RESEARCH ARTICLE

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The Benefit of Upfront Cytoreductive Surgery on the Effect of Immunotherapy After Tyrosine Kinase Inhibitor Therapies in Clear Cell Renal Cell Carcinomas

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The Benefit of Upfront Cytoreductive Surgery on the Effect of Immunotherapy After Tyrosine Kinase Inhibitor Therapies in Clear Cell Renal Cell Carcinomas

Berrak Hücreli Böbrek Hücreli Karsinomlarda Tirozin Kinaz İnhibitörleri Sonrası İmmünoterapide Ön Sitoredüktif Cerrahinin Etkisi

ABSTRACT

Objective

This study aimed to evaluate the effect of upfront cytoreductive nephrectomy on survival outcomes in patients with metastatic clear cell renal cell carcinoma (RCC) who received tyrosine kinase inhibitor (TKI) therapy followed by immunotherapy (nivolumab).

Materials and Methods

This retrospective, single-center study included 38 patients treated between 2010 and 2023. All patients received sunitinib as first-line and nivolumab as second-line therapy. The patients were divided into two groups based on whether they underwent primary tumor resection (PTR group) or not (non-PTR group). Progression-free survival (PFS1, PFS2) and overall survival (OS) were assessed by Kaplan-Meier analysis.

Results

The objective response rate was 79% in the PTR group and 22% in the non-PTR group (p=0.003). The median PFS1 was 16.7 months in the PTR group and 7.1 months in the non-PTR group (p=0.006). Median PFS2 was not reached in the PTR group, whereas it was 54.1 months in the non-PTR group (p=0.290). Although the OS was longer in the PTR group, the difference was not statistically significant (p=0.108).

Conclusion

Upfront cytoreductive nephrectomy appears to improve response rates and progression-free survival in patients with metastatic RCC receiving sequential TKI and nivolumab therapy. However, this effect on overall survival was not statistically significant. These findings warrant validation through prospective, large-scale studies.

Keywords

Renal cell carcinoma, Cytoreductive nephrectomy, Immunotherapy, Tyrosine kinase inhibitor, Survival

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ÖZ

Amaç

Bu çalışmanın amacı, metastatik berrak hücreli renal karsinom (mRHK) tanısı almış ve birinci basamakta tirozin kinaz inhibitörü (TKİ), ikinci basamakta immünoterapi (nivolumab) ile tedavi edilen hastalarda ilk basamakta yapılan sitoredüktif nefrektominin sağkalım sonuçları üzerindeki etkisini araştırmaktır.

Gereç ve Yöntemler

Bu retrospektif, tek merkezli çalışmada 2010–2023 yılları arasında tedavi edilen 38 hasta incelendi. Tüm hastalara birinci basamakta sunitinib, ikinci basamakta nivolumab uygulandı. Hastalar ilk basamakta tümör rezeksiyonu yapılanlar (PTR grubu) ve yapılmayanlar (non-PTR grubu) olarak ikiye ayrıldı. Progresyonsuz sağkalım (PFS1, PFS2) ve genel sağkalım (OS) analizleri Kaplan-Meier yöntemiyle değerlendirildi.

Bulgular

PTR grubunda objektif yanıt oranı %79 iken no-PTR grubunda %22 idi (p=0,003). Medyan PFS1 PTR grubunda 16,7 ay, no-PTR grubunda 7,1 ay olarak saptandı (p=0,006). Medyan PFS2 PTR grubunda henüz ulaşılmamışken, non-PTR grubunda 54,1 ay idi (p=0,290). PTR grubunda OS daha uzun olmakla birlikte istatistiksel anlamlılık göstermedi (p=0,108).

Sonuç

TKİ sonrası nivolumab alan mHRK hastalarında ilk basamakta sitoredüktif nefrektomi, yanıt oranını artırmakta ve progresyonsuz sağkalımı uzatmaktadır. Ancak genel sağkalım üzerindeki etkisi istatistiksel olarak anlamlı bulunmamıştır. Prospektif ve geniş ölçekli çalışmalarla bu sonuçların doğrulanması gereklidir.

