvement, which are associated with overall survival. Second, registry and administrative claims data are subject to miscoding errors, which may affect treatment assignment and outcomes assessed in the study. Claims data is used for reimbursement purposes and may not accurately reflect patients' behavior. For example, prescription claims indicate that the prescription was filled at the pharmacy but do not guarantee actual use by patients. Third, SEER only began collecting information on metastasis to bone, liver, lung, and brain in 2010. Hence, for patients diagnosed before 2010, we used ICD9-CM codes to identify sites of metastasis. However, according to the NCI, this information could be underreported in ICD9-CM codes because physicians are not required to report site of metastasis to get reimbursed from CMS.[37] However, in our study population, there was a 90% agreement on the site of metastasis reported by SEER after 2010 and claims-based metastasis for patients diagnosed after 2010. Fourth, this study was conducted among Medicare patients aged ≥ 65 years at the time of diagnosis and living in SEER areas. Therefore, findings from this study may not be generalizable to younger mRCC patients or patients living outside of SEER areas. Fifth, SEER collects cancer stage and tumor-related information only at the first cancer diagnosis and does not measure disease progression. Therefore, we could not include patients diagnosed at earlier stages who may have later progressed to stage-IV.

Conclusions

About one-half of older mRCC patients on Medicare did not receive either CN or targeted therapy. One-third of patients receiving targeted therapy also underwent CN. In addition to the clinical factors, a geographical disparity exists in the receipt of CN, which may also affect survival among patients living in these areas. Our findings, when taken in the context of previously published studies, suggest that among clinically appropriate mRCC patients CN plays an important role in extending overall survival. Furthermore, use of CN among targeted therapy users is not associated with an increase in the lifetime total healthcare costs to Medicare.

Appendix for study 2

Appendix 3.1 Codes used for identifying targeted therapy and cytoreductive nephrectomy

Drug name	NDC codes (PDE file)	HCPCS (Outpatient, Carrier files)
Suntinib	00069055030, 00069055038, 00069077030, 00069077038, 00069083038, 00069098030, 00069098038, 54569598200, 54569598300	--
Sorafenib	00026848858, 50419048858	--
Pazopanib	00173080409, 00078067066	--
Everolimus	00078056651, 00078056661, 00078056751, 00078056761, 00078059451, 00078059461, 00078062051, 00078062061, 00078041420, 00078041520, 00078041720, 0078062851, 00078062861, 0078062751, 00078062761, 00078062661, 00078062651, 00078041761, 00078041561, 00078041461,	--
Axitinib	00069014501, 00069015111	--
Bevacizumab	50242006001, 50242006101	J9035, C9257
Temsirolimus	00008117901, 00008117905	C9239, J9330
Interferon alpha	--	J9212, J9213, J9214, J9215
Interleukin	--	J2355, J9015

Appendix 3.2 Codes for cytoreductive nephrectomy

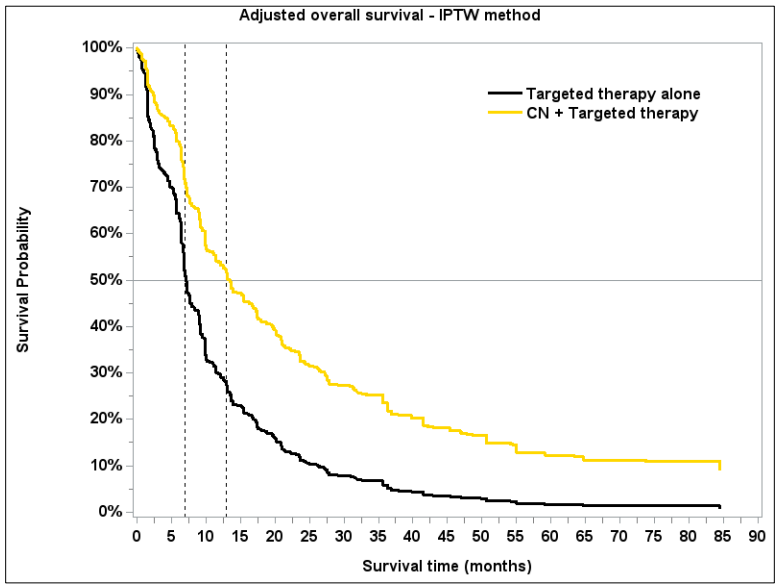
Files	Codes
SEER surgery codes	30, 40, 50, 70, 80
Carrier and outpatient files (HCPCS / CPT codes)	50220, 50225, 50230, 50234, 50236, 50240, 50280, 50290, 50542, 50543, 50545, 50546, 50548, 50549
Inpatient hospital file (ICD 9- CM procedure codes)	5501, 554, 5551, 5552, 5553, 5554, 5531, 5539, 5540

Appendix 3.3 ICD 9-CM codes for metastasis

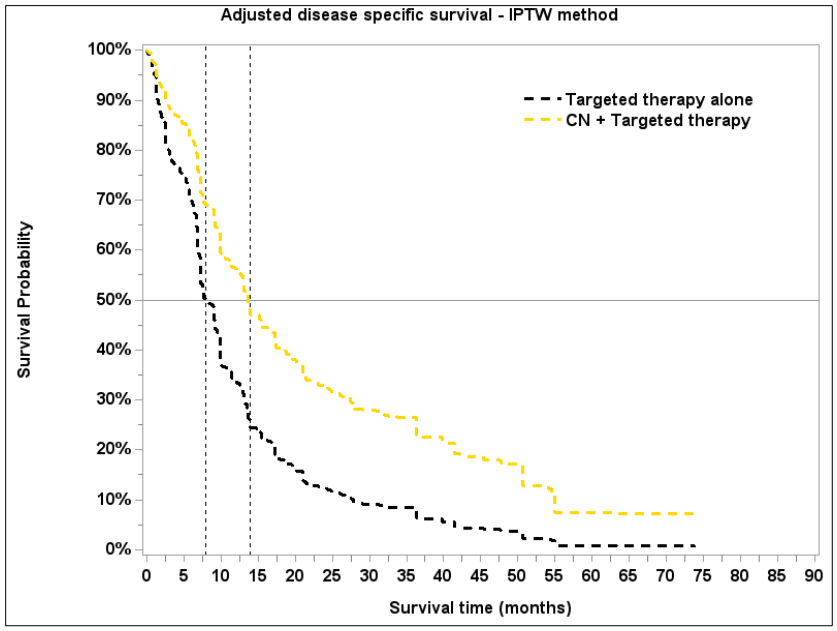
Site of metastasis	ICD9-CM codes
Bone	198.5
Brain	198.3, 198.4
Liver	197.7
Lung	197.0, 197.1, 197.2, 197.3

Appendix 3.4 Adjusted survival curves for CN + targeted therapy vs targeted therapy alone when survival was measured as a time from treatment initiation until death/end of the study period

a. Overall Survival



b. Disease-specific survival



Appendix 3.5 Multivariable Cox proportional hazard model assessing risk of death among mRCC patients who received CN + targeted therapy versus targeted therapy alone

	Hazard Ratio (HR)	95%CI for HR	p-value
Overall survival (n = 561)			
Targeted therapy alone	Reference	--	
CN + targeted therapy	0.37	0.28 - 0.49	<0.0001
Disease specific survival (n = 499)			
Targeted therapy alone	Reference	--	
CN + targeted therapy	0.34	0.25 - 0.46	<0.0001

Note: Covariates included age, gender, race, marital status, zip code level income, zip code level education, SEER region, urban rural status, NCI comorbidity index, tumor size, tumor grade, tumor extent (T), lymph node extent (N), cell type, era of diagnosis, metastases to liver / lung/bone/brain, claims-based performance status

Appendix 3.6 Multivariable generalized linear model assessing total healthcare costs, medical costs and prescription drug costs mRCC patients who received CN + targeted therapy versus targeted therapy alone

Average costs per month	CN + targeted therapy (n = 154) Mean (95%CI)	Targeted therapy alone (n = 326) Mean (95%CI)	p-value
Total healthcare costs	16,680 (13,578 - 20,491)	22,677 (18,907 - 27,199)	0.0003
Medical costs	14,244 (11,197 - 18,121)	12,992 (9,956 - 16,954)	0.4215
Prescription drug costs	3,318 (2,365 - 4,655)	6,932 (5,208 - 9,229)	<0.0001

Note: Covariates included age, gender, race, marital status, zip code level income, zip code level education, SEER region, urban rural status, NCI comorbidity index, tumor size, tumor grade, tumor extent (T), lymph node extent (N), cell type, era of diagnosis, metastases to liver / lung/bone/brain, claims-based performance status

Appendix 3.7 Predictors of receiving targeted therapy among older mRCC patients.

