



Research Article/Özgün Araştırma

The effect of tumor laterality on prognosis in metastatic renal cell carcinoma

Metastatik renal hücreli karsinomda tümör lateralitesinin prognoza etkisi

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Abstract

Aim: In metastatic renal cell carcinoma (RCC), prognosis relies on various factors. Tumor lateralization's role is still debated. Our study examined how tumor localization affects survival in metastatic RCC patients.

Materials and Methods: The study retrospectively analyzed 80 patients with metastatic renal cell carcinoma, diagnosed between January 1999 and December 2021.

Results: Eighty patients were evaluated. The median age at diagnosis was 60 (range 37-86). Tumors were in the right kidney for 39 patients (48.8%) and in the left kidney for 41 patients (51.2%). Of these patients, 58 (72.5%) had de novo metastatic disease, while 22 (27.5%) had recurrences during follow-up. Tumor localization showed no significant association with age ($p=0.684$), gender ($p=0.761$), ECOG performance status ($p=0.326$), primary tumor surgery ($p=0.697$), or lung metastasis ($p=0.495$). However, a significant association was found with liver metastasis ($p=0.032$). There was no significant difference in median survival between right and left-sided tumors ($p=0.266$).

Conclusion: In our study, survival showed no correlation with tumor lateralization in metastatic RCC.

Keywords: Renal cell carcinoma; Lateralization; Metastasis; Kidney.

Öz

Amaç: Metastatik renal hücreli kanserlerde (RCC) prognoz prognostik faktörlere bağlıdır. Tümör lateralizasyonun bu faktörlerden biri olup olmadığı halen tartışmalıdır. Çalışmamızda metastatik RCC ile takip edilen hastalarda tümörün yerleşiminin sağkalım üzerine etkisini araştırdık.

Gereç ve Yöntem: Çalışmada Ocak 1999 ve Aralık 2021 arasında metastatik renal hücreli kanser tanısı alan 80 hasta retrospektif olarak incelendi.

Bulgular: 80 hasta değerlendirildi. Median tanı yaşı 60 (37-86) idi. 39 (%48,8) hastada tümör sağ böbrekte, 41(%51,2) hastada sol böbrekte idi. Hastaların 58'i (%72,5) denova metastatik iken 22 (%27,5) hastada takipte nüks gelişmişti. Tümör lokalizasyonu ile yaş ($p=0.684$), cinsiyet ($p=0.761$), ECOG ps ($p=0.326$), tümör primerine cerrahi yapılması ($p=0.697$) ve akciğer metastazı ($p=0.495$) arasında anlamlı ilişki yokken, karaciğer metastazı arasında anlamlı ilişki saptandı ($p=0.032$). Sağ ve sol lokalizasyonlu tümör arasında median sağkalım açısından anlamlı fark yoktu ($p=0.266$).

Sonuç: Çalışmamızda, metastatik RCC'de sağkalım ile tümör lateralizasyonu arasında ilişki bulunamadı.

Anahtar Kelimeler: Renal hücreli karsinom; Lateralizasyon; Metastaz; Böbrek.

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Introduction

Renal cancer is the 13th most common cancer with a gradually increasing incidence.¹ Approximately 90% of kidney cancers are renal cell cancers.² Renal cell cancer, seen 2 times more in men than in women, is responsible for 5% of the malignities seen in men and 3% in women.^{1,3} Most of the patients are diagnosed at the age of 60-70 years.⁴

Due to the increased use of ultrasonography and computed tomography in recent years, its incidence has been increasing, so most patients are diagnosed at an early stage.^{5,6} Surgery is the main treatment method in these patients. While approximately 30% of the patients are metastatic at the time of diagnosis, recurrence develops in 30-40% of the patients during follow-up after curative surgery.⁷⁻¹⁰ Approximately 75% of the metastases involve lung, 36% lymph nodes, 20% bone, 18% liver, and less than 10% brain and skin.¹⁰ The prognosis in metastatic disease is generally poor depending on the prognostic factors at the time of diagnosis, and the median survival is less than 12 months. Various studies have been carried out for predicting prognosis, and some prognostic models have been developed.¹¹⁻¹⁶ Accordingly, age, Karnofsky performance status (KPS), histological grade and tumor subtype, tumor size, lymph node involvement and stage, some laboratory values (hemoglobin, albumin, calcium, etc.) were defined as prognostic, and started to be used in these models.^{13-15,17}

