

Efficacy and Safety of Combined Embolization and Radiofrequency Ablation in Stage 1 Renal Cell Carcinomas

Wirksamkeit und Sicherheit von kombinierter Embolisation und Radiofrequenzablation bei Nierenzellkarzinomen im Stadium 1

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ABSTRACT

Purpose To retrospectively evaluate outcomes of a combined interventional approach to stage 1 (cT1cN0cM0) renal cell carcinomas (RCCs) by transarterial embolization (TAE) followed by percutaneous CT-guided radiofrequency ablation (RFA) in patients ineligible for surgery.

Materials and Methods 13 patients (9 male, 4 female, 69.6 ± 16.6 y/o) with 14 RCCs (largest diameter: 40.4 ± 6.7 mm, cT1a: 4, cT1b: 10) were treated by RFA a median of one day after TAE in a single center. Indications for minimally invasive interventional therapy were bilateral RCCs ($n = 4$), RCCs in a single kidney after nephrectomy ($n = 3$), increased surgical risk

due to comorbidities ($n = 4$), and rejection of surgical therapy ($n = 2$). Technical success, effectiveness, safety, ablative margin, cancer-specific survival, overall survival, and tumor characteristics were analyzed.

Results All RCCs were successfully ablated after embolization with a minimum ablative margin of 1.2 mm. The median follow-up was 27 (1–83) months. There was no residual or recurrent tumor in the ablation zone. No patient developed metastasis. Two minor and two major complications occurred. Four patients with severe comorbidities died during follow-up due to causes unrelated to therapy. The 1-year and 5-year overall survival was 74.1 % each. Cancer-specific survival was 100 % after 1 and 5 years. There was no significant decline in mean eGFR directly after therapy ($p = 0.226$). However, the mean eGFR declined from 62.2 ± 22.0 to 50.0 ± 27.8 ml/min during follow-up ($p < 0.05$).

Conclusion The combination of TAE and RFA provides an effective minimally invasive therapy to stage 1 RCCs in patients ineligible for surgery. The outcomes compare favorably with data from surgery.

Key Points:

- Interventional treatment by TAE and ablation is a safe and effective alternative to surgery in stage 1 RCCs.
- Focal therapy of RCCs preserves renal function.
- A small ablative margin appears to be sufficient in the ablation of RCCs.

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ZUSAMMENFASSUNG

Ziel Retrospektive Evaluation der Ergebnisse eines kombinierten Behandlungsansatzes aus blander Embolisation und perkutaner, CT-gesteuerter Radiofrequenzablation (RFA) bei Nierenzellkarzinomen (NZK) im Stadium 1 (cT1cN0cM0) bei Patienten, die für eine operative Therapie nicht geeignet sind.

Material und Methode 13 Patienten (9 Männer, 4 Frauen, $69,6 \pm 16,6$ Jahre) mit 14 NZKs (größter Durchmesser: $40,4 \pm 6,7$ mm, cT1a: 4, cT1b: 10) wurden in einem Zentrum mittels blander Embolisation gefolgt von einer RFA behandelt.

Behandlungsindikationen für diese interventionelle Therapie waren bilaterale NZKs (n=4), NZKs in einer Einzelniere nach Nephrektomie (n=3), erhöhtes chirurgisches Risiko aufgrund von Komorbiditäten (n=4) und Ablehnung einer operativen Therapie (n=2). Technischer Erfolg, Wirksamkeit, Sicherheit, Ablationszone, tumorspezifisches Überleben, Gesamtüberleben und Tumorcharakteristika wurden untersucht.

Ergebnisse Alle NZKs wurden erfolgreich nach Embolisation abladiert. Der minimale Ablationsrand betrug 1,2 mm. Die mediane Nachsorgedauer betrug 27 (1–83) Monate. Es wurden weder Residualtumore noch Lokalrezidive beobachtet. Kein Patient entwickelte Metastasen. Es traten 2 “minor”- und 2 “major”-Komplikationen auf. 4 Patienten mit schweren Komorbiditäten verstarben während der Nachsorge. Die Todesursachen waren nicht therapieassoziiert. Das 1-Jahres- und 5-Jahres-Überleben betrug je 74,1 %. Das tumorspezifische Überleben nach 1 und 5 Jahren betrug je 100 %. Die eGFR zeigte direkt nach der Behandlung keine signifikante

Veränderung ($p=0.226$). Im Verlauf der Untersuchung reduzierte sich die eGFR jedoch von $62,2 \pm 22,0$ auf $50,0 \pm 27,8$ ml/min ($p<0,05$).