Characteristics	Total (n = 1,263) n (%)	Tagreted therapy use		Odds Ratio (95 % CI)
		Yes (n = 561)	No (n = 702)	
Age at diagnosis (years)				
- 65-69	293 (23)	170 (30)	123 (18)	Reference
- 70-74	346 (27)	190 (34)	156 (22)	0.95 (0.68 - 1.35)
- 75-79	297 (24)	133 (24)	164 (23)	0.69 (0.48 - 0.99)*
- 80 or more	327 (26)	68 (12)	259 (37)	0.26 (0.18 - 0.39)*
Sex				
- Male	690 (55)	336 (60)	354 (50)	1.12 (0.85 - 1.47)
- Female	573 (45)	225 (40)	348 (50)	Reference
Race/Ethnicity				
- White	1083 (86)	482 (86)	601 (86)	0.84 (0.58 - 1.22)
- Black /others	180 (14)	79 (14)	101 (14)	Reference
Marital status				
- Married	610 (48)	316 (56)	294 (42)	1.50 (1.14 - 1.97)*
- Single/Divorced/Separated	653 (52)	245 (44)	408 (58)	Reference
Zip code- college educated				
- 0 to 15%	366 (29)	147 (26)	219 (31)	Reference
- 16-20%	217 (17)	94 (17)	123 (18)	1.31 (0.87 - 1.97)
- 21-30%	279 (22)	121 (22)	158 (23)	1.32 (0.87 - 1.99)
- 31% and above	401 (32)	199 (35)	202 (29)	1.55 (0.96 - 2.49)
Zip code level median household income (USD)				
- < 40k	301 (24)	124 (22)	177 (25)	Reference
- 40k - 50 k	300 (24)	123 (22)	177 (25)	0.76 (0.51 - 1.14)
- 51k - 70k	358 (28)	163 (29)	195 (28)	0.86 (0.56 - 1.32)
- > 70 k	304 (24)	151 (27)	153 (22)	0.91 (0.52 - 1.57)
Urban/Rural Status				
- Big Metro	595 (47)	262 (47)	333 (47)	0.98 (0.62 - 1.53)
- Metro /Urban	482 (38)	218 (39)	264 (39)	0.94 (0.62 - 1.44)
- Less urban / Rural	186 (15)	81 (14)	105 (14)	Reference
SEER region				
- Northeast	218 (17)	93 (17)	125 (18)	Reference
- South	349 (28)	154 (27)	195 (28)	1.29 (0.83 - 2.00)
- North Central	168 (13)	67 (12)	101 (14)	0.98 (0.59 - 1.62)
- West	528 (42)	247 (44)	281 (40)	1.29 (0.89 - 1.87)
Year of diagnosis				
- 2007 to 2009	525 (42)	206 (37)	319 (45)	Reference
- 2010 to 2013	738 (58)	355 (63)	383 (55)	1.48 (1.13 - 1.93)*
NCI comorbidity index (mean, SD)	1.47 (1.8)	1.21 (1.4)	1.68 (1.9)	0.86 (0.78 - 0.95)*
NCI comorbidity index score				
- 0	476 (38)	225 (40)	251 (36)	NA
- 1	337 (27)	173 (31)	164 (23)	
- 2	169 (13)	65 (12)	104 (15)	
- 3 or more	281 (22)	98 (17)	183 (26)	

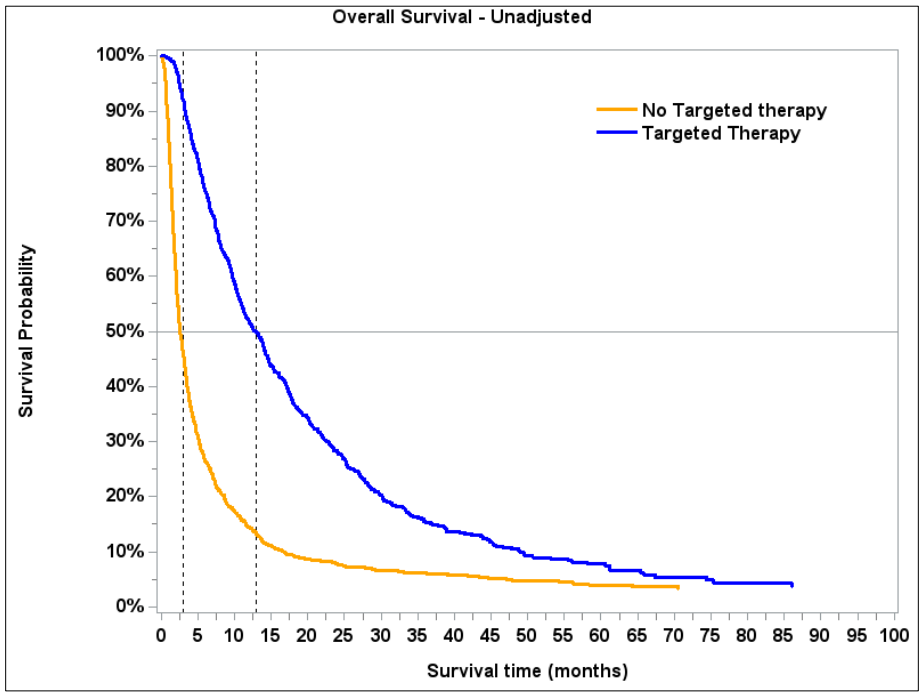
Note: Odds ratios were calculated from multivariable logistic regression

