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Oncological outcomes of surgery for isolated retroperitoneal recurrence in renal cancer patients after radical nephrectomy

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Abstract

Aims: Isolated retroperitoneal recurrence (IRR) in renal cancer patients after radical nephrectomy (RN) is a rare event and poses a therapeutic dilemma. We evaluated oncologic outcomes in surgically treated patients with IRR and established prognostic factors associated with survival. The benefit of metastasis-directed therapy (MDT) in those with clinical progression after extirpation of IRR was assessed.

Methods: This was a retrospective single-institutional study in which 60 renal cancer patients after previous RN underwent surgery for suspicion of IRR within the period of 2004-2019; in 55 of them, RCC recurrence was histologically confirmed. No patient had distant metastatic disease at the time of IRR diagnosis. In cases of clinical progression after IRR surgery, MDT (metastasectomy, stereotactic radiotherapy) was selectively used. Kaplan-Meier curves were used to estimate survival outcomes. Univariable and multivariable Cox proportional hazards regression analyses were used to evaluate associations between clinicopathological parameters and cancer-specific survival.

Results: Median age at IRR diagnosis was 64 years (range 23−81). IRR was diagnosed at a median of 42 months (IQR 19−99) after RN. Surgical complications of grade 3-5 after IRR extirpation were rare (7%). Median follow-up time was 50 months (IQR 19−80).

Five-year recurrence-free survival and cancer-specific survival rates were 32% and 66%, respectively. Radiographic progression was observed in 34 (62%) patients at a median of 11 months after IRR surgery, out of which 22 patients (40%) underwent MDT. When compared with 12 patients without MDT, the MDT patients had a prolonged median time to systemic treatment of 58 (vs. 16 months), and median cancer-specific survival of 88 (vs. 46 months). Upon multivariable analysis, the interval from nephrectomy ≤12 months (HR 7.77), tumour grade 3-4 (HR 13.24) and female sex (HR 7.42) were determined to be independent prognostic factors of cancer-related mortality.

Conclusion: Aggressive surgical therapy of IRR is feasible with relatively low morbidity. More than half of the patients experience long-term survival. The interval from nephrectomy to IRR less than 12 months, tumour grade 3-4 and female sex were negative prognostic predictors. In the case of progression, metastasis-directed therapy may prolong the interval to initiation of systemic treatment.

Keywords: Renal cancer; Nephrectomy; Local neoplasm recurrence; Metastasis; Metastasectomy

1. Introduction

Approximately 20% to 40% of patients with renal cancer experience disease progression despite radical nephrectomy, with the progression rate as high as 50% in high-risk patients [1]. The vast majority of the cases relapse in distant organs; isolated retroperitoneal recurrences (IRR) are, in

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comparison, relatively rare in 1% to 3% of cases [2,3]. The "true local recurrence" is defined as relapse confined to the renal fossa. However, most retrospective studies follow broader definitions to also include recurrences in regional lymph nodes and/or ipsilateral adrenal glands [3−5].

IRR poses a therapeutical challenge as these patients have a high risk of metastatic progression and locoregional surgical retreatment may be demanding after previous surgery [3−7]. Only a few retrospective studies reported on outcomes and prognosis in this subgroup of patients [8]. In the largest study, Thomas et al. reported a 5-year cancer-specific survival (CSS) rate of 52% [5]. Importantly, in case of oligometastatic progression, further metastasis-directed therapy (MDT) such as metastasectomy or stereotactic radiotherapy (SBRT), seems to be of value in selected patients and may lead to postponement of systemic therapy [9].

We present one of the largest cohorts of patients surgically treated for IRR with frequent use of MDT in case of progression and long-term follow-up. We assessed prognostic factors, value of imaging methods, complications of surgery, oncologic outcomes, and potential benefits of MDT.

2. Methods

A total of 60 patients with renal cancer after radical nephrectomy had been diagnosed with clinical IRR during the course of their disease and subsequently underwent extirpative surgery within the period of 2004-2019. This cohort of patients was identified from the institutional cancer registry. The study has been approved by the Ethical Committee of Masaryk Memorial Cancer Institute.

IRR was defined as a recurrence of renal cancer in the renal fossa (RF), lymph nodes (LN) or ipsilateral adrenal gland (IAG) in the absence of distant metastases. In 55 patients with IRR, the renal cancer relapse was histologically confirmed, and this cohort forms the core of the study.