Schlussfolgerung Die Kombination aus Embolisation und RFA ist eine sichere und effektive Therapie zur Behandlung von Patienten mit NZKs im Stadium 1, die für eine operative Therapie nicht geeignet sind. Die Ergebnisse dieser Studie sind mit den Ergebnissen der operativen Therapie vergleichbar.

Kernaussagen:

- Eine interventionelle Therapie aus Embolisation und Ablation ist eine sichere und effektive Alternative zur operativen Therapie des frühen NZK.
- Eine fokale Therapie des NZK schont die Nierenfunktion.
- Zur ablativen Behandlung des NZK scheint ein geringer Sicherheitsabstand ausreichend zu sein.

Introduction

The mean age of diagnosis in patients with kidney cancer, e. g., RCC, is 64 years in the USA with the highest cumulative incidence in the age group of 65–74 years [1]. The current standard therapy of T1 RCCs is partial nephrectomy (PN) according to the guidelines of the American Urological Association (AUA) and the European Association of Urology (EAU) [2, 3]. Due to the age distribution of kidney cancer, a minimally invasive and nephron-sparing alternative to PN is needed since patients over the age of 65 years typically have more than two preoperative risk factors and 38 % of US-Americans in this age group are diagnosed with chronic kidney disease [4, 5].

Percutaneous radiofrequency ablation (RFA) is a well-accepted minimally invasive nephron-sparing technique in the therapy of RCCs, which can safely achieve good oncologic and functional outcomes in T1a RCCs [6–10]. While RFA equals surgery in well selected T1a RCCs, it is more complicated in larger lesions or tumors in complex locations, e. g., close to the renal hilum. For instance, it is known that a blood flow-induced heat sink effect can limit heat-induced coagulation necrosis [11, 12] and that RFA of larger kidney tumors and/or tumors with central components (central or mixed location according to the Gervais et al. classification [13]) is less likely to be successful [8]. Transarterial embolization (TAE) prior to RFA reduces blood flow and increases the achievable area of ablation [11], which suggests the use of this combination in the treatment of larger and/or mixed or central T1 RCCs in patients ineligible for surgery.

There are already a few case series on the combination of embolization and RFA in the therapy of RCCs in small numbers of patients that have provided promising results [14–16].

The aim of this retrospective study is to show that the combination of TAE and RFA is a feasible minimally invasive therapy in patients with larger, mixed, or centrally located stage 1 RCCs.

