Dissertation

Pattern and Prognostic Impact of radiographic and pathological lymph node metastases in patients with kidney cancer

submitted by

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Declaration

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the “Guidelines of the
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Disclosures

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All co-authors have agreed to the inclusion of their published data in the dissertation. A signed statement confirming their approval has been submitted alongside the thesis.

This cumulative thesis incorporates the following three publications, all of which have been included with the formal approval of the respective publishers:

1. **“Regional differences in clear cell metastatic renal cell carcinoma patients across the USA”**(1)

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2. **“Prognostic Significance of Pathologic Lymph Node Invasion in Metastatic Renal Cell Carcinoma in the Immunotherapy Era”**(2)

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3. **“Prognostic Significance of Radiographic Lymph Node Invasion in Contemporary Metastatic Renal Cell Carcinoma Patients”** (3)

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Table of Contents

Abbreviations and Definitions

Abbreviation	Full Term
ALK	Anaplastic Lymphoma Kinase
BHD	Birt-Hogg-Dubé Syndrome
BMI	Body Mass Index
CaIX	Carbonic Anhydrase IX
CKD	Chronic Kidney Disease
CN	Cytoreductive Nephrectomy
CRP	C-Reactive Protein
CSS	Cancer-Specific Survival
CSM	Cancer-Specific Mortality
CT	Computed Tomography
CTLA-4	Cytotoxic T-Lymphocyte-Associated Protein 4
EAU	European Association of Urology
eGFR	Estimated Glomerular Filtration Rate
EORTC	European Organisation for Research and Treatment of Cancer
FCM	Fluorescence Confocal Microscopy
FLCN	Folliculin (BHD gene)
HIF	Hypoxia-Inducible Factor
HPRC	Hereditary Papillary Renal Carcinoma
HR	Hazard Ratio
RR	Relative Risk
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
IO	Immuno-Oncology
ISUP	International Society of Urological Pathology
KPS	Karnofsky Performance Status
LDH	Lactate Dehydrogenase
LND	Lymph Node Dissection
LNI	Lymph Node Invasion
mRCC	Metastatic Renal Cell Carcinoma
MSKCC	Memorial Sloan Kettering Cancer Center
mTOR	Mammalian Target of Rapamycin
NCDB	National Cancer Database
NLR	Neutrophil-to-Lymphocyte Ratio
NOS	Not Otherwise Specified
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OM	Overall Mortality
OS	Overall Survival
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death Ligand 1
PDGFs	Platelet-derived Growth Factors

PN	Partial Nephrectomy
PTEN	Phosphatase and Tensin Homolog
RCC	Renal Cell Carcinoma
RCT	Randomized Controlled Trial
RN	Radical Nephrectomy
SEER	Surveillance, Epidemiology, and End Results
SNP	Single Nucleotide Polymorphism
SMARCB1	SWI/SNF Related, Matrix Associated, Actin Dependent Regulator of Chromatin Subfamily B Member 1
TCEB1	Transcription Elongation Factor B Subunit 1
TFE3	Transcription Factor E3
TFEB	Transcription Factor EB
TKI	Tyrosine Kinase Inhibitor
TNM	Tumor, Node, Metastasis (Staging System)
US	United States of America
VEGF	Vascular Endothelial Growth Factor
VHL	Von Hippel-Lindau
WHO	World Health Organization

Abstract in German

Lymphknotenmetastasen (LNI) stellen einen etablierten ungünstigen prognostischen Faktor beim metastasierten Nierenzellkarzinom (mRCC) dar. Ihre prognostische Relevanz im Kontext moderner systemischer Therapien ist jedoch bislang unzureichend geklärt. Die vorliegende Dissertation untersucht die prognostische Bedeutung sowohl pathologisch (pN1) als auch radiologisch (cN1) nachgewiesener Lymphknotenmetastasen bei Patient:innen mit mRCC. Grundlage der Arbeit bilden drei populationsbasierte Studien, die im Rahmen eines Forschungsaufenthalts an der Cancer Prognostics and Health Outcomes Unit in Montreal (Kanada) unter Verwendung der SEER-Datenbank durchgeführt wurden.

In der ersten Studie wurden regionale Unterschiede hinsichtlich Patientencharakteristika, Behandlungsmustern und Überlebensraten von mRCC-Patient:innen in den Vereinigten Staaten analysiert. Es zeigte sich eine deutliche Heterogenität im Lymphknotenstaging sowie in der therapeutischen Vorgehensweise, was die Notwendigkeit standardisierter prognostischer Bewertungskriterien unterstreicht. Die zweite Studie fokussierte auf Patient:innen, die einer zytoreduktiven Nephrektomie (CN) unterzogen wurden, und konnte zeigen, dass ein pathologisch bestätigter Lymphknotenbefall (pN1) mit einem signifikant schlechteren krebsspezifischen Überleben assoziiert ist. Die dritte Studie widmete sich Patient:innen ohne CN und identifizierte auch hier radiologisch nachgewiesene Lymphknotenmetastasen (cN1) als unabhängigen Prädiktor für eine ungünstige Prognose.

Die Ergebnisse aller drei Arbeiten verdeutlichen die prognostische Relevanz von LNI – unabhängig von der Durchführung einer Nephrektomie. Aktuell etablierte Prognosemodelle wie IMDC oder MSKCC berücksichtigen den Lymphknotenstatus bislang nicht. Die vorliegenden Daten sprechen dafür, LNI künftig in prognostische Scores zu integrieren, um die Risikostratifizierung zu verbessern und therapeutische Entscheidungen gezielter treffen zu können. Prospektive Studien sind erforderlich, um den potenziellen therapeutischen Nutzen einer Lymphknotendissektion vom rein prognostischen Wert abzugrenzen.

Abstract in English

Lymph node invasion (LNI) is a known adverse prognostic factor in metastatic renal cell carcinoma (mRCC), yet its relevance in the era of modern systemic therapies remains unclear. This dissertation investigates the prognostic significance of both pathological and radiographic LNI in contemporary mRCC patients. The work is based on three population-based studies conducted during a research fellowship at the Cancer Prognostics and Health Outcomes Unit in Montreal, Canada, utilizing the SEER database.

The first study explored regional differences in mRCC patient characteristics, treatment patterns, and outcomes across the United States. It revealed notable variability in lymph node staging and treatment utilization, highlighting the need for consistent prognostic evaluation. The second study focused on patients undergoing cytoreductive nephrectomy (CN), demonstrating that pathological LNI (pN1) is independently associated with significantly worse cancer-specific survival compared to pN0 patients. The third study examined patients who did not undergo CN and found that radiographic LNI (cN1) was also a significant predictor of poor prognosis.

Collectively, these findings underscore the prognostic value of LNI—both pathological and radiographic—in mRCC patients, regardless of surgical intervention. Current prognostic models, such as IMDC and MSKCC, do not incorporate lymph node status. Our findings suggest that integrating LNI into future prognostic tools may improve patient stratification and guide therapeutic decision-making. Nonetheless, prospective studies are needed to determine whether lymph node dissection offers a therapeutic benefit or simply reflects disease severity.

Introduction

Definition and Overview

Renal cell carcinomas (RCC) are a heterogenous group of tumors that originate from the renal epithelium and are responsible for up to 85% of all neoplasms of the kidney. (4)The second most common form of kidney tumors are transitional cell carcinomas of the renal pelvis, comprising around 8% of all renal tumors.(5) In total, RCC includes more than ten histological and molecular subtypes, with clear cell renal cell carcinoma (ccRCC) being the most prevalent of them. (4)

Epidemiology and Incidence

RCC is the 12th most common malignancy worldwide with approximately 400.000 new cases in 2020. (6) However, the incidence of RCC shows significant regional variation, suggesting differences in genetic, environmental, and lifestyle factors among patients. Notably, the highest incidence rates were observed in the Czech Republic as well as North America. (7) Moreover, RCC demonstrates a clear gender disparity, with males being approximately twice as likely to develop the disease compared to females.(8) This difference may be attributed to differences in genetics, as well as higher exposure to risk factors among males, such as smoking, hypertension, and occupational hazards.(9) The median age at diagnosis for RCC is 64 years. (10)

Risk Factors and Etiology

Several risk factors, including lifestyle habits, occupational hazards, different disease as well as genetic predispositions have been associated with the development of RCC. The key risk factors associated with RCC will be described in detail in the sections below.

Smoking

Cigarette smoking is considered to be a well-established risk factor for RCC. (11)A meta-analysis of 24 studies revealed a relative risk (RR) of 1.31 for all smokers, 1.36 for current smokers, and

1.16 for former smokers. (12) Additionally, increased cigarette use correlates with more advanced stages of RCC at initial diagnosis. (13) Conversely, smoking cessation reduces that risk. (13,14)

Hypertension

Hypertension has been recognized as a risk factor for RCC, regardless of the use of antihypertensive medication or the presence of obesity. (15) However, the underlying biological pathways connecting hypertension to RCC are largely unknown. It is of note that hypertension has similar common risk factors as RCC, which can act as confounding factors during the investigation of the underlying causality.(16) A potential hypothesis is that hypertension may lead to chronic inflammation, resulting in renal hypoxia. This hypoxic environment could upregulate the expression of hypoxia-inducible factors, subsequently promoting the overexpression of vascular endothelial growth factor (VEGF) and platelet-derived growth factors (PDGFs), thereby facilitating tumorigenesis. (17)

Obesity

Excessive bodyweight is associated with an increased risk for RCC. (18) In a large study containing more than 300.000 individuals, the risk of developing RCC was strongly correlated to the body-mass-index (BMI). (18) However, weight gain only increased the risk for RCC up to the age of 50, whereas weight gain was unrelated to risk of RCC after the age of 50. (18)

Interestingly, some evidence suggests that obesity may also be associated with a better prognosis for RCC patients. For example, in patients with newly diagnosed RCC, increased body weight is associated with lower stage and grade disease. (19) Moreover, in patients with metastatic disease, increased body weight is associated with better overall survival and progression-free survival compared to patients with normal or lower body weight. (20)

Chronic Kidney Disease

In patients with chronic kidney disease, lower eGFR is associated with an increased risk of developing RCC. (21) In patients with acquired polycystic disease who require dialysis, the risk of

developing RCC is up to 30 times greater compared to healthy individuals. (22) In addition to an increased risk for developing RCC, a reduction in GFR is also associated with an increased risk for urothelial carcinoma. Possible pathological mechanisms for the relationship between chronic kidney disease and increased risk for RCC are chronic inflammation, oxidative stress, accumulation of cancerogenic compounds, changes in the intestinal microbiota as well as impairment of the DNA repair system. (23)

Occupational Exposure

Occupational exposure to certain compounds or chemicals has been associated with a higher risk for the development of RCC. In a German population-based multicenter study from 2000 long exposures in the chemical, rubber and printing industries were associated with an increased risk for RCC. (24) Additionally, substantial exposure to solvents, lead, solder fumes, mineral oils, cutting fluids, benzene, polycyclic aromatic hydrocarbons and asbestos was also associated with RCC development. (24)

Analgesic Use

Several studies suggest an association between regular analgesic use and RCC development. (25–27) The increased risk for RCC has been described for aspirin, nonsteroidal anti-inflammatory drugs (NSAIDS) and acetaminophen, with regular acetaminophen use having the strongest association. (25–27)

Genetic Factors

Several pathogenic genetic variants have been identified to contribute to the inherited risk of cancer in some families with a predisposition to RCC.(28) However, these variants are estimated to be responsible for only 5-8% of all RCC cases in total. (28,29) An inherited predisposition to RCC is suggested by an early onset (under 40 years of age), a family history of renal cancer, and the presence of bilateral or multifocal renal tumors. (30) Some of the more well-known inherited renal cancer syndromes include Von Hippel-Lindau disease (VHL; VHL gene), Hereditary papillary renal

carcinoma (HPRC; MET gene) or Birt-Hogg-Dubé syndrome (BHD; FLCN gene). It is likely that additional, yet-to be discovered genes and underlying genetic factors, are also involved in the development of RCC

Classification and Staging of kidney cancer

The classification of RCC has evolved from relying primarily on morphology to incorporating the complex molecular differences among the various carcinoma types. (31) The broad spectrum of RCC types is reflected in the World Health Organisation (WHO) classification of renal tumours from 2022, which consists of the following subtypes. (31)

01.I Clear cell renal tumours
- Clear cell RCC
- Multilocular cystic renal neoplasm of low malignant potential

01.II Papillary renal tumours
- Papillary adenoma
- Papillary RCC

01.III Oncocytic and chromophobe renal tumours
- Oncocytoma of the kidney
- Chromophobe RCC
- Other oncocytic tumours of the kidney

01.IV Collecting duct tumours
- Collecting duct carcinoma

01.V Other renal tumours
- Clear cell papillary renal cell tumour
- Mucinous tubular and spindle cell carcinoma
- Tubulocystic RCC
- Acquired cystic disease-associated RCC
- Eosinophilic solid and cystic (ESC) RCC
- RCC NOS (Not Otherwise Specified)

01.VI Molecularly defined renal tumours
- *TFE3*-rearranged RCCs
- *TFEB*-altered RCC (*TFEB*-rearranged RCC and *TFEB* amplified RCC)
- *ELOC* (formerly *TCEB1*)-mutated RCC

Fumarate hydratase-deficient RCC Succinate dehydrogenase-deficient RCC *ALK*-rearranged RCCs *SMARCB1*-deficient renal medullary carcinoma

Table 1: Overview of RCC subtypes according to WHO classification of renal tumors 2022.

Staging

All histological types of RCC are staged using the eighth (2017) Tumor, Node, Metastasis (TNM) staging system. In the eighth edition of the TNM staging system, kidney-confined tumors are categorized as T1 or T2, depending on their size. Tumors classified as T3 have grown into the renal vein or surrounding perinephric tissue but remain contained within the Gerota fascia. Tumors designated as T4 have extended past the Gerota fascia, which may include direct invasion into the nearby adrenal gland on the same side. Lymph node involvement and distant metastasis are straightforwardly indicated as either present or absent. (32)

T stage	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤7 cm in greatest dimension, limited to the kidney
T1a	Tumor ≤4 cm in greatest dimension, limited to the kidney
T1b	Tumor >4 cm but ≤7 cm in greatest dimension, limited to the kidney
T2	Tumor >7 cm in greatest dimension, limited to the kidney
T2a	Tumor >7 cm but ≤10 cm in greatest dimension, limited to the kidney
T2b	Tumor >10 cm, limited to the kidney
T3	Tumor extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota's fascia

T3a	Tumor extends into the renal vein or its segmental branches, or invades the pelvicalyceal system, or invades perirenal and/or renal sinus fat but not beyond Gerota's fascia
T3b	Tumor extends into the vena cava below the diaphragm
T3c	Tumor extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)
N stage	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
M stage	
M0	No distant metastasis
M1	Distant metastasis

Table 2: TNM stages of RCC

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3 T1, T2, T3	N0 N1	M0
Stage IV	T4 Any T	Any N Any N	M0 M1

Table 3: Overview of the American Joint Commission on Cancer (AJCC) staging for RCC

Prognostic factors

The size of the tumor, as well as the anatomic extent of the disease based on the TNM staging system is one of the most reliable prognostic factors in RCC. Thus, the TNM classification serves as a basic framework for risk assessment in RCC.

Stage I

Patients with stage I renal cell carcinoma (RCC) typically experience excellent outcomes, with a five-year survival rate exceeding 90%. (33) The risk of recurrent disease or metastasis in this stage is low.

Stage II

For stage II RCC, survival rates generally range from 75% to 95%. (34)However, prognosis significantly worsens when there is invasion of the urinary collecting system. (35)For T1 and T2 lesions with such invasion, the reported 5- and 10-year survival rates are 43% and 41%, respectively. (36)

Stage III

The five-year survival rate for stage III RCC is approximately 53%. (32) The impact of perinephric fat invasion (T3a) is debated, but tumor size remains a crucial prognostic factor even in stage III, with 10-year survival rates of 77% for tumors under 4 cm, 54% for 4–7 cm, and 46% for those over

7 cm. (37–39) In this stage, renal vein and inferior vena cava invasion are also significant prognostic factors. (40)

Stage IV

Survival rates for stage IV RCC have improved significantly with modern therapies, namely with the introduction of immunotherapies. Previously, median overall survival was just over one year with cytokine treatments. Current therapies, including immunotherapy combinations such as nivolumab and ipilimumab, have extended the median survival up to five years. (41)

Histology

RCC histological subtypes, tumor grade, lymph vascular invasion, tumor necrosis and invasion of the collecting system all represent important histological factors according to the current EAU guidelines for RCC. (42)

The prognostic implications of RCC subtypes are not as straightforward as other prognostic factors. Previous studies have shown that the chromophobe RCC subtype had the best prognosis, followed by papillary RCC and lastly clear cell histology. However, this is based on univariable analyses. (43) In multivariable models where tumor stage is considered, the prognostic implications of histological subtypes are lost. (44)

In contrast to the above, tumor grade is an independent histological prognostic marker. The current EAU guidelines on RCC suggest the use of the WHO/ISUP grading classification instead of the Fuhrman grading system. (45) This suggestion is based on various studies reporting superior prognostic information compared to the historic Fuhrmann grading system. (46,47) The WHO/ISUP grading system is suitable to use with both clear-cell RCC and papillary RCC, however,

it is not recommended to grade chromophobe RCC. (45) Additionally, all RCC subtypes can exhibit rhabdoid and sarcomatoid histological features, which are classified as an equivalent to grade 4 tumors. (45)

Molecular factors

With the shift from a primarily histological approach to one that recognizes complex molecular differences in RCC classification, various molecular markers are now being considered for their potential prognostic value. The number of these novel markers is rapidly increasing and includes carbonic anhydrase IX (CaIX), VEGF, HIF, Ki67, p53, p21, PTEN, E-cadherin, osteopontin, CD44, CXCR4, PD-L1, miRNA, SNPs, several gene mutations as well as gene methylations.