Appendix 3.7 Continued

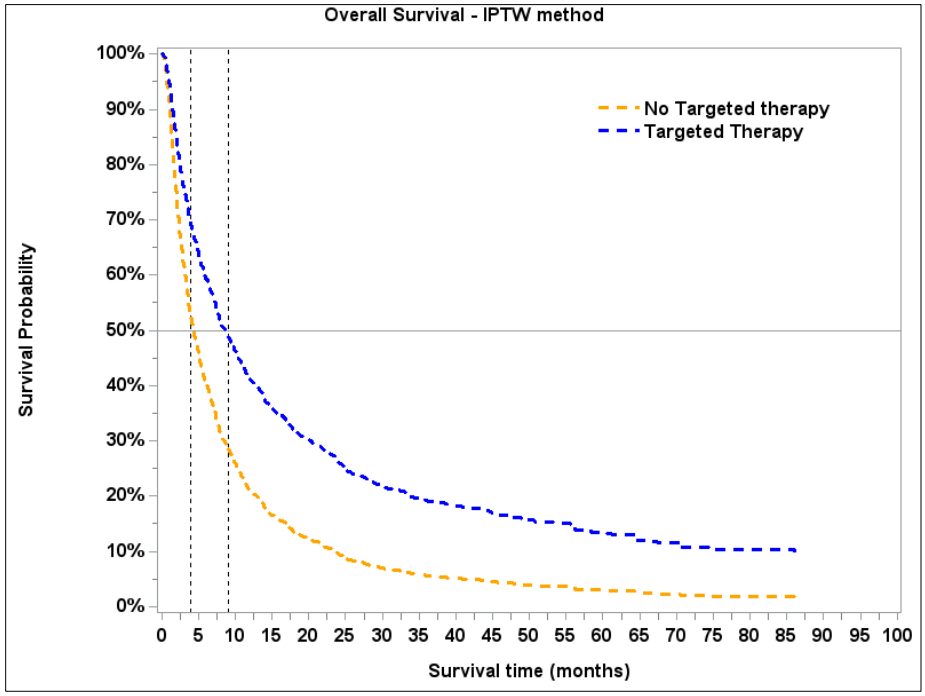
Characteristics	Total (n = 1,263) n (%)	Tagreted therapy use		Odds Ratio (95 % CI)
		Yes	No	
Histology				
- Clear cell	1,148 (91)	507 (90)	641 (91)	1.13 (0.73 - 1.74)
- Non clear cell	115 (9)	54 (10)	61 (9)	Reference
Tumor size				
- Unknown / < 5 cm	460 (36)	169 (30)	291 (41)	Reference
- 5 to 7.9 cm	327 (26)	144 (26)	183 (26)	1.05 (0.74 - 1.47)
- ≥ 8 cm	476 (38)	248 (44)	228 (32)	1.21 (0.83 - 1.75)
Tumor grade				
- Well/ moderate	130 (10)	86 (15)	44 (6)	Reference
- Poor / undifferentiated	244 (19)	136 (24)	108 (15)	0.50 (0.30 - 0.83)*
- Unknown	889 (70)	339 (60)	550 (78)	0.42 (0.27 - 0.65)*
Tumor extent (T) - TNM				
- T0 / T1/ unknown	603 (48)	217 (39)	386 (55)	Reference
- T2	183 (15)	91 (16)	92 (13)	1.21 (0.78 - 1.89)
- T3	359 (28)	201 (36)	158 (23)	1.46 (1.03 - 2.08)
- T4	118 (9)	52 (9)	66 (9)	1.19 (0.74 - 1.94)
Lymph Node (N) - TNM				
- N0 /NX	949 (75)	403 (72)	546 (78)	0.77 (0.58 - 1.89)
- N1 /N2	314 (25)	158 (28)	156 (22)	Reference
Bone metastasis				
- Absent	750 (59)	327 (58)	423 (60)	Reference
- Present	513 (41)	234 (42)	279 (40)	1.22 (0.93 - 1.60)
Lung metastasis				
- Absent	573 (45)	244 (44)	329 (47)	Reference
- Present	690 (55)	317 (57)	373 (53)	0.97 (0.74 - 1.26)
Liver metastasis				
- Absent	1,004 (79)	465 (83)	529 (77)	Reference
- Present	259 (21)	96 (17)	163 (23)	0.65 (0.47 - 0.90)*
Brain metastasis				
- Absent	1,086 (86)	493 (88)	593 (84)	Reference
- Present	177 (14)	68 (12)	109 (16)	0.55 (0.39 - 0.81)*
Performance status indicators				
Average number of services				
- ED visits	3.5 (3.2)	4.0 (3.4)	3.1 (2.9)	1.15 (1.10 - 1.21)*
- hospital days	1.16 (5.3)	0.53 (2.0)	1.65 (6.9)	0.94 (0.90 - 0.98)*
- physician claims	33.2 (30.4)	30.8 (25.0)	35.2 (34.0)	1.00 (0.99 - 1.01)
- home health claims	0.24 (0.8)	0.12 (0.6)	0.33 (0.9)	0.76 (0.62 - 0.94)*
DME use (Yes vs No)	487 (39)	199 (35)	288 (41)	0.98 (0.69 - 1.75)
Assisting devices (Yes vs No)	240 (19)	96 (17)	144 (21)	1.15 (0.76 - 1.21)

Appendix 3.8 Overall survival between mRCC patients that received targeted therapy versus patients who did not

A) Unadjusted



B) IPTW adjusted method



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Chapter 4

Study 3: Prescribing Patterns of Targeted Therapies, Overall Survival, and Total Healthcare Cost among Older Adults with Metastatic Renal Cell Carcinoma in the U.S

ABSTRACT

OBJECTIVES

Several targeted therapies have been approved since 2005 to treat metastatic renal cell carcinoma (mRCC). The first aim of this study was to describe prescribing patterns of targeted therapies among mRCC patients. The second aim was to describe overall survival (OS) and total healthcare costs (THC) for commonly observed targeted therapy patterns.

METHODS

This study analyzed 2007-2014 Surveillance Epidemiology and End Result (SEER)-Medicare data. Patients with mRCC were defined as those who were diagnosed at stage-IV as well as those who were diagnosed at earlier stages but were currently using targeted therapies. Further, we restricted our sample to patients who initiated targeted therapy and were continuously enrolled in Medicare Fee for Service plans. We described the frequencies of the most commonly used first and second line targeted therapies for clear-cell and non-clear cell mRCC. We also described the most frequently used sequences among patients who received two or more lines of targeted therapies. Oral targeted therapies were identified using generic names and National Drug Codes. Injectable targeted therapies were identified using the HealthCare Common Procedure Coding System (HCPCS) codes. Median OS and THC per month were described for the most common treatment patterns from the date of the first targeted therapy prescription until the end of 2014 or

until death. Median OS was calculated using Kaplan Meier survival curves. All analyses were conducted using SAS v.9.4.

RESULTS

Of 915 patients, 521 (57%) used only one line, 240 (26%) used two lines and 154 (17%) used three or more lines of targeted therapies. Among clear cell mRCC patients, sunitinib (384, 48%) and everolimus (101, 13%) were the most commonly used first and second line targeted therapies. Of 109 non-clear cell patients, sunitinib (n = 35, 32%) and temsirolimus (n = 26, 24%) were the most commonly prescribed first line targeted therapies. Only 44 non-clear cell mRCC patients received second line therapies. Among patients who received multiple lines, VEGF-mTOR was the most commonly prescribed sequence. The median OS was 6.0 months, 13.7 months and 23.7 months for patients with clear cell mRCC who received one line, two lines and 3 or more lines of targeted therapies respectively. The median monthly THC was significantly higher ($p < 0.05$) for patients who received only one line of therapy ($ 14,243) than patients who received two lines ($ 9,985) and three or more lines of therapies ($ 10,110). The median OS and median monthly THC was similar across targeted therapy sequences.

CONCLUSIONS

About fifty percent of mRCC patients who had at least one targeted therapy received multiple lines of therapies. Sunitinib and everolimus were the most common first and second line targeted therapies among mRCC patients. The descriptive analysis suggested that OS and THC were similar across targeted therapy sequences.