Materials and Methods

Patients and Tumors

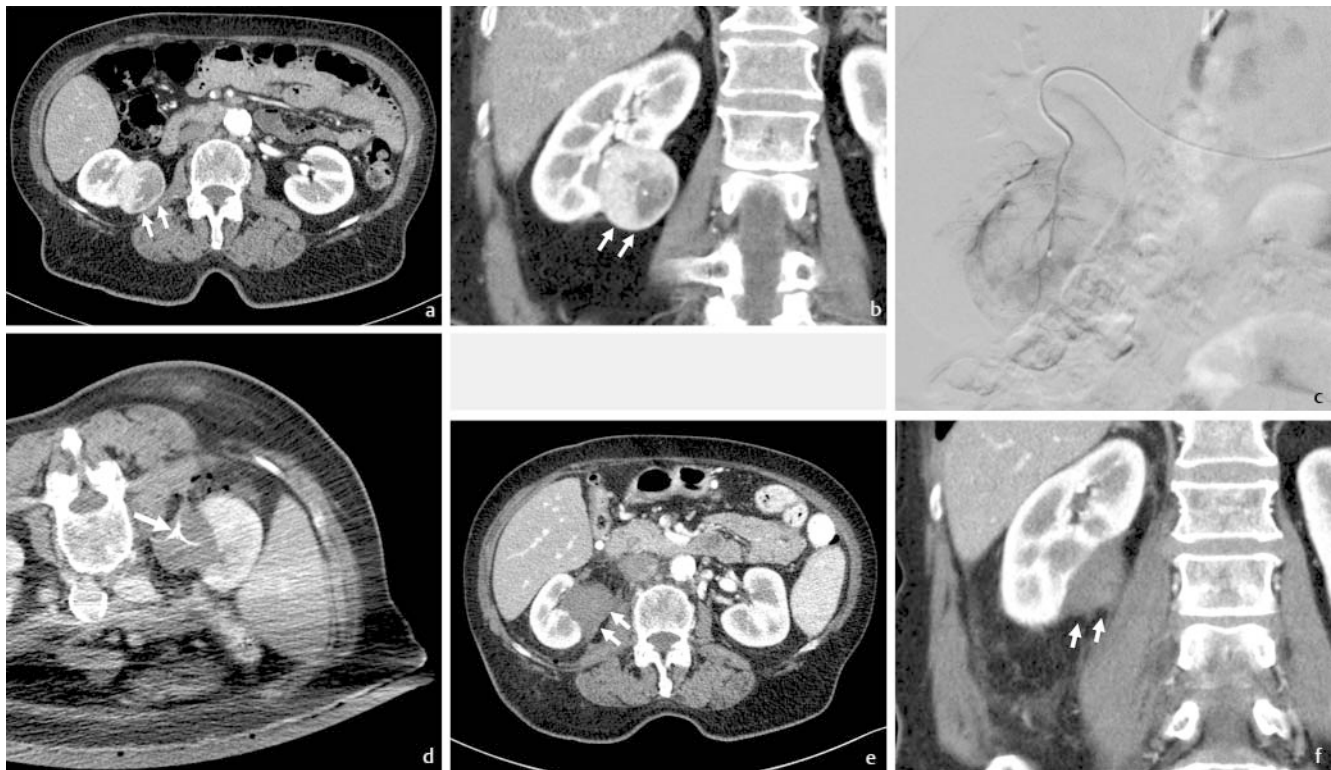
The study was performed with a waiver from the hospital's ethics committee. All patients with stage 1 RCCs who were treated with a combination of TAE and RFA in a single tertiary referral center were identified from a hospital information system. Patient data was anonymized and retrospectively evaluated.

Tumor diameters, TNM scores, and tumor location according to the definition of Gervais et al. [13] were evaluated using contrast-enhanced CT (n=12) or MRI (n=2) before therapy (► Fig. 1). The baseline eGFR was determined before TAE using the MDRD equation.

All treatment decisions were based on multidisciplinary team meetings. Indications for choosing this interventional therapy over surgery were bilateral RCCs (n=4), RCCs in a single kidney after contralateral nephrectomy (n=3), increased surgical risk due to comorbidities (n=4), and rejection of surgery (n=2). The indication for embolization was a case-by-case decision depending on tumor size >3.5 cm or central or mixed location since tumors with these characteristics were expected to benefit the most from TAE before RFA.

Therapy

All interventional procedures were performed by two EBIR (European Board of Interventional Radiology) certified interventional radiologists. TAE was performed under local anesthesia via a retrograde femoral approach. Tumor staining was proven by selective angiography of the tumor-bearing kidney. Thereafter, a 2.7F microcatheter was used to superselectively embolize tumor-feeding arteries with 250–700 µm microparticles and additional microcoils as needed (► Fig. 1). Percutaneous RFA was performed under CT guidance a median of 1 day after embolization using a posterolateral approach as previously described [17] (► Fig. 1).



► **Fig. 1** **A** Contrast-enhanced CT on the day prior to TAE displays a 4.4 cm × 4 cm × 3.5 cm T1b RCC (arrows) on the lower pole of the right kidney of a 74-year-old patient in axial images **A** and coronal MPR **B**. Superselective angiography depicts the tumor feeding vessels confirming correct catheter position **C** before TAE with 250–355 µm embolization particles. One day after TAE, a LeVein electrode is placed inside the embolized tumor (arrow) for RFA **D**. Postinterventional absence of contrast enhancement in the ablation zone (arrows) in axial images **E** and coronal MPR **F** from contrast-enhanced CT two days after RFA confirms complete ablation.

