THE EFFECT OF ADJUVANT AND NEOADJUVANT SYSTEMIC THERAPY ON THE TREATMENT OUTCOMES OF RENAL CELL CARCINOMA PATIENTS

by

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(Under the Direction of Henry Young)

ABSTRACT

Renal cell carcinoma is one of the most commonly diagnosed urological malignancies in the United States of America. The clinical management of renal cell carcinoma has evolved over the years with the emergence of novel therapy such as systemic therapy. This present study examined the effect of adjuvant and neoadjuvant systemic therapy on the survival and mortality of renal cell carcinoma patients. Our study also assessed the sociodemographic and clinical factors associated with time to systemic therapy initiation. This retrospective study utilized Surveillance, Epidemiology, and Ends Results (SEER) Research Plus dataset of patients 55 years and older, diagnosed with renal cell carcinoma from 2010-2019. Deidentified data from 122 patients who received neoadjuvant systemic therapy and 943 patients received adjuvant therapy was used in the analyses. The outcome variables for this study include all cause-mortality, overall survival, cancer-specific survival, and time to treatment initiation. Demographic and clinical variables of interest include age, sex, race, income group, region of residence, ethnicity, tumor size, tumor grade, tumor stage, and presence of distant organ metastases. Findings from this study suggest that adjuvant systemic therapy, older age, race, and metastases to the lungs are associated with all-cause mortality and are also associated with poor overall and cancer-specific survival. Time to systemic

treatment was found to be significantly associated with race, gender, ethnicity, marital status, and tumor stage.

INDEX WORDS: Renal cell cancer, systemic therapy, time to treatment initiation.

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DEDICATION

I dedicate this dissertation to my loving parents whose unwavering support and encouragement have been the foundation of my academic journey. Their belief in my potential, love and understanding have provided me with a nurturing environment throughout my academic pursuits.

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CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

Epidemiology of Renal Cell Carcinoma

Renal cell carcinoma (RCC) is a common cancer globally, as of 2018 approximately 400,000 people were diagnosed with RCC .[1] There has been a notable increase in RCC incidence rates with time with RCC being one of the ten most common malignancies in the United States.[1,2] Most renal cancers are adenocarcinomas arising from the renal parenchyma.[3] Renal cell tumors represent a group of histopathological and molecularly heterogeneous tumors with different sets of genetic and epigenetic abnormalities.[4] Smoking, obesity, and hypertension are established risk factors for RCC development.[5] Hereditary types of RCC exist, with von Hippel-Lindau (VHL) related RCC being the most common.[5] Cancers of the kidney are more common in men than in women, over the last few decades, the incidence has been increasing in many parts of the world with about 59% of renal cancer cases occurring in more developed countries.[6] The global incidence rates are highest in Europe, North America, and Australia and lowest in Africa, India, and China.[6] Due to the several risk factors that are characteristic of modern societies, the RCC is the seventh most common neoplasm in developed countries.[7,8]

In terms of racial trends, despite having limited access to care at the population level, the rates of RCC have increased more rapidly among black patients compared to whites.[9] Comparative analyses of black and white patients with RCC showed that black patients present with a lower stage of RCC but have a worse prognosis.[10,11] For those with metastatic disease, the prognosis is

extremely poor despite advances in RCC multimodal treatment.[6] Few studies have examined the survival trends for RCC. Research has shown that about 75% of patients with localized disease will have a five-year survival after treatment, while only less than 10% of patients with higher stage disease will survive five years after treatment.[12]

Subtypes and Molecular Characterization

The pathological epidemiologic features of subtypes of renal cell tumors are based on the provisional classification of renal cell tumors which has been revised and published in the 2016, the World Health Organization (WHO) classification.[4] The revised WHO classification is based on advances in the understanding of newly identified characteristics of the molecular pathological epidemiology of renal cell tumors. The Majority of the International Society of Urological Pathology (ISUP) Vancouver classification of renal neoplasia[13] was adopted for the revised 2016 WHO classification of renal cell tumors.[14] The ISUP molecular characterizations have guided the clinical and therapeutic management of the different subtypes of RCC.[13] The four main subtypes of renal cell carcinoma in adults are clear cell, papillary, chromophobe and collecting-duct carcinoma RCC.

According to the 2004 WHO classification system, the most common type of RCC is clear cell RCC which accounts for 70 - 85% of the histopathological subtype cancer.[15] The remaining subtypes comprise papillary, chromophobe, collecting duct, unclassified, and Xp11.2 transposition; they are often classified as non-clear cell RCC.[15] Approximately four to six percent of RCC tumors cannot be assigned to any specific RCC subtypes.[16] There are also rare benign primary renal tumors with unique microscopic features called oncocytomas.[6] The ISUP characterizations summarized the molecular pathology of genitourinary tumors for consideration by clinicians when formulating treatment plans.[17]Studies have demonstrated a relationship

between polygene mutation (the tumor suppressor gene Von Hippel–Lindau) and RCC. VHL is the prototypical hereditary renal cancer syndrome, associated with multiple clear cell RCC tumors and renal cysts; patients with von Hippel-Lindau disease have a germline mutation of the VHL gene, which is also commonly mutated in sporadic renal cancer.[18] The VHL disease is caused by an autosomal-dominant constitutional mutation in the VHL gene that predisposes to clear cell RCC and other proliferative vascular lesions.[18 19]

RCC proves to be an extremely heterogeneous disease beyond the seminal genetic alteration (mutation, deletion or hypermethylation) of the VHL tumor suppressor gene, which is present in the vast majority of sporadic RCCs.[20] Other genetic alterations may occur, especially over time,[21] hence worsening the prognosis of patients harboring these tumors.[22] Three of these genes (PBRM1, BAP1 and SETD2) are located on the same short arm of *chromosome 3* where the VHL gene is also located.[22] Some RCCs are characterized by mutations in the mammalian target of rapamycin (mTOR) pathway, and especially in the highly conserved FAT (FRAP, ATM, TTRAP) and kinase domains of the mTOR gene.[23] These cancers have been defined as metabolic RCCs.[23]

A comprehensive molecular characterization has shown papillary RCCs, type 1 and type 2 papillary RCCs to be clinically and biologically distinct. [24] Alterations in the MET pathway was associated with type 1 and activation of the NRF2-ARE pathway was associated with type 2, while CDKN2A loss and a CpG island methylator phenotype in type 2 contributed to a poor prognosis.[24] A different molecular subtype of renal cell carcinoma, the fumarate hydratase (FH)-deficient RCC, occurs in younger patients (median age: 39–45 years).[25] The FH-deficient RCC is associated with hereditary leiomyomata renal cell cancer syndrome (HLRCC), an autosomal dominant disorder characterized by uterine and cutaneous leiomyomas and increased predisposition to an aggressive

form of RCC.[25-27] For clear cell RCC, VHL mutations are well known, while the papillary RCC is now known to include likely several different molecular entities, such as FH deficient RCC.[17]

Clinical Management of Renal Cell Carcinoma

Surgical resection of clinically localized RCC remains the mainstay for curative intervention.[28] Approximately 20%–40% of patients will develop disease recurrence, and two-thirds of these patients will have their disease recur within the first year after nephrectomy.[28] Partial nephrectomy is considered to be the surgery of choice in the treatment of localized RCC.[29,30] Radical nephrectomy is commonly used in clinical practice, in cases of renal hilar tumors or large tumors ,ret4agreater than four cm that could significantly impair patient survival with a decrease in glomerular filtration rate and quality of life.[31-33] Multiple systemic treatment options have emerged to treat metastatic RCC by targeting the molecular pathways that promote angiogenesis of metastatic RCC.[34] The VEGF protein and related receptors have been the main target of these systemic therapies and have produced robust clinical effects in metastatic RCC,[34] leading to the regulatory approval of two agents, sorafenib (Nexavar®; Bayer Pharmaceuticals, West Haven, CT and Onyx Pharmaceuticals, Richmond, CA) and sunitinib (Sutent®; Pfizer Inc., New York, NY) for advanced RCC.[35,36] Additionally, bevacizumab (Avastin®; Genentech, South San Francisco, CA), a VEGF ligand-binding agent, has also demonstrated anti-tumor activity in metastatic RCC.[37,38] and temsirolimus (CCI-779; Wyeth Pharmaceuticals, Collegeville, PA), an inhibitor of mTOR, demonstrated an overall survival improvement in RCC patients with multiple adverse risk features.[39]

Table 1. shows a list of a few selected approved systemic therapies for RCC. Adjuvant therapy in patients with high-risk RCC is a challenging scenario for patients and their oncologists.[40] Tumor size reduction can prompt kidney preservation, resulting in significant

preferences for the patient, this goal can be achieved using neoadjuvant targeted therapy.[41] One of the most critical issues for adjuvant treatment is patient selection, identifying which patients with localized disease are at increased risk of relapse and may benefit from treatment in addition to surgery. [42]With RCC being an immunologically influenced malignancy, immune checkpoint inhibitors have shown significant antitumor activity with prolonged and durable responses in metastatic RCC, which led to an interest in evaluating these agents in the adjuvant setting.[40] Pembrolizumab and nivolumab have shown some efficacy for some tumors such as melanoma in the adjuvant setting.[42]

A recent phase III double-blind, randomized clinical trial, the Keynote-564 trial, recruited patients diagnosed with RC, at high risk for recurrence after nephrectomy and compared adjuvant therapy with pembrolizumab with placebo for up to 1 year until disease recurrence or unacceptable toxicity.[43] In the Keynote study, patients who were at high risk for recurrence after nephrectomy, with or without metastases removal, received either adjuvant pembrolizumab (at a dose of 200 mg) or placebo intravenously once every 3 weeks for up to 17 cycles (approximately 1 year).[43] The primary end point was disease-free survival (DFS), while overall survival was a key secondary end point.[43] Pembrolizumab therapy was associated with significantly longer disease-free survival than placebo (DFS at 24 months, 77.3% vs. 68.1%; hazard ratio for recurrence or death, 0.68; 95% confidence interval [CI], 0.53 to 0.87; P = 0.002).[43] The estimated percentage of patients who remained alive at 24 months was 96.6% in the pembrolizumab group and 93.5% in the placebo group (hazard ratio for death, 0.54; 95% CI, 0.30 to 0.96).[43]The results from the Keystone trial showed that the risk of recurrence or death was 32% lower with pembrolizumab (HR 0.68, 95% CI 0.53 to 0.87, p = 0.002) compared to placebo.[43] The findings from this trial supports the use of pembrolizumab as adjuvant immunotherapy in patients with renal-cell carcinoma and an

intermediate-to-high or high risk of disease recurrence. These results led to the FDA approval of adjuvant pembrolizumab in November 2021, a landmark moment in the history of RCC.[42]

Tyrosine kinase inhibitors (TKIs) have been the focus of extensive efforts in developing an effective adjuvant RCC treatment.[44] Adjuvant therapy with TKIs such as axitinib, pazopanib, sorafenib, and sunitinib failed to substantially improve disease-free survival outcomes in randomized Phase III trials, including in the double-blind, three-group Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma (ASSURE) trial of sunitinib or sorafenib as compared with placebo.[45-49] However, sunitinib as adjuvant treatment for patients at high risk of recurrence of RCC following nephrectomy showed a significant disease-free survival (primary end point) with sunitinib compared with placebo.[50] Sunitinib also improved overall survival by almost five months compared to IFN-α in a phase III clinical trial.[51]

Previous randomized clinical trials have been conducted focused on tyrosine kinase inhibitors in an effort to develop an effective adjuvant RCC treatment. These studies include the ASSURE, S-TRAC, PROTECT, ATLAS, SORCE and EVEREST clinical trials. ASSURE (Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma) was the first phase III trial assessing the efficacy of TKIs in adjuvant RCC patients.[46] No significant difference was found in the primary endpoint of DFS for either sunitinib or sorafenib relative to placebo (median DFS: 5.8, 6.1 and 6.6 years for sunitinib, sorafenib and placebo, respectively; OS: 77.9%, 80.5% and 80.3%, respectively). S-TRAC (Sunitinib Trial in Adjuvant Renal Carcinoma) was a randomized, double-blind phase III study comparing sunitinib versus placebo for one year in 615 patients at high-risk of recurrence from 99 centers.[50] The S-TRAC study considered a higher risk population than ASSURE, with locoregional high-risk stage T3-T4 disease.[50] When compared to the ASSURE study, DFS was prolonged in the sunitinib group, however, this must be balanced against

toxicity and quality of life considerations; 48% of the patients in the treatment group experienced grade three to four adverse events. The difference in outcomes could be due to the fact that ASSURE included patients with early stage (T1) tumors while S-TRAC focused on a higher risk population with T3-T4 disease. ATLAS (Adjuvant Axitinib Therapy of Renal Cell Cancer in High-Risk Patients) was a phase III double-blind trial comparing adjuvant axitinib versus placebo in 724 patients with locoregional RCC.[49]