BACKGROUND

Metastatic renal cell carcinoma (mRCC) is a deadly disease with a 5-year survival rate of about 12%.[1] About 15%-20% of RCC patients are diagnosed at the metastatic stage and about 30-33% of patients diagnosed at early stages eventually progress to the metastatic stage. The median age of RCC diagnosis is 64 years and Medicare covers about 46% of total RCC patients in the U.S.[2, 3]

In the last 15 years, systemic therapy has become the main treatment for mRCC patients. Before 2005, systemic therapy mainly included cytokines such as high dose interleukin-2 and interferon-alpha. However, both drugs were associated with low tumor response rates, high toxicity, and improvement of less than 6-12 months in overall survival (OS).[4, 5] In 2005, the first targeted therapy, sorafenib, was approved by the U.S Food and Drug Administration (FDA) to treat mRCC. Since then, several additional targeted therapies have become available to treat mRCC.[6-10] These include vascular endothelial growth factor inhibitors (VEGFi) like the tyrosine kinase inhibitors (TKI) sunitinib, pazopanib, and axitinib; the mammalian target of rapamycin inhibitors (mTORi) everolimus and temsirolimus; and the anti-VEGF monoclonal antibody bevacizumab. While most of the targeted therapies are approved as first and second line therapies, everolimus and axitinib are approved only as second-line therapies. Patients treated with first-line targeted therapy often develop resistance within 6-11 months and as a result, need subsequent lines of therapy to control disease progression. [6, 8]

The availability of several options has complicated decision making regarding the optimal choice of targeted therapy to treat mRCC patients. The National Comprehensive Cancer Network (NCCN) develops evidence-based guidelines to help healthcare professionals to decide appropriate treatment strategies for cancer patients.[11, 12] A category-1 recommendation indicates uniform

consensus about appropriateness of the intervention among NCCN panel members based on a high-level of evidence; Category-2A indicates uniform consensus based on a lower level of evidence; category-2B indicates some consensus based on lower level of evidence and category-3 indicates major disagreement about appropriateness of intervention. In the targeted therapy era, NCCN guidelines included sunitinib, pazopanib, and bevacizumab/interferon as category-1 recommendations and sorafenib as Category-2A recommendation for first-line treatment. Recommendations for second line therapy included all of the above agents and everolimus. However, only axitinib and everolimus have a Category-1 recommendation as second-line treatments while other agents have either category 2-A or 2-B recommendation. No recommendations were made for the use of third-line targeted therapies.[11, 12]

Several studies have analyzed prescribing patterns of targeted therapies among mRCC patients.[13-17] Miller et al. (2016) examined targeted therapy patterns using Humana claims data and assessed their consistency with the NCCN guidelines. They found that the largest proportion of patients received sunitinib (44%) as first and everolimus (29%) as second-line therapy; both have category-1 recommendations. Most treatment patterns were consistent with the NCCN recommendations for first-line therapy, but 5% of patients received everolimus as first-line, nearly 20% received bevacizumab as second line, and 15% received temsirolimus as second-line therapies.[15] These have a lower level of evidence (category 2-B) according to NCCN guidelines. Bevacizumab is approved by the FDA and recommended to be given in combination with interferon-α. However, several patients who received bevacizumab did not receive interferon-α. Similar findings regarding the most common first and second-line treatments were reported by two other studies.[14, 17]

A majority of previously published studies were conducted using commercial claims data and included patients diagnosed at younger ages. A number of them compared utilization of individual drug therapies, mainly sunitinib and pazopanib, but few described patterns that covered the entire therapeutic landscape. Few studies were conducted among older mRCC patient on Medicare.[18] Pal et al. (2017) compared survival among Medicare patients receiving first-line targeted therapies. The authors found that patients diagnosed in the late-targeted therapy era (2010-2012) had significantly higher OS than patients from the early- targeted therapy era (2006-2009). Additionally, patients prescribed pazopanib had higher OS than patients on sunitinib and sorafenib.[20] The study, however, did not describe second or subsequent lines of therapies. Rasca et al. (2015) compared prescribing patterns and survival among patients from Medicare Advantage plans. In contrast to Pal et al., no significant difference in OS was observed among sunitinib and pazopanib users.[19] Older adults with mRCC represent a special population for study because they are under-represented in randomized controlled trials. Additionally, comorbid conditions and frailty can complicate their treatment and may affect health outcomes. In addition, Medicare is the single largest payer for RCC patients, covering about 46% of them. The high costs of targeted therapies, which range from US $6,000 to $15,000 per month and the costs of managing adverse events and complications, may result in a significant economic burden on Medicare. The first aim of this study was to describe patterns of first line and subsequent lines of targeted therapies among older mRCC patients. The second aim was to describe the overall survival and healthcare costs for the first and the subsequent line targeted therapy users.

METHODS

Data Source

SEER-Medicare

We used 2007-2014 SEER-Medicare data. The Patient Entitlement and Diagnosis Summary File was used to obtain demographics and cancer diagnosis-related information. Resource use and cost-related information were obtained from Medicare Provider Analysis and Review (MEDPAR), outpatient, carrier, Part D event (PDE), home health agencies (HHA), hospice (HS) and durable medical equipment (DME) files. The MEDPAR file was used to obtain inpatient hospital and skilled nursing facility (SNF) claims. The HS file provided data on hospice care utilization. The carrier file provided information on non-institutional physician-provided services whereas the outpatient file provided information on institutional physician-provided services. The PDE file provided data related to prescription medication use (Medicare Part D). DME files provided data on the use of durable medical equipment while HHA files were used to get information on services provided in patients' homes.[20]