Although the kidneys are known as a pair of identical organs, there are some anatomical and physiological differences between each other. How these differences affect tumor prognosis is the subject of research. The effect of tumor localization either in the right or left kidney on the prognosis has not been clarified. Studies have shown that the right or left kidney localization rate of renal cancers was almost equal or close to equal.^{18,19} Nevertheless, in a few studies, several results were found on the relationship between the location of the tumor in the right or left kidney and survival.^{17,18,20} Therefore, tumor localization has not been accepted as prognostic yet.

In this study, we aimed to determine the effect of tumor location, either on right or left kidney, on survival in patients followed-up due to metastatic renal cell cancer.

Materials and Methods

We retrospectively screened a cohort of 100 patients diagnosed with metastatic renal cell cancer between January 1999 and December 2021. Patients classified as intermediate or high risk based on IMDC risk scoring were included in our study. Those with incomplete medical records were excluded. Ultimately, 80 patients met our inclusion criteria. Patient information was sourced from both written medical files and computerized records. Demographic and clinicopathological data were collected for analysis.

Statistical Analysis

Windows Statistical Package for the Social Sciences (SPSS) version 20.0 was used. (Chigo, Illinois, USA). The Kolmogorov-Smirnov test was used to examine whether continuous variables had a normal distribution. Depending on the aim, continuous variables were given as mean + SD or median (minimum-maximum). The Fisher exact test or the chi-square test were used to evaluate categorical variables. Using the Kaplan-Meier long rank test, the impact of tumor localization on survival was examined.

Ethics committee approval

The study was conducted according to the principles of the Helsinki Declaration and was approved by the Ankara Etilik City Hospital Ethics Committee on April 5, 2023, with approval number 2023-043.

Results

52 (65%) of the 80 patients were men. The median age of diagnosis was 60 (37-86) years. 49 (61.2%) of the patients were under the age of 65. There were 20 (25%) patients with 0 points performance score (PS), 24 (30%) patients with 1 point, 27 (33.8%) patients with 2 points, and 9 (11.2%) patients with 3 or 4 points. The tumor was located in the right kidney in 39 (48.8%) patients, and in the left kidney in 41 (51.2%) patients. While 58 (72.5%) of the patients were de novo

metastatic, 22 (27.5%) patients developed recurrence during follow-up. In 23% of patients with de novo metastatic disease, the tumor was located in the right kidney, while in 22% it was in the left kidney, and this difference was not statistically significant in terms of survival. Primary tumor surgery was performed on 57 patients (71.3%). Liver metastases were present in 21 (26.6%) patients and lung metastases were present in 38 (47.5%) patients (Table 1).

Table 1. Demographic characteristics of patients

| Gender | |
|-----------------------|----------|
| Female | 28(35) |
| Male | 52(65) |
| Age | |
| <65 years | 49(61.2) |
| ≥65 years | 31(38.8) |
| Tumor location | |
| Right | 39(48.8) |
| Left | 41(51.2) |