Not all trials of tyrosine kinase inhibitors in adjuvant settings have demonstrated increased overall or disease-free survival. The PROTECT trial evaluated efficacy and safety of pazopanib in 1538 patients with localized or locally advanced RCC at high-risk of relapse following nephrectomy.[47] The trial was stopped following interim analysis due to there was no significant difference detected in DFS in either treatment or placebo groups.[44,49] However, in the highest-risk subpopulation (pT3 disease with Fuhrman grade 3 or above, or pT4 and/or lymph node positive, any T and any Fuhrman grade), reduction in risk of a DFS event of 36% and 27% was detected by investigators and independent review committee, respectively.[44] In terms of clinical presentation, up to 10% of RCC cases present with characteristic clinical symptoms consisting of hematuria, lateral dorsal or flank pain and palpable abdominal mass,[6]with over 60% being detected incidentally in routine ultrasound examination.[52]RCC has the highest fatality rate among urological neoplasms. Although the overall 5-year survival rate is 76%, this value drops dramatically to 12% in patients with stage IV disease.[7] Approximately 30% of patients newly diagnosed with RCC have metastatic disease, while 20–50% of patients treated for localized disease will eventually relapse and progress to the metastatic stage.[7,53] Late presentation has been shown to affect timely diagnosis of RCC. Despite the advances in diagnosis, especially improved imaging techniques, about 20–30% of all patients are diagnosed with metastatic disease.[6]The

management of advanced or metastatic RCC has changed dramatically over the past 30 years.[54] The NCCN Guidelines for Kidney Cancer provide multidisciplinary recommendations for the clinical management of patients with renal cell carcinoma.[55] RCC has long been treated primarily by surgery and cytokine-based therapy.[56] An enhanced understanding of the underlying biology of RCC has led to systemic therapy targeting the vascular endothelial growth factor (VEGF) and the mammalian target of rapamycin (mTOR) pathways or inhibiting the interaction of the programmed death 1 receptor with its ligand. Novel agents blocking these pathway elements have demonstrated efficacy and offer useful treatment options for patients with RCC.[55]

For advanced RCC cases, interferon alpha (IFN-α) therapy has been known to slightly improve survival, and interleukin-2 therapy produced durable complete remission in only a small number of patients.[57,58] In 2005, the molecular-targeted agent sorafenib was approved in the USA for use in the treatment of advanced RCC, opening the new era of molecular-targeted therapy.[56] Before the introduction of molecular-targeted drugs, radical nephrectomy was the preferred treatment, especially in patients with good performance status, based on the results of randomized clinical trials.[59,60] Therapeutic options for RCC are limited due to resistance to chemotherapy and radiotherapy and to the low efficiency and toxicity of immunotherapy.[61,62] The mechanisms of resistance to chemotherapy in RCC remain unclear. [63] Single agent cytotoxic chemotherapies in RCC such as gemcitabine, and the fluoropyrimidine derivative vinblastine failed to show a benefit when given either weekly or as continuous infusions.[64-66]

Traditional chemotherapy and radiation therapy are largely ineffective in the treatment of all RCC subtypes.[67] The lack of sensitivity to chemotherapy and radiation therapy prompted research efforts into novel treatment options.[67] The development of targeted therapeutics, including multi-targeted TKIs and mTOR inhibitors, has been a major breakthrough in RCC therapy

especially for clear cell RCC which represents about 85% of all RCC tumors.[67] Ongoing studies continue to evaluate the efficacy of targeted therapy in combination with cytotoxic chemotherapy in patients with aggressive phenotypes.[63] Although surgery continues to be the mainstay of therapy even in the setting of locally advanced disease, resection in the setting of large or complex tumor may be high risk and involve adjacent organ resection or great vessel reconstruction or both.[68] More than 20% of patients undergoing nephrectomy will develop metastases during follow-up.[69] For patients with non-metastatic disease, surgical resection through partial or radical nephrectomy is the current standard-of-care.[70] Surgical removal of the localized renal tumor, in some cases combined with removal of metastases, remains the only curative treatment for RCC. Patients with advanced disease might benefit from modern systemic therapy, which has contributed towards a better understanding of RCC biology and carcinogenesis.[71] Around 30–40% of patients with high-risk features such as high nuclear grade, locally advanced stage, and/or regional lymph node involvement experience disease recurrence which is generally incurable.[72] The optimal treatment strategy for such high-risk patients may involve offering an effective anticancer perioperative systemic treatment with the goal of eradicating micro-metastatic disease and potentially improving cure rates, without subjecting patients to significant toxicity.[72]

Systemic Adjuvant and Neoadjuvant Therapy

Until the last decade, pharmacological treatment options for RCC were limited. The lack of sensitivity to chemotherapy and radiation therapy prompted research efforts into novel treatment options for renal cell carcinoma.[67] Systemic therapy for RCC includes targeted therapy, chemotherapy, hormone therapy and immunotherapy. Before the advent of targeted therapies, the two most used agents were the immunomodulatory cytokines interleukin (IL-2) and IFNa.[73] Initially based on a non-specific immune approach (high-dose IL-2 and interferon-α), this strategy

evolved to target the tumor vasculature, intracellular oncogenic pathways and the immune system signaling cascade. Despite inducing highly durable responses in a limited number of patients, the efficacy of IL-2 and IF-a were considerably low (reported response rates were 12% for interferon-α and 15% for IL-2), and their toxicity rather high, particularly that of IL-2.[74,75] Cytokine-based systemic therapy were the first-line pharmacologic agents for RCC for almost two decades. They still do not fulfill the treatment needs of patients with RCC due to limitations in treatment outcomes and safety.[73]

The treatment of advanced clear cell RCC has dramatically changed over the last decade with the introduction of targeted agents including tyrosine kinase inhibitors.[76] Although cytokine based therapy and tyrosine kinase inhibitors have significantly improved outcomes, studies show that they rarely result in complete responses.[77,78] Renal cell carcinoma is considered to be an immune-responsive tumor and immunotherapy with high dose IL-2 has been used in select patients leading to complete and durable responses in a subset of patients.[58] Interferon- α and IL-2 were later replaced by targeted approaches directed at either the endothelium of the tumor vasculature (anti-VEGF drugs) or at the tumor's oncogenic pathways (mTOR inhibitors).[54]

Anti-VEGF drugs include orally available TKIs targeting circulating VEGF itself or its receptors (axitinib, cabozantinib, lenvatinib, pazopanib, sorafenib, sunitinib and tivozanib), as well as an intravenously administered anti-VEGF antibody (bevacizumab combined with interferon alfa-2a), whereas mTOR inhibitors include temsirolimus and enviroximes.[75,79] More refined and novel immunotherapies have been developed due to improved understanding of T-cell function and associated immunosuppressive molecules such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), program death 1 (PD-1) and PD-1 ligand 1 (PD-L1), called immune checkpoints.[80] Molecular-targeted drugs, particularly tyrosine kinase inhibitors cause shrinkage of primary

tumors, making them great candidates for use in preoperative therapy in locally advanced cancer.[56] Targeted systemic therapy in RCC clinical management can be done in a neoadjuvant (pre-surgery) and adjuvant (post-surgery) settings. Preoperative neoadjuvant therapy should be considered to enable surgery or to decrease surgical invasiveness (including sparing of renal function); postoperative systemic therapy could prevent recurrence and improve prognosis.[56] Adjuvant therapy in RCC management may help reduce recurrence or tumors and to decrease the rate of relapse after nephrectomy. Their use in preventing recurrence and improving prognosis in patients with a high risk of recurrence should be considered, apart from their tendency to decrease surgical complexity.[56] The substantial responses observed with targeted agents in the treatment of patients with RCC have sparked interest in their use in the neoadjuvant and adjuvant setting.[73] Potential benefits with such therapy include reduction of the patient's overall tumor burden and tumor down staging.[81] Targeted therapies have demonstrated improved survival outcomes over traditional immunotherapeutic regimens with better tolerability.[74,82,83]

Recent studies have evaluated the role of systemic adjuvant and neoadjuvant therapy in the treatment and clinical management of locally advanced or metastatic RCC.[68] Neoadjuvant targeted therapy offers the potential advantage of tumor cytoreduction, which may make surgical interventions possible in some patients who would not otherwise be surgical candidates because of locoregional disease otherwise unresectable or in the setting of imperative indication for nephron-sparing surgery when partial nephrectomy is thought not to be safe or feasible.[68] Localized RCC has an associated risk of recurrence after nephrectomy.[40]Although systemic therapies targeting angiogenic pathways that are effective in metastatic RCC failed to show an improvement in overall survival in the adjuvant setting, immune checkpoint inhibitors have shown significant antitumor activity with prolonged and durable responses in metastatic RCC which led

to an interest in evaluating these agents in the adjuvant setting.[40]. While many patients with non-metastatic RCC can be cured with surgery alone, upward of 40% of patients recur in a short delay, raising the question of additional perioperative treatments.[84]

Multiple trials have investigated the addition of systemic therapy after surgery in localized or locally advanced RCC.[84] Neoadjuvant therapy facilitates surgery, reducing risks for patients and increasing the possibility of removing the mass thereby improving oncological results in terms of risk of progression and survival. [85] Several TKIs have been reported to decrease tumor size in most patients with localized and locally advanced RCC, including sunitinib and pazopanib.[48,86,87] Localized RCCs are best managed with nephrectomy, irrespective of the surgical approach.[88] Radical/cytoreductive nephrectomy or partial nephrectomy is unsuitable in some patients with localized or locally advanced RCC due to large tumor, unfavorable tumor location or the involvement of adjacent organs.[88] TKIs can possibly downsize a primary RCC tumor[89]. In a study on 17 patients with metastatic RCC, sunitinib induced a 31 % shrinkage in tumor size.[90] The rationale for the use of TKIs in neoadjuvant setting is to preoperatively shrink the tumor size and restrain the tumor from adjacent important structures. TKIs are used as first line treatment options for both clear and papillary cell RCC.[91] Figures 1.1 and 1. 2 show the rank order of first and second line options for the management of clear cell RCC and papillary RBCC.*[91]* The effect of preoperative TKIs neoadjuvant therapy on tumor reduction and surgical facilitation has been demonstrated previously[88,92] with a tumor volume reduction rate of 21–47%.[88,93,94]

Zhang et al, evaluated the clinical efficacy of sorafenib as preoperative neoadjuvant therapy in patients with high risk RCC.[88] The researchers analyzed the clinical data of eighteen patients with high risk RCC who received surgery done successfully after preoperative neoadjuvant therapy with sorafenib from April 2007- October 2013.[88]Preoperative neoadjuvant therapy with sorafenib

for high risk RCC patients significantly decreased primary tumor volume as well as tumor thrombus, which could increase the success of the nephron-sparing surgery or radical nephrectomy.[93] Another multicenter study of patients who received neoadjuvant sunitinib before planned nephron-sparing surgery (NSS) was done from February 2006 to February 2009 evaluated the effect of neoadjuvant sunitinib on the reduction of tumor size .[94] All patients underwent confirmatory biopsy for clear cell renal cell carcinoma and received two 28-day cycles of sunitinib before NSS.[94] The researchers assessed the demographic and tumor characteristics including tumor response, outcomes and complications.[94] The study by Zhang et al found that neoadjuvant sunitinib followed by imperative NSS is safe and feasible, with all patients achieving a reduction in maximum tumor diameter, and with NSS being achievable with negative margins and with no requirement for postoperative dialysis.[94]

Neoadjuvant systemic therapy may not always be tolerable in neoadjuvant and adjuvant settings. A study examined the effects of neoadjuvant axitinib for the treatment of localized renal cell carcinoma has on body compartment composition.[95] This clinical trial enrolled 24 patients with locally advanced non-metastatic biopsy-proven clear cell renal cell carcinoma.[95] Patients received axitinib orally for up to 12 weeks.[95] Computed tomography scans were completed before the start of treatment, after 7 weeks of treatment and at the completion of 12 weeks of treatment.[95] Chery et al in this study found that axitinib resulted in a decrease in skeletal muscle and subcutaneous adipose tissue, as well as weight loss.[95] They also found that patients with baseline sarcopenia tended to have a lower response rate to neoadjuvant axitinib.[95].Although the study done by Cheryl et al enrolled patients with non-metastatic disease, the findings are relevant since sarcopenia has been shown to be predictive of treatment related toxicity in patients with metastatic RCC receiving sunitinib or sorafenib.[96-98] Axitinib an oral tyrosine kinase inhibitor,[99]is used to

treat metastatic RCC and has also been used in the neoadjuvant or preoperative setting, mostly in the context of clinical trials.[100] It has been shown to be clinically active and reasonably well tolerated in the neoadjuvant setting in patients with locally advanced nonmetastatic RCC.[100]Neoadjuvant therapy of advanced RCC mainly aims to prevent local progression and possible metastasis, increasing the feasibility of tumor resection for certain patients.[101] The use of targeted systemic therapy before surgery, primary and metastatic tumor shrinkage or stabilization could be achieved in 70%–80% of metastatic RCC patients.[102] Although no direct study showed that neoadjuvant targeted therapy could prolong overall survival, it has been proven to be able to make some unresectable renal tumors respectable or make partial nephrectomy possible for some complex renal tumors.[103]

Studies have documented racial disparities in survival and outcomes for patients with RCC. Black patients with RCC have been shown to have poorer outcomes compared with White patients regardless of the stage at presentation.[104] Socio-economic factors and differences in prevalence of various histology have been proposed as some of the reasons for these observations.[11,105] Some studies show that there are possibly racial and ethnic differences in treatment and surgical outcomes for renal cell carcinoma patients. Elderly patients, women, and Black patients appear to have worse outcomes and these disparities merit further investigation.[104] Axitinib, which is in the same drug class as sunitinib [106,107] is approved globally for the treatment of metastatic RCC in the second-line setting.[108] A subgroup analyses with the focus on axitinib dosing and by ethnicity, time on treatment, dose modification and toxicity showed no DFS benefit for Asian patients (HR) 0.883 [95% CI 0.638-1.220] treated with masitinib or placebo.[108] Racial and ethnic disparities in RCC treatment outcomes may be associated by sociodemographic factors. A recent study assessed surgical treatment disparities across racial/ethnic groups and impacts of neighborhood

socioeconomic characteristics on surgical treatments and overall mortality in Stage1 RCC patients.[109] When compared to non-Hispanic Whites (NHWs), American Indians/Alaska Natives and non-Hispanic Blacks (NHBs) were more likely not to receive surgical care and all racial/ethnic minority groups had significantly increased odds of undergoing radical rather than partial nephrectomy, even after adjusting for neighborhood characteristics.[109] Racial/ethnic minority patients were found to be least likely to receive surgical treatment, when they do, they are likely to have less optimal surgical treatment (radical rather than partial nephrectomy).[109] This study finding suggests that surgical treatment disparities may account for high RCC mortality in the NHB population.[109] A retrospective cohort study within the Kaiser Permanente healthcare system using records of RCC patients examined differences between Hispanics and non-Hispanic whites diagnosed with and treated for renal cell carcinoma in an equal access healthcare system.[110] With an equal access healthcare system, Hispanics appeared to be diagnosed at younger ages, have greater comorbidities and to present more frequently with clear cell renal cell carcinoma compared with non-Hispanic white patients.[110] For this study, the researchers concluded that despite lower stage and greater receipt of surgery, Hispanic ethnicity was found to be an independent predictor of mortality.[110]