Anahtar Kelimeler

Renal hücreli karsinom, Sitoredüktif nefrektomi, İmmünoterapi, Tirozin kinaz inhibitörü, Sağkalım

INTRODUCTION

Renal cell carcinoma (RCC) is the third most common urological cancer worldwide and its incidence varies widely across regions (1). RCC is approximately two-fold more prevalent in males than in females and occurs mostly in the sixth to eighth decades of life, with a median age of 64 years (2). The prognosis is poor. Thirty percent of patients develop metastases at the time of diagnosis, and approximately 30% of patients develop metastases during follow-up (3). Clear cell RCC is the most common pathological subtype with a rate of 75%. Non clear cell RCC represents a heterogeneous group of papillary RCC, chromophobe RCC, translocation-associated RCC, medullar RCC and collecting duct carcinoma (4). Surgery can be curative for patients with localized RCC and selected patients with oligometastatic RCC. Barney and Churchill reported that a patient with RCC with lung metastases lived 23 years after nephrectomy and metastasectomy (5). Various studies have found that metastatic RCC patients undergoing metastasectomy have a longer OS (6-8).

With the development of systemic treatments for metastatic renal cell carcinoma, the perspective of surgical treatment is changing. In the interferon era, cytoreductive nephrectomy (CN) was considered the standard treatment for patients with metastatic renal cell carcinoma (mRCC) because it was associated with improved overall survival. However, the CARMENA trial showed that sunitinib alone was not inferior to cytoreductive nephrectomy followed by sunitinib, challenging the routine use of upfront CN in patients requiring systemic therapy (9,10). Another trial, SURTIME, suggested that the deferred approach to CN in patients who begin treatment with sunitinib and are offered nephrectomy only if their disease does not progress might be superior to performing CN upfront followed by sunitinib therapy (11). Immune checkpoint-based combination therapy has now become the standard-of-care with progression-free survival (PFS) and overall survival (OS) advantage in the frontline setting for clear cell RCC (12-15). The benefit of nephrectomy in patients receiving checkpoint inhibitor immunotherapy combination will be determined by the PROBE (SWOGS1931) trial (NCT04510597) (16). In our study, we retrospectively evaluated the efficacy of nivolumab and its impact on survival according to the CN status of patients who received first-line tyrosine kinase inhibitor (TKI) therapy and subsequently received nivolumab after disease progression on TKI therapy.

MATERIALS and METHODS

Study design and data collection

Our study was a retrospective, single center, cross sectional study. Patient data were collected from the database of the Medical Oncology Department at Antalya Training and Research Hospital. Inclusion criteria were 1) de novo metastatic clear cell renal cell carcinoma diagnosis; 2) age older than 18 years; 3) patients without autoimmune extra disease; 4) tyrosine kinase inhibitor treatment performed in a first-line setting; and 5) immunotherapy performed in a second-line setting. Patients with missing data on diagnosis,

treatment procedures or surgical procedures were excluded. All participants in the research were administered sunitinib as first-line treatment, followed by nivolumab as second-line therapy. The consistent application of sunitinib did not depend on a predetermined study premise. Instead, it reflected the institutional treatment methodologies and prescribing trends throughout the study duration. Despite the availability of alternative tyrosine kinase inhibitors such as pazopanib, they were not commonly utilized in the study cohort. Consequently, patients administered TKIs other than sunitinib were excluded from the analysis to preserve treatment homogeneity. The data were collected from patients treated between 2010 and 2023.

Descriptive oncological outcomes

PFS1 was calculated as the duration between the first line TKI treatment date and the first progression date of TKI treatment. PFS2 was determined as the time between the second-line immunotherapy starting date and the progression date of immunotherapy. OS was defined as the time interval between the diagnosis date and death or the last follow-up date.

Immunologic markers

The lymphocyte-to-monocyte ratio (LMR) was chosen as an exploratory immunological marker due to its recognized correlation with systemic inflammation and antitumor immune response.