In the era of precision medicine, identifying biomarkers that aid in prognosis and in the assessment of therapeutic response has become crucial. Non-invasive molecular biomarkers, have shown promise for early diagnosis, prognosis prediction, and assessment of therapy response in RCC patients. However, despite the increasing demand for such biomarkers, few have been approved for RCC. (42) Most of these markers show prognostic relevance, however, few studies have focused on validating these findings externally. At present, molecular markers are not routinely recommended in clinical practice. (42)

Clinical factors

Various clinical factors, including low performance status, presence of paraneoplastic syndromes (such as anemia, hypercalcemia, thrombocytosis, fever, and weight loss), elevated C-reactive protein, and neutrophil-to-lymphocyte ratio (NLR), have shown prognostic value in RCC. (48,49)

There are several models that incorporate these clinical features together with both anatomic staging and histology(50,51) The EAU guidelines recommends the use of integrated prognostic systems to evaluate oncologic outcomes following surgery in patients with localized RCC. Several

models exist that rely on anatomic extent as well as clinical and histological prognostic factors. The most established are the UISS, the Leibovich 2003, the Leibovich 2018, the VENUSS, the GRANT and the Karakiewicz model. (52–57) In a recent systematic review, all of these models showed comparable prognostic performance for clear cell RCC. (58) However, the VENUSS and UISS models have been shown to be the most accurate for predicting outcomes in papillary and chromophobe RCC, respectively. Therefore, selecting an appropriate prognostic model should take into account the specific histologic subtype. (59)

For metastatic RCC, The Memorial Sloan Kettering Cancer Center (MSKCC) model and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model are well-established prognostic model with significant validation. The MSKCC model, introduced by Motzer et al., incorporates five clinical and laboratory parameters: time from diagnosis to treatment, Karnofsky performance status (KPS), hemoglobin levels, serum calcium, and lactate dehydrogenase (LDH) levels. This model was initially proposed in the pre-targeted therapy era and has since been validated in patients receiving targeted therapies. (60,61)

The IMDC model, developed by Heng et al., includes six factors: time from diagnosis to treatment, KPS, hemoglobin, neutrophil count, platelet count, and serum calcium. (62)

Most of the contemporary randomized control trials (RCT) rely on the IMDC model as it was created in the targeted therapy era. As such, the IMDC model is the preferred model in clinical practice at the moment. (42)

Management of localized disease

For T1 tumors (<7cm), nephron-sparing surgery, namely partial nephrectomy (PN), is the preferred treatment choice in order to preserve kidney function. (63) PN can be performed using open, laparoscopic, or robot-assisted laparoscopic techniques. When PN is not technically feasible, open or robot-assisted laparoscopic radical nephrectomy (RN) is advised as an alternative. (42)

In recent years non-surgical approaches such as cryoablation, radiofrequency ablation, and microwave ablation have gained attention as an alternative treatment to PN, especially in small renal masses (<4cm). (64,65) In a recent systematic review, performed by the guideline panel of the current EAU RCC guidelines, tumor ablation for T1 tumors was found to be safe regarding complications and adverse events, however, its long-term oncological effectiveness relative to PN remains uncertain.(66) Given the limited available data, current guidelines recommend tumor ablation primarily for frail and/or comorbid patients with small renal masses. (42)

For T2 tumors, the use of PN should be more selective, taking into account specifics such as tumor location and patient comorbidities. (67) Despite limited data, PN for T2 tumors has been associated with improved OS and CSS, although at the expense of increased blood loss and a higher chance for postoperative complications.(67,68)

For T3 tumors, clinical studies suggest that 38-70% of patients are curable with surgery alone. (69)A meta-analysis found no significant differences in OS or CSS outcomes between PN and RN in T3a patients, suggesting that PN is a viable nephron-sparing option when technically feasible even in this stage. (70)

The question whether to perform lymph node dissection (LND) or not in locally advanced RCC (T3+) remains unclear, as multiple retrospective studies and systematic reviews have examined LND with mixed findings. (71,72) According on the current EAU guidelines, currently only one randomized controlled trial (RCT) compared RN with complete LND to RN alone in clinically N0M0 RCC patients. (73) In this trial, no survival benefit was shown in patients undergoing RN with complete LND compared to RN alone, however only 28% of included patients harbored T3 tumors. (73)

In patients with cN+ status, removing visible and palpable lymph nodes during surgery is warranted, though evidence for improved cancer control remains unproven. The decision to extend LND in cases of cN1 remains unclear.(42)

Management of advanced disease

Advanced RCC patients show considerable variability in treatment outcomes and disease progression. Prognostic models, including the MSKCC and IMDC classifications, have been established to categorize patients with advanced RCC into distinct risk groups (favourable, intermediate and poor). This prognostic stratification can help in the subsequent treatment decisions.

Cytoreductive nephrectomy

Cytoreductive nephrectomy (CN) involves the removal of the primary tumor in patients with metastatic disease. The main hypothesis behind this procedure is that reducing the tumor burden helps the immune system control any remaining disease and removes a possible source for additional metastases. Evidence supporting this approach comes from studies conducted in both pre-targeted and targeted therapy eras. (74,75)

However, in recent years, results from the CARMENA and SURTIME trials have changed the clinical approach to CN in metastatic RCC. The CARMENA trial challenged the role of CN by demonstrating that targeted therapy alone (sunitinib) could achieve comparable survival outcomes in mRCC patients with intermediate or poor risk disease compared to patients who underwent additional CN. (76) Additionally, the randomised EORTC SURTIME trial further explored the importance of CN timing. Specifically, the objective of the study was to test whether a period of sunitinib therapy before CN (deferred) improves the outcome of mRCC patients compared with immediate CN followed by sunitinib therapy. (77)

The study showed that patients who underwent deferred CN, allowing for an initial course of sunitinib therapy, experienced improved OS compared to patients who underwent immediate CN. This approach appears to select patients with inherent resistance to systemic therapy. (77) Together, these trials have led to a more individualized approach to CN, emphasizing patient selection and sequence of CN as critical factors for optimal outcomes.

However, the CARMENA and SURTIME trials, relied on sunitinib as the standard treatment, and did not incorporate modern immune checkpoint inhibitors or their combinations. (76,77) Therefore, these trials may not fully capture the potential advantages of newer therapeutic approaches. Ongoing randomized trials are investigating the role of deferred versus no cytoreductive nephrectomy in combination with novel immune checkpoint inhibitors. (78)Based on the current EAU RCC guidelines, mRCC patients in the IMDC intermediate- and poor-risk groups with an intact primary tumor should be treated with upfront IO-based combination therapies. (42)For those who show a clinical response, a subsequent cytoreductive nephrectomy may be considered.(42)

Systemic therapy

Despite advances in surgical management options, a significant proportion of patients with RCC either presents with metastatic disease at diagnosis (approx. 25%) or develop recurrence after initial treatment. (79) Advancements in systemic therapy, foremost the rise of immunotherapy, have drastically improved the prognosis of mRCC patients in the last decade. (80) This is especially notable given the poor historic efficacy of traditional cytotoxic therapies for RCC. (81)

Currently, systemic therapy for metastatic renal cell carcinoma typically involves combinations of agents from several therapeutic classes. These include immune checkpoint inhibitors targeting the programmed cell death protein 1 (PD-1) pathway, such as nivolumab and pembrolizumab, or its ligand, PD-L1, with agents like avelumab and atezolizumab. Additionally, anti-cytotoxic T-

lymphocyte-associated protein 4 (CTLA-4) antibodies, such as ipilimumab, are used to enhance T-cell-mediated antitumor responses. (82) Antiangiogenic agents targeting the vascular endothelial growth factor (VEGF) pathway, including axitinib, sunitinib, pazopanib, cabozantinib, lenvatinib, and bevacizumab, remain important components of treatment regimens. (42)Mammalian target of rapamycin (mTOR) inhibitors, such as everolimus, are also used in selected cases. (42)

Risk stratification models are used to guide treatment decisions. The IMDC classification is most commonly used and is based on six adverse factors: a Karnofsky performance status below 80 percent, a time from diagnosis to treatment of less than one year, hemoglobin levels below the lower limit of normal, elevated serum calcium above the upper limit of normal, and increased neutrophil and platelet counts.(62) Patients are categorized into risk groups based on the number of these adverse factors. Patients are considered as favorable risk if they have no adverse factors, intermediate risk if they have one or two factors, and poor risk if they have three or more factors.(62)

For patients with IMDC favourable risk mRCC, who are asymptomatic and have limited disease burden, active surveillance can be considered. (42,83) By opting for active surveillance, treatment associated toxicities can be postponed until evidence of significant disease progression occurs.(83) During active surveillance, CT imaging of the chest, abdomen and pelvis are recommended every three months during the first year, every four months in the second year, and every six months after completion of the second year. (83)

Treatment is recommended for patients with favorable-risk disease who present with a significant disease burden, symptoms, or rapidly progressing disease. Preferred options typically include immunotherapy-based combinations such as pembrolizumab with axitinib, nivolumab with cabozantinib, or lenvatinib with pembrolizumab. (42)

For patients with IMDC intermediate or poor-risk disease, preferred treatment options include nivolumab combined with ipilimumab, nivolumab with cabozantinib or pembrolizumab paired with axitinib or lenvatinib. (42)Alternatively, for patients who cannot receive or tolerate immune checkpoint inhibitors or combination therapies, sunitinib, cabozantinib or pazopanib alone may be considered. (42)

Discussion

Metastatic RCC is a heterogeneous disease with significant variability in clinical presentation, treatment response, as well as prognosis. As such, prognostic biomarkers are essential for guiding personalized treatment strategies, optimizing therapeutic decisions, and improving overall patient outcomes. The goal of this dissertation was to explore the prognostic role of lymph node invasion (LNI) in a large, contemporary cohort of mRCC patients. Historically, the detection of LNI has been recognized as an independent prognostic factor associated with poorer survival outcomes in patients undergoing cytoreductive nephrectomy (CN) for mRCC. (84) However, the prognostic relevance of LNI in the era of modern therapeutic strategies remains uncertain.

This dissertation is based on three distinct studies completed during my research fellowship at the Cancer Prognostics and Health Outcomes Unit, under the leadership of Professor Karakiewicz, in Montreal, Canada. These studies represent an outtake of my work completed during my research fellowship between 2022 and 2023. The first study is titled "Regional differences in clear cell metastatic renal cell carcinoma patients across the United States" and was the ground work for the following two studies. (2) The second study titled "Prognostic significance of pathological lymph node invasion in metastatic renal cell carcinoma in the immunotherapy era" aimed to explore the prognostic role of LNI in contemporary mRCC patients who underwent CN.(1) Finally, the third study titled "Prognostic significance of radiographic lymph node invasion in metastatic renal cell carcinoma patients" examined whether radiographic LNI in patients who did not undergo CN also affects prognosis. (3) Collectively, these studies address an important knowledge gap regarding the prognostic significance of LNI in contemporary mRCC patients, providing a foundation for future research and the development of novel prognostic models.

For all studies, we relied on a large, United States (US) population-based database, namely the Surveillance, Epidemiology, and End Results (SEER) database. The SEER database captures data for approximately 30% of the US population regarding cancer diagnosis, treatment and survival.(85)

The SEER program collects comprehensive data on patient demographics, clinical characteristics, as well as outcomes for all cancers diagnosed within specific geographic regions and subpopulations within the US. These regions are chosen based on their capacity to establish and maintain a high-quality, population-based cancer registry, as well as to enhance the demographic and geographic representation of the SEER dataset. (85) At the moment, there are currently 18 SEER registries. (85) The population covered by the SEER program closely reflects the broader U.S. population in terms of socioeconomic factors such as education and poverty levels. As a result, SEER data regarding cancer incidence, treatment, as well as outcomes are widely regarded as representative of the overall U.S. healthcare system.(85) The SEER program is considered to be the gold standard for data quality among large-scale population-based cancer registries both in the US and internationally. A high standard of quality control is upheld through strict contractual agreements with participating regional registries, ensuring compliance with SEER's protocols. (86)

The extensive scope of the SEER program ensures the inclusion of large cohorts, that provide significant statistical power even for the study of rare diseases. This scale of data collection enables analyses that are often beyond the reach of single or even multi-institutional databases, which may lack the necessary sample size and patient diversity. As for our studies, relying on such a large and comprehensive database was crucial in order to compare patient, tumor and treatment characteristics as well as the subsequent outcomes within distinct geographical regions in the US. Moreover, the large cohort of mRCC patients allowed for comprehensive multivariable adjustments in our models, enhancing the robustness of our analyses. However, the large sample size within the SEER database can present a challenge in interpreting the results and drawing clinically meaningful conclusions. While larger datasets increase the likelihood of detecting statistically significant differences, these differences may not always correspond to clinically meaningful conclusions. For critical endpoints such as survival or mortality, even small differences can hold significant clinical relevance that warrant further research. (87) In contrast, for less impactful outcomes, statistically significant findings may not always equate to clinically meaningful conclusions, a point frequently raised in criticisms of studies relying on the SEER

database. Therefore, the use of confidence intervals alongside p-values, as well as reporting absolute risk differences, is especially important when working with large-scale databases where statistical significance alone may be misleading. (88)

In the first study titled “Regional differences in clear cell metastatic renal cell carcinoma patients across the United States” we relied on the SEER database to assess differences in patient, tumor and treatment characteristic across different geographic regions within the US.(1)We hypothesized that patient and tumor characteristics as well as patterns of care may differ between geographic regions and that such differences may translate into differences in overall mortality (OM). As hypothesised, we reported significant differences in patient characteristics such as age, sex and race/ethnicity. Moreover, we observed pronounced differences in rates of nephrectomy as well as systemic therapy even after adjusting for differences in patient and tumor characteristics. Interestingly, for rates of nephrectomy, we observed only marginal variability in the two regions (based on distinct SEER registries) with the highest patient count (Δ=3%). As a subsequent step, we analyzed five-year OM across the individual SEER registries. Our findings revealed that the OM HR was significantly elevated in five registries with smaller patient counts compared to the registry with the largest patient count. To mitigate potential biases arising from differences in patient, tumor, or treatment characteristics, we recalculated the OM HR following comprehensive multivariable adjustments. Notably, in two smaller registries, the HR remained significantly elevated even after these adjustments. These findings raise the possibility of a systematic disadvantage associated with smaller SEER registries, warranting further investigation.(1)

In addition to the above-discussed findings, we observed differences in the distribution of lymph node status across the SEER registries. Specifically, the proportion of patients staged as N1 and those with unknown lymph node staging (NX) varied significantly among registries. These discrepancies may reflect differences in patient populations or staging practices across different geographic regions within the US. Moreover, when we performed our analyses, N1 status

emerged as a significant independent predictor for worse survival despite the presence of distant metastasis. Currently, the most commonly used risk stratification tool for mRCC patients is the IMDC model, developed by Heng et al. (89) This model was created in the targeted therapy era and is used in most contemporary RCTs to stratify mRCC patients into favourable, intermediate and poor risk groups. It consists of six distinct factors: time from diagnosis to treatment, KPS, hemoglobin, neutrophil count, platelet count, and serum calcium. However, the lymph node status is not considered.