Rationale and Hypothesis

Very few retrospective and prospective studies have attempted to examine the impact of adjuvant and neoadjuvant systemic therapy on the treatment outcomes of renal cell carcinoma patients. Studies have suggested that neoadjuvant systemic therapy such as tyrosine kinas inhibitors, used in the preoperative clinical settings for high risk RCC patients may significantly decrease primary tumor volume and the risk of thrombus formation.[88]Although randomized clinical trials have investigated the roles of systemic adjuvant and neoadjuvant systemic therapy adjuvant in the

clinical management of high-risk metastatic RCC, the findings are still inconclusive. The effect of the systemic therapy on morality and survival outcomes of RCC patients has not yet been fully established by scientific research. Some benefits have been reported on using adjuvant systemic therapy over placebo for patients with locoregional RCC at high risk of recurrence after nephrectomy,[50] also systemic adjuvant tyrosine kinase inhibitors have been reported to reduce relapse after nephrectomy.[111] Clinical guidelines have suggested the use of systemic therapy to improve patient care and quality.[112,113] Since the adoption of these existing clinical guidelines for management of localized RCC, no existing literature has reviewed the effect of systemic therapy on the mortality and survival of RCC patients. Fewer studies have examined the gender and racial disparities in treatment outcomes for RCC patients receiving adjuvant and neoadjuvant systemic therapy. This study will add to the scientific knowledge by evaluating and describing the effect of systemic therapy on RCC patients 'survival and mortality and will also determine if there are disparities overall and cancer-specific survival.

Specific Aims

Specific Aim 1: To evaluate the effect of neoadjuvant and adjuvant systemic therapy on mortality and survival of renal cell carcinoma patients.

Hypotheses:

a) Neoadjuvant and adjuvant systemic therapy are associated with all-cause mortality and overall survival in renal cell carcinoma patients.
b) There are racial and gender disparities in overall and cancer specific survival for renal cell carcinoma patients.

Specific Aim 2: To investigate different demographic and clinical factors influencing time to treatment in a cohort of renal cell carcinoma patients.

Hypothesis:

a) Sociodemographic factors are associated with time to systemic treatment initiation in the management of renal cell carcinoma patients.
b) Clinical factors are associated with time to systemic treatment initiation in the management of renal cell carcinoma patients.

Table 1: List of Available Systemic Therapy for Renal Cell Carcinoma

Drug (Generic name)	**Drug Class**	**FDA Approval Date**	**Administration Route**
Axtinib	Tyrosine Kinase Inhibitor	2012	Oral
Pazopanib	Tyrosine Kinase Inhibitor	2009	Oral
Sunitinib	Tyrosine Kinase Inhibitor	2006	Oral
Sorafenib	Tyrosine Kinase Inhibitor	2005	Oral
Temsirolimus	mTOR inhibitor	2007	Injection
Ipilimumab	Immunotherapy	2011	Injection
Pembrolizumab	Immunotherapy	2021	Injection

Figure 1.1 Systemic First- and Second-Line Treatment of Advanced Clear Cell RCC

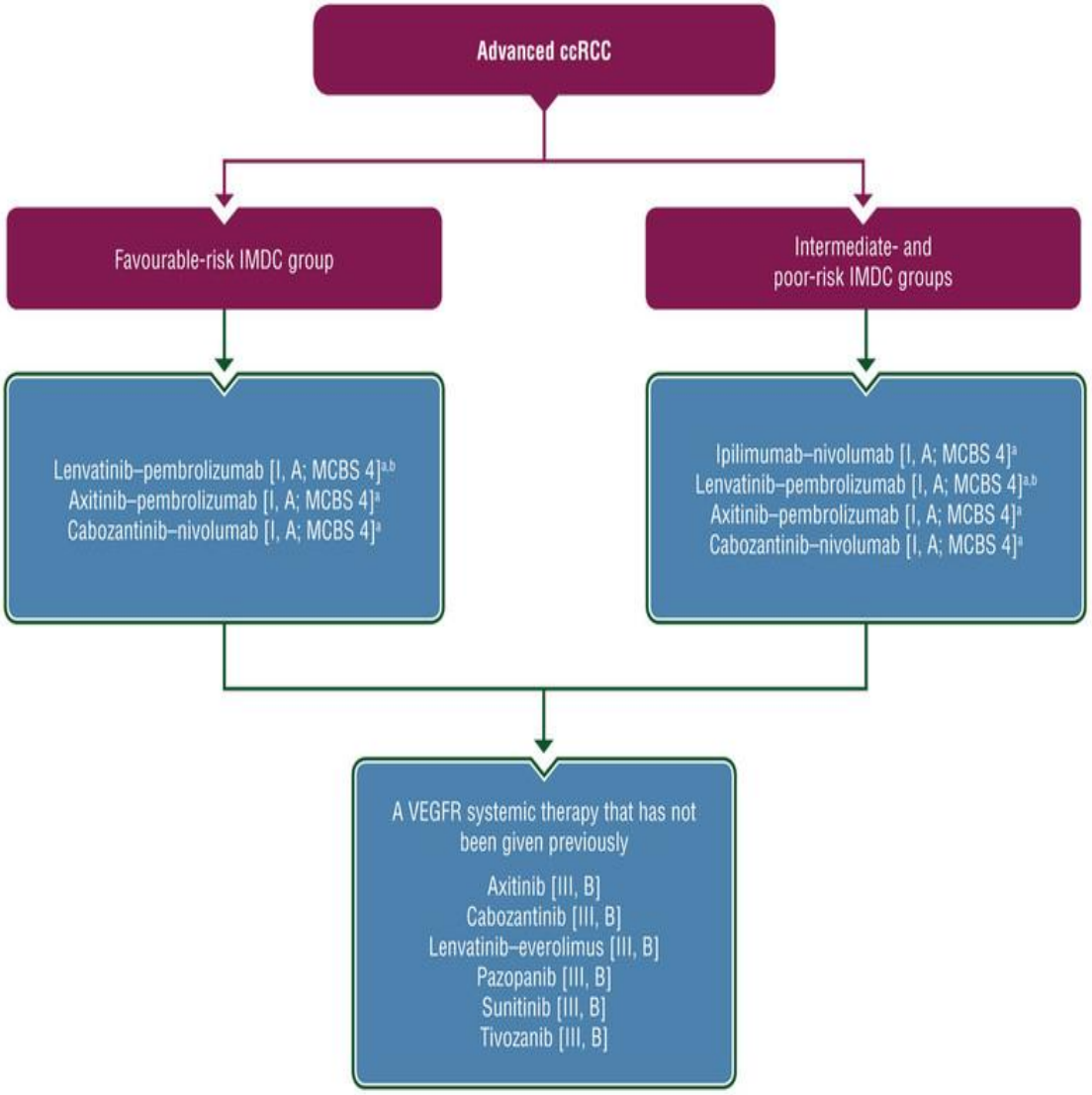

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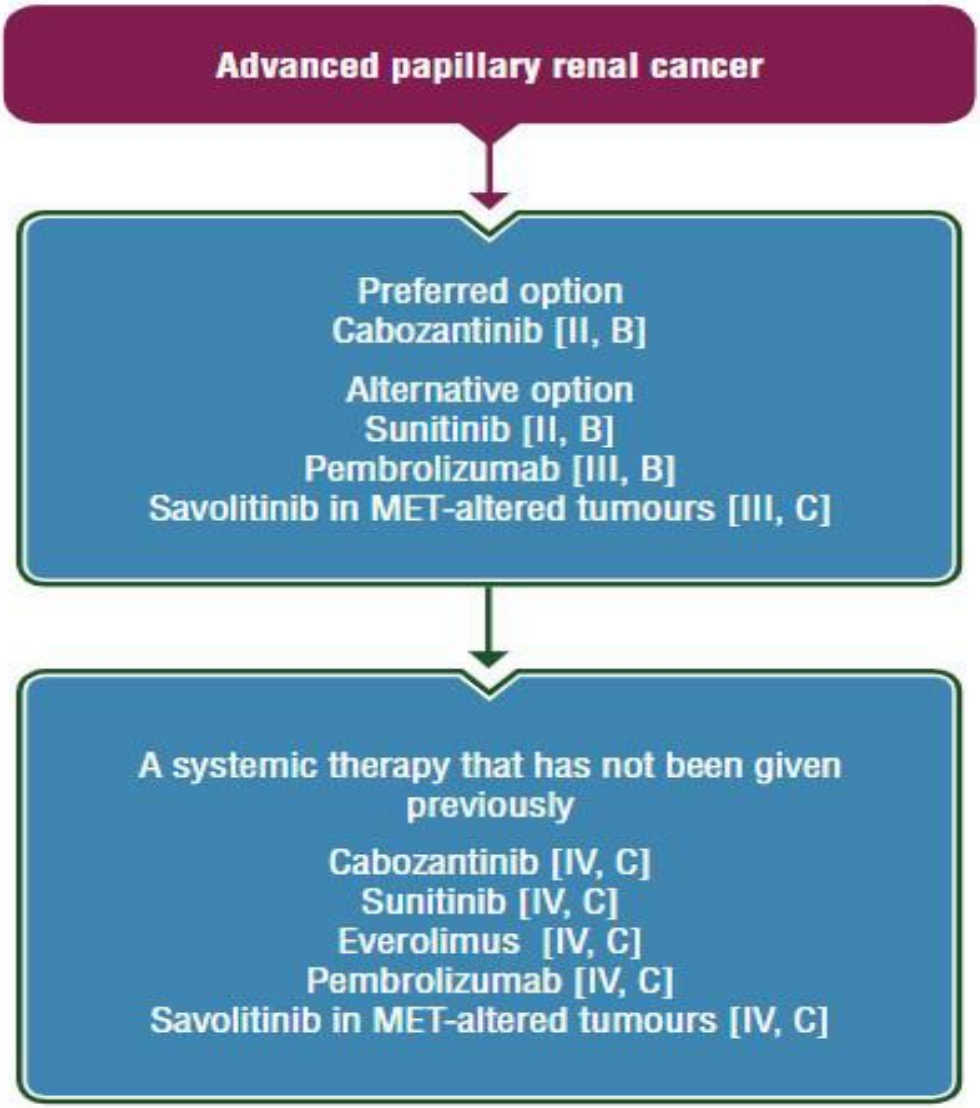
Figure 1.2 Systemic First-Line and Second-Line Treatment for Advanced Papillary RCC



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CHAPTER 2

THE EFFECT OF ADJUVANT AND NEOADJUVANT SYSTEMIC THERAPY ON THE MORTALITY AND SURVIVAL OF RENAL CELL CARCINOMA PATIENTS[1]

[1] Azih I, Young H, Tackett R, Shenoy S, Okosun I. To be submitted to the American Association of Cancer Research

Abstract

Background

Novel therapies such as systemic therapies have been developed and approved for the management of renal cell carcinoma. Very few studies have evaluated the effect of systemic therapy on the mortality and survival of renal cell carcinoma patients. This retrospective study describes the effect of adjuvant and neoadjuvant systemic therapy and other independent factors on the mortality and survival outcomes of renal cell carcinoma patients and also outlines the disparities in overall and cancer-specific survival.

Methods

Data analyzed were extracted from the Surveillance, Epidemiology, and End Results (SEER) Research Plus database and included a cohort of patients 55 years and older, with a diagnosis greater than stage T1 renal cell carcinoma from 2010 –2019, who received either adjuvant or neoadjuvant systemic therapies. Records of 1065 patients who received systemic therapy were analyzed, a total of 122 patients received neoadjuvant systemic therapy while a total of 943 received adjuvant therapy. The primary outcome was all cause-mortality, secondary outcomes were overall and cancer-specific survival. For this study, demographic and clinical variables of interest include age, sex, race, income group, region of residence, ethnicity, systemic therapy group (adjuvant or neoadjuvant) tumor grade, tumor stage, presence of adrenal gland involvement and presence of distant organ metastases. Binomial logistic regression analysis was used to determine the association between the independent prognostic factors and all-cause mortality. Multivariate Cox proportional hazards models and Kaplan Meir models were used to

estimate the effect of systemic therapy and other independent factors on the overall survival, and cancer-specific survival.