Prognostic factors collected at the time of IRR diagnosis were haemoglobin (Hb) level, Karnofsky performance score, thrombocyte and neutrophil count, calcium (Ca) levels and time from diagnosis to treatment for IMDC risk group assignment. In addition, other potential prognostic factors were collected, such as neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammatory index (SII; neutrophil * platelet / lymphocyte) or C-reactive protein (CRP).

All patients had at minimum computed tomography (CT) of the abdomen and the chest X-ray before surgery; in the last decade, a chest CT has replaced the chest X-ray. Seventeen patients (28%) had also positron emission tomography (PET) at the time of diagnosis of IRR.

2.1. Surgical procedure

The most frequent surgical approach for resection of IRR was extraperitoneal lumbotomy, usually performed through the 10th or 11th intercostal space. All patients had open surgery. Regional lymph node dissection was performed in all cases with suspicion of IRR located in LN. In other cases, the decision to perform lymph node dissection was left to the discretion of the surgeon.

The clinical progression after IRR surgery was defined by abnormal radiographic or clinical findings leading to detection of relapse. Progression was described as local relapse if the recurrence occurred in the IRR space. Systemic relapses were divided into oligometastatic (maximum of three metastases) and non-oligometastatic (more than three metastases). Metastasis-directed therapy included treatments such as metastasectomy, SBRT, or ablative therapy (cryotherapy or radiofrequency ablation).

2.2. Statistics

Kaplan-Meier curves were used to estimate 5-year recurrence-free (RFS), cancer-specific (CSS), and systemic therapy-free survival (STFS) rates and were compared between cohorts using log-rank test. RFS was calculated as the time from the extirpation of IRR to the date of recurrence or renal cancer-related death. STFS was calculated as the time from the extirpation of IRR to the date of initiation of systemic salvage treatment. CSS was calculated as the time from the extirpation of IRR to the date of renal cancer-related death. Univariable and multivariable Cox proportional hazards regression analyses were used to evaluate associations between clinicopathological parameters and oncological outcomes. Results were considered significant if P-value <0.05 was achieved. Statistical analysis was performed using SPSS (version 25) and STATA (version 14.2) software.

3. Results

3.1. Study cohort characteristics at the time of radical nephrectomy

Sixty patients after previous radical nephrectomy for RCC, underwent surgery for suspicion of IRR during the course of their disease, which was histologically confirmed in 55 of the patients. Table 1 shows the patients' characteristics. Men and women represented 67% and 33% of the patients, respectively. Median age was 64 years (range 23 −81). In almost 80% of nephrectomy specimens, the histology was clear cell renal cancer (ccRCC). Thirty-eight (69%) patients had nephrectomy in other hospitals and were referred to our institution with diagnosed IRR.

3.2. Clinical characteristics at the time of IRR diagnosis

IRR was diagnosed at a median of 42 months (IQR 19 −99) after radical nephrectomy. Table 2 shows the clinical data of patients at the time of IRR diagnosis. IRR was located in the renal fossa, adrenal gland and lymph nodes in 17 (31%), 15 (27%) and 23 (42%) cases, respectively. Patients with nodal IRR had higher grade disease (grade 3-4

Table 1
Demographic data and clinical characteristics of the cohort at the time of radical nephrectomy.