Statistical analyses

Continuous data are presented as median (min-max) and compared using the Mann-Whitney U test between the non-PTR and PTR groups. Categorical variables were presented as frequencies (n) and percentages (%) and were analyzed using Fisher's exact test. Normality assumptions were tested using the Shapiro-Wilk test. Survival curves were generated using the Kaplan–Meier method and the log-rank test was performed to compare overall and progression-free survival between the groups. The Cox proportional hazards model was used to estimate hazard ratios. Variables with $p<0.2$ in univariate analysis were included in the multivariate model. Hazard ratios (HR) with corresponding 95% confidence intervals (95% CIs) were reported. Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA). Statistical significance was defined as a two-sided p-value of less than 0.05. This single-center study included all patients who met the eligibility criteria during the study period; therefore, the sample size was not calculated prospectively. A post hoc power analysis was conducted using G*Power version 3.1.9.7 (two-tailed Fisher's exact test), based on the observed primary effect size.

RESULTS

Characteristics of study population

A total of 38 patients were included in this study. While cytoreductive nephrectomy was not performeda in nine (24%) patients, upfront primary tumor resection (PTR) was performed in 29 (76%) patients. The median age was 64 years; seven (18%) female and thirty-one (82%) male patients were included in the study (demographic and clinical data are shown in Table I).

Table I. Demographical and clinical features of the groups

Variables	All patients	PTR=No	PTR=Yes	p
No. of patients, (%)	38	9(23.7)	29(76.3)	-
Median age, years, (range)	64(40-82)	68(40-77)	63(42-82)	0.293
Gender, female-to-male, n(%)	7(18.4)/31(81.6)	3(33.3)/6(66.7)	4(13.8)/25(86.2)	0.322
Primary tumour size, n(%)				
T1	9(23.7)	3(33.3)[a]	6(20.7)[a]	**<0.001**
T2	17(44.7)	1(11.1)[a]	16(55.2)[b]	
T3	7(18.4)	0(0)[a]	7(24.1)[b]	
TX	5(13.2)	5(55.6)[a]	0(0)[b]	
IMDC risk skoru, n(%)				
Favorable	4(10.5)	0(0)[a]	4(13.8)[a]	**0.019**
Intermediate	20(52.6)	2(22.2)[a]	18(62.1)[b]	
Poor	14(36.8)	7(77.8)[a]	7(24.1)[b]	
Metastaz Alanı				
Lung	18(47.4)	4(44.4)	14(48.3)	0.999
Bone	15(39.5)	4(44.4)	11(37.9)	0.999
Liver	10(26.3)	2(22.2)	8(27.6)	0.999
Brain	2(5.3)	1(11.1)	1(3.4)	0.422
Median tanı LMR, (range)	2.66(0.18-9.21)	1.94(1.24-8.71)	2.97(0.18-9.21)	0.058
Median Nivo LMR, (range)	1.93(0.31-6.94)	2.07(0.84-3.82)	1.85(0.31-6.94)	0.736

All 38 patients were treated with sunitinib as the first-line treatment and nivolumab as the second-line treatment. The IMDC prognostic risk scores were higher in the PTR group (Table I). Metastatic sites were nearly balanced in each group. The primary tumor size was greater in the PTR group (Table I).

Oncological outcomes of the study population

At the time of data cutoff (February 2023), 10 and 4 deaths were reported in the PTR and non-PTR groups respectively. The objective response rate was higher in the PTR group (80% versus 22%; p= 0.003) (Table II). Compared with the non-PTR group, there was a 10-month advantage of PFS1 in the PTR arm (p= 0.006, Table II, Figure 1). While PFS2 for the non-PTR group was 54 months, the median PFS2 had not yet been reached in the PTR group (Table II, Figure 2). Mean PFS2 analysis was not different in both PTR and non-PTR groups (45 months (95%CI 32.6-56.5) in PTR group vs 35 months (95%CI 14.9-54.7) in non-PTR group, p=0.290). Although doubling the median OS with PTR, there was no statistically significant difference between two groups (Table I, Figure 3). Univariate analyses showed that factors associated with OS were poor. IMDC risk score (p=0.026), liver metastatic