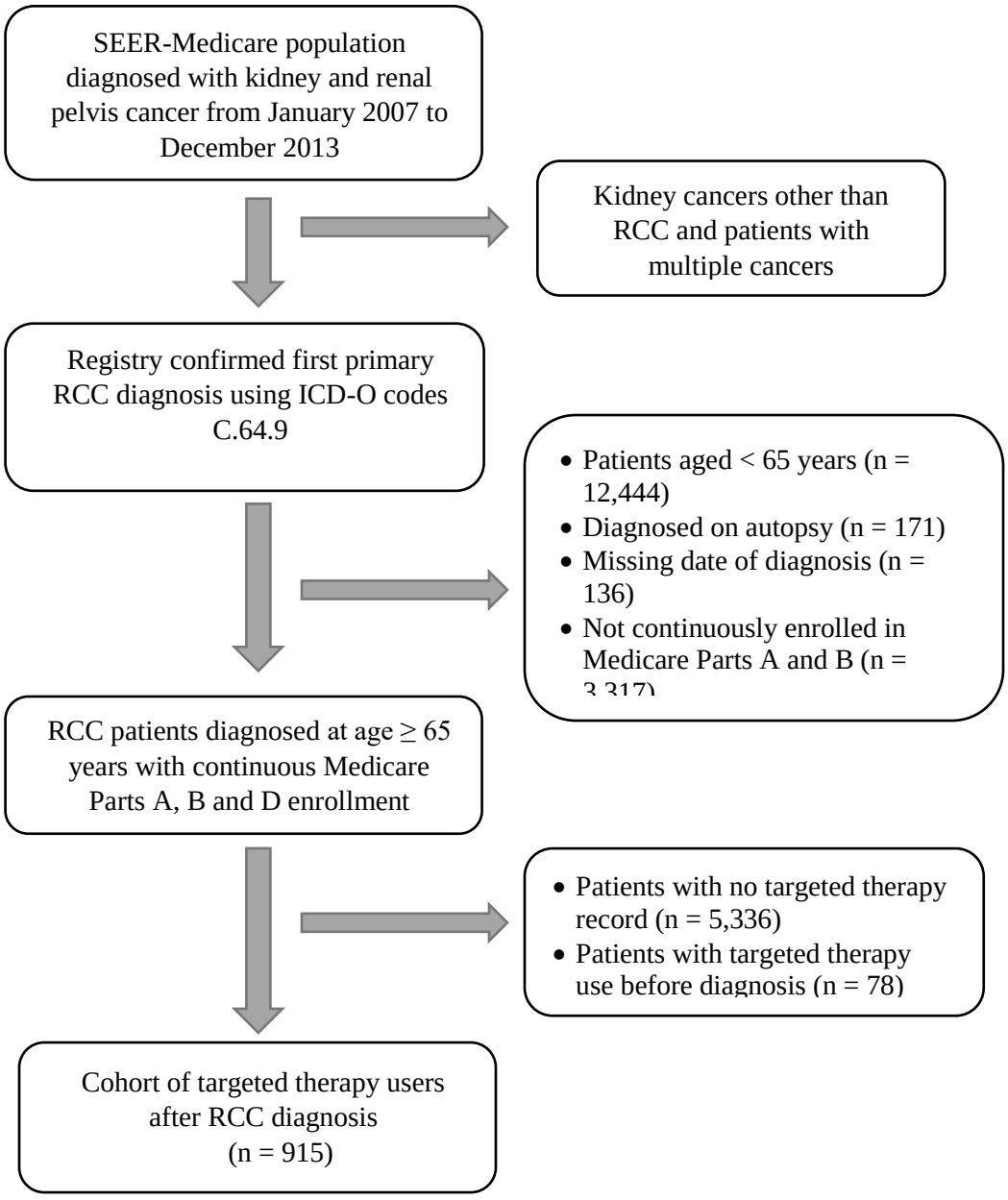
Study Design and Sample Selection

This was a retrospective cohort study. The study first identified patients with an incident diagnosis of RCC using the International Classification of Diseases for Oncology, 3rd edition codes C64.9 and relevant histology types ('8260', '8310', '8312', '8316', '8317', '8318'). Patients who initiated any systemic therapy between January 2007 and December 2013 were included in the study. The index date was defined as the date of the first prescription for a newly initiated systemic therapy. We excluded patients aged < 65 years, diagnosed with another cancer at the time of RCC diagnosis, diagnosed on autopsy, having cancer reported by death certificate, or enrolled in health maintenance organizations (HMOs). Figure 1 depicts the sample selection process. Treatment patterns and overall survival (OS) were measured in the follow-up period, which began after the index date and continued until death or the end of study period (end of December 2014). Total

healthcare cost (THC) over the lifetime was assessed among patients that had complete follow up until death. For cost analyses, patients who were still alive at the end of the study period were excluded. Baseline characteristics were assessed in the 1-year period prior to the index prescription date.

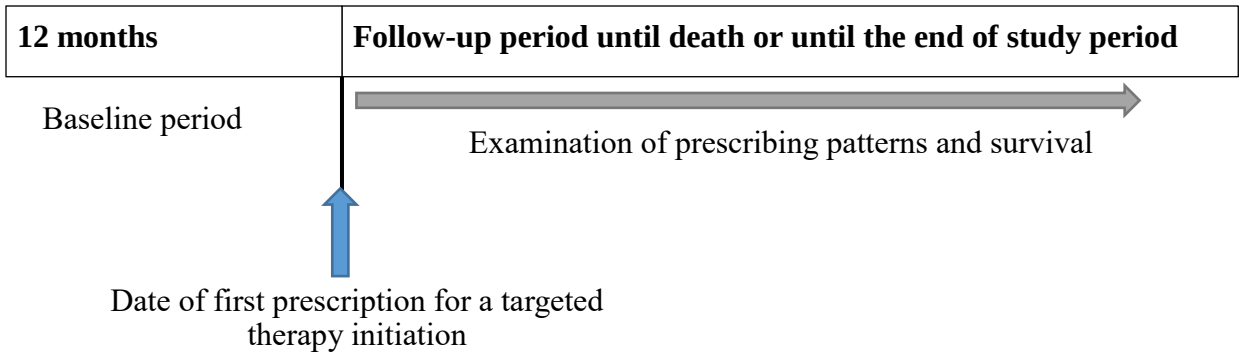
Oral targeted therapies were identified using generic names and National Drug Codes (NDCs) from Medicare Part D. Injectable-targeted therapies were identified using Healthcare Procedural Codes (HCPC) from Medicare Part B data.

Figure 4.1 Sample selection process for this study.



NOTE: For cost analysis, we excluded an additional 231 patients due to incomplete follow-up period from index date until death as these patients continued to live beyond December 2014.

Figure 4.2. Diagrammatic representation of study design



Study Measures

Prescribing patterns

Prescribing patterns included identification of the most common first line therapies. For patients who received more than one line, we identified the most common second line therapies. In addition, the most common treatment sequences were identified. Patterns were assessed separately for patients who had clear-cell and non-clear cell RCC.

Overall Survival

The study defined overall survival as the time in months from the date of the index prescription until the date of death or until the end of the study period. Patients that were alive beyond the follow-up period were censored.

Healthcare cost

Costs were the amounts reimbursed by Medicare for healthcare services. Costs for each component were calculated and aggregated to calculate total healthcare costs (THC). Costs were presented as monthly costs. All costs were converted to 2016 US dollars using the Consumer Price Index for medical care services and medical care commodities.[21]

Other variables

These variables included patient demographics, geographical region, tumor characteristics, site of metastasis, cancer staging specific details, histology, and the National Cancer Institute's (NCI) comorbidity index. Information on these variables was obtained in the baseline period.

Statistical Analysis

Sample characteristics were described using basic descriptive statistical procedures. The median overall survival for the most common treatment patterns and sequences was calculated using Kaplan Meier curves and Log-rank tests. Healthcare costs were described as mean and median costs per month. All analyses were conducted at an α level of 0.05 using SAS v.9.4 (SAS Institute Inc, Cary, NC) and Microsoft Excel 2016.

RESULTS

Sample Characteristics

The final study sample included 915 RCC patients who were prescribed at least one targeted therapy. About 58% patients were aged between 65-74 years, 61% were males, 85% were white and 56% were married or lived with a partner. About 47% patients lived in big metropolitan area, and in the West (47%). About 60% of patients were diagnosed in the later part of the targeted therapy era (2010-2013). About 68% had one or more comorbidities. A majority of patients were diagnosed at stage-IV (60%) while 40% were diagnosed at earlier stages. These patients were assumed to have the recurrent metastatic disease. The vast majority of patients (88%) had clear cell RCC while only 12% had non-clear cell RCC.

Table 4.1 Characteristics of older RCC patients who received at least one targeted therapy

Characteristics	Total (n = 915) Frequency n (%)
Age at diagnosis (years)	
- 65-69	264 (29)
- 70-74	264 (29)
- 75-79	214 (23)
- 80 or more	173 (19)
Sex	
- Male	560 (61)
- Female	355 (39)
Race/Ethnicity	
- White	778 (85)
- Black /others	137 (15)
Marital status	
- Married	515 (56)
- Single/Divorced/Separated	400 (44)
Zip code- college educated	
- 0 to 15%	260 (29)
- 16-20%	146 (16)
- 21-30%	184 (20)
- 31% and above	325 (36)
Zip code level median household income (USD)	
- < 40k	206 (23)
- 40k - 50 k	187 (20)
- 51k - 70k	276 (30)
- > 70 k	246 (27)
Urban/Rural Status	
- Big Metro	431 (47)
- Metro /Urban	350 (38)
- Less urban / Rural	134 (15)
SEER region	
- Northeast	156 (17)
- South	229 (25)
- North Central	104 (11)
- West	426 (47)
Year of diagnosis	
- 2007 to 2009	367 (40)
- 2010 to 2013	548 (60)
NCI comorbidity index score	
- 0	350 (38)
- 1	262 (29)
- 2	121 (13)
- 3 or more	182 (20)
Stage at diagnosis	
- I	111 (12)
- II	36 (4)
- III	175 (19)
- IV	553 (60)
- Unstaged	40 (4)

Table 4.1 Continued

Characteristics	Frequency n (%)
Histology	
- Clear cell	806 (88)
- Non clear cell	109 (12)
Tumor size	
- Unknown / < 5 cm	290 (32)
- 5 to 7.9 cm	250 (27)
- ≥ 8 cm	375 (41)
Tumor grade	
- Well/ moderate	211 (23)
- Poor / undifferentiated	305 (33)
- Unknown	399 (44)
Tumor extent (T) - TNM	
- T0 / T1/ unknown	351 (38)
- T2	128 (14)
- T3	375 (41)
- T4	61 (7)
Lymph Node (N) - TNM	
- N0 /NX	721 (79)
- N1 /N2	194 (21)
Metastasis (M) - TNM	
- M0 /MX	388 (42)
- M1	527 (58)

Lines of Therapies

Of 915 patients, 521 (57%) used only one line, 240 (26%) used two lines and 154 (17%) used three or more lines of therapies. This distribution was similar for clear cell and non-clear cell RCC patients.