N (%)/median (5th; 95th percentile)		Total N = 55	Renal fossa N = 17	Lymph node N = 23	Ipsilateral adrenal N = 15	P[a]
Gender	Male	37 (67.3)	12 (70.6)	17 (73.9)	8 (53.3)	0.403
	Female	18 (32.7)	5 (29.4)	6 (26.1)	7 (46.7)	
Age		64.0 (56.0; 70.0)	68.0 (65.0; 72.0)	62.0 (56.0; 68.0)	62.0 (54.0; 74.0)	0.032
Performance status	ECOG PS 0	47 (85.5)	13 (76.5)	21 (91.3)	13 (86.7)	0.427
	ECOG PS 1	8 (14.5)	4 (23.5)	2 (8.7)	2 (13.3)	
Charlson comorbidity index:	0–1	21 (38.2)	4 (23.5)	10 (43.5)	7 (46.7)	0.284
	2–3	21 (38.2)	6 (35.3)	10 (43.5)	5 (33.3)	
	≥4	13 (23.6)	7 (41.2)	3 (13.0)	3 (20.0)	
Time from nephrectomy		42.0 (17.0; 102.0)	40.0 (26.0; 102.0)	26.0 (7.0; 63.0)	62.0 (24.0; 108.0)	0.139
Histology	Clear cell	39 (70.9)	14 (82.4)	15 (65.2)	10 (100.0)	0.073
	Papillary t. 2	9 (16.4)	3 (17.6)	6 (26.1)	0 (0.0)	
	Other	2 (3.6)	0 (0.0)	2 (8.7)	0 (0.0)	
	Unknown	5 (9.1)				
Histology	ccRCC	39 (70.9)	14 (82.4)	15 (65.2)	10 (100.0)	0.028
	non-ccRCC	11 (20.0)	3 (17.6)	8 (34.8)	0 (0.0)	
	Unknown	5 (9.1)				
Tumour grade	1–2	18 (32.7)	9 (64.3)	6 (31.6)	3 (37.5)	0.158
	3–4	23 (41.8)	5 (35.7)	13 (68.4)	5 (62.5)	
	Unknown	14 (25.5)				
Staging at the time of nephrectomy: pT	pT1	18 (32.7)	7 (46.7)	8 (38.1)	3 (30.0)	0.928
	pT2	9 (16.4)	3 (20.0)	4 (19.0)	2 (20.0)	
	pT3	19 (34.5)	5 (33.3)	9 (42.9)	5 (50.0)	
	Unknown	9 (16.4)				
Staging at the time of nephrectomy: pN	pN0	1 (1.8)	0 (0.0)	1 (4.3)	0 (0.0)	0.079
	pN1	6 (10.9)	0 (0.0)	5 (21.7)	1 (7.1)	
	pNx	47 (85.5)	17 (100.0)	17 (73.9)	13 (92.9)	
	Unknown	1 (1.8)				
Thrombus	No	39 (70.9)	12 (75.0)	20 (90.9)	7 (63.6)	0.152
	Yes	10 (18.2)	4 (25.0)	2 (9.1)	4 (36.4)	
	Unknown	6 (10.9)				

ccRCC = clear cell renal cancer.
[a] Statistical difference between groups tested by ML chi-square test for categorical variables and by Kruskal-Wallis test for continuous variables.

in 75%), and more frequent non-ccRCC histology. The median size of IRR was 2.8 cm (IQR 2.1–3.9). According to Heng risk grouping, the patients were classified into favourable, intermediate, and poor risk groups as 54%, 44%, and 2% of patients at the time of IRR surgery, respectively.

3.3. Imaging of IRR

Preoperative CT was false positive in 5 out of 60 (8%) operated patients. The positive predictive value of CT was 92%. The 5 false-positive patients had suspicious masses of 1.1, 2.2, 2.8, 3.3, and 3.7 cm, respectively. Definitive histology showed suture granuloma in the area of renal vessels in 4 cases and desmoid in 1. Eighteen patients had preoperative PET/CT, for which the results were true positive in 12, false negative in 5, and false positive in one of them. Sensitivity and PPV were 71% and 92%, respectively.

3.4. Surgical procedure

All surgeries were performed with macroscopic negative margins; a microscopic positive margin was found positive in 1 case (2%). Median operative time was 150 minutes (IQR 118–195) and median blood loss was 200 ml (IQR 100–500).

Complications were seen in 17 patients (31%), the most frequent being transfusion; four of them (7%) experienced a grade 3-5 complication. One patient died due to multiorgan failure on day 65 (grade 5), and there were single cases of renal insufficiency (grade 4a), adrenal insufficiency (grade 4a) and percutaneous drainage of the abscess in the renal fossa (grade 3a).

3.5. Oncologic outcomes

Median follow-up time was 50 months (IQR 19–80). Figure 1 shows the course of the disease in 55 patients after extirpation of IRR. Clinical progression was observed in 34 (62%) patients at a median of 11 months after IRR surgery; for the whole cohort, 5-year RFS was 32%, with a median time to recurrence of 25 months (Fig. 2A). The relapse was local in 11 (20%) and systemic in 23 (42%) cases (14 oligometastatic and 9 non-oligometastatic). Five-year RFS was not significantly different between patients with IRR

Table 2
Clinical characteristics at the time of diagnosis of isolated retroperitoneal recurrence.

