available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Kidney Cancer

Treatment Facility Volume and Survival in Patients with Metastatic Renal Cell Carcinoma: A Registry-based Analysis

Shreyas S. Joshi[a], *Elizabeth A. Handorf*[b], *Matthew Zibelman*[c], *Elizabeth R. Plimack*[c], *Robert G. Uzzo*[a], *Alexander Kutikov*[a], *Marc C. Smaldone*[a], *Daniel M. Geynisman*[c,*]

[a] *Division of Urologic Oncology, Department of Surgical Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA;* [b] *Department of Bioinformatics and Biostatistics, Fox Chase Cancer Center, Philadelphia, PA, USA;* [c] *Department of Hematology/Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA*

Article info

Article history:
Accepted May 18, 2018

Associate Editor:
Giacomo Novara

Statistical Editor:
Andrew Vickers

Keywords:
Renal cell carcinoma
Facility volume
Cancer survival

Abstract

Background: Higher treatment facility (TF) volume has been linked with improved oncologic treatment outcomes.
Objective: To determine the association between TF volume and overall survival in patients with metastatic renal cell carcinoma (mRCC).
Design, setting, and participants: The National Cancer Database (NCDB) was queried for all patients with mRCC with survival data available (2004–2013, cohort A). Overall survival was assessed based on TF volumes, and increasingly narrow inclusion criteria were used to confirm the cohort A association: cohort B = mRCC patients with active treatment; cohort C = mRCC patients with systemic therapy; cohort D = mRCC patients with systemic therapy at the reporting institution; and cohort E = mRCC patients with systemic therapy at the reporting institution with known liver and lung metastatic status. Sensitivity analyses were also performed on subcohorts of mRCC who never underwent a nephrectomy (C1, D1, and E1).
Outcome measurements and statistical analysis: The effect of volume on time to death (from any cause) was determined using Cox regression models, adjusting for multiple clinical pathologic factors. Volume effects (assessed continuously) were modeled using flexible cubic splines, and adjusted 1-yr survivals were obtained from the model.
Results and limitations: A total of 41 836 mRCC patients were treated at 1222 TFs. The median age was 65 yr. Of the patients, 66% were men and 79% had clear cell mRCC. Median TF volume was 2.2 patients per year (pts/yr). Across all cohorts, higher TF volume was associated with improved outcomes. Adjusted 1-yr survival in cohort A was 0.36 at 2 pts/yr, 0.39 at 5 pts/yr, 0.42 at 10 pts/yr, and 0.46 at 20 pts/yr, with similar magnitudes of effect in cohorts B–E. Limitations include the retrospective nature of NCDB analysis and the lack of information on treatment regimens used at specific facilities, which may explain mechanisms of effects.
Conclusions: Higher facility volume is associated with improvements in survival for patients being treated for mRCC. Steps should be taken to standardize management of mRCC patients, such as evidence-based pathway development, clinical trial access, and multidisciplinary resource availability at lower-volume TFs.
Patient summary: In this report, we analyzed a large cancer database and found that patients with metastatic kidney cancer survived longer if they were managed at facilities that treated a higher volume of such patients. This information can help find the best treatment environment for patients with metastatic kidney cancer.

* Corresponding author. Department of Medical Oncology, Fox Chase Cancer Center, Temple University Health System, 333 Cottman Avenue, Philadelphia, PA 19111, USA. Tel. +1 215 728 3889; Fax: +1 215 728 3639.
E-mail address: daniel.geynisman@fccc.edu (D.M. Geynisman).

https://doi.org/10.1016/j.eururo.2018.05.025
0302-2838/

1. Introduction

Although mortality rates for patients with renal cell carcinoma (RCC) have declined over several decades, survival following the diagnosis of metastatic RCC (mRCC) continues to be poor [1]. Metastatic RCC is often an aggressive disease that is poorly responsive to traditional cytotoxic systemic therapies, with the 5-yr overall survival (OS) for patients as low as 8%, leading to over 14 000 deaths from RCC annually [1,2].

The landscape for systemic mRCC therapy has rapidly evolved over the last 10 yr, first with improvements in targeted therapies and more recently with the development of novel immunotherapies. Advanced knowledge of these ever-changing treatment options may be necessary to obtain optimal patient outcomes. Centers that manage higher volumes of cancer patients likely employ providers that have such advanced knowledge and treatment experience, as well as access to novel drugs via clinical trials. Indeed, treatment volume has historically been used as a surrogate marker for hospital and provider experience, and may also indicate the presence of more streamlined care processes that can impact patient outcomes.