Table 2. The relationship between clinicopathological characteristics of patients and tumor localization

| | Right sided | Left sided | Significance (p) |
|------------------------------|--------------------|-------------------|-------------------------|
| Age | | | |
| <65 years | 23(59) | 26(63.4) | 0.684 |
| ≥65 years | 16(41) | 15(36.6) | |
| Gender | | | |
| Female | 13(33.3) | 15(36.6) | 0.761 |
| Male | 26(66.7) | 26(63.4) | |
| ECOG PS | | | |
| 0,1, or 2 | 36(92.3) | 35(85.4) | 0.326 |
| 3 or 4 | 3(7.7) | 6(14.6) | |
| Primary tumor surgery | | | |
| No | 12(30.8) | 11(26.8) | 0.697 |
| Yes | 27(69.2) | 30(73.2) | |
| Liver metastasis | | | |
| No | 24(61.5) | 34(82.9) | 0.032 |
| Yes | 15(38.5) | 7(17.1) | |
| Lung metastasis | | | |
| No | 22(56.4) | 20(48.8) | 0.495 |
| Yes | 17(43.6) | 21(51.2) | |
| Denovo metastasis | | | |
| No | 16 (41) | 19 (46.3) | 0.632 |
| Yes | 23 (59) | 22 (53.7) | |

ECOG PS: Eastern Cooperative Oncology Group performance score

The median survival of all patients was 13 months. Patients with a right-localized tumor had a median survival of 16 months, whereas those with a left-localized tumor had a median survival of 11 months. No significant difference was found between right and left localized tumors ($p=0.266$; Figure 1). Three-year survival was 21% in patients with right-localized tumors, while it was 14% in left-localized tumors.

| Surgical excision of primary tumor | |
|---|----------|
| Yes | 57(71.3) |
| No | 23(28.8) |
| ECOG PS | |
| 0,1, or 2 | 71(88.8) |
| 3 or 4 | 9(11.2) |
| Liver metastasis | |
| Yes | 22(27.5) |
| No | 58(72.5) |
| Lung metastasis | |
| Yes | 38(47.5) |
| No | 42(52.5) |

ECOG PS: Eastern Cooperative Oncology Group performance score

Tumor localization did not significantly correlate with age ($p=0.684$), gender ($p=0.761$), ECOG PS ($p=0.326$), primary tumor surgery ($p=0.697$), or lung metastasis ($p=0.495$), but it did significantly correlate with the emergence of liver metastases ($p=0.032$). Liver metastasis was more common in right sided RCC (Table 2).

The median survival was 11 months in right kidney tumors with liver metastases, it was 28 months in those without liver metastases. There was no statistically significant difference between the patients with and without liver metastasis in right-sided tumors ($p=0.299$). Median survival was 3 months in patients with liver metastases in left kidney tumors, and 15 months in patients without liver metastases. No statistically significant difference was detected, despite a

quantitatively significant difference in median survival between individuals with a left-sided malignancy and those without liver metastases. ($p=0.512$).

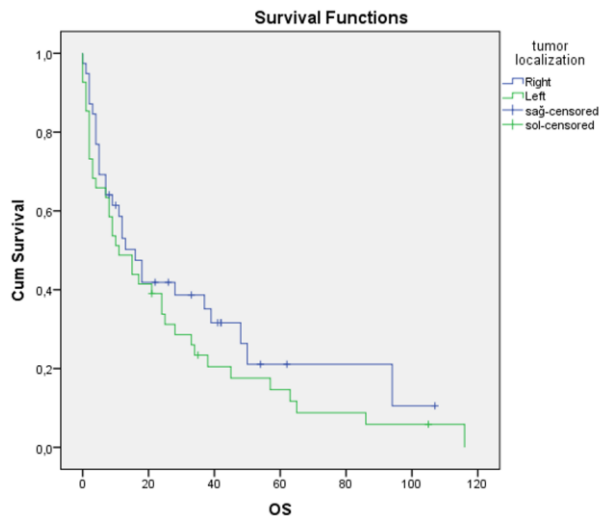


Figure 1. Kaplan Meier curve of the effect of tumor localization on survival

Discussion

Various prognostic models are used to determine the prognosis during the course of renal cell cancer.^{12,13} In these models, age, Karnofsky performance status (KPS), histological grade, tumor histological subtype, tumor size, lymph node involvement and stage, some laboratory tests (hemoglobin, albumin, calcium, etc.) are used. Another issue that has been researched in recent years is whether the location of tumor, either on right or left kidney, makes a difference in prognosis. The reason for this is some anatomical and physiological differences between right and left kidneys.