Table II. Efficacy

Variables	All patients (n=38)	PTR=No (n=9)	PTR=Yes (n=29)	p
Overall Response Rate, n(%)	25(65.8)	2(22.2)	23(79.3)	**0.003**
Stable Disease, n (%)	11(28.9)	6(66.7)	5(17.2)	**0.009**
Progressive Disease, n (%)	2(5.3)	1(11.1)	1(3.4)	0.422
Complete Response , n (%)	10(26.3)	1(11.1)	9(31)	0.396
Partial Response, n (%)	15(39.5)	1(11.1)	14(48.3)	0.061
Overall Survival, median (months) (95%CI)	138.3(NA)	58.9(NA)	138.3(NA)	0.108
Progression-free survival 1, median (months) (95%CI)	12.17(5.27-19.06)	7.133(0-16)	16.7(4.34-29.07)	**0.006**
Progression-free survival 2, median (months) (95%CI)	54.1(18.59-89.61)	54.1(NA)	NA	0.290
1-year OS, %	86.7	77.8	89.7	-
2-year OS, %	75.3	64.8	78.9	-
5-year OS, %	58.3	0	66.3	-
1-year PFS2, %	74.9	62.5	78.5	-
2-year PFS2, %	60.6	62.5	62	-
5-year PFS2, %	38.5	0	51.6	-