First and second line therapies among clear cell RCC patients

Of 806 clear-cell mRCC patients that received at least one targeted therapy, 384 (48%) received sunitinib, 139 (17%) received temsirolimus, 128 (16%) received pazopanib, and 71 (9%) received sorafenib as first-line therapy. A total of 350 patients received 2nd line therapy. Of 2nd line therapy users, 101 (29%) received everolimus and 84 (24%) patients received temsirolimus. Approximately equal proportion of patients (10-11%) received sorafenib, sunitinib, and pazopanib. (Table 2.)

First and second line therapies among non-clear cell RCC patients

Of 109 non-clear cell patients, sunitinib (n = 35, 32%), temsirolimus (n = 26, 24%), and bevacizumab (n = 18, 17%) were the most commonly prescribed first line targeted therapies. Only 44 patients received second line therapies. Temsirolimus, sunitinib, and everolimus were the most common second line therapies (n < 11).

Common sequences of targeted therapies among clear cell RCC patients

Of 350 patients that received two or more lines of therapies, the top five sequences included: - 1) sunitinib followed by everolimus (8%) 2) sunitinib followed by temsirolimus (6%) 3) sunitinib followed by sorafenib (5%) 4) pazopanib followed by everolimus (4%) and 5) sunitinib followed by pazopanib (4%). In terms of therapeutic classes, VEGF - mTOR (25%), VEGF-VEGF (21%), VEGF-mTOR-VEGF (11%), mTOR- VEGF (9%) and VEGF-VEGF-mTOR (6%) were the most common sequences.

Common sequences of targeted therapies among non-clear cell RCC patients

Only 44 patients received two or more lines of therapies. Temsirolimus followed by sunitinib (n<11) and temsirolimus followed by bevacizumab (n<11) were the top two sequences. In terms of therapeutic class, an equal proportion of patients received VEGF-mTOR and mTOR-VEGF.

Overall Survival (OS)

Median OS by the number of lines of therapies for clear cell and non-clear cell patients is described in Table 2 and Table 3 respectively. In the descriptive analysis, patients with clear cell RCC who received two lines of therapies had higher median OS than patients who received only one line. Similarly, patients who received 3 or more lines had higher OS than patients receiving one or two lines of targeted therapies. We also examined time since diagnosis for each group to

understand if there was any survivorship bias. The median time since diagnosis was 121 days for patients receiving one line of therapy, 106 days for patients receiving two lines, and 118 days for patients receiving three lines (p= 0.1933) Time since diagnosis also did not differ by number of line of therapies prescribed for patients that were directly diagnosed at stage-IV and patients diagnosed at earlier stages.

Kaplan Meier analysis suggested that pazopanib had significantly higher OS than sorafenib, sunitinib and temsirolimus ($p < 0.05$). Sunitinib followed by pazopanib had a median OS of 20.7 months compared to 13.7 months for sunitinib followed by everolimus. However, this difference was not statistically significant. Among patients who received multiple lines of therapies, no particular drug or a class sequence resulted in a significantly higher OS compared to other sequences. (Table 4.2)

Among non-clear cell RCC patients, those who received two or more lines of targeted therapies had higher OS than patients receiving a single line of targeted therapy. However, the difference in OS was not statistically significant. Time since diagnosis was 166 days for patients receiving one line of therapy, 112 for patients receiving two lines, and 121 days for patients receiving three lines ($p = 0.3547$). Time since diagnosis also did not differ by a number of line of therapies prescribed for patients that were directly diagnosed at stage-IV and patients diagnosed at earlier stages. Since very few non-clear cell RCC patients received two or more lines of therapies, we did not describe OS by drug-level sequencing. In terms of class-level sequence, patients who received mTOR-VEGF and VEGF-mTOR had similar median OS. (Table 4.3).

Table 4.2 Overall survival among clear cell Renal Cell Carcinoma patients receiving targeted therapy

	Median Overall Survival (months)	95%CI
Number of lines *		
First line only (n = 456)	6.0	5.0 - 7.0
First and second line (n = 212)	13.7	11.8 - 15.2
Three or more lines (n = 138)	23.7	20.3 - 26.0
First line therapy users		
• Sunitinib (n = 214)	3.9	2.8 - 5.1
• Sorafenib (n = 42)	5.6	2.9 - 6.8
• Pazopanib (n = 65)	9.4	6.6 - 20.8
• Bevacizumab (n = 50)	NA	NA
• Temsirolimus (n = 74)	5.2	4.0 -7.1
Most common drug sequences		
• Sunitinib-Everolimus (n = 28)	13.7	7.6 - 21.2
• Sunitinib-Temsirolimus (n = 20)	11.6	7.4 - 17.2
• Sunitinib - Sorafenib (n = 19)	13.9	7.5 - 22.3
• Sunitinib-Pazopanib (n = 14)	20.7	NA
• Pazopanib - Everolimus (n = 14)	13.7	7.1 - 22.4
Most common class sequences		
• VEGF-mTOR (n = 88)	13.9	11.3 - 16.5
• VEGF-VEGF (n = 73)	15.1	11.9 - 18.2
• VEGF-mTOR-VEGF (n = 39)	18.0	14.4 - 22.7
• mTOR-VEGF (n = 31)	10.5	5.4 - 20.4
• VEGF-VEGF-mTOR (n = 20)	17.8	13.0 - 25.7

NA: median survival or confidence intervals were not available due to a higher frequency of censoring.

** Statistically significant, $p<0.05$

Following comparisons were statistically significant:

First line therapy only: Sunitinib vs pazopanib, sorafenib vs pazopanib, temsirolimus vs pazopanib

Table 4.3 Overall survival among non-clear cell Renal Cell Carcinoma patients receiving targeted therapy

	Overall Survival in months Median	95%CI
Number of lines [NS]		
First line only (n = 65)	6.4	3.9 - 14.1
First and second line (n = 28)	11.6	7.6 - 13.0
Three or more lines (n = 16)	16.3	9.3 - 19.3
First line therapy users		
• Sunitinib (n = 25)	5.2	2.7 - 11.3
• Bevacizumab (n =17)	54.6	NA
• Temsirolimus (n = 11)	3.4	1.3 - 4.2
Most common class sequences		
• mTOR-VEGF (n = 12)	14.0	7.6 - 31.3
• VEGF-mTOR (n<11)	10.4	7.3 - 12.8

Note: OS is not shown for drug sequences because all had n< 11
NA: median survival or confidence intervals were not available due to a higher frequency of censoring.
NS: not statistically significant

Total Healthcare Costs

Among clear cell RCC patients, median monthly total healthcare cost was higher among patients who received only one line of targeted therapy compared to patients who received multiple lines of therapies. Patients who received two lines and three or more lines of therapies had similar total healthcare costs. Among patients who received only one line of therapy, the median monthly total healthcare cost was highest for sunitinib users. Wilcoxon Mann Whitney tests indicated that median monthly THC for sunitinib users was significantly higher than for bevacizumab, temsirolimus and pazopanib users ($p<0.05$). Sorafenib, temsirolimus and pazopanib users had similar total healthcare costs whereas bevacizumab users had lowest total healthcare costs. For patients who received two or more sequences, median monthly total healthcare costs were similar for all the targeted therapy sequences. (Table 4.4)

Among non-clear cell RCC patients, median monthly total healthcare cost was higher

among patients who received only one line than for patients who received multiple lines of therapies. No other cost differences were statistically significant.