N (%)/median (5th; 95th percentile)		Total N = 55	Renal fossa N = 17	Lymph node N = 23	Ipsilateral adrenal N = 15	P[a]
Number of tumours at the time of recurrence	1	33 (60.0)	9 (52.9)	12 (52.2)	12 (80.0)	0.160
	≥2	22 (40.0)	8 (47.1)	11 (47.8)	3 (20.0)	
Location of recurrence	Renal fossa	17 (30.9)				
	Lymph node	23 (41.8)				
	Adrenal	15 (27.3)				
Size of the tumour		28.0 (20.0; 40.0)	29.0 (23.0; 32.0)	25.0 (20.0; 40.0)	29.5 (23.0; 50.0)	0.742
Heng risk groups	Favourable	26 (47.3)	6 (40.0)	12 (57.1)	8 (66.7)	0.417
	Intermediate	21 (38.2)	9 (60.0)	8 (38.1)	4 (33.3)	
	Poor	1 (1.8)	0 (0.0)	1 (4.8)	0 (0.0)	
	Unknown	7 (12.7)				
Neutrophile-to-lymphocyte ratio (NLR)	≤3	32 (58.2)	9 (60.0)	16 (76.2)	7 (53.8)	0.354
	>3	17 (30.9)	6 (40.0)	5 (23.8)	6 (46.2)	
	Unknown	6 (10,9)				
Calcium	Normal	39 (70.9)	13 (81.3)	16 (76.2)	10 (83.3)	0.869
	Abnormal	10 (18.2)	3 (18.8)	5 (23.8)	2 (16.7)	
	Unknown	6 (10.9)				
Hemoglobin	Normal	43 (78.2)	11 (64.7)	19 (82.6)	13 (92.9)	0.131
	Abnormal	11 (20)	6 (35.3)	4 (17.4)	1 (7.1)	
	Unknown	1 (1.8)				
CRP	≤5	15 (27.3)	9 (81.8)	4 (33.3)	2 (50.0)	0.054
	>5	12 (21.8)	2 (18.2)	8 (66.7)	2 (50.0)	
	Unknown	28 (50.9)				
SII	≤600	28 (50.9)	7 (46.7)	15 (71.4)	6 (46.2)	0.210
	>600	21 (38.2)	8 (53.3)	6 (28.6)	7 (53.8)	
	Unknown	6 (10.9)				
Type of the tumour	Clear cell	43 (78.2)	12 (70.6)	16 (69.6)	15 (100.0)	0.065
	Papillary t. 2	7 (12.7)	3 (17.6)	4 (17.4)	0 (0.0)	
	Other	5 (9.1)	2 (11.8)	3 (13.0)	0 (0.0)	
Type of the tumour	ccRCC	43 (78.2)	12 (70.6)	16 (69.6)	15 (100.0)	0.012
	non-ccRCC	12 (21.8)	5 (29.4)	7 (30.4)	0 (0.0)	
Tumour grade	1–2	22 (40)	10 (66.7)	5 (25.0)	7 (63.6)	0.022
	3–4	24 (43.6)	5 (33.3)	15 (75.0)	4 (36.4)	
	Unknown	9 (16.4)				

ccRCC = clear cell renal cancer; CRP = C-reactive protein; SII = systemic immune-inflammatory index.
[a] Statistical difference between groups tested by ML chi-square test for categorical variables and by Kruskal-Wallis test for continuous variables.