The organs, that right and left kidneys are adjacent in the abdomen, differ. The right kidney is positioned anatomically in the lower abdomen, compared to the left, due to its adjacency to the liver.²¹ Because the left kidney is positioned more cranially and is more difficult to visualize on ultrasonography, there may be a time difference between the two kidneys in terms of tumor diagnosis. Besides, there is a difference between arterial venous circulation and lymphatic drainages due to different embryonic sources.²² Because of this situation, right and left kidney metastases may progress differently from each other. Due to these factors, it is thought that tumor

lateralization may make a difference in survival.

Right-sided tumors had a better prognosis than left-sided tumors, with a 5-year survival rate for right-sided RCC of 47.6% and 39.6% for left-sided RCC ($p=0.34$), according to a study by Deluhan et al.¹⁸. In the same study it was stated that right-sided tumors were more localized, and the rate of radical surgery was higher Strauss et al.²³ also found in their study that the survival for left-sided tumor was lower than right-sided. Similarly, Guo et al.¹⁷, found that right-sided tumor had a better prognosis, was more associated with less frequent lymph node involvement and metastasis, stage 1-2 and low grade-tumor were more common, and had higher rate of partial nephrectomy. Nini et al.²⁴, also showed that left-sided RCC was associated with more frequent lymph node involvement than right-sided RCC. In terms of right and left localization and tumor incidence, Roychoudhuri et al. observed no statistically significant difference between the two groups.²⁵ Similar findings were made by Russo et al.²⁶ who discovered no difference between right-sided and left-sided RCC in terms of 5-year progression-free survival and overall survival.

We investigated whether the prognosis of patients diagnosed with metastatic RCC in our center differed according to tumor laterality. In our study, similar to the literature, the number of male patients was approximately twice that of female patients, and the median age at diagnosis was 60 years. Nevertheless, similar to the literature, the ratio of right and left localized tumor was almost equal (right RCC 48.8%, left RCC 51.2%). Most of our patients were metastatic at the time of diagnosis. The reason for this may be that the primary treatment of early-stage tumor is surgery, following up of patients by urology department during post-surgical period, or applying of patients to oncology unit during metastatic stage. There was no significant relationship between tumor localization and age, gender, ECOG PS, primary tumor surgery, and lung metastasis. There was a significant relationship between tumor localization and development of liver metastasis. Liver metastases were present in 38.5% of our patients with right

RCC and 17.1% of our patients with left RCC ($p=0.032$). The rate of liver metastasis was higher in patients with right-sided tumor due to its adjacency to liver. Although there was a quantitatively significant difference in median survival between patients having left sided RCC with and without liver metastases, this difference was not statistically significant ($p=0.512$). The median survival of all patients was 13 months, while it was 16 months in patients with right sided tumor and 11 months in those with left sided. The 3-year survival rate was 21% in patients with right-localized tumors, while it was 14% for those with left-sided tumors. Similar to previous studies, no significant difference was found in 3-year survival between right and left localized tumors.^{18,26}

Our study has some limitations such as being single-centered and having retrospective design with a small sample size.

Conclusion

This study did not detect a median overall survival difference between right and left-sided metastatic RCCs. The relationship between disease course and laterality remains uncertain due to differing data in many studies. Perhaps future research investigating the molecular and genetic basis of RCC may yield definitive results.

Ethics Committee Approval

The study was conducted according to the principles of the Helsinki Declaration and was approved by the Ankara Etlik City Hospital Ethics Committee on April 5, 2023, with approval number 2023-043.

Informed Consent

All authors have approved the manuscript and consent for publication.

Author Contributions

O.D. took part in the planning, data collection, ethics committee application and writing of the manuscript. H.S. contributed to the statistical analysis and writing of the data. Y.D. contributed to the planning and data collection of the manuscript. P.P. and E.Z. contributed to data collection.

Conflict of Interest

The authors declare that there is no conflict of interest for this article.

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