Table 4.4 Total healthcare costs per month among clear cell Renal Cell Carcinoma patients receiving targeted therapy

	Mean (SD) US $	Median (IQR: Q1 - Q3) US $
Number of lines		
• First line only (n = 336)	20,837 (20,987)	14,243 (8,402 - 25,306)
• First and second line (n = 164)	11,866 (6,785)	9,985 (7,579 - 14,080)
• Three or more lines (n = 105)	10,998 (4,851)	10,110 (7,710 - 12,754)
First line therapy users		
• Sunitinib (n = 179)	23,750 (21,169)	16,976 (10,000 - 31,891)
• Temsirolimus (n = 64)	16,098 (16,605)	10,592 (6,696 - 19,215)
• Sorafenib (n = 38)	21,078 (22,874)	14,347 (8,776- 19,176)
• Pazopanib (n = 34)	19,696 (27,524)	12,141 (7,751 - 18,382)
• Bevacizumab (n = 12)	9,788 (6,032)	9,254 (4,523 - 13,150)
Most common drug sequences		
• Sunitinib-Everolimus (n = 22)	12,237 (7,553)	10,429 (7,428 - 13,205)
• Sunitinib-Temsirolimus (n = 18)	11,380 (6,008)	10,712 (8,006 - 12,210)
• Sunitinib - Sorafenib (n = 16)	9,351 (4,429)	7,760 (5,960- 13,584)
• Pazopanib - Everolimus (n = <11)	10,243 (2,913)	10,405 (7,749 - 11,952)
• Sunitinib-Pazopanib (n = <11)	14,448 (7,157)	12,266 (9,079 - 20,237)
Most common class sequences		
• VEGF-mTOR (n = 71)	11,516 (6,056)	10,724 (7,428 - 13,283)
• VEGF-VEGF (n = 49)	10,888 (4,925)	9,481 (7,532 - 13,621)
• VEGF-mTOR-VEGF (n = 35)	11,227 (3,773)	10,313 (8,782 - 13,665)
• mTOR-VEGF (n = 26)	15,519 (9,901)	12,790 (9,170 - 18,447)
• VEGF-VEGF-mTOR (n = 15)	11,101 (2,748)	11,598 (9,689 - 12,676)

Note: Significant differences were observed for following comparisons
Number of lines: One line vs two lines: p <.0001, One line vs three or more lines: p <.0001
First line therapy users only: Sunitinib vs pazopanib (p = 0.0293), Sunitinib vs temsirolimus (p = 0.0002), Sunitinib vs bevacizumab (p = 0.0025), Sorafenib vs bevacizumab (p = 0.0332)

Table 4.5 Total healthcare costs per month among non-clear cell Renal Cell Carcinoma patients receiving targeted therapy.

	Mean (SD)	Median (IQR: Q1 - Q3)
Number of lines [NS]		
• First line only (n = 42)	23,619 (26,398)	14,664 (9,612 - 26,010)
• First and second line (n = 23)	12,490 (5,835)	10,403 (7,760 - 17,192)
• Three or more lines (n = 14)	12,180 (6,470)	11,116 (9,766 - 13,790)
First line therapy users		
• Sunitinib (n = 20)	32,045(35,942)	15,144 (9,893 - 40,586)
• Temsirolimus (n = 11)	18,499 (6,936)	20,169 (11,002 - 24,262)
Most common class sequences		
• mTOR-VEGF (n = <11)	11,271 (5,862)	8,011 (7,119 - 17,643)
• VEGF-mTOR (n<11)	14,660 (7,329)	11,608 (9,826 - 18,450)

NS: not statistically significant

Note: Significant differences were observed for the following the comparison

Number of lines: One line vs two lines: p = 0.0323

DISCUSSION

This study examined the prescribing patterns of targeted therapies among older mRCC patients in the targeted therapy era. To our knowledge, this is the first study which used SEER-Medicare data to describe the full spectrum of targeted therapies given over the lifetime of older mRCC patients. The study assessed the number of lines of targeted therapies, most common first and second lines and most common sequences prescribed to clear cell and non-clear cell mRCC patients. In addition, overall survival and total healthcare costs per month from Medicare's perspective were described.

The patterns of prescribing for first line treatments, for the most part, were consistent with the NCCN guidelines. Prescribing patterns in terms of the choice of first and second line therapy were similar to patterns observed in previous studies.[13-15, 17] Some patients in our study received bevacizumab and sorafenib which have category 2-A recommendations. Among patients who received a second line therapy, temsirolimus, which has a category 2B recommendation, was given to 84 (24%) patients. This may be considered a deviation from the NCCN guidelines. A similar finding was also reported by Miller et al.[15] In addition, sorafenib, which has a category-2A recommendation was less frequently used than temsirolimus. Axitinib, approved in 2012, which has a category-1 recommendation as a second line therapy was not frequently observed in this study, probably because the follow-up period ended on December 2014. Additional analysis among mRCC patients who were diagnosed after 2012 suggested that axitinib use increased in 2013 and 2014.

OS increased with the increase in the number of targeted therapies used among mRCC patients. The descriptive analysis suggested that pazopanib had higher OS than other targeted therapies. Pal et al. also assessed SEER-Medicare data and reported that pazopanib had higher OS

than sunitinib.[18] However, Rasca et al. found no difference in OS or risk of death between pazopanib and sunitinib.[19] Our results are primarily descriptive and did not control for prognostic risk, performance status or sociodemographic factors.

Patients who received multiple lines of therapies had higher OS but OS did not differ across sequences. Among patients who received two lines, OS was similar between VEGF-mTOR and VEGF-VEGF classes. Similarly, among patients who received three lines, VEGF-mTOR-VEGF and VEGF-VEGF-mTOR sequence resulted in a similar OS. Our findings are consistent with previous studies, which did not find a significant difference in the progression free survival or OS between targeted therapy sequences.[13, 17, 22]

The median monthly total healthcare cost was significantly higher for patients who received only one line of targeted therapy. This could be because patients who received only one line had more severe or advanced disease or had poorer prognoses, as indicated by their lower OS. In contrast, patients who received multiple lines could have had better prognoses and performance status, as suggested by their longer OS. Among patients who used a single line of therapy, median cost was highest for sunitinib and lowest for bevacizumab. Vogelzang et al. in a recently published study using Medicare data found that the THC among sunitinib users were higher than pazopanib users.[23] However, McLean et al did not find any significant difference between sunitinib and pazopanib users.[24] Our findings related to sunitinib and sorafenib users were consistent with Kim et al. who did not find a significant difference between sunitinib and sorafenib users.[25] We also did not find any significant differences across targeted therapy sequences. However, it is important to note that our cost analyses were descriptive in nature and we did not control for prognosis, performance status or sociodemographic factors. Also, sample sizes for some drug sequences were low (n <20).