Results

Adjuvant systemic therapy (OR 1.75, p<0.01), older age (OR 2.02, p<0.01), black race (OR 1.54) , metastases to the lungs (OR: 2.17, p < 0.0001) , lymph nodes metastases (OR 1.79; p< 0.02) and metastases to other organs (OR 1.60, p < 0.05) were found to be associated with higher odds for all-cause mortality. Although there were no differences in all-cause mortality between black and white patients, AAPI patients had significantly lower odds of all-cause mortality (HR: 0.58, p<0.05) when compared to white patients. The three-year overall survival (OS) and cancer specific survival (CSS) rates for the entire cohort of RCC patients were 49.2% and 53.8%, respectively. Patients who received adjuvant systemic therapy had poorer overall and cancer specific survival (HR 1.64, 1.57; $p < 0.01$) compared to those who received neoadjuvant therapy. Patients aged 76 and above had poorer overall and cancer-specific survival compared to those in the 55- 65 years age group (HR 1.64, 1.54; p < 0.01). The presence of metastases to the lungs was associated with higher odds of mortality and poor overall and cancer specific survival (HR 1.87, 1.97; p <0.0001). Black patients had the poorest overall and cancer- specific survival compared to white patients and patients in the other racial (AAPI) group (HR 2.03 1.92; p < 0.01). Gender was not significantly associated with all-cause mortality, overall and cancer-specific survival.

Conclusion

The result of this study shows that the use of adjuvant systemic therapy is associated with a higher odd for all-cause mortality and poor survival compared to treatment with neoadjuvant

therapy. Older age, race, and metastases to the lungs were also found to be associated with all-cause mortality and poor overall and cancer-specific survival.

Keywords: Renal Cell Carcinoma, Systemic Therapy, Mortality, Survival

Introduction

Renal Cell Carcinoma (RCC) is a common cancer globally and is among the top ten most common malignancies in the United States.[1,2] The incidence of RCC varies geographically, with the highest incidence in developed countries.[3] RCC incidence in men is 1.5 to 2.0 times higher than in women and 60–70 years of age is the prime age for its occurrence. [4] The reason for the higher incidence in developed countries and in men is not clear.[5] Smoking, obesity, and hypertension are established risk factors for RCC development.[6] Hypertension, smoking, and obesity are increasing in developed countries therefore a higher prevalence of RCC is expected in those regions.[7] Hereditary types of RCC also exist, with von Hippel-Lindau (VHL) disease being the most common.[6] VHL disease is caused by an autosomal-dominant constitutional mutation in the VHL gene that predisposes to clear cell RCC and other proliferative vascular lesions.[8-10]

More than 50% of RCCs are currently detected incidentally during clinical examination, making the classical triad of flank pain, gross hematuria, and palpable abdominal mass less frequent than in the past.[11] Surgical resection, radiotherapy, chemotherapy, and immunotherapy are therapeutic options applicable for solid tumors like RCC.[12] The treatment of RCC has changed greatly over the past fifteen years. Progress in the surgical management of the primary tumor and increased understanding of the molecular biology and genomics of the disease have led to the development

of new therapeutic agents. About three quarters of people with RCC present with localized disease. Definitive local treatment remains the gold standard for managing patients with localized tumors with no evidence of distant metastasis.[5]

Multiple systemic treatment options have emerged to treat advanced or metastatic RCC.[13] Systemic therapies targeted at the molecular pathways inherent to RCC biology that promote angiogenesis have been shown to produce robust clinical effects in metastatic RCC.[13] Vascular endothelial growth factor (VEGF) and related receptors have been the main target of systemic therapeutic agents and have produced robust clinical effects in metastatic RCC, leading to regulatory approval of two tyrosine kinase inhibitors: Sorafenib and Sunitinib.[14,15] Tyrosine kinases play critical roles in RCC blood vessel formation via the growth factor signaling pathway. [16] RCC is one type of immunogenic tumors,[17]and immunotherapy has been approved as a more effective therapeutic option.[12] Though several immunotherapy-based drugs are available, cytokine-based immunotherapy such as IL-2 is still the most commonly used. [12] Bevacizumab, a recombinant human monoclonal antibody against VEGF and temsirolimus, an inhibitor of mammalian target of rapamycin (mTOR) have also shown substantial clinical activity in metastatic RCC.[13] Nivolumab, a human immunoglobulin, is the most recent immunotherapeutic agent to get approval for the use against RCC. [12] Systemic therapies have been used in neoadjuvant and adjuvant settings in the medical management of renal cell carcinoma. Results from several randomized clinical trials of adjuvant sunitinib (S-TRAC, ASSURE), sorafenib (ASSURE) and pazopanib (PROTECT) have been reported.[18] [19] [20] For all these trials (S-TRAC, ASSURE and PROTCECT), only S-TRAC had a positive primary end point, for sunitinib in terms of disease-free survival (DFS) by independent review, but without any overall survival (OS) benefit. [11] This result led to approval of sunitinib by the United States

Food and Drug Administration (FDA).[11] Cytoreductive nephrectomy before systemic therapy is recommended in select patients with a potentially surgically resectable primary tumor mass.[6] Sorafenib and sunitinib were tested in the adjuvant setting soon after their FDA approval for the treatment of metastatic disease. A retrospective analysis conducted indicated that patients most likely to benefit from cytoreductive nephrectomy before systemic therapy were those with lung-only metastases, good prognostic features, and good performance status.[21] Previously, studies have noted that tyrosine kinase inhibitors could downsize primary RCC tumor. [22]

A study on patients with metastatic RCC showed that sunitinib induced a 31 % shrinkage in tumor size.[23] For localized RCC, neoadjuvant treatment may be beneficial to downsize or downstage primary tumors that are considered unresectable, such as tumors associated with vascular invasion, bulky regional lymphadenopathy, or proximity to vital organs.[24] Considering age, racial and gender disparities in survival with targeted therapies, elderly patients, women, and Black patients appear to have worse outcomes.[25] Several analyses of the Surveillance, Epidemiology, and End Results (SEER) database suggest that African American patients with RCC have decreased overall survival compared to Caucasian patients regardless of age, sex, stage, and histologic subtype.[26-28] It remains unclear how the availability of these novel targeted agents for RCC has influenced the racial disparity in survival in advanced RCC, or if the survival of African American patients with advanced RCC has improved as much as that of Caucasian patients.[29]

The survival disadvantage of African American patients may be more prominent in the last decade compared with the 1990's,[26-28,30] implying that AA patients have showed less benefit from the introduction of targeted therapy than Caucasian patients.[29] Some studies have

suggested that the survival disparity seen in African American patients may be related to access to treatment and lower rates of nephrectomy, even among patients with metastatic RCC.[27,31,32]

Very few retrospective and prospective studies have attempted to describe the effects of adjuvant and neoadjuvant systemic therapy such as tyrosine kinase inhibitors and immunotherapy, on the mortality and survival outcomes of RCC patients. Fewer studies have examined the age, gender, and racial disparities in mortality and survival outcomes of RCC patients who received systemic therapy. This retrospective study describes the effect of systemic therapy on RCC patients' mortality and survival and also outlines the age-related, racial and treatment disparities in overall and cancer-specific survival.

Methods

Study Design and Data Source

This retrospective cohort study utilized the Surveillance, Epidemiology, and Ends Results (SEER) Research Plus data set. The SEER dataset used for this study includes patients diagnosed with Renal Cell Carcinoma from January 2010 through December 2019. The SEER registry is a United States (US) nationally representative population-based cancer surveillance system that collects data and information on the incidence and survival rates of cancer, covering approximately 28% of the US population.[33] The SEER data was obtained using the SEER*Stat software which is available through the National Cancer Institute (NCI).[34] The SEER database records various demographic and clinical characteristics, patient sex, race and ethnicity, state and county of residence, method of diagnostic confirmation, age at diagnosis, the month and year of diagnosis, and the month and year of last follow-up or of death.

The SEER data including age, sex, race/ethnicity, and marital status at the time of diagnosis; localized or in-situ malignancies, year of diagnosis are obscured so that it does not identify individuals. In the SEER database, tumor grade was ascertained based on the degree of an abnormal cell's resemblance to its normal counterpart as well, differentiated, moderately differentiated, poorly differentiated, and anaplastic.[35] The tumor size captured in millimeters and the tumor stage were listed as stages I - IV. [35] The number of primary tumors, survival time and vital status were all extracted from the SEER databse.[35-37] The SEER histological broad groupings were listed as adenocarcinoma, transitional cell papilloma and squamous or ductal renal cell carcinoma.[37] Data on time to treatment initiation (in months), survival time and cause of death were also extracted from the SEER Research Plus database.

Study Population and Cohort Selection

The study was restricted to 1065 adults 55 years and older with a confirmed diagnosis of renal cell carcinoma from 2015 to 2019, with SEER summary tumor stage of T1 or greater. Figure 2.1 shows the derivation of the final analytical cohort based on the inclusion and exclusion criteria. Patients diagnosed with RCC before 2005 were excluded due to insufficient data on systemic therapy use before 2005. In the SEER database, systemic therapy for RCC includes targeted therapy, chemotherapy, hormone therapy and immunotherapy. For this study, patients that received systemic therapy before surgery (neoadjuvant systemic therapy) and those patients that received systemic therapy after surgery (adjuvant systemic therapy) were included in this analytical cohort. In terms of racial groups, the cohort will include Black, White, and American Indians, Alaskan Natives, Asians, and Pacific Islanders, (AAPI) patients with complete records of survival time information and systemic treatment assignments.

Definition of Study Outcomes and Covariates

The primary outcome for this study is the all-cause mortality (ACM). In the SEER registry, deaths were linked to individuals regardless of whether they died within or outside of a SEER registry.[35] Cause of death was defined based on listings from the death certificates using the 3-digit ICD 10 code.[35]. In the SEER registry, cause of death was recorded according to the 10th edition of the International Classification of Diseases.[38] All-cause mortality will be defined using the SEER "vital status" variable, which is represented as a binary outcome of "dead" or "alive". The secondary outcomes are overall survival (OS) and cause specific survival (CSS). Survival time was captured in the SEER database in months. Any death within 30 days of initial diagnosis was defined as perioperative death and was recorded as zero in survival time. Overall survival (OS) is defined in this study as the length of time from diagnosis with RCC that patients diagnosed with the disease are still alive. The SEER event that was used to capture overall survival is the vital status (dead or alive). The cancer- specific survival (CSS) is a net survival measure representing survival of a specified cause of death in the absence of other causes of death. The SEER event that will be used to capture CSS will be the cause -specific death, defined as the time from diagnosis to the date of cancer-specific death. This cause-specific death was recorded in the SEER database for analyzing cause-specific survival.[34]

The covariates for this study include demographic, tumor and clinical (tumor specific) variables. Demographic covariates include age, sex, race, ethnicity, marital status, income level, year of diagnosis and geographical locality (urban versus rural). In this study, age was categorized into 55- 65 years, 66- 75 years, and 76+ years. Race was classified as "white," "black" and "other" race group which includes American Indians, Asians, and Pacific Islanders (AAPI)". Ethnicity was classified as Hispanic and non- Hispanic. Income level was classified as

$55,000 - $74, 999, less than $75,000 or greater than $75,000. Marital status was classified as married, single (never married or with a domestic partner) or divorced (separated and divorced), and widowed. In terms of region or locality of residence, patients were grouped into urban, rural, or unknown residences. In the SEER database, each patient was designated as an urban dweller (metropolitan) or rural (nonmetropolitan) dweller according to the 2003 rural-urban continuity codes within the SEER data set based on Office of Management and Budget (OMB) metropolitan area delineations for the 2000 Census.[38,39] The clinical covariates of interest include tumor stage, tumor size, histology, grade, primary tumor involvement, laterality, presence or absence of adrenal involvement, presence of and visceral metastases. The SEER summary stage was used to classify the tumor stage (I, II, III and IV) at diagnosis. Tumor laterality was classified as right, left, or paired (bilateral) occurrence. Visceral metastases were categorized into metastasis to the lung, metastases to lymph nodes and metastases to other organs.

Statistical Analysis

Statistical programs that are available in SAS 9.4 (SAS Institute, Cary, NC, USA) were utilized for this study. The baseline patients 'characteristics were summarized by means and standard deviation for continuous variables and as number and frequency for categorical variables. Patients' clinical and demographic characteristics were compared between patients that received systemic therapy before surgery (neoadjuvant systemic therapy) and those that received systemic therapy after surgery (adjuvant systemic therapy) using chi-squared tests. To analyze all-cause mortality, univariate logistic regression was used first to screen out the variables without statistical significance. This was followed by a stepwise approach multivariate logistic regression model which was used to evaluate the effect of neoadjuvant and adjuvant systemic therapy and other covariates on all-cause mortality. To estimate the effect of systemic therapy and other

clinical and demographic factors on survival, Cox proportional hazards regression analysis was performed to obtain hazard ratios (HRs) and 95% confidence intervals (CIs) for all factors associated with OS and CSS. In the multivariate Cox regression analyses, the stepwise regression procedures were also utilized to determine the most significant factors. For the entire cohort (n= 1065), OS and CSS at year 1 and year 3 was estimated, the Kaplan Meier curves were generated for OS and CSS, stratified by age (55-65 years, 66-75 year and ≥ 76 years) racial groups (black, white, and other races), gender (male, female) and type of systemic therapy received (adjuvant, neoadjuvant). In all analyses, statistical significance level was set at $P < 0.5$.

Results

Characteristics of the Study Cohort

The final analytical cohort included 1065 eligible patients, diagnosed with renal cell carcinoma between 2010 and 2019. There were more males than females in the study sample (66.7% versus 33.3%). The mean age of the study cohort was 67.4 years, 476 (44.7%) of the patients were 55-65 years, 404 (37.9 %) were 66 - 75 years and 185 (17.4%) were 76 years and older. A higher proportion of the patients (86.3%) were white, 63 (5.9%) were blacks and 83(7.8%) were of the other (AAPI) racial group. The majority of patients 919 (86.3%) were non- Hispanic while 146 (13.7%) were Hispanic. A total of 122 (11.5%) patients received neoadjuvant systemic therapy while 943 (88.5%) patients received adjuvant systemic therapy. Table 2.1 shows the distributions of demographic and clinical characteristics of the patients by systemic therapy (neoadjuvant and adjuvant). Statistically significant differences were observed in several demographic and clinical parameters such as gender, primary tumor involvement, tumor stage, grade histology, adrenal involvement and metastases to the lungs and lymph nodes ($p < 0.05$). There were no statistically

significant differences observed across the two systemic therapy groups for age, race, ethnicity, region of residence, and income level.