Another commonly used risk stratification tool is the MSKCC model, introduced by Motzer et al. (61) This model, which predates the IMDC model, incorporates five clinical and laboratory variables: the time from diagnosis to treatment, KPS, hemoglobin levels, serum calcium, and LDH levels. Like the IMDC model, the MSKCC model is widely used in clinical settings to predict prognosis and guide therapeutic decisions. However, it also does not account for the presence or absence of lymph node metastases. Even the more complex Leibovich model, which consists of 9 factors (constitutional symptoms at nephrectomy, metastases to the bone or liver, metastases in multiple simultaneous sites, metastases at nephrectomy or within 2 years of nephrectomy, complete resection of all metastatic sites, tumor thrombus level I to IV, nuclear grade 4, histological tumor necrosis), does not consider N stage. (90)

The prognostic nomogram developed by Karakiewicz et al. is one of the few prognostic models that incorporate LNI as a factor in assessing prognostic outcomes for RCC, including metastatic cases. (91) However, this nomogram is not limited to the metastatic disease and incorporates patients of all stages. (91) Moreover, the number of patients with mRCC in this nomogram was limited. (91) It is possible that the prognostic significance of lymph node status observed in this prognostic model is predominantly derived from its impact in nonmetastatic RCC patients, rather than reflecting its role in advanced disease. (91) Although our data pointed to a significant prognostic impact of N stage in patients with mRCC, current prognostic models largely overlook lymph node status as a relevant factor. Recognizing this knowledge gap, we wanted to further

investigate the relationship between LNI and prognosis in patients with advanced RCC. This investigation led to our second study, titled, “Prognostic Significance of Pathological Lymph Node Invasion in Metastatic Renal Cell Carcinoma in the Immunotherapy Era”. (2)We hypothesized that in patients with mRCC who underwent CN, the presence of pathological lymph node involvement would be associated with poorer survival outcomes. Again, we relied on the SEER database to identify a large cohort of mRCC patients who underwent CN (3,149). Of these 3,149 mRCC patients, 40% (1255) underwent additional lymph node dissection during CN. Next, we relied on Kaplan-Meier plots and multivariable Cox-regression analyses to test for differences in cancer-specific mortality (CSM) for pN0 vs. pN1 vs. pNx patients. Kaplan-Meier analyses revealed significant differences in CSM-free survival based on N status, with median survival times of 15 months for pN1, 40 months for pN0, and 35 months for pNx ($p<0.001$). Furthermore, multivariable Cox regression analyses identified pN1 status as an independent predictor of higher CSM compared to pN0 (HR 1.88, $p<0.01$).

These results established the prognostic importance of pathological LNI (pN1) in a contemporary cohort of surgically treated mRCC patients. Unfortunately, direct comparisons to other studies exclusively examining this association in the immunotherapy era are not feasible, as to the best of our knowledge, no comparable studies have been conducted. However, earlier investigations in historical cohorts have demonstrated comparable findings. These studies, conducted in both the pre-TKI and TKI therapy eras, consistently identified pN1 status as an independent predictor of poorer survival outcomes, mirroring the results of our analysis.(92,93) Specifically, Lughezzani et al. reported a median CSM-free survival for surgically treated mRCC patients with pN1 vs. pN0 vs. pNx status of 10 months vs. 22 months vs. 18 months. (92) Notably, these findings not only demonstrate a similarly strong association between LNI and worse prognosis in mRCC patients that are consistent with our more contemporary results, but also highlight the significant improvements in survival for surgically treated mRCC patients over time. This is particularly relevant given that the study by Lughezzani et al., which also utilized the SEER database, offers a valuable historical comparison.

Taken together, our findings suggest that even with modern treatment options, pN1 status remains a critical factor for prognostic stratification in surgically treated mRCC patients. Specifically, in cases where LND is performed, individuals with pN1 disease experience significantly worse survival outcomes compared to those with pN0 status.

However, the current role of LND in CN is a topic of ongoing debate. In our analyses, only 40% of all CN-treated mRCC patients underwent additional LND. Despite the association between LNM and poor prognosis, it is unclear whether LND has an impact on survival outcomes in mRCC patients treated with modern therapies. While the phase 3 EORTC 30881 trial reported no significant advantage of LND in terms of OS, recurrence-free survival, or progression-free survival (PFS), the study primarily included low-stage tumors with a negligible risk for nodal involvement, limiting its applicability to higher-risk populations. (94) Retrospective studies, however, have highlighted that LNI is especially prevalent in patients with high-risk features, such as advanced tumor stage, large tumor size, high Fuhrman grade, sarcomatoid differentiation, or tumor necrosis.(95) Moreover, in contrast to the EORTC trial, a retrospective study suggested that LND in highly selected mRCC patients is associated with improved survival. (96)

The limited use of LND in routine clinical practice can be attributed not only to the inconclusive evidence but also to significant changes in the surgical management of RCC. In recent years, there has been a significant transition from open radical surgery with the possibility of extensive LND to minimally invasive approaches, predominantly robotic surgery, which typically only allows for limited hilar LND. (97)Consequently, in modern clinical practice, LND is primarily reserved for high-risk patients and is performed with a diagnostic purpose rather than a curative intent.(98)
Although our results show a strong association between LNI and poorer survival outcomes, randomized prospective trials are needed to definitively determine the role of LND during CN in patients with mRCC.

In addition to the above, recent evidence from pivotal trials has further reshaped the role of CN in mRCC. Specifically, the CARMENA trial, a prospective study, established the non-inferiority of sunitinib alone compared to sunitinib plus upfront CN. Patients treated with sunitinib alone had a median overall survival (OS) of 18.4 months, slightly exceeding the 13.9 months observed in those who underwent CN followed by sunitinib. (76) However, the trial's findings are limited by the exclusion of low-burden disease patients, who were managed surgically outside the trial. Subgroup analyses suggest that intermediate-risk patients, particularly those with a single International Metastatic RCC Database Consortium (IMDC) risk factor or isolated lung metastases, may benefit from upfront CN. (99)Additionally, 18% of patients in the sunitinib-only arm who underwent deferred CN experienced a significantly improved median OS of 48.5 months compared to 15.7 months for those continuing systemic therapy alone.(99)

The SURTIME trial added further insights. Although limited by its small sample size (99 patients instead of the planned 458), the study compared immediate CN followed by sunitinib with delayed CN after three cycles of sunitinib. (77)Patients in the delayed CN arm demonstrated a median OS of 32.4 months, significantly longer than the 15 months in the immediate CN arm. (77)While the trial failed to meet its primary endpoint, it highlighted the potential benefit of selecting patients who respond well to systemic therapy for delayed CN.

The results of these two landmark trials have reshaped the role of CN in the treatment of mRCC. In detail, current guidelines do not recommend CN for IMDC poor risk patients anymore. (42)Additionally, immediate CN is not advised for intermediate-risk patients with an asymptomatic synchronous primary tumor who require systemic therapy. (42)Taken together, these recommendations have led to a significant reduction in performed CN. (100) A recent NCDB study by Chakiryan et al. published in 2022, reported that 61% of all mRCC patients do not undergo CN. (101)

As such, despite strong prognostic implications, information regarding pathological lymph node status is often not available. With this in mind, we wanted to explore whether radiographic information regarding lymph node status offers similar prognostic value in patients who do not undergo CN. Specifically, in our third paper titled “Prognostic significance of radiographic lymph node invasion in metastatic renal cell carcinoma patients”, we investigated the prognostic significance of radiographic lymph node status in a contemporary cohort of mRCC patients treated with systemic therapy without CN. As the SEER database does not offer information on MSKCC or IMDC criteria, we only included mRCC patients with low metastatic burden (single site of metastases) in this analysis. In accordance with these inclusion criteria, all patients included in this analysis did not undergo CN. Consequently, they most likely represent cases with more advanced disease and poorer prognosis that were either unfit for surgery or benefited from immediate systemic therapy. By confining our patient cohort to patients with low metastatic burden, we aimed to archive a more comparable cohort to mRCC patients who underwent surgery. Moreover, in patients with a high metastatic burden, the presence or absence of radiographic lymph node involvement is unlikely to affect CSM. In these patients, the prognosis is primarily driven by the presence of multiple distant metastases. (102) In a similar fashion to the previous study, we relied on Kaplan-Meier plots and multivariable Cox-regression models to address CSM according to radiographic N-stage (cN1 vs. cN0). Specifically, we identified 1,596 mRCC patients of which 545 (31%) were radiographic cN1. In Kaplan-Meier analyses, the median CSM-free survival was 8 vs. 14 months for cN1 vs. cN0 mRCC patients ($p<0.001$). Interestingly, radiographic N1 (cN1) remained an independent predictor for worse CSM compared to cN0 mRCC patients (HR 1.39; $p=0.01$). To the best of our knowledge, no other study has investigated the prognostic impact of radiographic N-stage in mRCC patients. As such, our results cannot be compared to other studies. Nevertheless, our results suggest that patients with radiographic N1 stage are predisposed to less favourable outcomes compared to those without radiographic evidence of lymph node involvement. Therefore, these patients should ideally receive systemic therapy without delay.

Taken together, our detailed investigation, that resulted in three distinct publications, highlights the prognostic significance of LNI mRCC patients. Nevertheless, several key questions remain unanswered. First, the role of LND in mRCC remains controversial, given that the evidence regarding the therapeutic benefit of LND in this setting is limited. While our findings suggest that pathological LNI is a strong predictor of poor survival outcomes, it is unclear whether LND itself confers a survival advantage or merely serves as a prognostic marker. Given the increasing importance of systemic therapies, particularly immune checkpoint inhibitors, future studies should explore whether the removal of metastatic lymph nodes during CN influences response rates or disease progression in mRCC patients. Additionally, as surgical strategies continue to evolve, the optimal extent of LND in the setting of CN remains uncertain.

Second, the therapeutic implications of LNI in mRCC patients warrant further investigation. While our findings suggest that LNI is associated with significantly worse survival outcomes, it remains unclear whether the presence of LNI should alter treatment strategies. Specifically, whether mRCC patients with LNI benefit from more aggressive systemic therapy or enhanced surveillance protocols remains to be determined.

Finally, our study highlights the need for novel prognostic models for mRCC. The IMDC and MSKCC risk stratification models remain the most widely used risk stratification tools in clinical practice, yet neither model incorporates lymph node status as a prognostic variable. Given the strong independent association between LNI and survival observed in our study, future efforts should ideally explore the integration of lymph node status into existing or novel prognostic models in an effort to increase the prognostic capabilities. Well designed and up to date risk stratification models can lead to improved treatment decision-making in the treatment of mRCC patients.

Lastly, despite the novel findings of our research, several limitations need to be discussed. First and foremost, all three studies are retrospective studies. The retrospective nature of these analyses inevitably lead to a selection bias. However, this limitation is shared with all other non-

prospective, non-randomized studies. Second, patient stratification according to the routinely used MSKCC or IMDC risk stratification tool was not possible. As such, adjusting for these criteria was also not possible in our multivariable models. Unfortunately, neither the SEER database or the comparable NCDB offer information regarding these two risk stratifications. Third, the SEER database does not offer information on the exact composition or specific timing of postoperative systemic therapy, such as whether it was administered immediately or delayed. Furthermore, our analysis was limited to mRCC patients diagnosed between 2010 and 2018, when immunotherapy became the standard first-line treatment. However, it's essential to recognize that not all patients who received systemic therapy during this period were necessarily treated with immunotherapy or other guideline recommend agents. Fourth, in our studies, N stage was either classified into pathological N stage, as recorded in the SEER database, or radiographic N stage, in cases where histopathological data was unavailable. However, the SEER database does not specify the exact imaging modalities used to determine radiographic N stage. Fifth, the SEER database lacks information on the exact number of metastatic lesions. Therefore, we used the number of metastatic sites as a surrogate to identify patients with low metastatic burden. However, it can be argued that the number of metastatic sites may be a more robust predictor of mortality than the absolute count of metastatic lesions.(103) Sixth, in our first study, we relied on the SEER database to assess differences in RCC patients according to 12 specific SEER registries. Although each registry, is linked to a specific geographic region in the U.S., the 12 registries may not fully represent the entire U.S. population. Additionally, as SEER is designed to reflect U.S. demographics, our findings may not be directly applicable to patients in other countries.

Lastly, although these three studies were conducted in subsequent order and built upon one another, some inconsistencies exist in patient cohorts, methodology, as well as terminology. These discrepancies stem at least partially from the fact that each study underwent an independent peer-review process and was published in a different journal with distinct recommendations and guidelines. While we only implemented reviewer suggestions that we deemed appropriate, these suggested modifications contributed to the observed inconsistencies. Although these variations may appear discordant when the studies are compiled in this thesis, it is important to recognize

that a rigorous peer review is an essential component of scientific research and plays a crucial role in maintaining research quality and integrity.

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Appendix

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ORIGINAL ARTICLE

Regional differences in clear cell metastatic renal cell carcinoma patients across the USA

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Abstract

Purpose To test for regional differences in clear cell metastatic renal cell carcinoma (ccmRCC) patients across the USA.

Methods The Surveillance, Epidemiology, and End Results (SEER) database (2000–2018) was used to tabulate patient (age at diagnosis, sex, race/ethnicity), tumor (N stage, sites of metastasis) and treatment characteristics (proportions of nephrectomy and systemic therapy), according to 12 SEER registries. Multinomial regression models, as well as multivariable Cox regression models, tested the overall mortality (OM) adjusting for those patient, tumor and treatment characteristics.

Results In 9882 ccmRCC patients, registry-specific patient counts ranged from 4025 (41%) to 189 (2%). Differences across registries existed for sex (24–36% female), race/ethnicity (1–75% non-Caucasian), N stage (N1 25–35%, NX 3–13%), proportions of nephrectomy (44–63%) and systemic therapy (41–56%). Significant inter-registry differences remained after adjustment for proportions of nephrectomy (46–63%) and systemic therapy (35–56%). Unadjusted 5-year OM ranged from 73 to 85%. In multivariable analyses, three registries exhibited significantly higher OM (SEER registry 5: hazard ratio (HR) 1.20, $p=0.0001$; SEER registry 7:HR 1.15, $p=0.008$M SEER registry 10: HR 1.15, $p=0.04$), relative to the largest reference registry ($n=4025$).

Conclusion Important regional differences including patient, tumor and treatment characteristics exist, when ccmRCC patients included in the SEER database are studied. Even after adjustment for these characteristics, important OM differences persisted, which may require more detailed analyses to further investigate these unexpected differences.

Keywords SEER · Metastatic RCC · Regional · Outcome · Clear cell · Population

Introduction

Overall survival of clear cell metastatic renal cell carcinoma (ccmRCC) patients improved over the past decade [1, 2]. The introduction of new systemic therapies, specifically immunotherapies, has significantly contributed to this improvement [3]. However, most improvements were reported in the context of prospective randomized trials that may not apply to patients at large. It is possible that patient characteristics and patterns of care may differ between geographic regions of patient's residence. Moreover, these differences could potentially lead to discrepancies in survival outcomes that should ideally not exist. Indeed, such differences across geographic regions have been reported for other urologic malignancies such as prostate or penile cancer [4–6]. It is currently unknown, whether such differences also exist for ccmRCC patients in the USA. We tested this hypothesis within the Surveillance, Epidemiology, and End Results (SEER) database (2000–2018). We hypothesized that such differences exist and that they may be associated with differences in overall mortality (OM) between specific geographic regions of residence (SEER registries).

Methods

Study population

The SEER database (2000–2018) was used to identify patients aged ≥ 18 years with histologically confirmed

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unilateral metastatic RCC (International Classification of Disease for Oncology [ICD-O] site codes C64.9), who harbored clear cell histology (ICD-O-3 code 8310). Cases identified only at autopsy were excluded. The SEER database is divided into 13 geographic registries. We excluded the smallest registry due to the limited sample size ($n = 20$). In accordance with the SEER data agreements and limitations, names of individual registries were omitted from the report [7]. These selection criteria resulted in an overall cohort of 9882 assessable patients within 12 SEER registries, namely from SEER registry 1 to SEER registry 12, in descending order of patient count. Death was defined according to the SEER mortality codes [8]. For the purpose of this study, OM (defined as death from any cause) was considered.

Statistical analyses

Descriptive statistics included frequencies and proportions for categorical variables. Medians and interquartile ranges (IQR) were reported for continuously coded variables. Kruskall–Wallis rank sum and Pearson Chi-square tested for statistical significant differences in medians and proportions, respectively. Statistical analyses relied on three steps. First, baseline patient (age at initial diagnosis, sex, race/ethnicity: Caucasian vs. non-Caucasian), tumor (N stage according to the American Joint Committee on Cancer (AJCC) TNM system, 8th edition, sites of metastasis) and treatment (rate of nephrectomy (radical or partial) and systemic therapy) characteristics were tabulated and displayed graphically, according to the above defined SEER registries. Second, we relied on multinomial regression models to display adjusted proportions of nephrectomy and systemic therapy exposure. Here, multinomial models were fitted for each registry, and the adjusted treatment proportion was derived from the predicted probability of receiving the said outcome on the entire selected SEER population (including all registries) from the multinomial model of each registry. For proportions of nephrectomy, multinomial models relied on age, sex, year of diagnosis, race/ethnicity, as well as N stage as covariates. For systemic therapy exposure, multinomial models relied on age, sex, year of diagnosis, race/ethnicity, N stage, as well as nephrectomy proportions as covariates. Finally, 5-year OM was computed for each SEER registry. Moreover, unadjusted and adjusted OM hazard ratios (HR) were computed for each SEER registry, relying on Cox regression analyses. Adjustment variables consisted of year of diagnosis, baseline patient (age at diagnosis, sex, race/ethnicity), tumor (N stage, sites of metastasis) and treatment (nephrectomy and systemic therapy exposure) characteristics. All tests were two sided with a level of significance set at $p < 0.05$ and R software environment for statistical computing and graphics (version 4.1.2) was used for all analyses (7). Owing to the anonymously coded design of the SEER database, study-specific ethics approval was waived by the institutional review board.