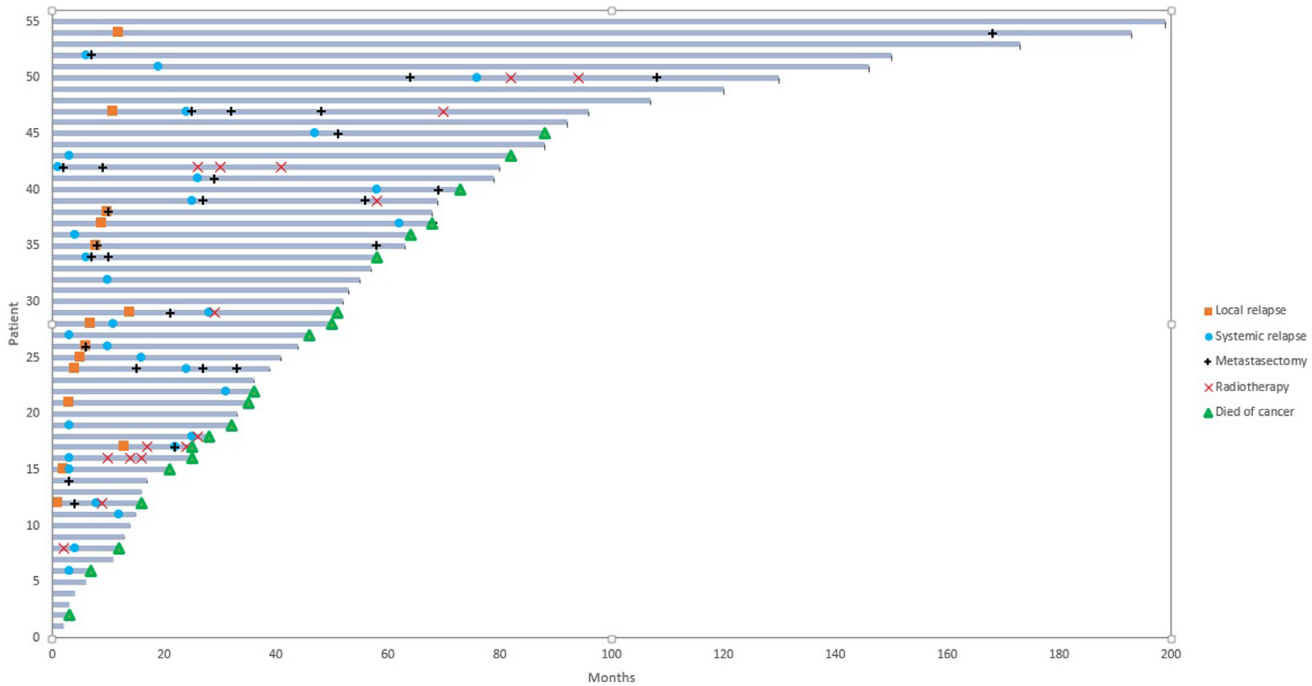

Fig. 1. Swimmer plot representation of the individual patients' course of the disease.

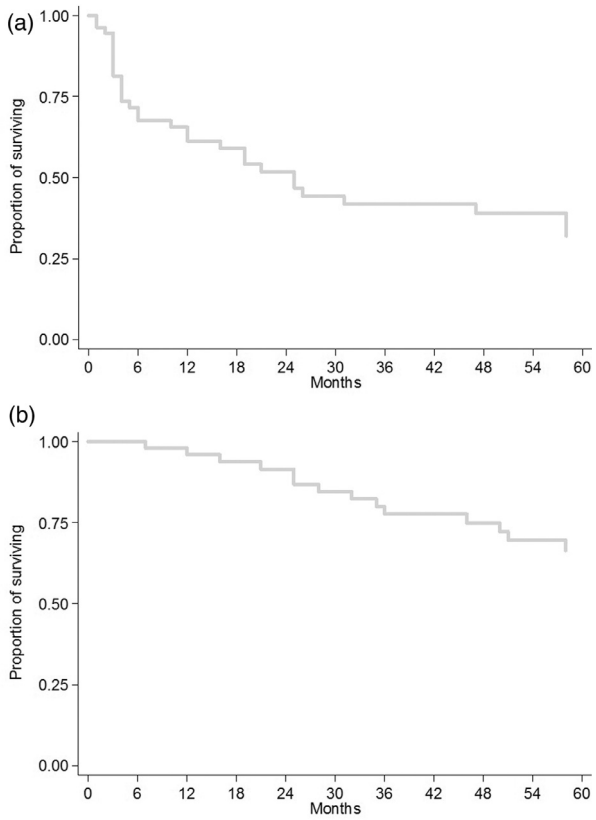

Fig. 2. (A) Recurrence-free survival and (B) cancer-specific survival for the complete patient cohort.

located in RF, LN and IAG with respective survival rates of 45%, 22% and 29% ($P = 0.204$).

Overall, 19 patients died of renal cancer after a median of 36 months (IQR 25−61). One-, 3- and 5-year CSS were 96%, 78% and 66%, respectively (Fig. 2B). Five-year OS was 62%. Patients with IRR located in RF, LN and IAG had 5-year CSS of 75%, 57% and 74%, respectively ($P = 0.560$). Oligometastatic type of progression was associated with the best outcomes. The 5-year CSS rate was 71%, with median survival not reached. Respective 5-year CSS in local and non-oligometastatic relapses were 49% and 23% ($P = 0.230$) (Fig. 3).