All-Cause Mortality (ACM).

The results of the multivariable logistic regression analysis show that age, race, adrenal involvement, metastasis (to the lungs and lymph nodes) and systemic therapy use were significantly associated with ACM (Table 2.2). Older age was found to be a poor prognostic predictor of ACM with patients 76 years and older having higher odds of mortality (OR 1.02, 95% CI: 1.11– 1.35) when compared to patients in the 55-65 years group. There were no significant differences in ACM between patients in the 55-65 years group and ≥ 76 years groups. Race was found to be significantly associated with ACM. The odds of ACM among patients in the other (AAPI) race group decreased by 42% (OR 0.58, 95% CI:0.35, 0.97, $p = 0.04$) when compared to white patients. There were no significant differences in ACM between Black and white patients. Patients who had no adrenal involvement had lower odds for ACM (OR 0.56 95% CI:0.39, 0.71, p <0.001) compared with unspecified adrenal involvement. Distant metastasis was found to be associated with higher odds of ACM. Patients with metastases to the lungs, lymph nodes and other sites had 2.17 (95% CI: 1.61, 2.94, $p < 0.0001$), 1.79 (95% CI: 1.19, 2.67, p = 0.02) and 1.60 (95% CI: 1.04,2.49, p = 0.04) times higher odds of death, respectively compared to patients without metastases to those sites. Patients who received adjuvant therapy were found to have higher odds of ACM (OR 1.75, 95% CI: 1.13, 2.70) compared to patients who received neoadjuvant therapy.

Overall Survival (OS) and Cancer Specific Survival (CSS)

The results of the multivariate Cox regression analyses are shown in Table 2.3. Age, race, metastases to the lungs and adrenal involvement were found to be associated with OSS and CSS. Figures 2.2 and 2.3 show the OS and CSS for the entire RCC cohort. The 1-year, 2-year, and 3-year OS estimates for the analyzed cohort of RCC patients (n= 1065) were 75.5%, 59.2% and 49.2%, respectively. The 1-year, 2-year and 3-year CSS estimates were 77.2%, 62.3% and 53.8% respectively. The OS and CSS were further stratified by age, gender, race, and systemic therapy groups as shown in the Kaplan Meir survival curves (Figures 2.4 – 2.11). For the different age groups, there were significant differences in survival rates between the different age groups with patients in the 76+ age group having the lowest OS and CSS rates, ($p < 0.01$). The 3-year OS rates for patients that received neoadjuvant, and adjuvant systemic therapy were 65.9 % and 47.2%, respectively, while the 3 -year CSS estimates were 68.2% and 52.0 %, respectively. There were no statistically significant gender differences observed for OS and CSS.

The 3-year OS rates for the 55-65 years, 66-75 years, and 76+ years age groups were 52.3%, 51.11% and 38.3%, respectively. The 3-year CSS rates were 55.1%, 56.1% and 44.1%. When compared to patients in the 55-65 years group, patients in the 76+ years group had poorer survival outcomes (HR 1.65; $p < 0.0001$), while there were no differences in OS and CSS between the 55-65 years patients and 66-75 years patients. The age-specific survival findings are consistent with the results of the multivariate Cox regression analysis for association of age with ACM as shown in Table 2.2. In terms of adrenal involvement, patients without adrenal involvement had the better OS and CSS compared to patients who had no adrenal involvement assessment (HR 0.55, $p < 0.01$). Patients with metastases to the lungs had poorer OS and CSS (HR; 1.87; $p < 0.0001$), compared to patients without metastases to the lungs. Figures 2.4- 2.11

show the Kaplan Meir curves of OS and CSS stratified by age, gender, race systemic therapy and demonstrated differences in OS and CSS. Comparing the OS of Black patients with white patients and patients AAPI patients, black patients (HR 2.03, $p = 0.01$) and white patients (HR 1.50; $p = 0.04$) had poor OS compared to AAPI patients. For CSS, there were no differences among white patients and AAPI patients while black patients had poorer CSS (HR 1.92; $p = 0.01$) compared to white patients and AAPI patients. Patients who received adjuvant therapy had poorer OS (HR 1.64 95%CI; p= 0.01) and CSS (HR 1.57 95%CI; p= 0.01) compared to those who received neoadjuvant therapy.

Discussion

In this retrospective cohort study, data from the SEER database was used to describe the all-cause mortality as well as overall and cancer-specific survival in patients diagnosed with greater than stage I renal cell carcinoma. Adjuvant systemic therapy was found to be an independent risk factor for all-cause mortality. Patients who received adjuvant therapy had poorer survival rates and higher odds of all-cause mortality compared to those who received neoadjuvant systemic therapy. The findings from this study are of importance in the management of renal cell carcinoma and have the potential to inform clinicians as they weigh the benefits of initiating systemic therapy before or after surgery. Neoadjuvant therapy before partial or total nephrectomy has been shown to reduce the tumor size and have clinical advantage in the operability of the tumor with respect to adjacent organs. Previous research has shown that targeted systemic therapy may have side effects in the adjuvant settings.[40] Since patients in the present analyzed cohort received either neoadjuvant or adjuvant systemic therapy, it is important to consider systemic therapy as a possible additive factor to mortality and survival. The side-effect profile of systemic RCC therapeutic drugs such as the tyrosine kinase inhibitors represents a significant

barrier to their use, particularly in the adjuvant settings. For TKI, discontinuation due to adverse events ranged from 23% to 45% across clinical trials.[40]

A phase II study reported adverse events occurred in 93%, 98%, 93% and 93% of patients receiving systemic sunitinib, cabozantinib, crizotinib and savolitinib, respectively.[41] One of the major reported adverse events was death within 30 days of the last dose of treatment reported in one patient receiving cabozantinib, secondary to a thromboembolic event.[41] In surgical settings, when considering survival and mortality risks, adjuvant systemic therapy may not be the optimal ancillary treatment modality for RCC patients after surgery and may be reserved for advanced higher stage tumors to reduce recurrence. In this present study, older age was found to be associated with higher odds of all-cause mortality. RCC incidence increases steadily with age, with a worldwide median age at diagnosis of approximately 75 years.[42] A recent SEER based analysis of RCC trends in the US found that the overall incidence-based mortality rates of RCC was higher in patients older than 65 years (30.876 [95% CI, 30.548,31.207]).[43]

Findings from this present study also showed that patients in the older age group (76 years and above) had poorer overall and cancer-specific survival compared to patients in the 55–65-year group. Patents in the older age group category may have a higher prevalence of other comorbidities which may affect cancer survivorship. It is also important to note that the age distribution of survivors has been shown to vary substantially by cancer type.[44] The majority of prostate cancer survivors (62%) are aged 70 years or older, whereas less than one-third (32%) of melanoma survivors fall within the older age group.[44] Adjuvant systemic therapy have been associated with higher mortality rates in older women with RCC.[45] Considering race as a predictor of mortality and survival, in this present study, AAPI patients had significantly lower odds for ACM compared to white patients, but there were no significant differences in ACM

observed between black and white patients. In terms of survival rates, black patients had the poorest overall and cancer-specific survival rates compared to white patients and AAPI patients. This is consistent with findings from a previous National Cancer Database (NCDB) study which noted that Black patients had worse overall survival for renal cell carcinoma. [46] The NCDB study found that while black patients presented at a younger age with lower stage tumors, they had worse overall survival.[46] The NCDB study also found that blacks experienced disparities in socio-demographic characteristics, clinical presentation, treatment-related factors, and had an independently increased hazard of death.[46] Similarly, an International Marker Consortium for Renal Cancer database (INMARC) study found that despite presenting with more indolent histology and lower stage, blacks were at greater risk for diminished survival, faring worse in overall survival for all stages and cancer-specific survival.[47]

In terms of gender disparities for mortality and survival outcomes, this study found no statistically significant gender differences in all-cause mortality, overall and cancer-specific survival. A recent SEER analysis found that for gender, the disparity of relative survival risks was obvious among patients who were 30-59 years old, but not among those younger than 29 years or older than 60 years.[48] Other demographic factors such as marital status, region and income were not associated with all-cause mortality and cancer survival. Tumor size and laterality (right, left, or bilateral occurrence) were not associated with mortality or survival in this cohort of RCC patients. Bilateral occurrence does not influence overall and cancer-specific survival in patients with renal cell carcinoma especially among those who have undergone radical nephrectomy.[49]

The findings from this study may have future implications especially in the development of recommendations and guidelines for neoadjuvant and adjuvant systemic therapy use in RCC

management. It is important to consider patients' demographic factors such as age when using systemic therapy in adjuvant settings since this study found older age to be significantly associated with higher odds of mortality and poorer survival. Long term research and development efforts could be directed at identifying the optimal systemic therapy for different age categories. It is also crucial to consider the patient survival benefits before adding any form of systemic therapy to the surgical or conservative management of RCC.

In the present study, patients that received adjuvant systemic therapy had a significantly lower overall and cancer-specific survival compared with those that received neoadjuvant therapy. Besides survival benefits, the gains of using systemic therapy to improve tumor operability, and reducing tumor progression should outweigh the risk of minimal survival benefits and potential side effects. Larger clinical trials may be needed to explore the comparative survival benefits of the different classes of systemic therapy for renal cell carcinoma, especially for higher tumor stages (stage III and IV) and tumors presenting with distant metastases. This study also found that metastases in the lungs were associated with poor overall and cancer specific survival. Therefore, in the management of tumors with distant metastases, the lifesaving and survival benefit of using any form of systemic therapy with or without partial or total nephrectomy should be important considerations and factored in as part of the preoperative patient work up. Furthermore, in clinical and surgical settings, the use of systemic neoadjuvant or adjuvant therapy should be customized or triaged in the presence of other comorbidities which may contribute to mortality and affect cancer survivorship.

Limitations

The main focus of this study is to evaluate the effect of adjuvant and neoadjuvant systemic therapy and independent clinical and demographic factors on mortality and survival outcomes in

renal cell carcinoma patients. The individual effects of classes of systemic therapy were not evaluated in this study due to information available in the SEER Research Plus Database. Another limitation of this study is that other clinical and social determinants of cancer survivorship, such as co-existing acute or chronic medical conditions, inpatient and outpatient patient information, hospitalization information, insurance status, provider information and the effect of other medications on mortality and cancer survivorship were not explored in this study.

Conclusion

The use of adjuvant systemic therapy, older age and black race were identified in this study as factors associated with higher odds for all-cause mortality and poorer survival outcomes. Disparities in mortality survival rates were observed across the different age groups with older patients having higher odds of all-cause mortality and worse overall and cancer specific survival. Black patients had the highest odds for all-cause mortality and also had poorest survival rates. There were no statistically significant gender disparities in mortality and survival. There is a need for further research on the comparative effectiveness and survival benefits of the different classes of systemic therapy in renal cell carcinoma management.

Table 2.1. Characteristcs of Renal Cell Carcinoma Patients By Systemic Therapy Group

Demographic and Clinical Variables	**Neoadjuvant Systemic Therapy** *n*= 122	**Adjuvant Systemic Therapy** *n*= 943	**p-value**
Age			
Mean ± SD = 67.4 ± 7.7 years			
55-65 years	58 (47.5)	418 (44.3)	0.67
66-65 years	46 (37.7)	358 (40.0)	
≥ 76 years	18 (14.8)	167 (17.7)	
Sex			
Male	71 (58.2)	639 (67.8)	0.03*
Female	51 (41.8)	304 (32.2)	
Race			
White	111 (90.9)	808 (85.7)	0.18
Black	3 (2.5)	60 (6.4)	
Other (AAPI)	8 (6.6)	75 (8.0)	
Ethnicity			
Non- Hispanic	104 (85.3)	815 (86.4)	0.72
Hispanic	18 (14.7)	128 (13.6)	
Marital Status			
Single	11 (9.02)	108 (11.5)	0.38
Married	86 (70.5)	615 (65.2)	
Divorced/Separated	10 (8.2)	108 (11.5)	
Widowed/Unknown	15 (18.0)	112 (11.9)	
Region			
Urban	107 (87.7)	823 (87.3)	0.47
Rural	14 (11.5)	118 (12.5)	
Unknown	1 (0.8)	2 (0.2)	
Primary Tumor			
Yes	88 (72.1)	761 (80.7)	0.03*
No	34 (27.9)	182 (19.3)	
Income Level			
Less than $55,000	21 (17.2)	154 (16.3)	0.52
$55.00- 74,999	48 (39.3)	421 (44.6)	
$ 75,000	53 (43.4)	368 (39.0)	
Laterality			
Right	56 (45.9)	495 (52.5)	0.30
Left	64 (52.4)	440 (46.7)	
Paired	2 (1.6)	8 (0.9)	
Stage			
I	19 (15.6)	35 (3.7)	<.0001**
II	9 (7.4)	21 (2.2)	
III	35 (28.7)	257 (27.3)	
IV	59 (48.4)	630 (66.8)	