Results

Descriptive characteristics

A total of 9822 ccmRCC patients were identified. Median age at initial diagnosis was 63 years (interquartile range (IQR) 56–71), 31% were female and 30% were non-Caucasians. N stage distribution was as follows: N0 6,085 (62%) vs. N1 3,192 (32%) vs. NX 605 (6%). Proportions of treatment were as follows: 5,666 patients (57%) received either radical (55%) or partial (2%) nephrectomy and 4,749 (48%) received systemic therapy (Table 1).

Differences in patient and tumor characteristics, across SEER registries

Registry-specific patient counts ranged from 4025 (41%) in SEER registry 1 to 189 (2%) in SEER registry 12 (Fig. 1). The proportion of females ranged from 24 (SEER registry 6) to 36% (SEER registry 4; $p < 0.001$, Fig. 2b). The proportion of race/ethnicity other than Caucasians ranged from 1 (SEER registry 7) to 75% (SEER registry 12; $p < 0.001$; Fig. 2c). Regarding N stage, the proportions of N0 ranged from 56 (SEER registry 6) to 67% (SEER registry 2) vs. 25 (SEER registry 11) to 35% (SEER registry 9) for N1 ($p < 0.001$; Fig. 2d) vs. 3 (SEER registry 5) to 13 (SEER registry 6) for NX ($p < 0.001$; Fig. 2e). There were no statistically significant differences in patients' age at initial diagnosis across the different SEER registries ($p = 0.18$;

Table 1 Descriptive characteristics of 9882 clear cell metastatic renal cell carcinoma (ccmRCC) patients within the Surveillance, Epidemiology, and End Results (SEER) database (2000–2018)

Characteristic	*N*	Overall, $N = 9882$[1]
Age	9882	63 (56, 71)
Race	9882	
Caucasian		6948 (70%)
Non-Caucasian		1627 (30%)
N-Stage	9882	
N0		6690 (62%)
N1		3192 (32%)
NX		605 (6%)
Systemic therapy		4749 (48%)
Surgery	9863	5666 (57,3%)
Radical nephrectomy		5439 (55%)
Partial nephrectomy		227 (2.3%)
Female		3047 (31%)

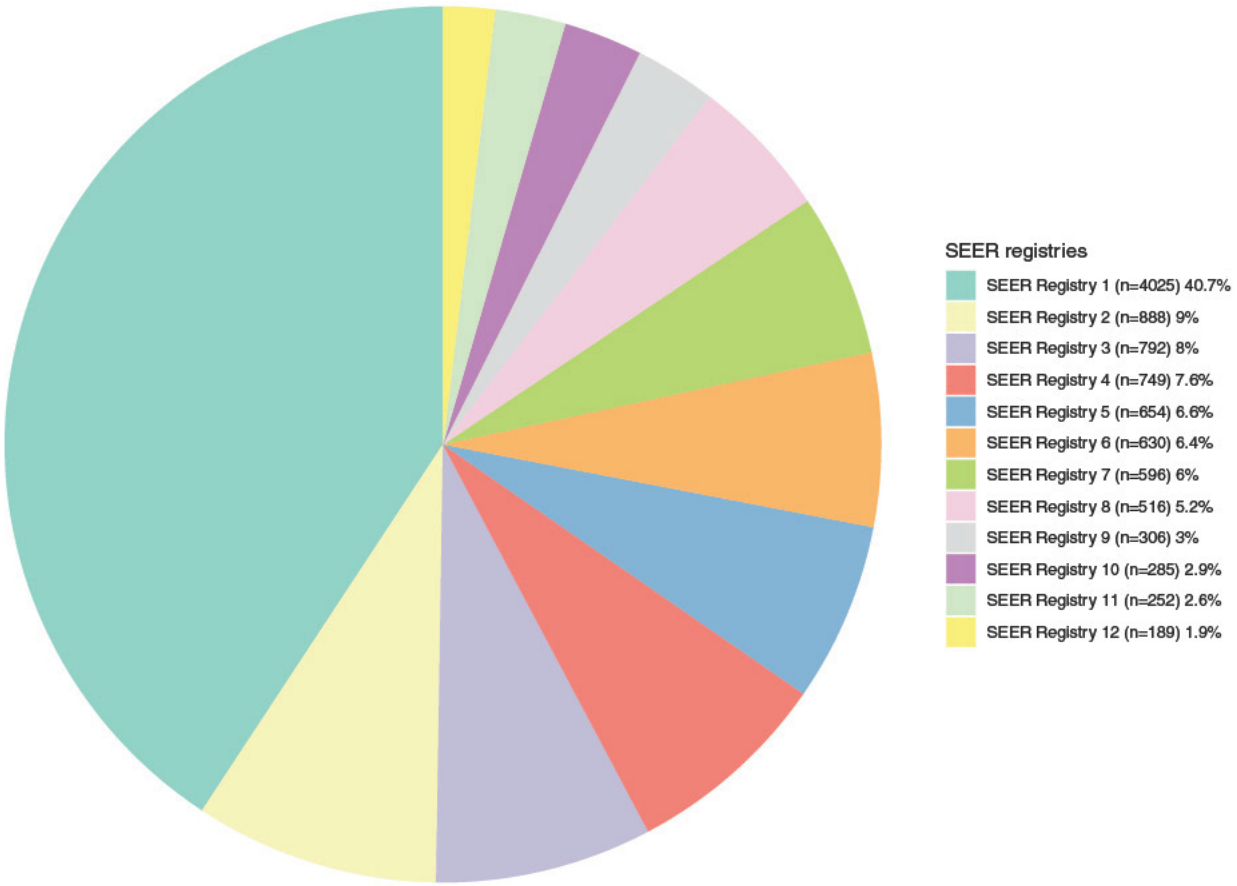


Fig. 1 Pie chart depicting the distribution of 9882 clear cell metastatic renal cell carcinoma (ccmRCC) patients, according to the Surveillance, Epidemiology, and End Results (SEER) 2000–2018 geographic registries across the USA

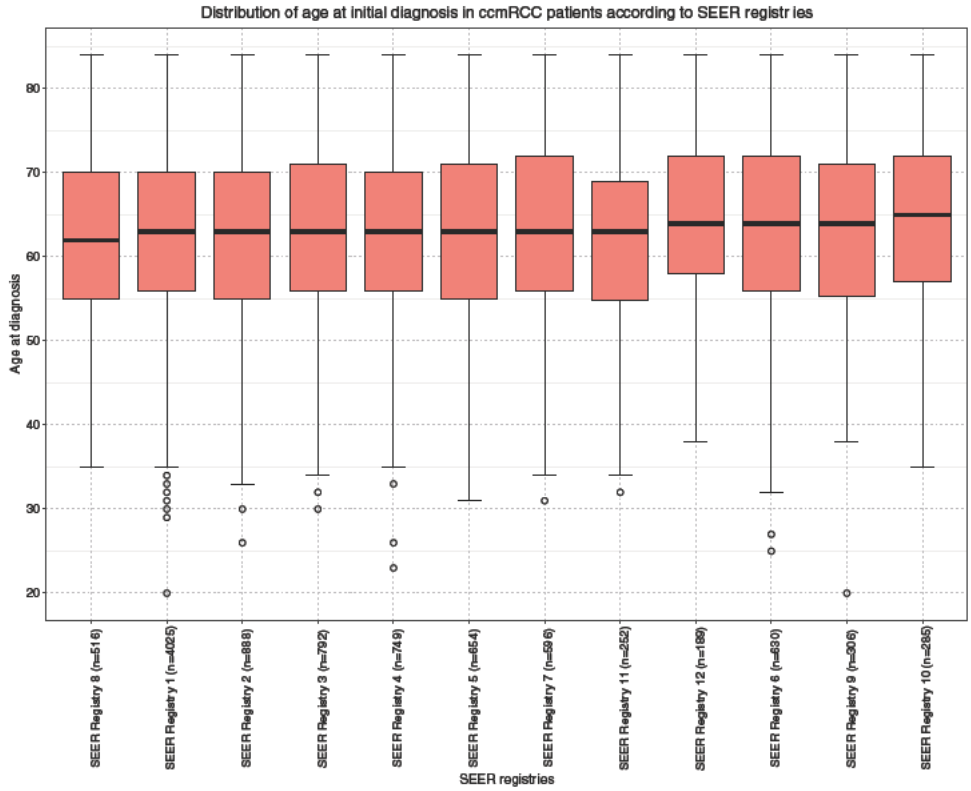
Fig. 2a). Regarding the location of metastasis, we recorded significant differences in the proportion of bone metastasis across the registries (21–31%; $p<0.001$). No statistically significant differences were observed for the proportion of liver, lung, brain and other metastasis across the SEER registries (Table 2).

Unadjusted and adjusted differences in treatment proportions across SEER registries

The rate of nephrectomy ranged from 46 (SEER registry 8) to 64% (SEER registry 12; $p<0.001$, $\Delta=18\%$). After adjustment, differences in nephrectomy proportions persisted (46–63%, $\Delta=17\%$, $p<0.001$). When focusing on the two registries with the highest patient count (SEER registry 1–2), proportions ranged from 56 to 59% ($\Delta=3\%$). In the ten remaining registries with lower patient count (SEER registry 3 to 12), proportions ranged from 46 to 63% ($\Delta=17\%$; Fig. 3a). Rate of systemic therapy ranged from 41 (SEER registry 12) to 56% (SEER registry 7; $p<0.001$, $\Delta=15$). After adjustment, differences in systemic therapy proportions persisted (35–56%, $\Delta=21$, $p<0.001$). When focusing on the two registries with the highest patient count (SEER registry 1–2), proportions ranged from 47 to 53% ($\Delta=6\%$). In the ten remaining registries with smaller patient count (SEER registry 3 to 12), proportions ranged from 35 to 56 ($\Delta=21\%$; Fig. 3b).

Overall mortality and unadjusted and adjusted differences in overall mortality across SEER registries

Five-year OM was 80% for all 9882 ccmRCC patients. Five-year registry-specific OM ranged from 73 to 85% (Table 3). When focusing on the two registries with the highest patient count (SEER registry 1–2), OM ranged from 79 to 80% ($\Delta=1\%$). In the ten remaining registries with lower patient count, 5-year OM ranged from 73 to 85% ($\Delta=12\%$). Unadjusted HR predicting OM ranged from 0.93 to 1.17. Adjusted HR predicting OM ranged from 0.88 to 1.20. The HR predicting OM recorded in three registries was statistically significantly higher than the recorded HR of SEER registry of reference (SEER registry 1, HR 1.0). Specifically, the HR recorded for SEER registry 5 was 1.20 ($p=0.0001$), the HR



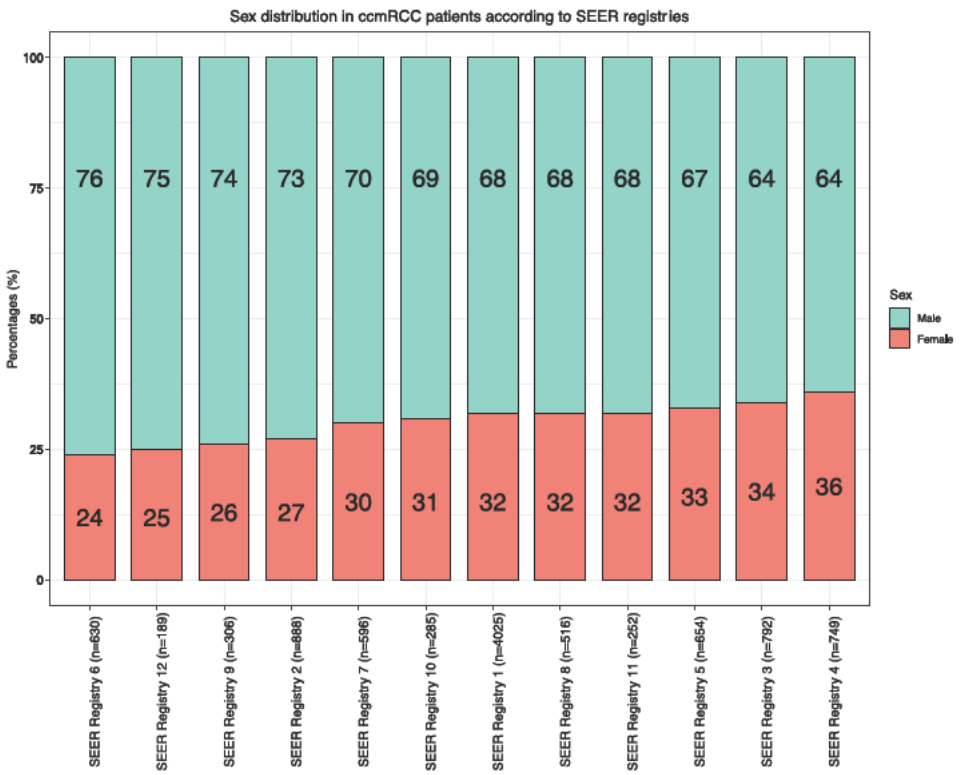
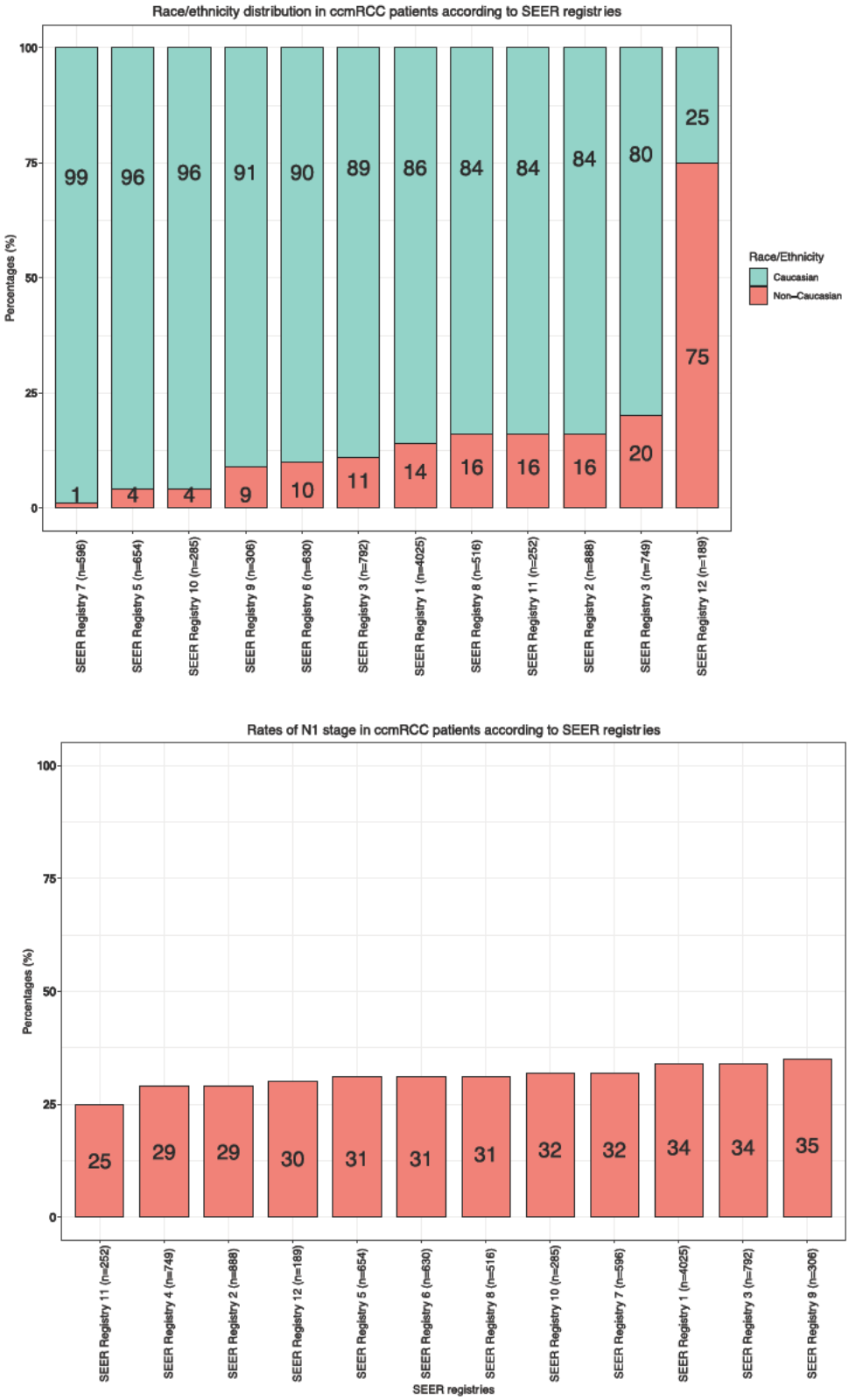