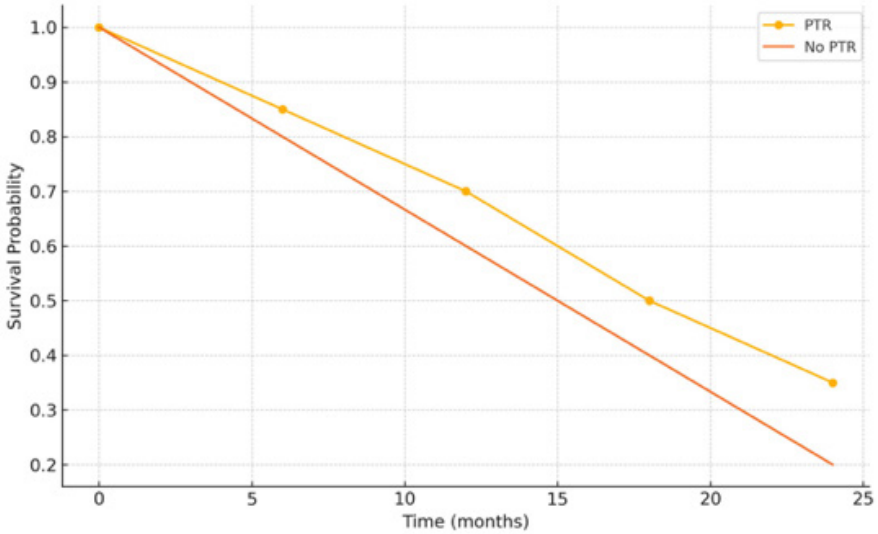


Figure 1. Progression Free Survival1 in patients who had PTR and no PTR

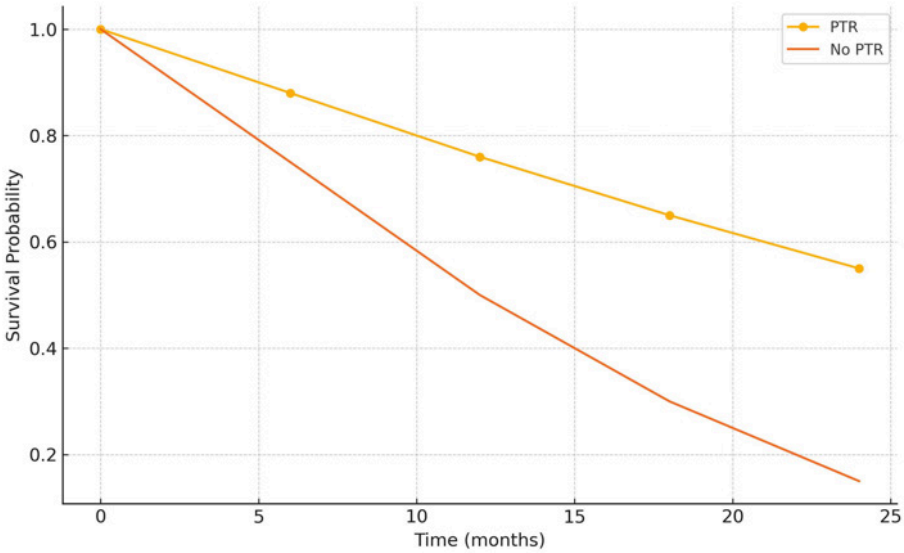


Figure 2. Progression Free Survival2 in patients who had PTR and no PTR

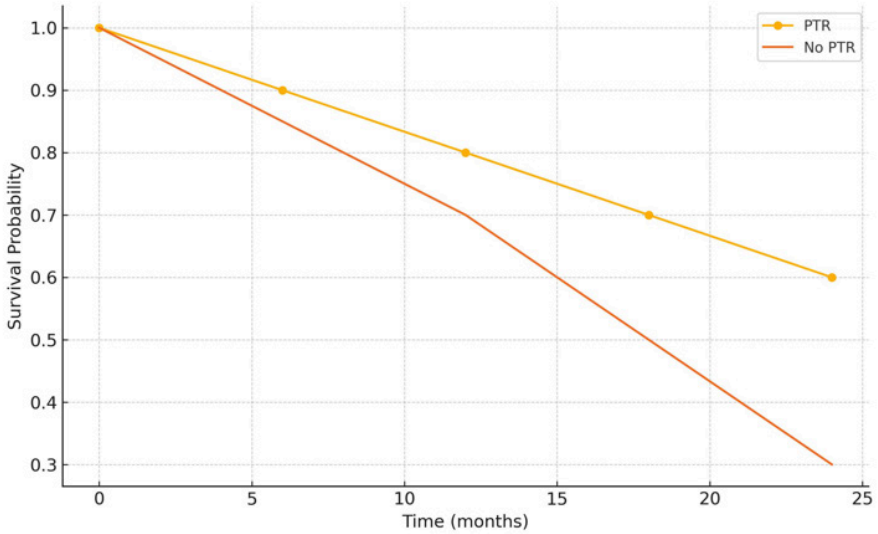


Figure 3. Overall Survival in patients who had PTR and no PTR

site (p=0.008), and PFS1 duration were shorter than the median PFS1 (p=0.003) (Table III). Factors associated with PFS2 were the liver metastatic site (p< 0.001) and shorter PFS1 (p=0.033) (Table III). On multivariable analyses, an OS benefit was observed in patients in the poor IMDC risk group (HR: 5.23; 95% CI, 1.07–25.50; p = 0.04), liver metastatic disease (HR: 16.16; 95% CI, 3.35–77.80; p = 0.001), and shorter PFS1 (HR: 22.54; 95% CI, 3.20–158.60; p = 0.002) (Table IV). PFS2 survival benefit was only observed in liver metastatic disease (p<0.001) and shorter PFS1 (p=0.011). Upfront cytoreductive nephrectomy was ineffective for OS (HR: 0.38; 95% CI, 0.11- 1.28, p= 0.12) and PFS2 (HR: 0.54; 95% CI, 0.17-1.71, p= 0.297) (Table III). Furthermore, the lymphocyte/monocyte ratio (LMR) at the start of immunotherapy had no prognostic effect on PFS2 or OS (Table III).