Grade			
Well, Differentiated	5 (4.1)	10 (1.06)	0.002*
Moderately Differentiated	10 (8.2)	79 (8.4)	
Poorly Differentiated	17 (13.9)	252 (26.7)	
Undifferentiated /Anaplastic	56 (45.9)	398 (42.2)	
Unknown	34 (27.9)	204 (21.6)	
Adrenal Involvement			
Yes	6 (4.9)	68 (7.2)	0.03*
No	32 (26.2)	378 (40.1)	
Not Determined	84 (68.9)	497 (52.7)	
Histology			
Adenocarcinoma	61(50.0)	680 (72.1)	<.0001**
Transitional Cell Papilloma	60 (49.1)	246 (26.1)	
Squamous/Ductal	1 (0.8)	17 (1.8)	
Metastases to Lymph Nodes			
Yes	7 (5.8)	144 (15.3)	0.02*
No	114 (93.4)	789 (83.7)	
Unknown	1 (0.8)	10 (1.1)	
Metastases to Lungs			
Yes	15 (12.3)	355 (37.6)	<.0001**
No	106 (86.9)	578 (61.3)	
Unknown	1 (0.8)	10 (1.1)	
Metastases to Other Sites			
Yes	12 (9.8)	133 (14.1)	0.40
No	109 (89.3)	799 (84.7)	
Unknown	1 (0.8)	11 (1.2)	

Table 2.2. Result of Multivariate Logistic Regression for Demographic and Clinical Variables Associated with All-Cause Mortality

Demographic and Clinical Variables	OR (95% CI)	P value
Age		**0.001**
55 - 65 years	Reference	
66 - 75 years	1.02 (0.77 – 1.36)	0.89
≥ 76 years	2.02 (1.38 – 2.97)	0.0003*
Race		**0.03**
White	Reference	
Black	1.54 (0.87 – 2.73)	0.14
Other (AAPI)	0.58 (0.35 – 0.97)	0.04*
Sex		0.92
Male	Reference	
Female	1.01 (0.77 – 1.33)	0.92
Ethnicity		0.16
Non-Hispanic	Reference	
Hispanic	1.30 (0.89 – 1.91)	0.14
Adrenal Involvement		**< 0.0001**
Yes	0.56 (0.32 -0.97)	0.04*
No	0.52 (0.39 – 0.71)	< 0.0001
Not Determined	Reference	
Metastases To Lungs		**< 0.0001**
Yes	2.17 (1.61 -2.94)	< 0.0001**
No	Reference	
Unknown	1.60 (0.27 – 9.49)	0.60
Metastases To Lymph Nodes		**0.02**
Yes	1.79 (1.19 – 2.67)	0.01*
No	Reference	
Unknown	0.69 (0.12 -4.13)	0.69
Metastases To Other Sites		**0.02**
Yes	1.60 (1.04– 2.49)	0.03*
No	Reference	
Unknown	4.30 (0.61- 9.34)	0.14
Systemic Therapy		**0.01**
Neoadjuvant	Reference	
Adjuvant	1.75 (1.13– 2.70)	0.01*

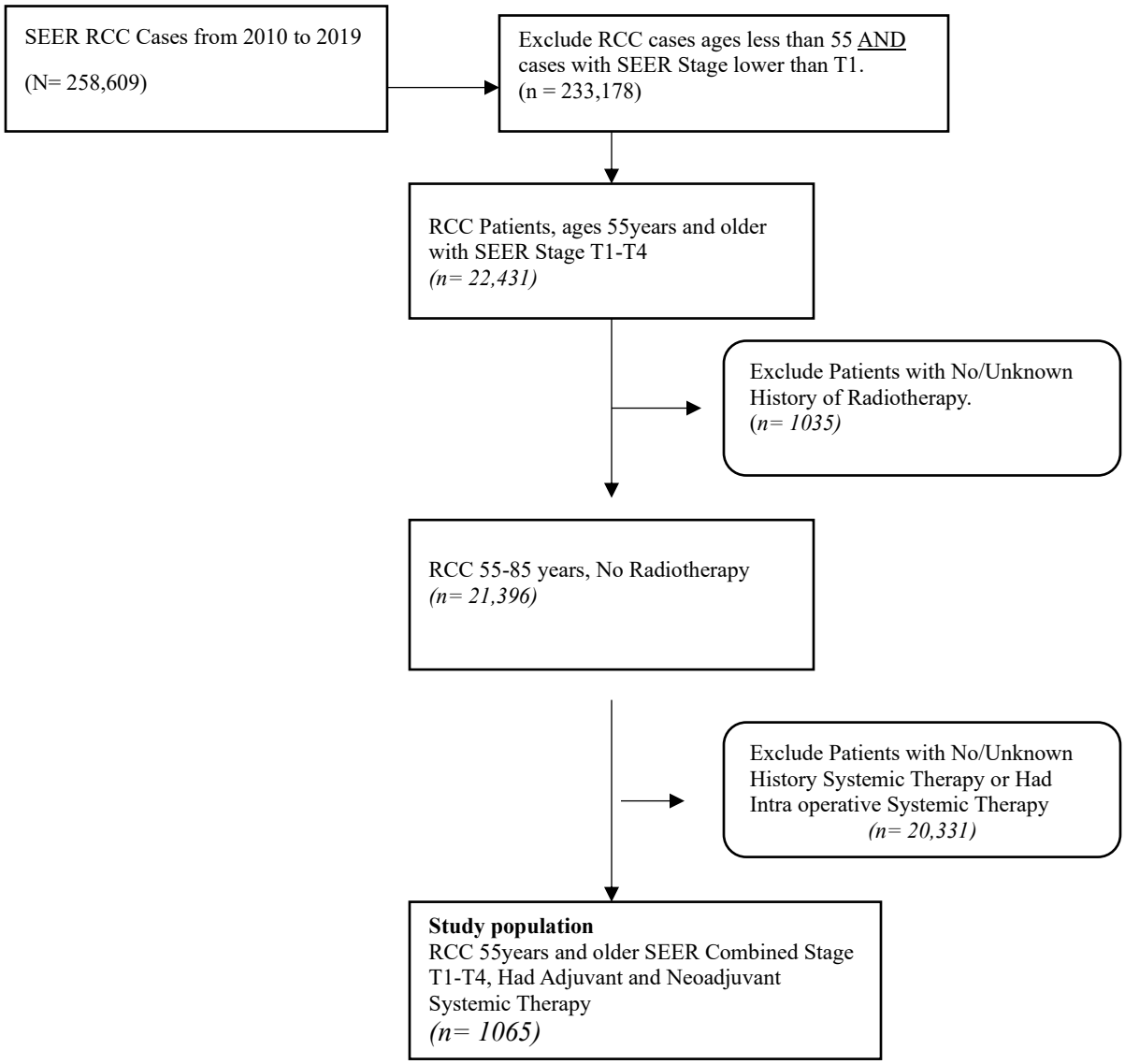
OR: Odds Ratio
CI: Confidence Interval

Table 2.3. Results of Multivariable Cox Proportional Regression Analysis of Overall Survival (OS) and Cancer Specific Survival (CSS)

Demographic and Clinical Factors	Overall Survival		Cancer Specific Survival	
	HR (95% CI)	P value	HR (95% CI)	P value
Age				
55-65 years	Reference		Reference	
66 - 75 years	0.96 (0.79 – 1.17)	0.70	0.89 (0.72 – 1.10)	0.29
≥ 76 years	1.65 (1.30 – 2.07)	<0.0001**	1.54 (1.20 -1.98)	0.01*
Sex				
Male	Reference			
Female	1.10 (0.91-1.32)	0.61	1.18 (0.97 – 1.43)	0.09
Ethnicity				
Non-Hispanic	Reference			
Hispanic	1.18 (0.92 – 1.52)	0.19	1.29 (1.00 – 1.67)	0.05
Race				
White	1.50 (1.02 – 2.09)	0.04*	1.34 (0.93- 1.94)	0.12
Black	2.03 (1.25 – 3.31)	0.01*	1.92 (1.15 – 3.18)	0.01*
Other (AAPI)	Reference		Reference	
Histology				
Adenocarcinoma	0.69 (0.39 – 1.23)	0.21	0.68 (0.37 - 1.25)	0.22
Transitional	0.54 (0.29 – 0.97)	0.04*	0.51 (0.27 – 0.95)	0.03*
Squamous/Ductal	Reference		Reference	
Adrenal Involvement				
Yes	0.81 (0.57- 1.15)	0.24	0.80 (0.56 - 1.17)	0.26
No	0.55 (0.45 – 0.68)	<0.0001**	0.60 (0.45 – 0.70)	<0.0001**
Not Determined	Reference		Reference	
Metastases to Lungs				
Yes	1.87 (1.53- 2.30)	<0.0001**	1.94(1.57 – 2.40)	<0.0001**
No	Reference		Reference	
Unknown	1.88(0.92 – 3.82)	0.08	2.12 (1.04 – 4.32)	0.04*
Systemic Therapy				
Neoadjuvant	Reference			
Adjuvant	1.64 (1.17 – 2.30)	0.01*	1.57(1.12- 3.18)	0.01*

HR: Hazard Ratio
CI: Confidence Interval

Figure 2.1. Flow Chart of the RCC Study Cohort Selection



Figures 2.2 and 2.3. Overall and Cancer Specific Survival Plots for the Entire RCC Cohort

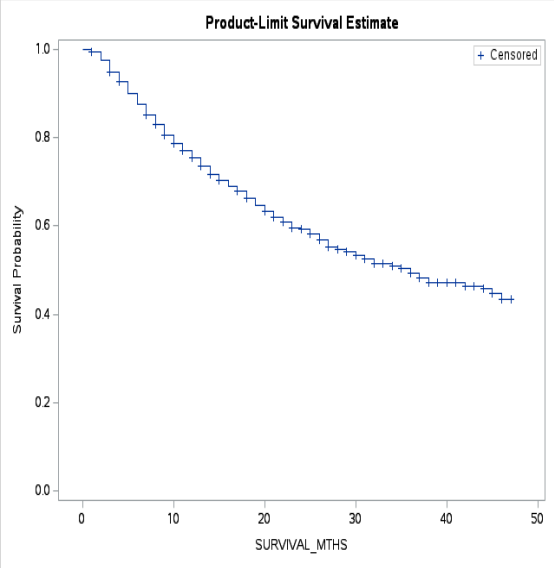


Figure 2.2 Overall Survival

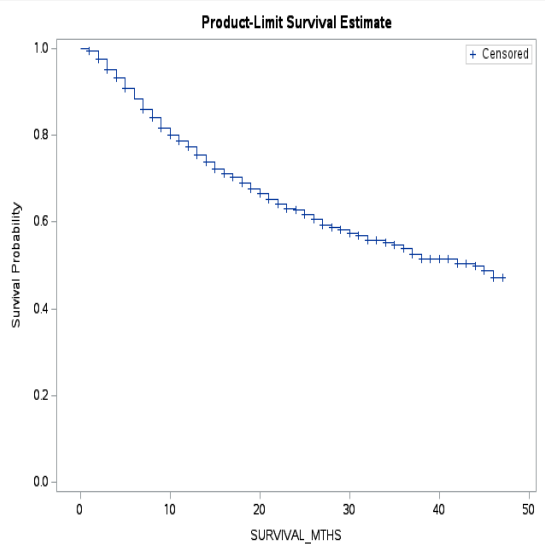


Figure 2.3. Cancer-Specific Survival

Figures 2.4 -2.7. Kaplan-Meier Curves of OS Stratified by Age, Gender, Race and Systemic Therapy Group

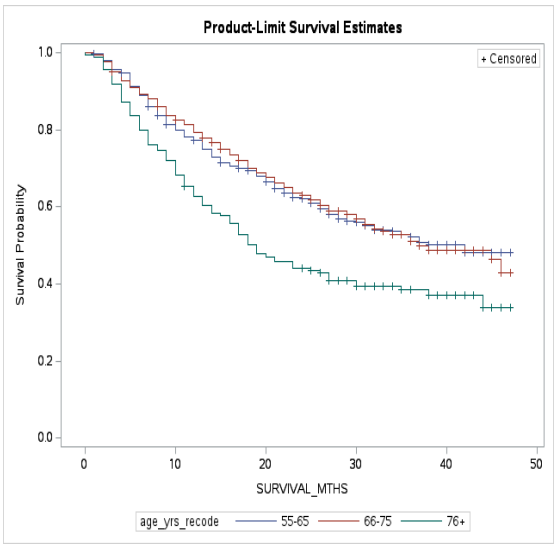


Figure 2.4.

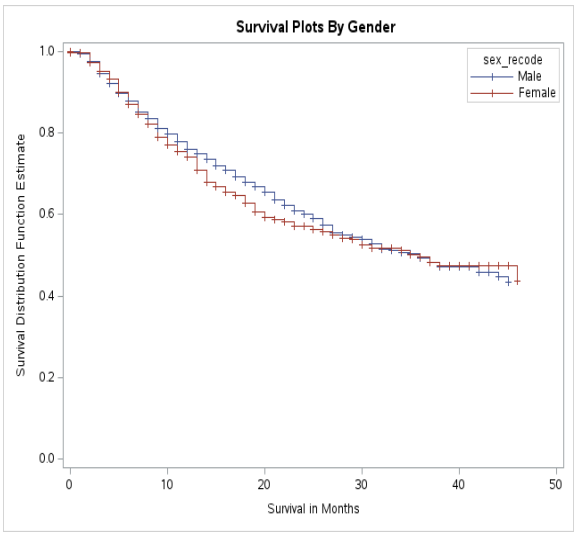


Figure 2.5.