Fig. 2 **a** Box and whisker plots depicting patient age at initial diagnosis distribution in 9882 clear cell metastatic renal cell carcinoma (ccmRCC) patients, according to the Surveillance, Epidemiology, and End Results (SEER) geographic registries (2000–2018). **b** Stacked bar plots depicting sex distribution in 9882 clear cell metastatic renal cell carcinoma (ccmRCC) patients, according to the Surveillance, Epidemiology, and End Results (SEER) geographic registries (2000–2018). **c** Stacked bar plots depicting race/ethnicity (Caucasian vs. Non-Caucasians) distribution in 9882 clear cell metastatic renal cell carcinoma (ccmRCC) patients, according to the Surveillance, Epidemiology, and End Results (SEER) geographic registries (2000–2018). **d** Stacked bar plots depicting rate of N1 stage in 9882 clear cell metastatic renal cell carcinoma (ccmRCC) patients, according to the Surveillance, Epidemiology, and End Results (SEER) geographic registries (2000–2018). **e** Stacked bar plots depicting rate of NX stage in 9882 clear cell metastatic renal cell carcinoma (ccmRCC) patients, according to the Surveillance, Epidemiology, and End Results (SEER) geographic registries (2000–2018)

Fig. 2 (continued)



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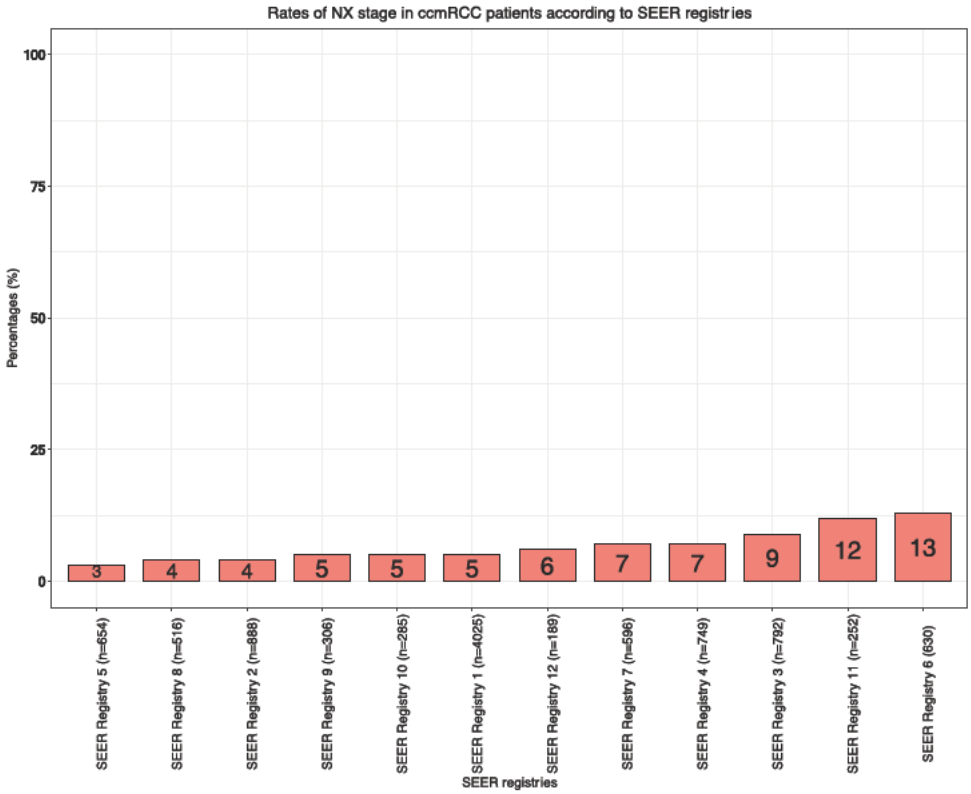

recorded for SEER registry 7 was 1.14 ($p=0.008$) and the HR for SEER registry 10 was 1.15 ($p=0.04$; Table 3).

Discussion

It is currently unknown whether regional differences regarding patient, tumor and treatment characteristics exist in ccmRCC patients and potentially even contribute to differences in overall mortality (OM). We hypothesized that higher than expected OM may be identified in select SEER registries, even after adjustment for patient, tumor and treatment characteristics. We tested this hypothesis within a large population of ccmRCC patients from within the SEER database (2000–2018). Our analyses resulted in several noteworthy observations.

First, we identified 9882 ccmRCC patients of 12 geographic registries within the SEER database over a period of 18 years (2000–2018). This number is comparable to a different study addressing ccmRCC within the SEER database over a similar time period [9]. Analyses on regional differences regarding patient, tumor and treatment characteristics as well as cancer control outcomes, as were done in this study, require use of large-scale population-based databases. Single-institution or even multi-institutional databases may suffer from deficient numbers of observations or patient populations, which limits this type of research. In consequence, large-scale epidemiologic databases such as SEER or the National Cancer Database (NCDB) are essential for the purpose of assessing regional differences in patient, tumor or treatment characteristic as well as OM outcomes in ccmRCC patients.

Second, we recorded important differences in patient, tumor and treatment characteristics between the SEER registries. Regarding patient characteristics, the proportions of female patients ranged from 24 to 36% ($p<0.001$) and the proportion of race/ethnicity other than Caucasians ranged from 1 to 75% across the SEER registries ($p<0.001$). Proportions of N1 stage ranged from 25 to 35% and proportions of unknown N stage (NX) ranged from 3 to 13% ($p=0.008$; Fig. 2d). In a recent National Cancer Database (NCDB) analysis, female sex was an independent predictor for worse OS in ccmRCC [10]. Similarly, a SEER-based analysis reported that non-Caucasians experience higher CSM in ccmRCC compared to Caucasians [11]. Last but not least, N1 status has been shown to be an independent predictor for worse CSM [12]. Regarding treatment characteristics, proportions of nephrectomy ranged from 46 to 64% ($p<0.001$). These differences persisted after adjustment for age, sex, year of diagnosis, race/ethnicity and N status (46–63%). Moreover, we observed marginal variability in the two registries with the highest patient count ($\Delta=3\%$). Conversely, the recorded variability between the ten registries with smaller patient count

Table 2 Patterns of metastasis of 9882 clear cell metastatic renal cell carcinoma (ccmRCC) patients according to Surveillance, Epidemiology, and End Results (SEER) 2000–2018 geographic registries across the USA

Characteristic	Overall, $N = 9882$[a]	SEER registry 1 ($n = 4025$)	SEER registry 2 ($n = 888$)	SEER registry 3 ($n = 792$)	SEER registry 4 ($n = 749$)	SEER registry 5 ($n = 654$)	SEER registry 6 ($n = 630$)	SEER registry 7 ($n = 596$)	SEER registry 8 ($n = 516$)	SEER registry 9 ($n = 306$)	SEER registry 10 ($n = 285$)	SEER registry 11 ($n = 252$)	SEER registry 12 ($n = 189$)	*P* value[b]
Bone	2443 (25%)	926 (23%)	255 (29%)	180 (23%)	201 (27%)	204 (31%)	141 (22%)	163 (27%)	127 (25%)	65 (21%)	77 (27%)	52 (21%)	52 (28%)	< 0.001
Liver	1005 (10%)	392 (9.7%)	115 (13%)	75 (9.5%)	89 (12%)	62 (9.5%)	51 (8.1%)	61 (10%)	58 (11%)	37 (12%)	21 (7.4%)	24 (9.5%)	20 (11%)	0.062
Lung	3990 (40%)	1609 (40%)	346 (39%)	306 (39%)	306 (41%)	275 (42%)	257 (41%)	241 (40%)	211 (41%)	116 (38%)	137 (48%)	100 (40%)	86 (46%)	0.3
Brain	770 (7.8%)	326 (8.1%)	70 (7.9%)	50 (6.3%)	50 (6.7%)	50 (7.6%)	36 (5.7%)	59 (9.9%)	38 (7.4%)	25 (8.2%)	20 (7.0%)	26 (10%)	20 (11%)	0.13
Other	976 (9.9%)	391 (9.7%)	83 (9.3%)	75 (9.5%)	67 (8.9%)	85 (13%)	64 (10%)	66 (11%)	42 (8.1%)	28 (9.2%)	25 (8.8%)	33 (13%)	17 (9.0%)	0.2

[a]Median (IQR); n (%)

[b]Kruskal–Wallis rank sum test; Pearson's Chi-square test

was more pronounced (Δ = 17%). Cytoreductive nephrectomy plays an integral role in the management of ccmRCC; however, its indication depends on multiple clinical variables and ultimately on an individualized clinician's assessment. In consequence, its use may vary and its variability may not be directly related to tumor characteristics. Additionally, we observed important differences in systemic therapy exposure, ranging from 41 to 56% across the SEER registries ($p < 0.001$). These differences persisted after adjustment (35–56%). Systemic therapy represents the key element in multimodal treatment of ccmRCC. The presence of such differences in systemic therapy exposure may potentially affect survival rates. Furthermore, all the above-mentioned registry-specific differences may result in OM outcome discrepancies. Therefore, it is crucial to include these patient, tumor and treatment characteristics in multivariable analyses addressing OM, as was done in the current analyses.

Third, we also identified important variability in registry-specific five-year OM ranging from 72.5% (SEER registry 11) to 84.5% (SEER registry 8). Additionally, unadjusted OM HR was significantly higher in five registries with lower patient count compared to the registry of reference (SEER registry 1) with the highest patient count: SEER registry 4 HR 1.15, SEER registry 5 HR 1.13, SEER registry 7 HR 1.14, SEER registry 8 HR 1.17 and SEER registry 10 HR 1.17. However, these rates may be biased, due to differences in patient, tumor and treatment characteristics. In consequence, we reassessed these rates after detailed multivariable adjustment. Despite this extensive adjustment, HR differences persisted (ranging from 0.88 to 1.20). Specifically, the OM HR remained significantly higher in three registries with lower patient count (SEER registry 5: HR 1.20, $p = 0.0001$; SEER registry 7: HR 1.14; $p = 0.008$; SEER registry 10: HR 1.15, $p = 0.04$). Taken together, these results indicate that only three out of twelve regions exhibit suboptimal survival data. Ideally, no statistically significant differences should be recorded after adjustment for patient case mix. Interestingly, these registries represent registries with lower patient count. In consequence it is possible that a systematic disadvantage may exist in smaller SEER registries. The structure of the SEER database does not allow investigating in more detail the specific association between low patient counts and worse survival. However, it is well established that according to the practice-makes-perfect hypothesis, small caseload and lack of regionalization tend to be associated with worse outcomes including worse survival [13]. In consequence, regionalizing the care for ccmRCC patients may represent a valid option for avoiding low patient counts at regional or institutional level. Regionalization of care, as well as standardization of care, in addition to multidisciplinary decision making at larger centers, all have the ability to improve survival, as well as all other outcomes.

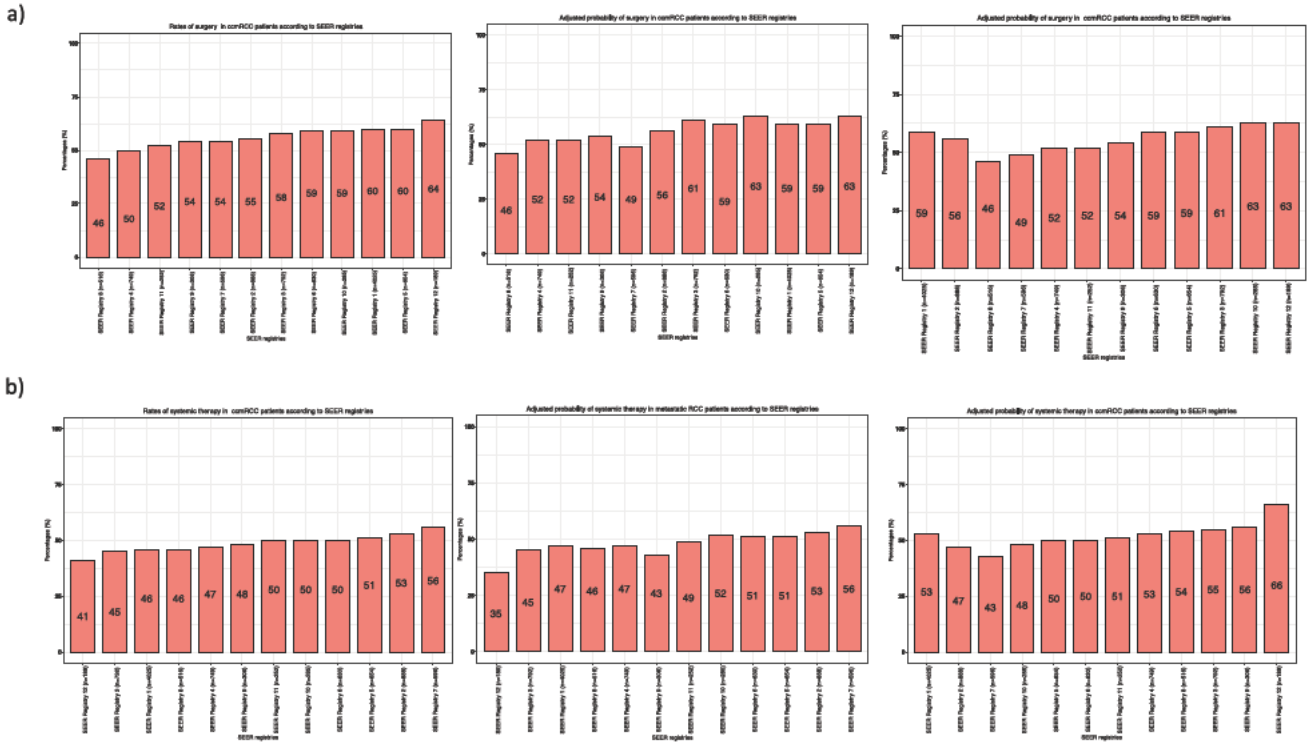

Fig. 3 Bar plots depicting rates of **a** surgery and **b** systemic therapy before and after multinomial adjustment in in 9882 clear cell metastatic renal cell carcinoma (ccmRCC) patients, according to the Surveillance, Epidemiology, and End Results (SEER) geographic registries (2000–2018). The first plot shows SEER registries in ascending order according to rates of treatment before adjustment, the second plot shows SEER registries in the same order after adjustment and the third plot shows the largest two SEER registries (1,2) and then the smallest in ascendant order after adjustment

Despite the novelty of the current study, our work has limitations and should be interpreted in the context of its retrospective and population-based design. First, the current SEER version provides sampling of patient from only 12 specific registries. This sample may not perfectly reflect the entire US population. Additionally, since the SEER database is designed with the intent of providing a representation of the US population, our findings cannot be applicable to patients from other countries and should be ideally validated after adjustment for ccmRCC characteristics using large-scale database in multi-collaborative studies even in other countries or macro-areas. Third, the SEER database does not allow stratifying or adjusting the analyses, according to the International Metastatic Database Consortium (IMDC) criteria. However, this limitation applies to all previous SEER and NCDB analyses. Fourth, limited details regarding treatment type is available. Specifically, the SEER database does provide information on systemic therapy. Therefore, a distinction between chemotherapies and immunotherapies is not possible, nor does it provide information on cycle number and duration of treatment administration. Fifth, multivariable adjustment relies on patient, tumor and treatment information available in the SEER database. It is possible that other unavailable patient, tumor and treatment characteristics also affected the observed rates, without being amendable for inclusion in either stratification or multivariable adjustment. Unfortunately, the SEER database does not provide data regarding baseline comorbidity status. Ideally, it could have been used for the purpose of further adjustment.

Conclusion

Important regional differences including patient, tumor and treatment characteristics exist, when ccmRCC patients included in the SEER database are studied. Even after adjustment for these characteristics, important OM differences persisted, which may require more detailed analyses to further investigate these unexpected differences.