The volume-outcome relationship of various medical treatments and procedures has long been established, although the magnitude of this association varies greatly [3,4]. This relationship also appears to hold true for cancer therapies, with mounting evidence to suggest that treatment facilities (TFs) that manage a higher volume of cancer patients might have improved survival outcomes [5–9].

For RCC, the volume-outcome relationship has been explored for the treatment of localized disease. Many studies have demonstrated that high-volume TFs lead to improved postoperative outcomes and fewer complications following renal cancer surgery [10–12]. Several studies showed improved in-hospital survival following high-risk nephrectomy for RCC, although it is unclear if surgery at high-volume surgical centers necessarily translates to overall longer-term survival [13,14]. However, there is little knowledge regarding the volume-outcome relationship for patients diagnosed with and treated for mRCC. We, therefore, analyzed a large national cancer database to determine if there is a relationship between TF volume and survival outcomes for patients diagnosed with mRCC.

2. Patients and methods

2.1. Data source

The National Cancer Database (NCDB), a program of the ACS CoC (Commission on Cancer) and the American Cancer Society, is a national cancer registry and comprehensive clinical surveillance resource for cancer care in the USA. The NCDB compiles data from over 1500 commission-accredited cancer programs in the USA and Puerto Rico, and captures approximately 70% of all newly diagnosed cancer cases [15]. The use of national deidentified registry data was exempt from institutional review board approval.

2.2. Study population

Patients with mRCC were identified in the NCDB based on ICD-O-3 site codes. All histologic subtypes of RCC were included (ICD-O-3 site code C649). Our study cohort included all patients who were diagnosed with primary RCC between 2004 and 2013. Only patients with metastatic (M1) disease at diagnosis were selected for analysis. Patients were excluded if survival data were unavailable or they did not receive any treatment at the reporting facility. To confirm any association between TF volume and survival, patients were divided into five cohorts defined by increasingly stringent inclusion criteria (Fig. 1): cohort A included all patients with mRCC and available survival data ($N = 41\,836$); cohort B was restricted to mRCC patients who underwent some active treatment (surgery or systemic therapy, $N = 27\,557$); cohort C was further restricted to mRCC patients whose treatment included systemic therapy (with or without primary surgery, $N = 19\,138$); cohort D required treatment with systemic therapy at the reporting institution ($N = 12\,000$); and cohort E was further subset to those with known sites of metastases (ie, known if liver/lung metastases present, $N = 4933$).

In order to isolate the influence of volume effects not related to surgery, subgroups were generated excluding patients who had surgical intervention in addition to systemic therapy. Cohorts C1 ($N = 10\,489$), D1 ($N = 6898$), and E1 ($N = 2866$) correspond to cohorts C, D, and E, respectively, after excluding patients who had surgery (partial or radical nephrectomy) as part of their treatment (Fig. 1).

2.3. TF volume, covariates, and study outcome

TF volume was defined as the mean number of mRCC patients treated per year. The regression models were adjusted by a set of covariates available in the NCDB. These included patient age, sex, race, Hispanic ethnicity, year of diagnosis, insurance type, income, education, location, Charlson-Deyo comorbidity score [16], and clinical characteristics (histology, and presence or absence of liver and lung metastasis). Our model did not adjust for facility type, due to potential collinearity with facility volume. It also did not adjust for treatment type (ie, surgery) because treatment differences were assumed to be the mechanism by which volume affects outcomes. Treatment type, therefore, was not considered a confounding covariate. A small proportion of data were missing for some of the (categorical) covariates, with the highest percentage of missing data being 6.3% for Hispanic ethnicity. For covariates with missing data, a missing category was added to the multiple regression models. The primary outcome was time until death from any cause.

2.4. Statistical analysis

The effect of TF volume on risk of mortality was determined using multivariable Cox regressions, using robust standard errors to account for clustering within facilities. We modeled the effect of TF volume as a continuous variable using flexible cubic splines [17]. Degrees of freedom for the spline effects were chosen via cross validation. Adjusted 1-yr survival probabilities were estimated based on the Cox regression models. Spline effects were summarized graphically and by presenting the resulting hazard ratios for mortality at specific volume thresholds (5, 10, and 20 cases/yr). Separate survival analyses were conducted on all treatment cohorts, including the subgroups C1–E1 that excluded surgical patients. In an additional analysis, we examined the effect of high (top 20%) versus low (lower 80%) TF volume on mortality (see the Supplementary material). Statistical analysis was performed with SAS version 9.3 and R version 3.3, with $p < 0.05$ being considered statistically significant.

Please cite this article in press as: Joshi SS, et al. Treatment Facility Volume and Survival in Patients with Metastatic Renal Cell Carcinoma: A Registry-based Analysis. Eur Urol (2018), https://doi.org/10.1016/j.eururo.2018.05.025