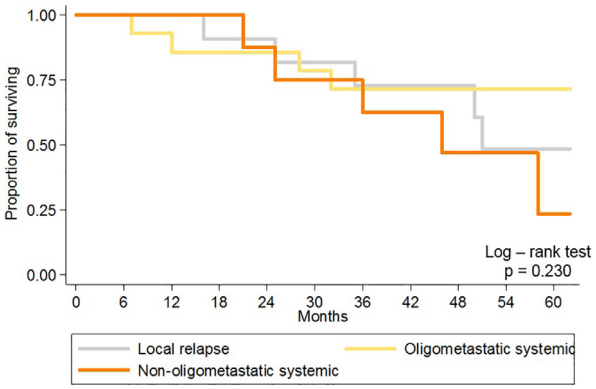

Fig. 3. Cancer-specific survival according to the type of relapse (local/oligometastatic/non-oligometastatic)

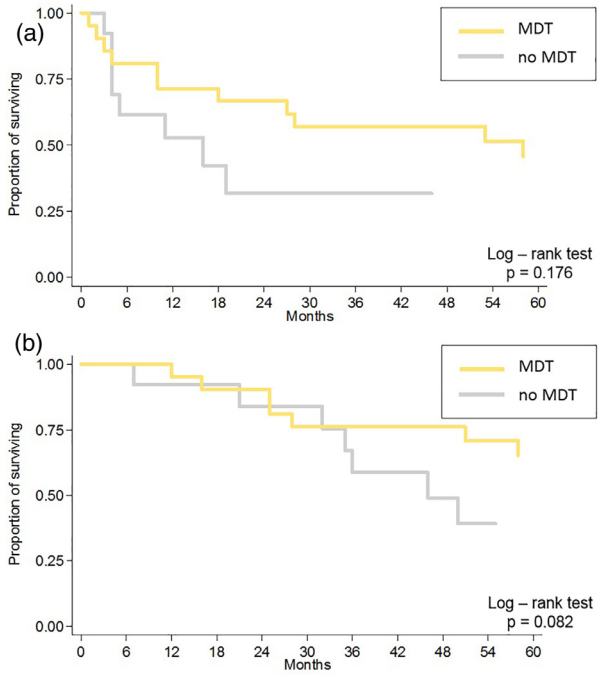

Fig. 4. (A) Systemic therapy-free survival and (B) cancer-specific survival according to the use of metastasis-directed therapy (MDT) in case of clinical progression after surgery for isolated retroperitoneal recurrence.

Out of 34 patients with clinical progression after IRR surgery, 22 patients (40%) underwent MDT. Figure 4 shows that, when compared to 12 patients without MDT, this group had prolonged median time to systemic treatment of 58 vs. 16 months (Fig. 4A), and median CSS times of 88 vs. 46 months (Fig. 4B). Five-year CSS in patients with MDT and without MDT were 65% and 39% ($P = 0.082$), respectively (Fig. 4B). The most frequent MDT was surgery in 18 patients, with a median time of 24 months after IRR extirpation. In total, 31 metastasectomies were performed with a median number of one per patient (range 1−3). Ten patients underwent stereotactic radiotherapy and 2 patients underwent ablative therapy, with median times of 25 and 8 months after IRR surgery, respectively.

3.6. Systemic treatment

No patients had neoadjuvant therapy before IRR surgery. Five patients received adjuvant treatment (interferon-alpha in 3 cases and tyrosine kinase inhibitor [TKI] in 2 cases). Palliative systemic treatment was started in 24 patients (44%), and a 5-year STFS rate was 56%. The analysis did not show any significant differences between subgroups with IRR located in RF, LN or IAG; the respective STFS rates were 52%, 46% and 72% ($P = 0.3$).

In general, the type of medication used reflected the advances in systemic treatment. Cytokine therapy was dominant in the period before 2006 (3 cases), TKI thereafter (22 cases), with a minority of patients receiving immune checkpoint inhibitors (ICI) from 2017 onwards (6 cases).

Table 3
Univariate Cox regression analysis for clinicopathological factors associated with cancer-specific survival.