This study had several limitations. First, SEER data does not measure cancer recurrence and progression. Targeted therapies were mainly approved for metastatic RCC, therefore we assumed that patients who were initially diagnosed at stages-I- III and had a prescription record for targeted therapy had recurrent metastatic disease. Second, the study could not control for baseline prognostic risk measured by Heng's criteria[26] or performance status measured by Eastern Cooperative Oncology Group (ECOG) scale[27]. This could affect OS and THC. Similarly, the study did not measure physician and patient preferences, which are important determinants of treatment selection. Third, this study was conducted among Medicare patients aged ≥ 65 years at the time of diagnosis and living in SEER areas. Therefore, findings from this study may not be generalizable to younger mRCC patients or patients living outside of SEER areas. Fourth due to a two year lag in the availability of the SEER-Medicare data, we could not measure the use of cabozantinib and nivolumab, which were approved in 2016. Future studies may assess prescribing patterns of immunotherapies among older adults with mRCC and use data from sources that allow measurement of risk of prognosis and performance status at the baseline.

Conclusions

Among mRCC patients who received targeted therapies, fifty percent received two or more lines of targeted therapies. Prescribing patterns of targeted therapies were generally consistent with NCCN recommendations. OS was significantly higher and THC was significantly lower for patients who received multiple lines of therapies compared to patients who received a single line. However, OS and total healthcare costs did not differ significantly by the type of targeted therapy sequence prescribed.

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Chapter 5: Discussion

Summary of findings

This dissertation focused on three specific issues related to healthcare cost, overall survival and treatment modalities among older mRCC patients. The first study examined the direct healthcare cost and the total economic burden of RCC on Medicare. It also examined cost drivers of total healthcare costs by stage at which RCC was diagnosed. The second study specifically included RCC patients newly diagnosed at stage-IV (metastatic) and examined the prevalence of cytoreductive nephrectomy (CN) and targeted therapy use and comparative effectiveness of the combined use of CN and targeted therapy versus targeted therapy alone strategy. The overall survival (OS) and total healthcare cost (THC) were the main outcomes. The third study specifically described the prescribing patterns and sequencing of targeted therapies among mRCC patients and described the OS and THC among the most common patterns.

Based on our analysis, the economic burden of RCC on Medicare was found to be between US $1.5 to 2.2 billion, the average THC associated with RCC was $7,419. Based on phase-based cost approach we found that for patients diagnosed at earlier stages, initial and late phase costs could be substantially higher than the continuing phase of care. For stage-IV patients though, THC was higher for all the phases of care due to shorter OS among these patients. This is the first study in the targeted therapy era, which assessed the healthcare costs by stage at which the RCC was diagnosed. Our findings suggested that the average THC and the economic burden varied substantially by the stage at which RCC was diagnosed. Despite of lower prevalence, patients diagnosed at stage-IV accounted for 50% of total economic burden. Patients diagnosed at stage-I accounted for the second largest component of the total economic burden. The average THC associated with stage-IV was 9 times higher than patients diagnosed at stage-I. Study findings

suggested that hospital costs was the primary drivers of THC for stages I-III whereas prescription drug cost was the primary drivers of THC among stage-IV patients. According to NCI, a 5-year survival rate for patients diagnosed at stage-IV is only 12%. Although targeted therapies have marginally improved OS among stage-IV patients, the unmet needs could be much higher among stage-IV patients compared to patients diagnosed at earlier stages as the OS is lowest but the average THC is the highest in this patient group.

Among newly diagnosed mRCC (stage-IV) patients, 29% received targeted therapy alone, 9% received CN alone, and 16% received both CN and targeted therapy. About 47% did not receive either targeted therapy or CN, which are considered as primary treatments for mRCC. Prevalence of patients who received targeted therapy or CN in our study was much lower than previously published studies on commercially insured patients. In addition to factors such as older age, NCI comorbidity index score, and presence of liver/ brain metastasis, we found that living in the south and north central region, and rural areas was associated with lower odds for receiving CN. Results from survival analysis suggested that combined use of CN and targeted therapy played an important role in improving the OS among mRCC patients. Patients who received CN + targeted therapy had a lower risk of death and a higher median OS compared to patients that received targeted therapy alone. These findings, when taken in the context of previously published studies, suggest that among clinically appropriate mRCC patients CN plays an important role in extending overall survival. Further, lifetime cost associated with the use of CN+ targeted therapy was similar to targeted therapy alone group, which suggested that use of CN prior to targeted therapy use may not increase the monthly THC on Medicare.

Prescribing patterns of targeted therapy among mRCC patients, for the most part, were consistent with the NCCN guidelines. Findings were also consistent with previous studies in terms

of drug-level and class level sequencing. About 25% of mRCC patients received temsirolimus as a second line therapy which can be considered as a deviation from the NCCN guidelines. About 50% of mRCC patients who received targeted therapy, received multiple lines of therapies. This number may increase in the future with the approval of several targeted / immunotherapies. Results from the survival analysis suggested that the median OS increased with the addition of an extra line of treatment. Study findings also suggested that among patients who received two or more lines of therapies, the OS and median monthly THC was similar across targeted therapy sequences. However, our findings related to treatment sequencing and OS or THC were descriptive and did not control for baseline prognosis or performance status.

Implications

Several targeted therapies and immunotherapies are being studied in clinical trials for mRCC as well as in the adjuvant setting for patients with recurrent disease. Findings from the economic burden study can be used as a baseline to assess the value of emerging therapies and to develop key value messages for payers. Interventions that prevent or detect RCC at earlier stages or manage RCC with fewer complications have the potential to generate cost savings. Understanding of cost drivers by stage at diagnosis would help Medicare in the allocation of resources and annual budget planning. Findings related to the association between the combined use of CN + targeted therapy and OS provided an additional evidence for the potential benefits of CN in the targeted therapy era. Assessment of predictors for CN or targeted therapy use would help to identify patients that are good candidates for RCTs and to explore reasons underlying disparities observed in our study. Findings on prescribing patterns of targeted therapies would be useful to understand the extent to which targeted therapies were prescribed as per the NCCN

guidelines. Further, our findings provided real-world evidence on the OS and THC for targeted therapy sequences among older adults.

Future research

This study assessed the economic burden of RCC using the prevalence-based design. Future research can be conducted using the incidence-based design to examine healthcare costs that occur during the lifetime of patients from diagnosis until death. Incidence-based cost studies may help to better understand healthcare cost during the initial, continuing and terminal phase of care. Future studies may also assess financial burden to patients and indirect costs to assess the societal impact of RCC. Our study could not examine the health-related quality of life (HRQoL) of mRCC patients who received targeted therapy and/or CN. Assessment of HRQoL in addition to the OS and healthcare cost would help in the complete assessment of the comparative effectiveness of CN and targeted therapy. Further, it would be interesting to understand the effects of timing and sequencing of CN and targeted therapy on the overall survival and HRQoL. Also, individually targeted therapies can be compared in the adjuvant setting (after CN) for their outcomes. Several studies including ours have assessed the combined use of CN and targeted therapy to targeted therapy alone. Sunitinib was the commonly assessed targeted therapy in these studies. Other targeted therapies and immunotherapies can be compared in the adjuvant setting for their effects on OS, HRQoL, and THC.

From 2016, several immunotherapies such as nivolumab have been approved to treat mRCC. Combinations of immunotherapies and/or targeted therapies are also being assessed in the RCTs. Future research may compare new therapies and their combinations among older adults for their OS, HRQoL, persistence and total healthcare costs. These outcomes can be studied using the electronic health records in addition to registry and claims data to get the information on laboratory

values that are used in the Heng's or MSKCC criteria. This would allow researchers to classify mRCC patients into risk groups based on their baseline prognosis and to study outcomes stratified by the baseline risk of prognosis. The landscape of systemic therapies has changed even further after 2016. As a result, selecting a systemic therapy for the first and subsequent lines has become more complicated. Future studies may assess prescribing patterns of immunotherapies, patient and physician-level factors associated with treatment choices and the effects of prescribing patterns on the health outcomes.

VITA

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