Table III. Univariate analysis of the factors associated with OS, PFS2

	Overall Survival		Progression-free Survival 2	
Variable	**HR (95%CI)**	**p**	**HR (95%CI)**	**p**
Female Gender	1,632(0,447-5955)	0,458	1,072(0,298-3,862)	0,915
Age	1(0,94-1,064)	0,997	1(0,949-1,054)	0,992
Size of Tumour				
T1	Reference	-	Reference	-
T2	0,849(0,21-3,426)	0,818	1,793(0,483-6,653)	0,383
T3	0,279(0,029-2,707)	0,271	0,302(0,031-2,931)	0,302
TX	1,965(0,396-9,75)	0,408	2,054(0,41-10,274)	0,381
IMDC skor				
Favorable or Intermediate	Reference	-	Reference	-
Poor	3,601(1,166-11,121)	**0,026**	2,037(0,762-5,443)	0,156
Lung metastasis	1,071(0,358-3,2)	0,903	0,806(0,3-2,166)	0,668
Bone metastasis	1,414(0,472-4,239)	0,536	0,851(0,303-2,384)	0,758
Liver metastasis	4,435(1,483-13,263)	**0,008**	6,964(2,398-20,227)	**<0,001**
PTR=Yes	0,385(0,116-1,285)	0,121	0,542(0,172-1,714)	0,297
PFS1≤12.17	9,832(2,137-45,228)	**0,003**	3,431(1,105-10,652)	**0,033**
Nivo LMR ≤1.93	1,429(0,475-4,303)	0,525	1,136(0,422-3,059)	0,801

Table IV. Multivariate analysis of the factors associated with OS, PFS2

	Overall Survival		Progression-free Survival 2	
Variable	**HR (95%CI)**	**p**	**HR (95%CI)**	**p**
IMDC skor				
Favorable or Intermediate	Reference	-	Reference	-
Poor	5,232(1,073-25,506)	**0,041**	2,347(0,801-6,874)	0,120
Liver metastasis	16,165(3,358-77,809)	**0,001**	15,672(4-61,398)	**<0,001**
PTR=Yes	1,726(0,318-9,358)	0,527		
PFS1≤12.17	22,545(3,205-158,603)	**0,002**	5,302(1,468-19,144)	**0,011**

DISCUSSION

Patients with advanced renal cell carcinoma have a 5-year mortality rate of 85%. Following advances in diagnostic testing, the incidence of patients diagnosed with RCC has rapidly increased over the past decade. The best therapeutic approaches to improve the survival outcomes of RCC have recently changed. However, the value of PTR in metastatic treatment remains controversial. The conflict between CARMENA and SWOG8949 and the EORTC trials hampered routine PTR performance (10,17,18). Recently it was reported in the SURTIME trial that deferred PTR with sunitinib in advanced disease showed better OS outcomes with 17 months benefit (11). However, these data were from the previous standard of care. A new standard of care for advanced RCC is the checkpoint inhibitor of immunotherapy (IO) and TKI combination. The PTR ratios in these IO-TKI trials were 82.6% in KN426 (12), 68.7% in CM9ER (13), 82% in CM214 (14), 73.8% in CLEAR (15), 54% in the IMDC-IPI/NIVO group, and 55% in the IMDC-TKI group (19). Most of the patients had undergone PTR during upfront treatment. However, in these trials, subgroup analysis of survivals in the PTR group compared to the non-PTR group was not performed, except in the IMDC trial (19). In our trial, different from the standard of care, the study population had to receive TKI as the first line treatment and nivolumab as the second line treatment due to the reimbursement conditions. We evaluated the survival outcome differences between the PTR and non-PTR groups that received sequential TKI and nivolumab. In our study, the ORR was higher in the PTR group (79% in the PTR group vs. 22% in the non-PTR group p=0.003) than in the CARMENA (27% vs 29%, respectively) (10) and EORTC trials (19% vs 12%, respectively) (18).

The median PFS-TKI (mPFS1) of the PTR group was 17 months vs. 7 months in the non-PTR group (p=0.006), and the median PFS-nivo (mPFS2) was not reached in PTR group vs. 54 months in non-PTR group (p=0.290). In the CARMENA trial (10) mPFS was the same in both

arms and shorter than our survival results (PFS-TKI 8.3 months vs PFS-TKI+PTR 7.2 months (HR:0.92, 95%CI 0.67-1.00)). The EORTC trial (18) reported time to progression (TTP), which was longer in the IFN+PTR group (HR:0.60; 95%CI 0.36-0.97) than in the IFN alone group. The primary end point of our study was that median OS (mOS) was found in favor of PTR with nonsignificant 6.5 years survival benefit which was longer than TKI and IFN trials (CARMENA: 18 months in non-PTR vs 14 months in PTR, HR:0.89 (95%CI 0.71-1.1); IMDC-TKI: 13 months vs 25 months, respectively, HR:0.72 (95%CI 0.67-0.78); SWOG8949: 8 months vs 11 months respectively, p=0.012). mOS results of the IMDC-IPI/NIVO trial were similar to our findings: 54 months in the PTR group vs 22 months in the non-PTR group, HR:0.61 (95%CI 0.41-0.90).