Table 3 Overall mortality (OM) in 9882 clear cell metastatic renal cell carcinoma (ccmRCC) patients according to Surveillance, Epidemiology, and End Results (SEER) 2000–2018 geographic registries across the USA

SEER Registries	1 ($n=4025$)	2 ($n=888$)	3 ($n=792$)	4 ($n=749$)	5 ($n=654$)	6 ($n=630$)	7 ($n=596$)	8 ($n=516$)	9 ($n=306$)	10 ($n=285$)	11 ($n=252$)	12 ($n=189$)
Five-year OM (%)	79.1	80.1	78.1	83.5	84.8	78.8	83.1	84.5	77.4	86.3	72.5	79.1
Unadjusted OM HR	Ref	1.05	0.97	**1.15**	**1.13**	0.97	**1.14**	**1.17**	0.97	**1.17**	0.93	0.97
95% CI***		(0.96–1.14)	(0.88–1.05)	**(1.05–1.26)**	**(1.02–1.24)**	(0.88–1.07)	**(1.03–1.25)**	**(1.05–1.29)**	(0.84–1.11)	**(1.01–1.33)**	(0.79–1.08)	(0.81–1.14)
p value		0.25	0.48	**0.001**	**0.01**	0.60	**0.008**	**0.003**	0.67	**0.02**	0.34	0.68
Adjusted OM HR*	Ref	1.08	1.00	1.09	**1.20**	0.96	**1.14**	1.03	0.91	**1.15**	0.88	0.97
95% CI***		(0.99–1.17)	(0.91–1.09)	(0.98–1.19)	**(1.09–1.32)**	(0.87–1.06)	**(1.03–1.26)**	(0.93–1.15)	(0.79–1.04)	**(1.01–1.32)**	(0.75–1.02)	(0.81–1.16)
p value		0.07	0.91	0.06	**0.0001**	0.48	**0.008**	0.48	0.18	**0.04**	0.10	0.76

Bold values indicate *p*-value < 0.05

*Adjusted for sex, age, systemic therapy, race/ethnicity, N stage, sites of metastasis, year of diagnosis and surgery

**p value < 0.05

***Confidence Intervals

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Data availability All data generated for this analysis were from the Surveillance, Epidemiology, and End Results Research Plus (SEER) database. The code for the analyses will be made available upon request.

Declarations

Conflict of interest The authors declare that there is no conflict of interest.

Ethics consent statement All analyses and their reporting followed the SEER reporting guidelines. Due to the anonymously coded design of the SEER database, study-specific institutional review board ethics approval was not required.

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ORIGINAL ARTICLE – UROLOGIC ONCOLOGY

Prognostic Significance of Pathologic Lymph Node Invasion in Metastatic Renal Cell Carcinoma in the Immunotherapy Era

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ABSTRACT

Background. This study aimed to test the prognostic significance of pathologically confirmed lymph node invasion in metastatic renal cell carcinoma (mRCC) patients in this immunotherapy era.

Methods. Surgically treated mRCC patients were identified in the Surveillance, Epidemiology, and End Results (SEER) database between 2010 and 2018. Kaplan-Meier plots and multivariable Cox-regression models were fitted to test for differences in cancer-specific mortality (CSM) and overall mortality (OM) according to N stage (pN0 vs pN1 vs. pNx). Subgroup analyses addressing pN1 patients tested for CSM and OM differences according to postoperative systemic therapy status.

Results. Overall, 3149 surgically treated mRCC patients were identified. Of these patients, 443 (14%) were labeled as pN1, 812 (26%) as pN0, and 1894 (60%) as pNx. In Kaplan-Meier analyses, the median CSM-free survival was 15 months for pN1 versus 40 months for pN0 versus 35 months for pNx ($P < 0.001$). In multivariable Cox regression analyses, pN1 independently predicted higher CSM (hazard ratio [HR], 1.88; $P < 0.01$) and OM (HR, 1.95; $P < 0.01$) relative to pN0. In sensitivity analyses addressing pN1 patients, postoperative systemic therapy use independently predicted lower CSM (HR, 0.73; $P < 0.01$) and OM (HR, 0.71; $P < 0.01$).

Conclusion. Pathologically confirmed lymph node invasion independently predicted higher CSM and OM for surgically treated mRCC patients. For pN1 mRCC patients, use of postoperative systemic therapy was associated with lower CSM and OM. Consequently, N stage should be considered for individual patient counseling and clinical decision-making.

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Keywords mRCC · Lymph node invasion · SEER · Population-based · CSM

Currently, the role of lymph node dissection (LND) in cytoreductive nephrotomy (CN) is controversial and not generally endorsed.[1] However, historic studies demonstrated that information about lymph node invasion (LNI) status represents an independent predictor of cancer-specific mortality (CSM).[2,3] Specifically, patients with LNI historically exhibited markedly worse survival than those without LNI (pN1 vs pN0). Based on the absence of contemporary data addressing the potentially added value of confirmed pN1 versus pN0 status at cytoreductive nephrectomy, we addressed this knowledge gap. Specifically, we investigated the prognostic significance of pathologic lymph node involvement in a contemporary cohort of surgically treated metastatic renal cell carcinoma (mRCC) patients relying on the Surveillance, Epidemiology, and End Results (SEER) database.

METHODS

Data Source and Study Population

In the SEER database (2010–2018), we identified patients 18 years old or older with histologically confirmed unilateral metastatic RCC (International Classification of Disease for Oncology [ICD-O] site code C64.9) who harbored clear-cell histology (ICD-O-3 code 8310). Cases identified only at autopsy were excluded. The study included only mRCC patients who received cytoreductive nephrectomy. Further exclusion criteria ruled out patients with unknown T stage, unknown grade, or missing data on pathologic lymph node status. Autopsy or death certificate-only cases also were excluded (consort diagram).

Variables of Interest

The demographic covariates consisted of age at diagnosis (years, continuously coded), sex, and race/ethnicity (Caucasians vs others). The tumor characteristics consisted of T stage (T1 vs. T2 vs. T3 vs. T4), grade (G1–G2 vs. G3 vs. G4), and pathologic N stage (pN0 vs. pN1 vs. pNx). Patients who did not undergo lymph node dissection (LND) were labeled pNx.

Systemic therapy comprised only postoperative therapy after cytoreductive nephrectomy and was coded as received or not received. Cancer-specific mortality (CSM) and overall mortality (OM) were the primary end points of the study.

Statistical Analyses

First, the baseline characteristics of the cohort were analyzed. Descriptive statistics included frequencies and proportions for categorical variables. Medians and interquartile ranges (IQRs) were reported for continuously coded variables.

Second, Kaplan-Meier plots were used to display rates of CSM and OM according to pN0 versus pN1 versus pNx. The association between pathologic N stage (pN0 vs pN1 vs pNx) and CSM as well as OM was further tested in multivariable Cox regression models. Adjustment variables consisted of age, year of diagnosis, sex, T stage, grade, ethnicity, and systemic therapy exposure status.

Third, we reapplied the previously described methodology in a subgroup analysis. Specifically, we analyzed CSM and OM hazard ratios (HRs) of pN1 mRCC patients according to systemic therapy exposure. In all statistical analyses, R software environment for statistical computing and graphics (R version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria) was used. All tests were two-sided, with the level of significance set at a P value lower than 0.05.[4]

RESULTS

Descriptive Characteristics

Between 2010 and 2018, we identified 3149 cytoreductive nephrectomy mRCC patients (Table 1). Of these patients, 1255 (40%) underwent LND and 1894 (60%) did not (pNx). In terms of disease stage, 443 patients (14%) were labeled as pN1, 812 (26%) as pN0, and 1894 (60%) as pNx. Overall, 29% of all the patients were female, and 13% were not Caucasian. Statistically, the ages of the groups differed significantly (median ages: 62 years for pN1 vs 60 years for pN0 vs 63 years for pNx; $P < 0.001$). Additionally, the pN1 patients exhibited higher rates of T3 tumors (70% for pN1 vs. 69% for pN0 vs. 59% for pNx) and T4 tumors (22% for pN1 vs. 18% for pN0 vs. 14% for pNx) as well as higher rates of G4 tumors (58% for pN1 vs. 39% for pN0 vs. 33% for pNx).

The median number of removed nodes was four for both the pN1 (IQR, 2–9) and pN0 (IQR, 1–8) patients. The median number of positive nodes was two for the pN1 patients (IQR, 1–3). The rates of postoperative systemic therapy exposure were 53% for the pN1 patients, 47% for the pN0 patients, and 52% for the pNx patients.

Cancer-Specific Mortality, Overall Mortality, and Cox Regression Analyses

The median CSM-free survival for the overall cohort was 33 months. According to pathologic lymph node stage, the median CSM-free survival was 15 versus 40

TABLE 1 Descriptive characteristics of 3149 metastatic renal cell carcinoma (mRCC) patients in the Surveillance, Epidemiology, and End Results (SEER) database (2010–2018)

Characteristic	*n*	Overall (*n* = 3149) *n* (%)	pN1 (*n* = 443, 14%) *n* (%)	pN0 (*n* = 812, 26%) *n* (%)	pNx (*n* = 1894, 60%) *n* (%)	*P* value[a]
Median age: years (IQR)	3149	62 (55–69)	62 (54–68)	60 (53–68)	63 (56–70)	< 0.001
Female	3149	924 (29)	138 (31)	251 (31)	535 (28)	0.3
Non-Caucasian	3149	415 (13)	59 (13)	106 (13)	250 (13)	> 0.9
T stage	3149					< 0.001
T1		332 (11)	12 (2.7)	42 (5.2)	278 (15)	
T2		330 (10)	22 (5.0)	68 (8.4)	240 (13)	
T3		1988 (63)	310 (70)	559 (69)	1119 (59)	
T4		499 (16)	99 (22)	143 (18)	257 (14)	
Grade	3149					< 0.001
G1–G2		633 (20)	28 (6.3)	145 (18)	460 (24)	
G3		1323 (42)	160 (36)	347 (43)	816 (43)	
G4		1193 (38)	255 (58)	320 (39)	618 (33)	
Median no. of removed nodes (IQR)	1255	4 (1–8)	4 (2–9)	4 (1–8)	–	0.3
Median no. of positive nodes (IQR)	1255	0 (0–1)	2 (1–3)	–	–	< 0.001
Systemic therapy received	3149	1601 (51)	236 (53)	380 (47)	985 (52)	0.025

[a]Kruskal-Wallis rank-sum test; Pearson's chi-square test

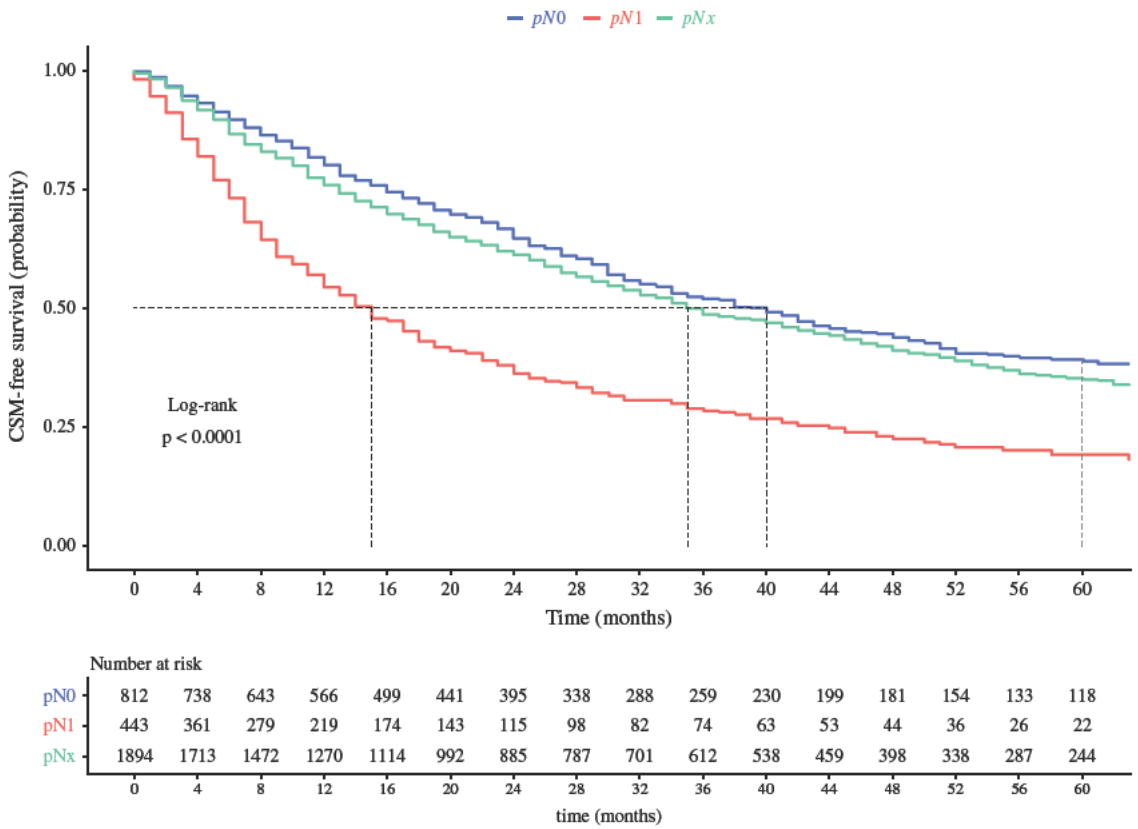

FIG. 1 Kaplan-Meier curves depicting five-year cancer-specific mortality (CSM)-free survival according to pathological N-stage in 3149 metastatic renal cell carcinoma (mRCC) patients within the Surveillance, Epidemiology, and End Results (SEER) database (2010–2018)

versus 35 months for pN1, pN0 and pNx, respectively ($P < 0.001$, log-rank test; Fig. 1). The 5-year CSM-free survival was 19% versus 39% versus 35% for pN1, pN0, and pNx, respectively. In univariable Cox regression models, the statistically significant predictors of CSM were pN1 stage (HR, 2.1; $P < 0.01$), T2 (HR, 1.3; $P = 0.01$), T3 (HR, 1.8; $P < 0.01$), T4 (HR, 2.0; $P < 0.01$), G3 (HR, 1.5; $P < 0.01$), G4 (HR, 2.5; $P < 0.01$), female sex (HR, 1.3; $P < 0.1$), year of diagnosis (HR, 1.0; $P < 0.01$), and systemic therapy exposure (HR, 1.3; $P < 0.01$) (Table 2). In multivariable Cox regression analyses, with adjustment for these variables, pN1 was an independent predictor of higher CSM (HR, 1.88; $P < 0.01$). Additionally, independent predictor status also was achieved by pNx (HR, 1.22; $P < 0.01$), T2 (HR, 1.34; $P < 0.01$), T3 (HR, 1.52; $P < 0.01$), T4 (HR, 1.63; $P < 0.01$), G3 (HR, 1.42; $P < 0.01$), G4 (HR, 2.17; $P < 0.01$), female sex (HR, 1.15; $P = 0.01$), and year of diagnosis (HR, 0.93, $P < 0.01$). The median overall survival according to pathologic lymph node stage was 14 versus 36 versus 32 months for pN1, pN0 and pNx, respectively ($P < 0.001$, log-rank test; Fig. S1). The 5-year overall survival rates were 16% versus 36% versus 31% for pN1, pN0, and pNx, respectively. In multivariable Cox regression analyses, pN1 was an independent predictor of higher OM (HR, 1.95; $P < 0.001$; Table S1).

TABLE 2 Cox regression analyses predicting cancer-specific mortality (CSM) for metastatic clear-cell renal cell carcinoma patients

	Univariable		Multivariable[a]	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
N stage (N0 ref.)				
N1	**2.10 (1.81–2.45)**	**< 0.01**	**1.92 (1.63–2.26)**	**< 0.01**
NX	1.12 (0.99–1.26)	0.06	**1.26 (1.10–1.43)**	**< 0.01**
T stage (T1 ref.)				
T2	**1.34 (1.07–1.67)**	**0.01**	**1.41 (1.10–1.79)**	**< 0.01**
T3	**1.79 (1.50–2.14)**	**< 0.01**	**1.57 (1.29–1.92)**	**< 0.01**
T4	**2.02 (1.65–2.47)**	**< 0.01**	**1.71 (1.36–2.14)**	**< 0.01**
Grade (G1–G2 ref.)				
G3	**1.49 (1.30–1.72)**	**< 0.01**	**1.48 (1.26–1.73)**	**< 0.01**
G4	**2.45 (2.12–2.82)**	**< 0.01**	**2.31 (1.97–2.72)**	**< 0.01**
Age	1.00 (0.99–1.01)	0.69	1.00 (0.99–1.01)	0.06
Female	**1.13 (1.03–1.26)**	**0.01**	**1.16 (1.04–1.28)**	**0.01**
Non-Caucasian	1.06 (0.92–1.22)	0.38	1.05 (0.95–1.26)	0.19
Year of diagnosis	**0.95 (0.93–0.97)**	**< 0.01**	**0.93 (0.90–0.95)**	**< 0.01**
Systemic therapy	**1.20 (1.08–1.34)**	**< 0.01**	1.06 (0.88–1.19)	0.22

$P < 0.05$ values are given in bold

HR hazard ratio, *CI* confidence interval

[a]Covariates in the multivariable model: age at diagnosis, sex, year of diagnosis, N stage, T stage, grade, systemic therapy

Subgroup Analyses Examining the Benefit of Postoperative Systemic Therapy for Patients With Pathologically Confirmed Lymph Node Invasion

The median CSM-free survival for pN1 mRCC patients who received postoperative systemic therapy was 15 versus 10 months for the patients who did not receive postoperative systemic therapy. After multivariable adjustment, postoperative systemic therapy status represented an independent predictor for lower CSM (HR, 0.73; $P < 0.01$) and OM (HR, 0.71; $P < 0.01$).