► **Abb. 1** **A** Kontrastangehobene CT in axialer **A** und koronarer Orientierung **B** einen Tag vor der Embolisierung zeigt ein 4,4 × 4 × 3,5 cm messendes Nierenzellkarzinom (cT1b) am Unterpol der rechten Niere eines 74-jährigen Patienten (Pfeile). Die superselektive Angiografie zeigt die tumorversorgenden Gefäße und bestätigt die korrekte Katheterposition vor blander Embolisierung mit 250–355 µm messenden Partikeln. Einen Tag nach der Embolisierung erfolgt die RFA mit einer LeVein-Elektrode (Pfeil). 2 Tage nach der Ablation bestätigt die fehlende Kontrastmittelaufnahme in der kontrastangehobenen CT die komplette Ablation des Tumors (Pfeil) **E**, **F**.

RFAs were either performed under general anesthesia (n = 12) or conscious sedation (n = 2). All RFA procedures were performed with the RF3000 system using a LeVein electrode (Boston Scientific Corp. Natick, MA). The applicator size was chosen to match or slightly exceed the tumor size by up to 5 mm. To improve ablation safety, cold pyeloperfusion with 0.9% saline solution (n = 3) and/or hydrodissection of the colon with 5% glucose solution (n = 8) were performed if the target tumor was closer than 5 mm to the ureter and/or bowel.

Follow-up

Laboratory testing and contrast-enhanced cross-sectional imaging were performed within 48 h after RFA (► **Fig. 1**). Thereafter, contrast-enhanced CT or MRI every 3–6 months was recommended for the first year and every 6–12 months thereafter. The change in eGFR immediately after therapy and the long-term change in eGFR during the complete follow-up were recorded.

Success of ablation, complications, ablation zone, and ablative margin were evaluated as previously described [18]. Ablation was considered complete if contrast enhancement was absent in the

area of the former target tumor. Furthermore, post-procedural cross-sectional imaging was used to analyze complications using the CIRSE classification of complications [19], the SIR Classification System for Complications by Outcome [20], and the Clavien-Dindo Classification [21]. Complications were also categorized into immediate (after 6–24 h), periprocedural (within 30 d), and delayed (> 30 d) complications according to Ahmed et al. [22].

Ablation zone size was measured by determining the three largest diameters that are perpendicular to each other. Ablative margins were determined from axial images and multiplanar reformats (MPR).

Statistics

All values for continuous measures are given as mean ± standard deviation (range) if not stated otherwise. The paired two-sample Student's t-test was used to analyze the changes in eGFR after the Kolmogorov-Smirnov test concluded normal distribution of eGFR values. A p-value < 0.05 was considered statistically significant. Eta coefficient test was used to analyze a correlation between preexisting medical conditions and long-term eGFR decline. The

► **Table 1** Summary of patient characteristics.

► **Tab. 1** Zusammenfassung der Patientencharakteristika.

Patient	Age (years)	Reason for interventional therapy	TNM score (location)	Oncologic outcome	Total eGFR change	Follow-up (months)
1	45	bilateral RCCs	cT1b (mixed)	tumor control	−39.72 %	55
2	62	bilateral RCCs	2x cT1a (mixed)	tumor control	−36.47 %	49
3	74	bilateral RCCs	cT1b (exophytic)	tumor control	−11.46 %	23
4	78	singular kidney	cT1b (mixed)	tumor control	−46.28 %	83
5	29	bilateral RCCs	cT1b (mixed)	tumor control	−79.06 %	63
6	79	singular kidney	cT1b (mixed)	tumor control	+ 6.56 %	55
7	80	liver cirrhosis	cT1a (central)	tumor control	+ 2.21 %	20
8	80	singular kidney	cT1a (exophytic)	tumor control	+ 20.46 %	43
9	82	cardiovascular comorbidities	cT1b (mixed)	tumor control	−13.19 %	8
10	69	cardiovascular comorbidities	cT1b (exophytic)	tumor control	−55.74 %	9
11	84	rejection of surgical therapy	cT1b (mixed)	tumor control	−7.87 %	27
12	82	cardiovascular comorbidities	cT1b (mixed)	tumor control	−8.29 %	1
13	61	rejection of surgical therapy	cT1b (exophytic)	tumor control	−3.07 %	5

correlation was assessed as statistically significant for $\eta \geq 0.2$. Statistical analysis was performed using IBM SPSS Statistics 27 (International Business Machines Corporation, Armonk, NY, USA).