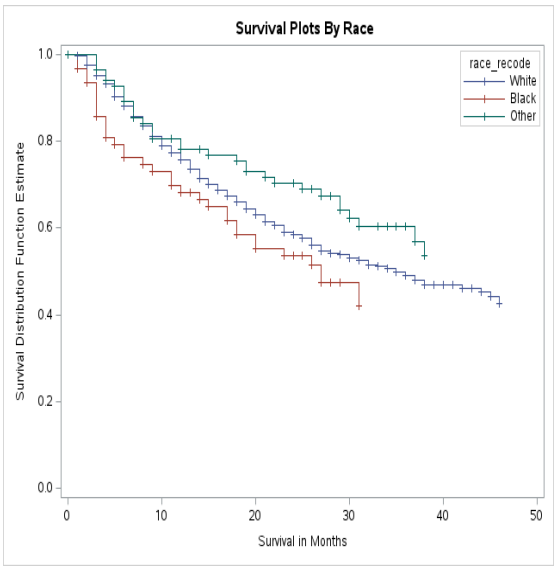


Figure 2.6

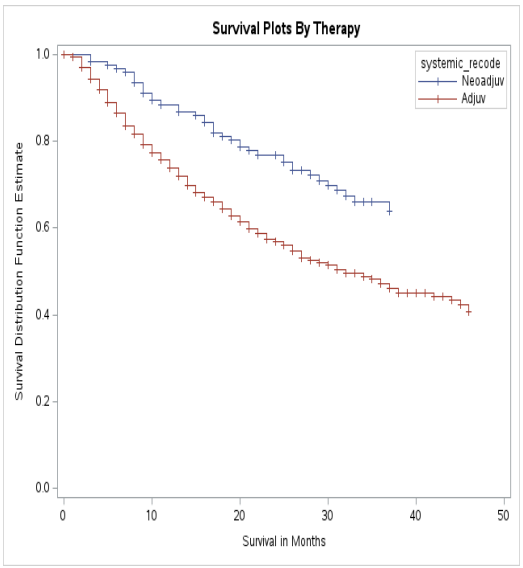


Figure 2.7

Figures 2.8 – 2.11. Kaplan-Meier Curves of CSS Stratified by Age, Gender, Race and Systemic Therapy Group

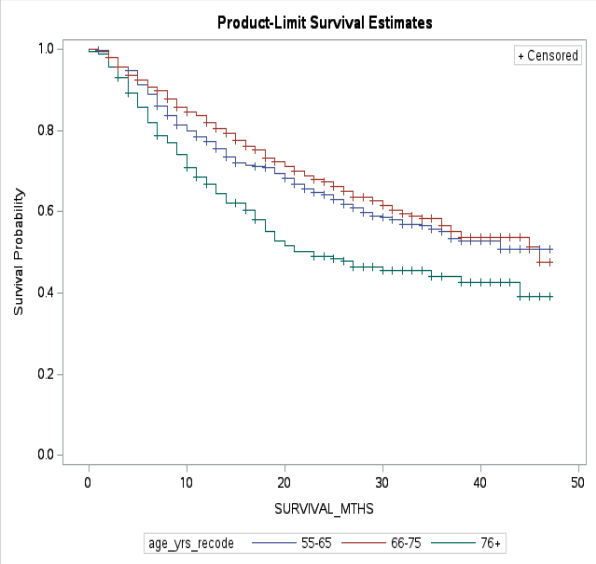


Figure 2.8

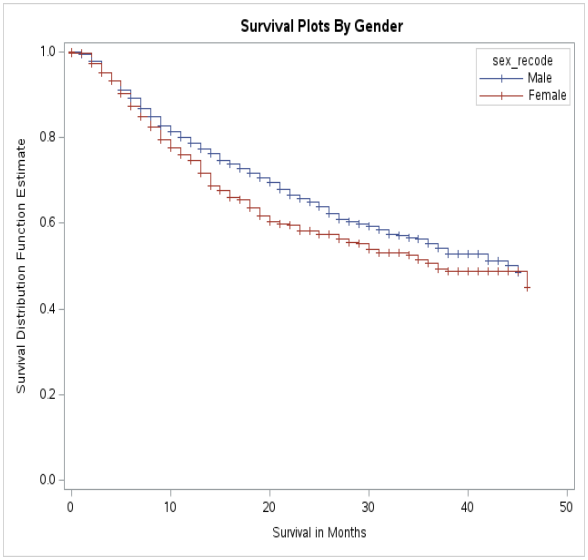


Figure 2.9

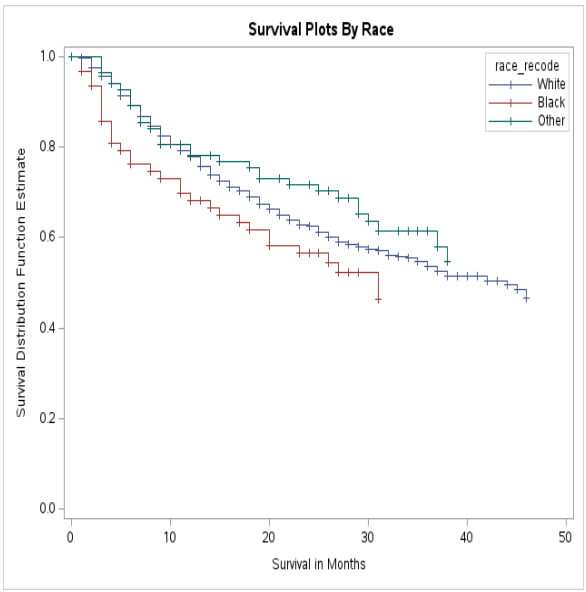


Figure 2.10

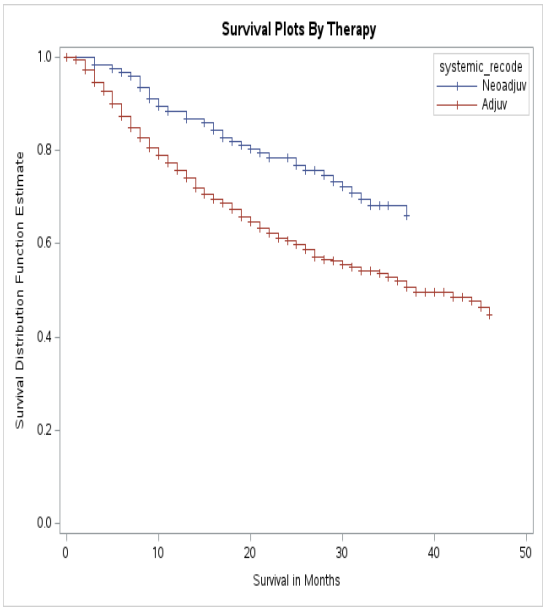


Figure 2.11

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CHAPTER 3

FACTORS ASSOCIATED WITH TIME TO TREATMENT INITIATION IN A COHORT OF RENAL CELL CARCINOMA PATIENTS[2]

[2] Azih I, Young H, Tackett R, Shenoy S, Okosun I. To be submitted to the American Association of Cancer Research

Abstract

Background

Time to treatment initiation is an important treatment indicator for most malignancies including renal tumors. Currently, there is a paucity of literature on factors associated with time to systemic therapy initiation in cancer patients. This study will identify and evaluate the sociodemographic and clinical factors associated with time to treatment initiation (TTI) in a cohort of renal cell carcinoma patients receiving systemic therapy. Understanding the prognostic role of these factors is necessary for clinicians to optimize treatment outcomes for renal cell carcinoma patients.

Methods

The Surveillance, Epidemiology, and Ends Results (SEER) database was used to extract de-identified patient information. The analytical cohort includes patients 55 years and older with a confirmed diagnosis of renal cell carcinoma from 2010 to 2019, with a tumor stage of T1 or greater who received systemic therapy. Patients younger than 55 years of age, who received radiotherapy and those with incomplete systemic therapy information were excluded. The primary outcome for this study is the time to treatment initiation as defined in the SEER database as time in months from diagnosis to the date of systemic therapy initiation. Demographic covariates include age, sex, race & ethnicity, marital status, income level, and geographical locality (urban versus rural). Clinical covariates of interest include the tumor stage and primary tumor involvement. Frequencies, proportion for all the demographic and clinical characteristics and the mean time to treatment initiation were estimated. Multivariate Poisson regression analysis was performed to identify independent predictors of time to treatment initiation.

Results

The mean TTI for the entire cohort of RCC patients was 1.03 months (SD= 1.2). Race, ethnicity, gender, marital status, and tumor stage were found to be significantly associated with TTI. TTI was longer in Black (p=0.04), AAPI (p= 0.01) and patients of Hispanic ethnicity (p = 0.002) compared to white non-Hispanic patients. Female patients had a shorter TTI compared to male patients (p= 0.01). Married and common law patients had a shorter TTI compared to widowed patients (p=0.01). Patients with stage IV RCC had significantly shorter TTI compared to stage III (P=0.002) and stage II (< 0.0001) patients.

Conclusion

Time to systemic treatment is significantly associated with race, gender, ethnicity, marital status, and tumor stage in this cohort of renal carcinoma patients. Income status, urban/rural residence, and primary tumor involvement were not found to be independent predictors of time to treatment.

Key words: Renal Cell Carcinoma, Systemic therapy, Time to Treatment

Introduction

Time to treatment initiation (TTI) is crucial in the treatment of most malignancies. Delay in the treatment of cancer could have adverse consequences on treatment outcomes.[1] TTI is an increasingly important factor for cancer treatment outcomes and has gained recent attention in literature.[2] Cancer treatment delay is a problem in health systems worldwide and is associated with increased mortality across surgical, systemic treatment, and radiotherapy indications.[1] The

need for an in-depth understanding of the impact of treatment delay on outcomes came sharply into focus during the coronavirus (COVID-19) pandemic.[1] The COVID-19 pandemic resulted in global deferral and cancellation of cancer treatment. The need for deferral of elective cancer surgery and radiotherapy, and reductions in the use of systemic treatments[3,4] was established during the pandemic because global health systems had to reassign healthcare resources to pandemic preparedness.[5] Clinical factors such as preexisting medical conditions, tumor-related factors and social determinants of health could affect TTI for most malignancies. Social determinants of health (SDH) are non-medical factors that account for 30–55% of health outcomes. These are conditions in which people are born, grow, live, work, and age.[6,7] According to the World Health Organization, SDH factors could have a more significant influence on health than health care, underscoring the importance of comprehensive approaches to addressing health inequities.[7] SDH factors include income, education, employment status, housing, and access to affordable health services of decent quality. Patients with cancer who live in rural communities face unique barriers to receiving high-quality cancer care.[8] Geographic misdistribution of health systems that provide screening, preventive services, oncology specialty care, and clinical trials reduces access to care for rural patients.[9,10] Rural patients are more likely to be uninsured or underinsured through Medicaid or Medicare compared with their urban counterparts.[11]

Time-to-treatment has been shown to differ significantly across racial and ethnic groups, patient-reported stressors also predict delays in time to evaluation and treatment initiation.[12] Minority patients have higher odds of treatment delays compared to non-Hispanic white patients for all types of initial treatment.[6] Research has shown that black females have delayed initiation of treatment compared to white patients.[13,14] In breast cancer patients, factors

such as being unmarried, living in rural areas, distance to providers, local stage cancer and time of diagnosis are known to be associated with late receipt of adjuvant therapy.[14]

Improving time to treatment initiation (TTI), a potential surrogate for access and could be an effective strategy to improve outcomes for rural patients with cancer.[15] Lengthy time to treatment initiation leads to delayed treatment in cancers such as lung, kidney, and pancreas,[16] with inconsistent effects over time.[17] [18] Delays in treatment initiation have also been linked with increased mortality. For head and neck cancers, TTI beyond two months was associated with a three-fold increase in mortality.[19-22] For breast cancer, increasing TTI has been associated with worse survival, especially for underserved patients.[23-25] While there is limited evidence of the effects of treatment delays on survival, early evidence points to a possible negative effect.[26,27]

While there is paucity of literature on time to systemic therapy initiation for renal cell carcinoma patients, few studies have examined factors associated with treatment intuition for other cancers such as breast, lung, head, and neck cancers and leukemias. This present study is the first to evaluate factors associated with time to systemic therapy initiation in a cohort of RCC patients and will provide a better understanding on the disparate effects of these prognostic factors on treatment outcomes.

Methods

Study Population and Cohort Selection

This retrospective cohort study utilized data from the Surveillance, Epidemiology, and Ends Results (SEER) Research Plus database. The SEER registry contains nationally representative population-based cancer surveillance data and contains information on the incidence and survival rates of cancer, covering approximately 28% of the US population.[28]

The study sample includes patients with a diagnosis of renal cell carcinoma from 2010 to 2019, aged 55 years and older, with tumor stage of T1 or greater who received systemic therapy. Patients who received radiotherapy and with incomplete or unknown systemic therapy information were excluded from this study. Information on the RCC patients including demographics (age, sex, race/ethnicity, marital status, income, and region/locality) and clinical characteristics (time to treatment initiation. primary tumor involvement and tumor stage) were extracted from the SEER database. Deidentified patient data was retrieved using the SEER*Stat software version 8.4.0.1.[29]

Definition of Study Outcomes and Covariates

The primary outcome for this study is the time to treatment initiation, defined as time in months from diagnosis to the date of systemic therapy initiation. The demographic covariates are age, sex, race & ethnicity, marital status, income level, and geographical locality (urban versus rural). Age is categorized into 55- 65 years, 66- 75 years, and 76+ years. Race was classified as "white," "black" and "AAPI' (. American Indian/Asian/Pacific Islander. Ethnicity was classified into non-Spanish Hispanic and Spanish Hispanic. Income level was grouped into $55,000 - $74, 999, less than $75,000 or greater than $75,000. Patients' marital status was classified into married, single (never married or with a domestic partner) or divorced (separated, divorced, and widowed). In terms of region or locality, each patient was designated as an urban (metropolitan) or rural (nonmetropolitan) dweller according to the 2003 rural-urban continuity codes within the SEER data set based on Office of Management and Budget (OMB) metropolitan area delineations for the 2000 Census. [30,31] Clinical covariates of interest are tumor stage and primary tumor involvement. The SEER summary staging was used to classify the tumor stage at

diagnosis (stages I, II, III and IV). Primary tumor involvement was classified as “yes” (primary tumor involved) and “no” (primary tumor not involved).