	Risk group	HR (95% CI)	P^a
Gender	Female	0.95 (0.37; 2.45)	0.917
Age	Age/10 yrs	1.08 (0.75; 1.57)	0.669
Performance status	Yes	2.44 (0.65; 9.14)	0.184
Charlson Comorbidity index	0−1	1 (. . .)	
	2−3	1.20 (0.42; 3.42)	0.733
	≥4	1.61 (0.51; 5.10)	0.418
Time from nephrectomy	>12 mo	0.22 (0.08; 0.57)	0.002
	>24 mo	0.33 (0.13; 0.81)	0.016
	≤12 mo	4.54 (1.54; 13.42)	0.006
	13−36 mo	2.38 (0.83; 6.80)	0.105
	>36 mo	1 (. . .)	
Staging at the time of nephrectomy: pT	pT2-4	1.46 (0.50; 4.31)	0.489
	pT3-4	0.96 (0.35; 2.75)	0.962
Staging at the time of nephrectomy: pN	pN1	0.62 (0.18; 2.14)	0.447
Number of tumours at the time of recurrence	≥2	0.78 (0.30; 2.07)	0.623
Location of recurrence	Renal fossa	1.69 (0.47; 6.01)	0.421
	Lymph node	2.31 (0.73; 7.29)	0.154
	Adrenal	1 (. . .)	
Size of the tumour	>3 cm	1.45 (0.58; 3.60)	0.422
	Change by 1 cm	1.07 (0.82; 1.39)	0.591
Type of the tumour	non-ccRCC	0.87 (0.29; 2.63)	0.799
Tumour grade	3−4	3.73 (1.18; 11.80)	0.025
Heng risk groups	Intermediate	1.18 (0.44; 3.19)	0.745
Neutrophile-to-lymphocyte ratio (NLR)	>3	1.31 (0.48; 3.55)	0.598
CRP	>5	2.39 (0.57; 10.02)	0.234
SII	>600	1.67 (0.64; 4.34)	0.292
Hemoglobin	Abnormal	2.19 (0.71; 6.78)	0.174

HR = Hazard ratios obtained by Cox - Proportional hazard model; ccRCC = clear cell renal cancer; CRP = C-reactive protein; SII = systemic immune-inflammatory index.
[a] Statistical significance of HR.

Table 4
Multivariate Cox regression analysis for clinicopathological factors associated with cancer-specific survival.

	Risk group	HR (95% CI)	P[a]
Gender	Female	7.42 (1.60; 34.36)	0.010
Age	Age/10 yrs	1.00 (0.95; 1.06)	0.942
Time from nephrectomy	<12 mo	7.77 (1.50; 40.20)	0.014
Tumour grade	3−4	13.24 (2.08; 84.30)	0.006
Hemoglobin:	Abnormal	3.31 (0.66; 16.65)	0.147
Location of recurrence	Renal fossa	2.72 (0.36; 20.58)	0.333
	Lymph node	0.65 (0.10; 4.38)	0.654
	Adrenal	1 (. . .)	

HR − Hazard ratios obtained by Cox - Proportional hazard model.
[a] Statistical significance of HR.

3.7. Predictors of CSS

Univariable Cox proportional hazards regression analysis showed the interval from nephrectomy to IRR ≤12 months (HR 4.54; 95% CI 1.54−13.42, $P = 0.006$) and grade 3-4 (HR 3.73; 95% CI 1.18−11.8, $P = 0.025$) were associated with higher risk of dying of renal cancer (Table 3). Multivariable analysis showed that both intervals from nephrectomy ≤12 months (HR 7.77; 95% CI 1.50 −40.20, $P = 0.014$), grade 3-4 (HR 13.24; 95% CI 2.08 −84.30, $P = 0.006$) and female sex (HR 7.42; 95% CI 1.60 −34.36, $P = 0.010$) were independent prognostic factors of cancer-related mortality (Table 4).

4. Discussion

Local recurrence after radical nephrectomy is a rare situation, seen in 1% to 3% patients [2,3]. The mainstay of treatment is aggressive surgical excision in appropriately selected patients with long-term survival in about half of cases [2−7,10]. We report oncological outcomes and predictors of survival in a relatively large cohort of patients from a single institution with IRR after previous nephrectomy for renal cancer. Our results support the principle of meticulous surgical resection of IRR and MDT in case of clinical progression [8]. Twenty-one patients (38%) remained free of the disease after surgery and the 5-year CSS rate was 66%.