DISCUSSION

Historically, the presence of lymph node invasion represented an independent predictor of worse survival for cytoreductive nephrectomy (CN) mRCC patients.[2] However, no contemporary data support the prognostic significance of pN1 for CN-treated mRCC patients. Consequently, we addressed this knowledge gap and investigated the prognostic significance of pathologic lymph node status in a contemporary cohort of surgically treated mRCC patients.

Our analyses resulted in several important observations. First, the population of CN-treated mRCC patients represents a relatively rare entity, in which patient counts generally are low. Consequently, population-based data are necessary for meaningful assessments of tumor characteristics. In the current study, we identified 3149 mRCC patients in the SEER database who underwent cytoreductive nephrectomy between 2010 and 2018. This sample size was comparable with those of other large-scale analyses. For example, in a previous SEER analysis, Zhang et al.[5] identified 2352 CN mRCC patients between 2010 and 2015.

Second, according to the current analysis, 1255 CN mRCC patients (40%) underwent LND. Of those patients, 443 (35%) were labeled pN1 and 812 (65%) were labeled pN0. The rate of pN1 patients in the current study is similar to those reported in previous studies. Specifically, Feuerstein et al.[6] reported a 33% pN1 rate in mRCC patients ($n = 258$). Similarly, Tappero et al.[7] reported a 25% pN1 rate in surgically treated mRCC patients ($n = 814$) with primary tumors 4 cm in size or smaller. Notably, a comparison of pN1 and pN0 patients showed that the pN1 patients had higher rates of T4 tumors (22% pN1 vs 18% pN0; $P = 0.04$) and G4 tumors (58% pN1 vs 39% pN0; $P < 0.01$). Conversely, the rate of G1–G2 tumors was significantly lower among the pN1 patients (6.3% pN1 vs 18% pN0; $P < 0.01$).

Third, we tested for CSM differences in these patients according to pathologic N stage. Specifically, the 5-year CSM-free rates were 19% versus 39% versus 35% for pN1, pN0 and pNx, respectively ($P < 0.01$). In multivariable analyses, pN1 was an independent predictor of higher CSM (HR, 1.88; $P < 0.01$).

To the best of our knowledge, we are the first to confirm the prognostic significance of pathologic lymph node invasion in contemporary, surgically treated mRCC patients. Consequently, our results cannot be compared directly with similar, contemporary studies that relied on immunotherapy-era patients. However, previous historical studies demonstrated the same phenomenon. These studies applied to both pre-TKI therapy-era patients and TKI-era patients.[2,3] In these studies, pN1 stage represented an independent predictor of worse survival in the same fashion as was recorded in the current study.

To further test the prognostic significance of pathologic lymph node invasion, we reapplied the methodology described earlier, relying on overall mortality as the end point. After multivariable adjustment, pN1 remained an independent predictor of higher OM (HR, 1.95; $P < 0.01$), further adding to the robustness of our data.

Taken together, our observations indicate that even in this immunotherapy era, pN1 stage harbors added value regarding prognostic stratification of CN mRCC patients. Specifically, when LND is performed, those with pN1 status exhibit significantly worse survival than those with pN0 status. Such stratification may improve clinical decision-making regarding early versus delayed use of systemic therapy for mRCC patients who underwent CN.

Finally, we tested the benefit of postoperative systemic therapy (ST) administration for pN1 patients based on the hypothesis that early ST administration, captured in the current database, may be associated with a stronger protective effect when CSM represented an end point. Our analyses indeed recorded lower CSM rates for the patients treated with postoperative ST than for those who were not (HR, 0.73; $P < 0.01$). This observation further validates that pathologic N1 status may indeed improve decision-making regarding postoperative ST administration. It may be argued, that patients with confirmed pN1 status should ideally receive the earliest postoperative ST.

Despite the novelty of our findings, several limitations of our study need to be acknowledged. First, our data reflect CSM patterns of North American CN mRCC patients. Consequently, estimates shown in this report cannot be applied to CN mRCC patients outside the United States.

Second, the SEER database does not allow stratification or adjustment of the analyses according to Memorial Sloan Kettering Cancer Center (MSKCC) or International mRCC Database Consortium (IMDC) criteria. This limitation is shared with all previous SEER and National Cancer Database (NCDB) analyses.

Third, the SEER database does not provide detailed information about the composition or the exact timing of postoperative systemic therapy (immediate vs deferred). Moreover, our study included only patients with mRCC diagnosed between 2010 and 2018, a period in which immunotherapy was recommended as a first-line systemic treatment option. However, it is important to note that not all patients who received systemic therapy during this period necessarily received immunotherapy. Finally, our report represents a retrospective analysis with high potential for selection biases.

CONCLUSIONS

Pathologically confirmed lymph node invasion independently predicted higher CSM and OM in surgically treated mRCC patients. For pN1 mRCC patients, use of postoperative systemic therapy was associated with lower CSM and OM. Consequently, N stage should be considered for both individual patient counseling and clinical decision-making.

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DATA AVAILABILITY All data generated for this analysis were from the Surveillance, Epidemiology, and End Results Research Plus (SEER) database. The code for the analyses will be made available upon request.

DISCLOSURE There are no conflict of interest.

INFORMED CONSENT All analyses and their reporting followed the Surveillance, Epidemiology, and End Results Research Plus (SEER) reporting guidelines. Due to the anonymously coded design of the SEER database, study-specific institutional review board ethics approval was not required.

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Original Study

Prognostic Significance of Radiographic Lymph Node Invasion in Contemporary Metastatic Renal Cell Carcinoma Patients

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Abstract

We tested for the prognostic significante of radiographic N-stage in metastatic renal cell carcinoma (mRCC) patients with low metastatic burden (single metastatic site). After multivariable adjustment, radiographic N1 status was an independent predictor of higher cancer-specific mortality (CSM). In consequence, consideration of radiographic lymph node invasion might be of great value in this specific population of mRCC patients.

Purpose: To test the prognostic significance of radiographic cN-stage in metastatic renal cell carcinoma (mRCC) patients with low metastatic burden (1 site of metastasis), relying on the Surveillance, Epidemiology, and End Results database (SEER 2010-2020). **Methods:** Included were mRCC patients with 1 site of metastasis, treated with systemic therapy without cytoreductive nephrectomy (CN). Kaplan-Meier plots and multivariable Cox-regression models addressed cancer-specific mortality (CSM) according to radiographic cN-stage (ccN1 vs. ccN0). Separate subgroup analyses were performed, addressing radiographic N-stage in patients with distinct histology (clear-cell vs. RCC not otherwise specified [RCC NOS]). **Results:** Of 1756 mRCC patients, 545 (31%) were radiographic cN1. Overall, the median CSM-free survival of the cohort was 11 months. Median CSM-free survival was 8 vs. 14 months in radiographic cN1 vs. cN0 mRCC patients (HR 1.49, $P < .0001$). In multivariable Cox regression analyses, radiographic cN1 status was an independent predictor of higher CSM (HR 1.39; $P = .01$). In subgroup analyses, addressing patients with clear-cell histology and patients with RCC NOS separately, radiographic cN1 status remained independently associated with a higher CSM in both groups (clear-cell: HR 1.36; $P = .03$; RCC NOS: HR 2.06; $P = .009$). **Conclusion:** In mRCC patients with low metastatic burden, presence or absence of radiographic lymph node invasion results in a clinically meaningful discrimination between those with poor prognosis and others. In consequence, consideration of radiographic lymph node invasion might be of great value in this specific population of mRCC patients.

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Keywords: CSM, Population-based, SEER, RCC, Prognosis

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Introduction

In historic studies, presence of lymph node invasion represented an independent predictor of worse survival for mRCC patients who underwent cytoreductive nephrectomy.[1,2] However, the number of patients who undergo cytoreductive nephrectomy is decreasing.[3,4] Moreover, even if patients undergo cytoreductive nephrectomy, lymph node dissection is not routinely performed in most centers.[5] As a consequence, a search for prognostic markers that do not rely on histology are increasingly relevant. The importance of radiographic cN1-stage is currently unknown in metastatic RCC patients treated with systemic therapy.[1,2] The current study addresses the knowledge gap regarding radiographic cN1. Specifically, we hypothesised, that presence of radiographic cN1 may represent an important predictor of higher cancer-specific mortality (CSM), specifically in patients with low metastatic burden defined as presence of a single site of metastasis. We tested this hypothesis within a large, contemporary population-based cohort of mRCC patients, that were exposed to systemic therapy and did not undergo cytoreductive nephrectomy.

Methods

Data Source and Study Population

Within the SEER database (2010-2020), we identified patients aged ≥18 years with histologically confirmed metastatic RCC (International Classification of Disease for Oncology [ICD-O] site codes C64.9) with either clear-cell (ICD-O 8310/3) or renal cell carcinoma not otherwise specified (RCC NOS, ICD-O 8312/3) subtype. Only mRCC patients that received systemic therapy were included. Additionally, only patients in whom only 1 site of metastasis was identified were included. Further exclusion criteria consisted of patients with missing data on clinical lymph node status. Autopsy or death certificate only cases were also excluded (Figure consort).[6]

Variables of Interest

Demographic covariates consisted of age at diagnosis (years, continuously coded) and sex (male vs. female). Tumor characteristics consisted of T-stage (T1 vs. T2 vs. T3 vs. T4), grade (G1-G2 vs. G3-G4), histology (clear-cell vs. RCC NOS) and radiographic N-stage (cN0 vs. cN1). Cancer-specific mortality (CSM) was the primary end point of the study.[7]

Statistical Analyses

First, baseline characteristics of the cohort were analyzed. Descriptive statistics included frequencies and proportions for categorical variables. Medians and interquartile ranges (IQR) were reported for continuously coded variables. Kruskal-Wallis (continuous variables) and Chi-square (categorical variables) tests were used to assess differences in medians and proportions. Second, Kaplan-Meier plots were used to display rates of CSM according to radiographic cN1 vs. cN0. The association between radiographic N-stage (cN1 vs. cN0) and CSM was further tested in multivariable Cox regression models. Adjustment variables consisted of sex, T-stage, grade and histology. Third, we reapplied the above-described methodology in a subgroup analyses. Specifically, we used Kaplan-Meier plots to display rates of CSM in mRCC patients who harbored clear-cell histology and in those with RCC NOS. Additionally, CSM Hazard ratios (HR) were tabulated, using both univariable and multivariable analyses. In all statistical analyses, R software environment for statistical computing and graphics (R version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria) was used.[8] All tests were 2 sided, with a level of significance set at $P < .05$.

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Results

Descriptive Characteristics

Between 2010 and 2020, we identified 1,756 mRCC patients that received systemic therapy (Table 1). Of those, 545 (31%) had radiographically suspected cN1 status. Statistically significant differences between cN1 and cN0 patients existed for age (median age: 63 for cN1 vs. 66 years for cN0; $P < .001$), T-stage (T3: 27% cN1 vs. 17% cN0; T4: 23% cN1 vs. 12% cN0; $P < .001$) histology (clear-cell: 32% cN1 vs. 45% cN0; $P < .001$), as well as site of metastasis (lung: 51% cN1 vs. 45% cN0; bone: 25% cN1 vs. 41% cN0; liver: 11% cN1 vs. 7.4% cN0; $P < .001$). No significant differences in the groups were recorded regarding sex, race/ethnicity, and grade.

Cancer-Specific Mortality and Cox Regression Analyses

Overall, the median CSM-free survival was 11 months. The median CSM-free survival according to radiographic N-stage was 8 vs. 14 months in cN1 vs. cN0 mRCC patients with low metastatic burden (Figure 1). In univariable Cox regression models, radiographic cN1 stage represented a statistically significant predictor of CSM (HR 1.49; $P < .0001$; Table 2). In multivariable Cox regression analyses, adjusting for sex, T-stage, grade and histology, radiographic cN1 status remained an independent predictor of CSM (HR 1.39; $P = .01$).

Prognostic Significance of Radiographic N-Stage in Metastatic Renal Cell Carcinoma With Clear-Cell Histology

The median CSM-free survival in clear-cell mRCC patients was 10 vs. 19 months in cN1 vs. cN0 patients (Figure 2). After multivariable adjustment, radiographic cN1 represented an independent predictor for higher CSM (HR 1.36; $P = .03$; Table 3).

Prognostic Significance of Radiographic N-Stage in Metastatic Renal Cell Carcinoma Not Otherwise Specified

The median CSM-free survival in mRCC patients with RCC NOS classification was 7 vs. 11 months in cN1 vs. cN0 patients (Figure 3). After multivariable adjustment, radiographic cN1 represented an independent predictor for higher CSM (HR 2.06; $P = .009$; Table 3).

Discussion

The importance of lymph node invasion (LNI) in cytoreductive nephrectomy (CN)-treated mRCC patients has been introduced prior to the advent of TKIs and was subsequentially validated in the early as well as in more contemporary TKI era.[1,2,5] In mRCC patients treated with CN, presence of LNI is associated with significantly higher mortality. For example, Lughezzani et al, reported

Table 1 Descriptive Table of 1756 Metastatic Renal Cell Carcinoma (mRCC) Patients Identified Within the Surveillance, Epidemiology, and End Results database (2010-2020)

Characteristic	N	Overall, N = 1756[a]	cN1, N = 545 (31%)[a]	cN0, N = 1211 (69%)[a]	*P*-value[b]
Age	1756	65 (58, 72)	63 (55, 70)	66 (59, 73)	<.001
Sex	1756				.13
Female		517 (29%)	174 (32%)	343 (28%)	
Stage	1756				<.001
T1		429 (24%)	89 (16%)	340 (28%)	
T2		366 (21%)	105 (19%)	261 (22%)	
T3		349 (20%)	148 (27%)	201 (17%)	
T4		272 (15%)	128 (23%)	144 (12%)	
TX		340 (19%)	75 (14%)	265 (22%)	
Grade	290				.14
G1-G2		148 (51%)	48 (45%)	100 (54%)	
G3-G4		142 (49%)	58 (55%)	84 (46%)	
Histology	1756				<.001
clear-cell		719 (41%)	176 (32%)	543 (45%)	
RCC NOS		1037 (59%)	369 (68%)	668 (55%)	
Site of metastasis	1756				<.001
Lung		826 (47%)	280 (51%)	546 (45%)	
Bone		630 (36%)	138 (25%)	492 (41%)	
Liver		149 (8.5%)	59 (11%)	90 (7.4%)	
Brain		52 (3.0%)	17 (3.1%)	35 (2.9%)	
Other		99 (5.6%)	51 (9.4%)	48 (4.0%)	

[a] Median (IQR); n (%).
[b] Wilcoxon rank sum test; Pearson's Chi-square test; Fisher's exact test.

Figure 1 Kaplan-Meier curve addressing cancer-specific mortality (CSM)- free survival in 1756 metastatic renal cell carcinoma patients identified within the Surveillance, Epidemiology, and End Results (SEER) database (2010-2020).