Results

Patient & Tumor Characteristics

A total of 13 patients (9 male; 4 female) with 14 RCCs (largest diameter: 40.4 ± 6.7 mm, cT1a: 4, cT1b: 10), who were treated between November 2013 and May 2021 with a combination of TAE and RFA, were included in this study (► **Table 1**).

Tumor Control and Survival

The initial procedure achieved complete ablation in all tumors resulting in a technical success rate and technique effectiveness of 100 %. The peak power output of the RF system ranged from 100–200 watts. The mean duration of ablation was 37.2 ± 17.4 min. (12–83 min.). No residual or recurrent tumor was found in the ablation zone. There was neither metastasis nor tumor seeding. The median follow-up was 27 (1–83) months. Four patients reached the endpoint for overall survival at 28 days (respiratory failure unrelated to the procedure), 8 months (respiratory failure), 9 months (ileus), and 63 months (complications from cerebral hemangioblastoma), respectively. The 1-year and 5-year overall survival rates were both 74.1 %. No patient died from RCC or the interventional therapy resulting in cancer-specific survival rates of 100 % at 1 and 5 years.

Renal Function

The immediate post-procedural laboratory parameters of two patients were not available. These patients were excluded from the analysis of the immediate post-interventional functional outcome. No patient required dialysis during follow-up.

There was no significant decline in eGFR directly after therapy ($P = 0.226$). During the follow-up period, the mean eGFR declined by -20.9 ± 28.3 % from 62.2 ± 22.0 to 50.0 ± 27.8 ml/min. ($P < 0.05$).

Long-term eGFR decline was shown to be correlated with pre-existing CKD ($\eta = 0.481$) and single kidney ($\eta = 0.292$) but not with arterial hypertension ($\eta = 0.017$) or diabetes ($\eta = 0.083$).

Ablation Zone and Ablative Margin

The post-procedurally assessed ablation zone contained the entire target tumor in all treated lesions. The minimum ablative margin was 1.2 mm.

Safety

Two minor complications and two major complications occurred during therapy (► **Table 2**). A subcapsular renal hematoma was the only complication causing prolongation of hospitalization. Three complications resulted from RFA, while a small urine leak with subsequent hematuria resulted from a complicated Mono-J catheter insertion in preparation for retrograde pyeloperfusion during RFA. None of the complications affected the long-term treatment result.

► **Table 2** Classification and therapy of complications (PCC = prothrombin complex concentrate, FFP = fresh frozen plasma).

► **Tab. 2** Klassifikation und Therapie der Komplikationen (PCC = Prothrombinkomplex-Konzentrat, FFP = gefrorenes Frischplasma).

Complication	Onset of complication	CIRSE classification	SIR classification	Clavien-Dindo classification	Therapy
Hematuria and urine leak in preparation for RFA	Immediate	3	Minor, B	1	Irrigation catheter
Urinary tract infection and hematuria	Periprocedural	3	Minor, B	2	Cefuroxime
Subcapsular hematoma	Immediate	3	Major, D	3	TAE, PCC, FFP, red cell concentrates
Ureteral stricture with urinoma and delayed psoas abscess	Delayed	5	Major, E	3	Nephrostomy and abscess drainage, Tazobac/Piperacillin

Discussion

The study results indicate that the combination of TAE and RFA is an effective minimally invasive therapy for patients with stage 1 RCCs who are ineligible for surgery. Every target tumor was successfully treated without local recurrence, resulting in a local tumor control rate of 100 % which is consistent with reports of similar therapy strategies (97–100 % local tumor control rate) [14–16] and comparable to PN (90–100 % local tumor control rate) [23]. Furthermore, no re-ablations were needed, which compares favorably with the literature [14, 16].