Statistical analysis

The frequencies, proportion, and the mean time to treatment initiation for all the demographic and clinical characteristics were calculated. Multivariate Poisson regression analysis was performed to identify independent predictors of TTI. Predictors included were determined by clinical significance a priori. Results are expressed as incidence rate ratios (IRR) and significance level was set at $P < 0.05$ for all statistical tests. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA

Results

A total of 1065 RCC patients who received systemic therapy were included in the analytical cohort. Table 3.1 shows the distribution of the demographic and clinical characteristics and mean time to treatment for the RCC patients. The mean age of the patients in this RCC cohort was 67.4 years (SD = 7.7) while the mean TTI for the entire cohort of patients was 1.03 months (SD= 1.2). For this study, majority of RCC patients were white (86.3%), male (66.7%), non-Hispanic (86.3%), married (65.8%), lived in urban areas (87.3%) and had stage IV tumors (64.7%). Table 3.2 shows the results of the multivariate Poisson regression analysis; race, ethnicity, gender, marital status, and tumor stage were found to be significantly associated with TTI. There was a 13% increase in TTI in AAPI patients (IRR 1,31, p = 0.01) compared to white patients while the TTI was 25 % shorter in blacks (IRR 0.74, p= 0.04) compared to whites. In terms of ethnicity, TTI was increased in Hispanic patients (IRR= 1.36. p <0.01) compared to non-Hispanics patients. Gender was associated with TTI; TTI was 17% shorter in female patients (IRR= 0.83,

p= 0.01). compared to male patients. The TTI in patients with stages II, III, and IV tumors were significantly decreased (IRR = 0.51.0.59.0.51 respectively, p<0.01) compared to patients with stage I tumors. Marital status was also identified as an important prognostic factor. There was a 25% significant reduction in TTI for married or common law patients (IRR = 0.75, p =0.01) compared to widowed patients. For this study, age, income level, geographical region of residence and primary tumor involvement were not found to be associated with TTI.

Discussion

The objective of this study was to identify and evaluate the social and clinical factors associated with time to systemic therapy initiation in a cohort of renal cell carcinoma patients. The mean TTI for patients was 1.03 months. Studies have shown that initiation of therapy within six weeks from diagnosis is associated with improved survival in cancer patients.[32] In this present study, gender was found to be significantly associated with time to treatment initiation with female patients having significantly shorter TTI compared to male patients. This is similar to findings from another study evaluating time to treatment in patients with stage III non-small cell lung cancer where male sex (p = 0.013) was significantly associated with longer TTI.[33] Similarly, National Cancer Database (NCDB) study on gender differences in time to treatment for primary malignant brain tumors (glioblastoma and lower grade glioma) found that males had a statistically significant association with delays to treatment initiation (OR = 1.09, CI 1.05-1.13, p < 0.001) although this association was not observed in the multivariable model (OR = 1.05, CI 0.96-1.16, p = 0.25).[34]

An interesting finding from this study was the significant association of black race with reduced time to treatment initiation compared to white patients. McGee et al. showed that younger black women experienced greater delays than white women of the same age.[13] A recent

Babatunde et al found that black female patients were more likely to have delayed initiation of adjuvant hormonal therapy compared to white patients.[14] A population-based study analyzing racial disparities in time to treatment for stage I non-small cell lung cancer showed that black patients had a statistically significantly longer median time to treatment for all three treatment modalities, with an average 8.2-day delay compared with white patients ($P < .001$).[35] Stokes et al conducted a SEER based study on time to treatment initiation for prostate cancer. African American patients with prostate cancer experienced a longer time from diagnosis to treatment than Caucasian patients with prostate cancer.[36] Although the definitive treatment modalities analyzed by Holmes et al, and Stokes et al, were not systemic therapy, black patients with lung and prostate cancer had increased time to treatment (radiotherapy and surgery) compared to white patients. A possible explanation for this notable finding from this present study could be that black patients presented with higher stage disease (stage III and IV) and sought treatment earlier, hence the shorter TTI. This study also found that American Indian/Asian/Pacific Islander patients had longer TTI compared to white patients. A retrospective study by Schermerhorn et al in patients with stages I-III breast cancer found that patients with breast cancer who identified as black, Hispanic, and other non-white races/ethnicities were exposed to longer treatment delays relative to white patients.[37] The racial ethnic -related treatment disparities observed by Schermerhorn et al were further explained by disparities in education, comorbidities, insurance, and facility type.[37]

This present study found that marital status was associated with TTI, with married/common law patients having significantly shorter TTI compared to widowed patients. A previous study done on bone cancer patients concluded that the marital status of middle-aged and elderly people can affect tumor stage at diagnosis, treatment, and survival prognosis.[38] Research

has also shown that widowed patients have worse prognosis compared to married patients.[38] Spousal support has been suggested to play a role in the visual surveillance in cancer patients and possibly leads to higher rates of treatment and better survival.[39] Ren et al evaluated factors influencing delayed treatment in breast cancer patients and found that patients' marital status ($p = 0.010$), was an independent predictor of delayed treatment. They noted that patients without life partners tended to delay medical diagnosis and treatment.[40]

Tumor stage was an important clinical factor associated with TTI in this study. Patients with stage IV RCC had significantly shorter TTI compared to stage III and stage II RCC patients. This important tumor-related finding is consistent with the results of a retrospective study by Khanna et al, which found that patients with stage IV disease had the shortest TTI (27.5 days) compared to patients diagnosed with earlier stages (overall $P=0.03$).[41] Khanna et al observed that stage IV patients had significantly shorter TTI compared to stage III ($p=0.05$) and stage II ($p=0.04$). The shorter TTI for stage IV patients observed in this present study may be explained by the fact that patients with stage IV disease may be prioritized for faster treatment based on the clinician's background knowledge of the poor prognosis of advanced disease. Patients with stage IV cancers at the time of diagnosis also present with substantial cancer-related pain and symptoms, hence they are most likely to seek expedited treatment.

Study Limitations

The SEER research database has limited demographic and clinical information. This study was limited by the variables available in the SEER database and hence did not address comorbid medical conditions as well as other clinical and sociodemographic factors such as treatment facility, provider information, insurance, and education level.

Conclusion

Time to systemic treatment is significantly associated with race, gender, ethnicity, marital status, and tumor stage in this cohort of renal carcinoma patients. Age, income status, urban or rural residence, and primary tumor involvement were not independent predictors of time to treatment. Further research is needed to elucidate the influence of other important factors such as access to specialized care, provider type and knowledge and access to health insurance on systemic treatment initiation for cancer patients.

Table 3.1. Patient Charactersitics and Mean Time to Treatment Initiation (TTI) in a Cohort of Renal Cell Carcinoma patients

Patient Characteristics	N (%)	Mean (SD) TTI (months)
Age (Mean ± SD = 67.4 ± 7.7 years)		
55-65 years	476 (44.7)	0.98 (1.05)
66-65 years	404 (37.9)	1.01 (1.20)
≥ 76 years	185 (17.4)	1.18 (1.69)
Sex		
Male	710 (66.7)	1.06 (1.25)
Female	355 (33.3)	0.96 (1.21)
Race		
White	919 (86.3)	1.03 (1.25)
Black	63 (5.9)	0.79 (1.19)
American Indian/Asian/Pacific Islander (AAPI)	83 (7.8)	1.19 (1.16)
Ethnicity		
Non- Hispanic	919 (86.3)	0.98 (1.18)
Hispanic	146 (13.7)	1.30 (1.54)
Marital Status		
Single	119 (11.2)	1.13 (1.28)
Married	701 (65.8)	0.98 (1.08)
Divorced/Separated	118 (11.1)	1.09 (1.24)
Widowed	88 (8.3)	1.30 (2.17)
Unknown	39 (3.7)	0.74 (0.75)
Region		
Urban	930 (87.3)	1.02 (1.21)
Rural	132 (12.4)	1.10 (1.41)
Unknown	3 (0.3)	0.67 (0.58)
Income Level		
Less than $55,000	175 (16.4)	0.96 (1.16)
$55.00- 74,999	469 (44.0)	1.08 1.20)
$ 75,000 0r more	421 (39.5)	1.00 (1.31)
Primary Tumor Involved		
Yes	849 (79.2)	1.05 (1.29)
No	216 (20.3)	1.02 (1.23)
Stage		
I	54 (5.1)	1.76 (2.76)
II	30 (2.8)	0.97 (1.30)
III	292 (27.4)	1.08 (1.10)
IV	689 (64.7)	0.95 (1.07)

Table 3.2: Results of Poisson Regression Analysis of Factors Associated with TTI

Variables	IRR	P value
Age		
55 - 65 years	Reference	
66 - 75 years	1.04	0.60
≥ 76 years	1.19	0.05
Race		
White	Reference	
Black	0.74	0.04*
Other (AAPI)	1.31	0.01*
Sex		
Male	Reference	
Female	0.83	0.01*
Ethnicity		
Non-Hispanic	Reference	
Hispanic	1.36	0.0002*
Marital Status		
Single	0.88	0.34
Married / Common law	0.75	0.01*
Divorced/Separated	0.87	0.29
Widowed	Reference	
Unknown	0.21	0.01*
Region		
Urban	Reference	
Rural	1.20	0.05
Unknown	0.74	0.73
Income Level		
Less than $55,000	Reference	
$55.00- 74,999	1.19	0.07
≥$ 75,000	1.07	0.45
Primary Tumor		
Yes	Reference	
No	0.94	0.47
Tumor Stage		
Stage I	Reference	
Stage II	0.51	0.002*
Stage III	0.59	< 0.0001**
Stage IV	0.51	< 0.0001**

IRR = Incidence Risk Ratio

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CHAPTER 4

CONCLUSIONS

This study aimed to describe the effect of systemic adjuvant and systemic therapy on the treatment outcomes of renal cell carcinoma (RCC) patients. Our analyses investigated the effect of neoadjuvant and adjuvant systemic therapy on survival and mortality and also described factors associated with time to systemic therapy initiation in a cohort of renal cell carcinoma patients. RCC is one of the commonly diagnosed urological tumors. The clinical management of RCC has evolved over the years with surgery still being the mainstay treatment for low grade non-metastatic tumors. Cytoreductive nephrectomy before systemic therapy is recommended in patients with a potentially surgically resectable primary tumor mass.[1] The emergence of novel therapies such as the use of systemic therapy as adjuvant or neoadjuvant therapy has become increasingly used in RCC management. Targeted therapy utilizing tyrosine kinase inhibitors (TKIs), and anti-VEGF antibodies, are widely used in first- and second-line treatments. Agents targeting the mammalian target of rapamycin (mTOR) and immune checkpoint inhibitors are other RCC treatment options.[1]

The results from this study show that adjuvant systemic therapy is associated with higher odds of all-cause mortality and poorer survival outcomes compared to treatment with neoadjuvant systemic therapy. Older age, black race, and metastases to the lungs were also found to be associated with all-cause mortality and poor overall and cancer-specific survival. We also found that time to systemic treatment is significantly associated with race, gender, ethnicity, marital status, and tumor stage in this cohort of renal carcinoma patients. American Indian, Asian Pacific

Islander (AAPI) and Black patients were found to have longer time to treatment when compared to White patients. Female patients and patients with higher stage tumors had a shorter TTT when compared to male patients and patients with lower stage tumors respectively. These findings may have future implications in the development of recommendations and guidelines for systemic therapy use in RCC management. In RCC management, patient stratification is considered a particularly important component of systemic therapy selection.[1] The efficacy of newer systemic therapies is challenging the standard in some patients with metastatic disease. [1]It is imperative to consider the patient's survival benefits before adding systemic therapy to the surgical or conservative management of RCC. It is important to consider demographic and clinical factors such as age, race and tumor stage when using systemic therapy in adjuvant and neoadjuvant settings.

A very important treatment outcome component analyzed in this study is the time to systemic treatment initiation. The diagnosis of RCC is usually incidental and may lead to late presentation and delayed treatment initiation. In the management of higher stage disease prognostic scoring systems have been developed to define risk groups of patients by combining independent prognostic factors for survival in patients with metastatic RCC.[2,3] The time interval from diagnosis to treatment has been identified as one of the important prognostic factors in the management of advanced RCC.[3,4] This present study showed that time to treatment was associated with sociodemographic factors such as race, ethnicity, gender and marital status. Access to treatment and specialty care may be a contributing factor to delayed treatment observed in AAPI and Black patients. Prioritizing redistribution of heath resources in Black and AAPI communities could reduce time to systemic treatment intuition and improve treatment outcomes.

This study was designed to help clinicians and oncologists make informed decisions that could potentially improve treatment outcomes for RCC patients. The survival benefit of systemic therapy initiation in RCC management should always be considered, especially in situations where there are advanced metastatic tumors or coexisting chronic medical conditions. An ideal clinical consideration would be tailoring and triaging systemic therapy based on the patients' demographic and tumor related factors. Age-related differences in mortality and survival after systemic therapy use is another important clinical consideration, as older patients may not have any survival or mortality benefit from receiving systemic therapy for RCC before or after surgery. Similarly, the use of systemic therapy in advanced metastatic RCC may not be beneficial to the patient with distant organ metastases and may result in treatment complications. In clinical situations where systemic therapy use is not deemed beneficial to the patient, partial or total nephrectomy could be considered as an alternative. We anticipate that the predictors of treatment outcomes identified from this present study will serve as a valuable resource to inform the development of treatment approaches and clinical guidelines for RCC patients. Ensuring clinician education on these guidelines could potentially enhance patient outcomes.

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