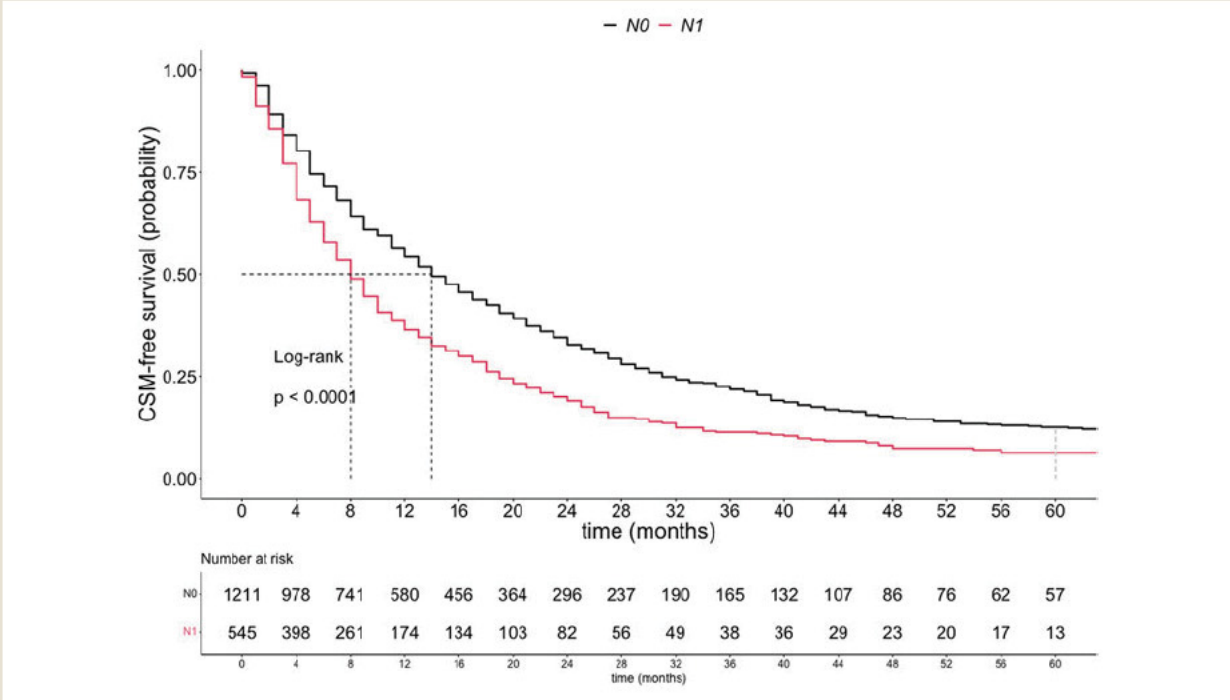


Table 2 Cox Regression Analyses Predicting Cancer-Specific Mortality (CSM) for Metastatic Renal Cell Carcinoma

	Univariable		Multivariable[a]	
	HR	*P*-value	HR	*P*-value
N-stage (N0 Ref.)				
N1	1.49 (1.33-1.67)	<.001	1.39 (1.2-1.87)	.01
T-stage (T1 Ref.)				
T2	1.18 (1.00-1.39)	.04	0.93 (0.60-1.44)	.75
T3	1.29 (1.09-1.52)	<.01	0.92 (0.59-1.43)	.72
T4	1.37 (1.15-1.64)	<.01	0.74 (0.45-1.20)	.23
Tx	1.22 (1.03- 1.44)	.01	1.16 (0.68-1.96)	.57
Grade (G1-G2 Ref.)				
G3-G4	1.40 (1.07-1.84)	.01	1.40 (1.06-1.85)	.01
Histology (cc. Ref)				
Other	1.46 (1.31-1.64)	<.001	1.33 (0.99-1.81)	.06
Female	1.16 (1.03-1.30)	.006	1.28 (0.93-1.76)	.11

[a] Covariates in multivariable model: N-stage, sex, T-stage, grade, histology.

Table 3 Cox Regression Analyses Predicting Cancer-Specific Mortality (CSM) for Metastatic Renal Cell Carcinoma According to Histology

	Clear-Cell		RCC NOS	
	Univariable	Multivariable[a]	Univariable	Multivariable[a]
N-stage (N0 Ref.)				
N1	**HR 1.45 (1.19-1.77); *P* < .001**	**HR 1.36 (1.09-1.58); *P* = .03**	**HR1.41 (1.23-1.63); *P* < .001**	**HR 2.06 (1.19-3.57); *P* = .009**

[a] Covariates in multivariable model: N-stage, sex, T-stage, grade.

Figure 2 Kaplan-Meier curve addressing cancer-specific mortality (CSM)- free survival in 719 clear-cell metastatic renal cell carcinoma patients identified within the Surveillance, Epidemiology, and End Results (SEER) database (2010-2020).

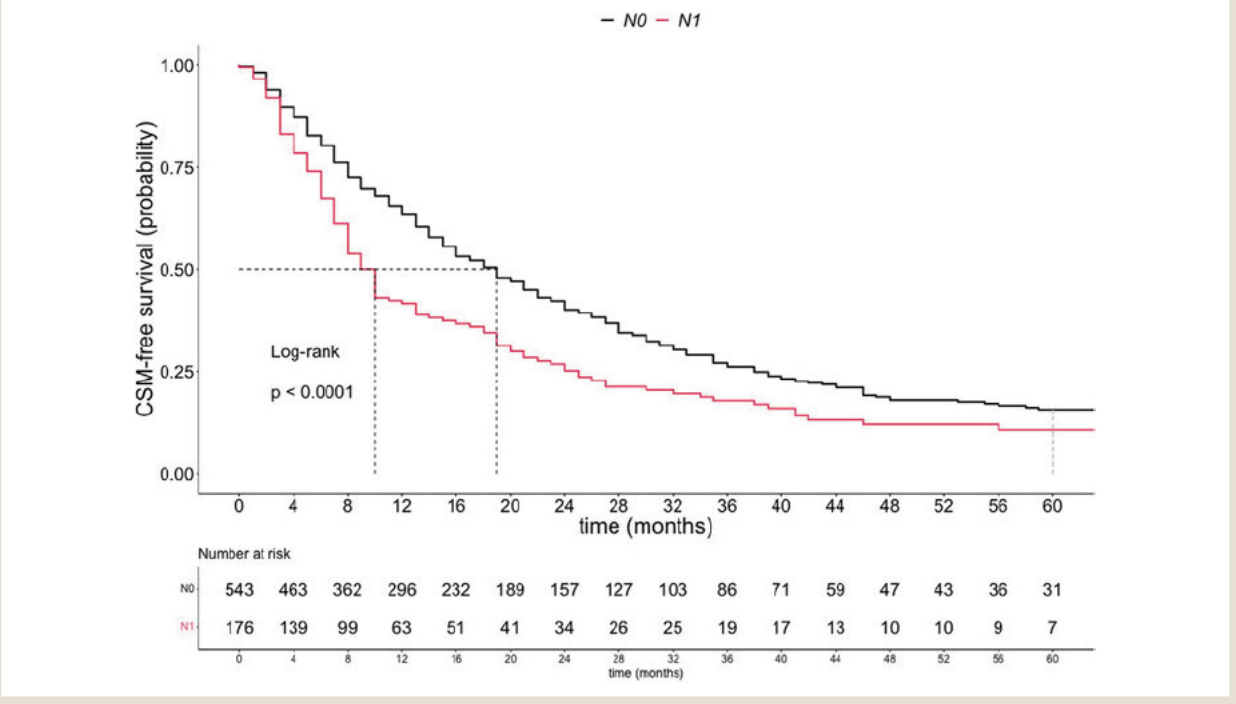
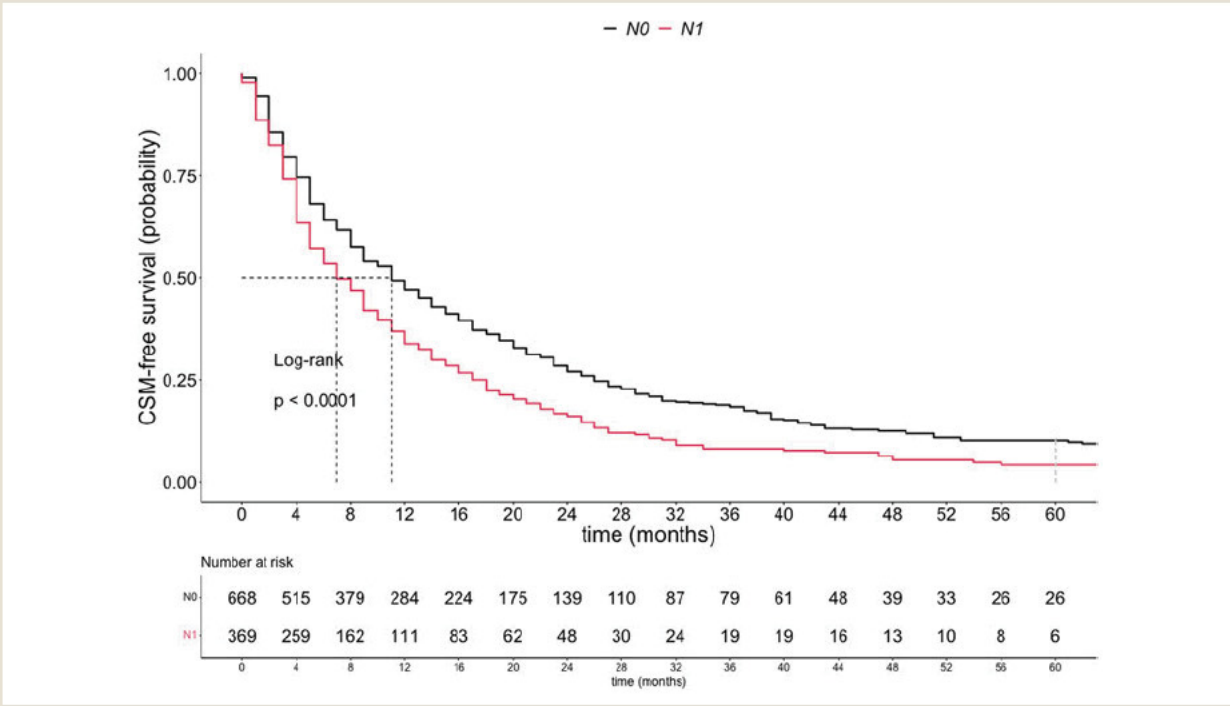


Figure 3 Kaplan-Meier curve addressing cancer-specific mortality (CSM)- free survival in 1037 metastatic renal cell carcinoma patients not otherwise specified (RCC NOS) identified within the Surveillance, Epidemiology, and End Results (SEER) database (2010-2020). In historic studies, presence of lymph node invasion represented an independent predictor of worse survival for metastatic renal cell carcinoma (mRCC) patients who underwent cytoreductive nephrectomy. However, the number of patients who undergo cytoreductive nephrectomy is decreasing. Moreover, lymph node dissection is not routinely performed in most centers. As a consequence, a search for prognostic markers that do not rely on histology are of increasing importance. It is currently unknown whether radiographic N-stage has a significant prognostic impact, and therefore act as a proxy to pathological N-stage. We relied on the Surveillance, Epidemiology, and End Results (SEER) database to address this knowledge gap. Indeed, our findings indicate that presence of radiographic N1 status is an important prognostic marker in patients with low metastatic burden and should be considersed in clinical decision making. Figure: Consort diagram of the study population. Abbreviations: SEER = Surveillance, Epidemiology and End Results, RCC = renal cell carcinoma, RCC NOS = renal cell carcinoma not otherwise specified, ST = systemic therapy.



CSM-free survival rates at 3 years after CN of 14 vs. 35% for cN1 vs. cN0 patients. However, the concept of LNI solely based on radiographic findings in systemically treated mRCC patients who did not undergo CN was never formally addressed in contemporary analyses. We addressed this unmet need and made several noteworthy observations.

First, within all 1756 contemporary mRCC patients with low metastatic burden, treated with systemic therapy, the rate of radiographic cN1 stage was 31%. The high prevalence of radiographic cN1-stage in mRCC patients with low metastatic burden validates the importance of conducting comprehensive analyses within this specific patient cohort. Previous studies addressing N-stage in mRCC patients, either relied on pathological N-stage or a combination of radiographic and pathological N-stage.[1,2,9] However, since the majority of mRCC patients do not undergo CN, pathological N-stage is often not available. A study by Chakiryan et al. published in 2022, relying on the NCDB database, reported that 61% of all mRCC patients do not undergo CN.[10] Moreover, the rate of CN-treated mRCC is decreasing with time.[11] In consequence, a search for prognostic factors in this population where surgical pathology is unavailable is of increasing importance. Radiographic cN-stage represents a potential candidate variable.

Second, all previous studies examined the importance of cN1 stage without accounting for metastatic burden. Exclusive consideration of patients with low metastatic tumor burden is crucial, since presence or absence of radiographic cN1-stage in patients with heavy metastatic burden will unlikely represent an important determinant of CSM. In such individuals, the mortality will be predominately and foremost defined by multiple distant metastasis, but not presence or absence of radiographic N-stage.[12] In consequence, only patients with low metastatic burden were included in the current study.

Third, we relied on formal survival analysis to test whether radiographic cN1 is an independent predictor of CSM and to quantify its magnitude. In Kaplan-Meier analyses, the median CSM-free survival was 8 vs. 14 months for cN1 vs. cN0 mRCC patients ($P < .001$). In multivariable analyses, radiographic cN1 status represented an independent predictor of higher CSM (1.39; $P = .01$).

These 2 observations cannot be directly compared to any previous study, since no such study has been reported. Unfortunately, several studies examining the effect of nodal stage on survival in mRCC were "contaminated" with surgically treated patients. In consequence, such studies provide uninterpretable results regarding the effect of radiographic N-stage. The implications of the current results are important. Specifically, our observations indicate that patients with radiographic cN1 stage in presence of low metastatic burden, are predisposed to less favourable treated natural history. In consequence, patients with radiographic cN1 stage should ideally be actively treated with systemic therapy from initial diagnosis. Additionally, delays between consecutive lines of therapy upon eventual disease progression should also ideally be avoided in this high-risk patient population.

Despite its novelty and important clinical observations, the current study has important limitations that acquire acknowledgment. First, our findings could not be adjusted according to the International mRCC Database Consortium (IMDC) criteria. However, his limitation is shared with all previous SEER and National Cancer Database (NCDB) analyses. Second, the current study relied on patients with clear-cell, as well as, RCC NOS histology. Exclusive consideration of clear-cell mRCC patients would result in a significantly smaller patient population that only includes a minority of individuals, since the majority of biopsy-confirmed mRCC cases in the SEER database fall into the category of RCC NOS. In consequence, a methodology that relies on combined analyses of clear-cell and RCC NOS histology, as well as on subgroup analyses that examine the histological groups separately, is warranted. This methodology was applied in the current study according to previous recommendations.[13] The current results validate the importance of radiographic cN1 in both clear-cell and NOS histology, since the effect of this variable represents an independent predictor for CSM in both subgroups. Third, unfortunately the SEER database does not provide information regarding the type of imaging modality used, nor does it provide information on specific systemic therapy type and its dose and duration. Fourth, the SEER database does not provide information regarding number of metastases. In consequence, we relied on number of metastatic sites to identify patients with low metastatic burden. However, it can be postulated that the number of metastatic sites is a stronger predictor for mortality than the specific number of overall metastases.[14] Last but not least, due to the retrospective nature of our study, our report has a high potential for selection biases. Therefore, these results must be interpreted within the boundaries of such limitation.

Conclusion

In mRCC patients with low metastatic burden, presence or absence of radiographic lymph node invasion results in a clinically meaningful discrimination between those with poor prognosis and others. In consequence, consideration of radiographic lymph node invasion might be of great value in this specific population of mRCC patients.

Clinical Practice Points

- In historic studies, presence of lymph node invasion represented an independent predictor of worse survival for metastatic renal cell carcinoma (mRCC) patients who underwent cytoreductive nephrectomy. However, the number of patients who undergo cytoreductive nephrectomy is decreasing. Moreover, lymph node dissection is not routinely performed in most centers. As a consequence, a search for prognostic markers that do not rely on histology are of increasing importance.
- It is currently unknown whether radiographic N-stage has a significant prognostic impact, and therefore act as a proxy to pathological N-stage. We relied on the Surveillance, Epidemiology, and End Results (SEER) database to address this knowledge gap.
- Our findings indicate that presence of radiographic N1 status is an important prognostic marker in patients with low metastatic burden and should be considersed in clinical decision making.

Disclosure

The authors have stated that they have no conflicts of interest.

CRediT authorship contribution statement

Lukas Scheipner: Conceptualization, Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Reha-Baris Incesu:** Data curation, Writing – review & editing. **Simone Morra:** Data curation, Writing – review & editing. **Andrea Baudo:** Investigation, Writing – review & editing. **Anis Assad:** Investigation, Writing – review & editing. **Letizia Maria Ippolita Jannello:** Investigation, Writing – review & editing. **Carolin Siech:** Investigation, Writing – review & editing. **Mario de Angelis:** Investigation, Writing – review & editing. **Zhe Tian:** Data curation, Formal analysis, Methodology, Software, Visualization, Writing – review & editing. **Fred Saad:** Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing. **Shahrokh F. Shariat:** Project administration, Resources, Validation, Writing – review & editing. **Alberto Briganti:** Project administration, Resources, Validation, Writing – review & editing. **Felix K.H. Chun:** Project administration, Resources, Validation, Writing – review & editing. **Derya Tilki:** Project administration, Resources, Validation, Writing – review & editing. **Nicola Longo:** Project administration, Resources, Validation, Writing – review & editing. **Luca Carmignani:** Project administration, Resources, Validation, Writing – review & editing. **Ottavio De Cobelli:** Project administration, Resources, Validation, Writing – review & editing. **Martin Pichler:** Project administration, Resources, Validation, Writing – review & editing. **Sascha Ahyai:** Project administration, Resources, Supervision, Validation, Writing – review & editing. **Pierre I. Karakiewicz:** Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing.

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