In cases of oligometastatic progression after IRR extirpation, a limited retrospective data reinforces the use of further metastasectomies and SBRT, deferring the need for systemic salvage treatment [4,5,10]. This is consistent with the approach to metastatic renal cancer in general, where even without high-quality data from randomized trials, it is generally recommended to perform metastasectomy in patients that are good surgical candidates, have limited metastatic burden, and the surgery is considered technically feasible [11−14].

In our study, 34 (68%) of patients experienced progression after IRR surgery. Twenty-two (40%) of patients underwent further MDT, significantly prolonging the time to initiation of systemic treatment in comparison to those without MDT, with median times of 58 and 16 months, respectively. However, it cannot be determined from the study, if the favourable outcome is a result of surgical therapy, indolent tumour biology or selection bias, as younger patients with better performance status and limited disease burden tend to undergo MDT.

In the largest retrospective study of 102 patients with IRR, Thomas et al. reported metastatic progression in 60 patients, out of which 16 underwent metastasectomy [5]. For the whole cohort, 5-year CSS rate was 52%. The risk factors of cancer-specific death were stage pN1 at prior nephrectomy and maximum diameter of IRR mass. Our study confirms these outcomes, with 5-year CSS rate of 66%. Interestingly, in the current study, different independent predictors of survival were identified: time from nephrectomy to IRR shorter than 12 months, grade 3-4 and female sex. In contrast to the aforementioned study, tumour size was not a significant predictor. However, the median

size of the tumour was smaller in our study (2.8 cm vs. 4.5 cm). These data support the adherence to close follow-up of high-risk patients after nephrectomy, with the intention to diagnose IRR when it is of relatively small size and asymptomatic.

The largest multicentric series of isolated lymph node recurrence was reported by Russell et al. [15]. Five-year PFS was 35%, which was favourable to 22% in our study. The strongest negative predictor was the interval from nephrectomy to recurrence (<12 months). It is noteworthy that at the time of initial staging of renal cancer, we frequently see false positive findings with clinically enlarged nodes having transverse diameter <20 mm, due to the inflammatory reaction associated with advanced tumours [16]. This is not the case at the time of IRR when the classic criteria of enlarged nodes (transverse diameter >10 mm) may be applied. Nevertheless, we experienced 5 cases (8%) of false positive CT findings with a median diameter of 28 mm; in most cases, the suture granuloma was histologically confirmed.

Heng risk groups are extremely useful in the metastatic setting to inform prognoses and guide therapy [17]. To our knowledge, our study is the first to assess its applicability to the scenario of IRR. In our cohort, no Heng risk factor or Heng risk group showed significance in relation to progression. The same was true for inflammatory prognostic predictors, such as C-reactive protein, neutrophil-to-leukocyte ratio, or SII. However, due to the small number of patients included in the study, the analysis was underpowered to detect differences in outcomes by Heng risk groups or other laboratory biomarkers.

Our study has several limitations. It is a retrospective study from a tertiary referral centre with a limited number of highly selected patients, which were good surgical candidates. The results should be interpreted with caution, because it is a heterogenous cohort with varying clinical behavior using a broad definition of IRR. The retrospective nature of the study and no comparison with other therapeutic approaches do not allow drawing strong conclusions from the study, as it is impossible to know if the favourable oncological outcomes resulted from aggressive surgical therapy or rather from indolent cancer biology. Moreover, this study cannot answer the question if favourable patients with small local recurrence would not have similar long-term survival with medical treatment only. The patients were treated over a long period of time, during which we witnessed a true paradigmatic change of systemic treatment. Recently, ICI-based combination therapy for metastatic renal cancer showed high response rates up to 71% and excellent survival, especially in the favourable IMDC risk group [18,19]. In the updated CheckMate-214 trial, 4-year OS was 65% with ICI and 68% with TKI [20]. Therefore, further studies are warranted to better define the role of surgical and medical therapies in this clinical scenario.

5. Conclusion

Aggressive surgical therapy of IRR after radical nephrectomy is feasible with relatively low morbidity in experienced hands, with a long-term survival in more than half of the patients. In case of progression, metastasis-directed therapy may prolong the interval to initiation of systemic treatment. Further studies are needed to assess the value and timing of multimodal treatment with emerging new systemic therapies.

Declaration of Competing Interest

None

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