In the current analysis, IMDC risk stratification emerged as the primary determinant of clinical outcomes in the study population. The disparities noted between the PTR and non-PTR groups were predominantly affected by the allocation of IMDC risk categories, with a greater percentage of poor-risk patients in the non-PTR cohort. This discovery highlights the essential function of IMDC risk assessment in prognostic evaluation and therapy decision-making for metastatic clear cell RCC. The increasing clinical applicability of the IMDC score, in addition to its recognized prognostic significance, necessitates additional examination, especially regarding patient selection for cytoreductive nephrectomy. Our findings indicate that IMDC risk criteria may assist in identifying patients who are more likely to benefit from first surgical intervention, hence preventing unnecessary morbidity in high-risk patients.

Recent studies have highlighted the prognostic relevance of systemic inflammatory markers in RCC. In particular, LMR has been proposed as an easily accessible and cost-effective marker that reflects the host immune response and tumor-promoting inflammation. A low LMR has been associated with poor survival outcomes in various malignancies, including RCC. Several retrospective studies have demonstrated that low pretreatment LMR is significantly correlated with worse progression-free survival and overall survival in patients receiving tyrosine kinase inhibitors or immune checkpoint inhibitors (20, 21). However, in our study, the baseline LMR measured at the initiation of immunotherapy did not show any significant predictive or prognostic value. This discrepancy might be due to the limited sample size, retrospective nature, and heterogeneous timing of the LMR assessment. Prospective studies are warranted to better define the role of LMR in treatment sequencing and patient stratification.

Limitations

The retrospective design and single-center nature of this study should be considered when interpreting the findings. In addition, the imbalance in IMDC risk groups between the PTR and non-PTR cohorts represents an important consideration in the evaluation of survival outcomes. Further prospective studies are needed to confirm these conclusions.

CONCLUSION

In conclusion, although upfront cytoreductive nephrectomy was associated with a higher objective response rate and numerically improved survival outcomes, its effect on PFS after IO and OS was not statistically significant in our cohort. Nevertheless, given its retrospective design and limited sample size, these results should be interpreted with caution. In this context, IMDC risk stratification appears to be a key determinant of clinical outcomes and may play an important role in guiding patient selection for cytoreductive nephrectomy. Our findings underscore the need for prospective, randomized studies to clarify the role of PTR in the era of sequential TKI–IO therapy. Moreover, the integration of immunological markers such as LMR may enhance prognostic modeling but remains to be validated in larger real-world populations.

Ethics Committee Approval

This research complies with all the relevant national regulations and, institutional policies, is in accordance with the tenets of the Helsinki Declaration, and has been approved by the University of Health Sciences Antalya Training and Research Hospital Ethical Committee (approval number: 2023/11/11).

Informed Consent

Owing to the retrospective nature of the study, informed consent was not required and was therefore waived. This was explicitly stated in the study protocol and approved by the Institutional Ethics Committee.

Author Contributions

Concept – E.A.K.; Design – D.K.S.; Supervision – D.K.S.; Resources – E.A.K., D.K.S.; Materials – E.A.K.; Data Collection and/or Processing – E.A.K.; Analysis and/ or Interpretation – D.K.S.; Literature Search – E.A.K.; Writing Manuscript – E.A.K.; Critical Review – D.K.S.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

The authors declared that this study has received no financial support.

Prior Presentation

This study was not presented at any congress as an oral or poster presentation.

Declaration of AI and AI-Assisted Technologies in the Writing Process: The authors declare that no artificial intelligence (AI) or AI-assisted technologies were used in the writing, editing, or preparation of this manuscript.

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