Indications for embolization before RFA are not agreed upon. In previously published studies, tumors were either embolized due to size > 3.5 cm [16] or the expected benefit of reduced tumor perfusion independent of size or location [14, 15]. The role of embolization in this study is to overcome RFA's dependency on small tumor size and exophytic tumor location for successful ablation, as described by Gervais et al. [8]. Therefore, both size and location were considered when deciding whether a tumor should be embolized. The combined interventional approach subsequently allows greater patient access to minimally invasive therapy. This case series and comparable data demonstrate successful outcomes of combined embolization and ablation strategies in the therapy of RCCs, which would be challenging for RFA alone [14–16]. A particularly notable finding from this study is the effect of embolization in the therapy of RCCs with central components. By combining TAE and RFA, complete ablation was achieved in every tumor independent of location. This compares favorably with Gervais et al.'s report of complete ablation in 61 % of mixed and 78 % of central tumors after RFA alone [8].

This study provides new information on the ablative margin after a combination of embolization and ablation. There is currently no consensus regarding the ablative margin when treating RCCs by RFA alone or by TAE combined with RFA, but it is known that an ablative margin > 5 mm is recommended for the RFA of hepatocellular carcinomas (HCCs) [22]. In this study, complete tumor ablation without local tumor recurrence was achieved in every case with a minimum ablative margin of 1.2 mm. The small ablative margin in this study can be considered as adequate, as

there were no local recurrences. Moreover, a small ablative margin may help to preserve renal function in patients with preexisting CKD and subsequently impaired renal function. Nevertheless, further investigation to determine the ideal ablative margin after renal ablation is warranted.

This study's total complication rate of 28.6 % (4/14) is consistent with the data from other studies analyzing the combination of TAE and RFA in the therapy of RCCs with total complication rates up to 33.3 % [14–16]. One of two major complications was a subcapsular hematoma in a patient with acquired Von Willebrand disease and essential thrombocythemia (ET). The therapy of patients with ET is complex since they have an increased risk for both thrombosis and hemorrhage [24]. This patient was known to have had an ischemic stroke in the past, so no systemic prevention of hemorrhage was conducted prior to RFA. It remains uncertain to which degree this complication is attributed to the therapy method and to which degree to the ET and if the hemorrhage would have been worse without TAE prior to RFA. Walach et al. compared the outcomes of PN in frail and non-frail patients and concluded a significantly higher rate of severe complications, readmissions, and longer hospital stays in the frail cohort than in the non-frail cohort [25]. This study's major complication rate of 14.3 % compares favorably with Walach et al.'s rate of severe complications in the frail cohort (25 %) and is comparable to the severe complication rate in the non-frail cohort (11.7 %) [25], which is consistent with Uzzo and Novick [23] who report major complication rates between 4 % and 30 % after PN without differentiation between frail and non-frail patients. These comparisons indicate that the combination of TAE and RFA is a safe method, which compares favorably with PN of frail patients without significant disadvantage in the therapy of non-frail patients.

All four deaths were shown to be unrelated to RCCs or the interventional therapy resulting in an excellent cancer-specific survival rate of 100 %. All deceased patients were severely morbid prior to therapy with major cardiovascular comorbidities (n = 3) or multiple cerebral hemangioblastomas combined with a history of small cell lung cancer (n = 1).

This study and comparable literature [14–16] show no significant decrease in eGFR directly after the combination of TAE and

RFA which indicates that this treatment is well suited for patients with impaired renal function. A unique feature of this study is the long-term functional outcome. The mean eGFR decline from 62.2 ± 22.0 to 50.0 ± 27.8 ml/min ($P < 0.05$) is considered as a satisfactory preservation of renal function since this study's cohort consists of patients with multiple comorbidities that negatively affect renal function. As a consequence, decline in renal function is considered to be due to underlying conditions.

The most important shortcoming of this study is the low number of patients and treated RCCs. The same is true for previous publications, reporting the combined treatment of 12 to 36 lesions [14–16]. Nevertheless, this study provides more detailed data on tumor location and new information on the long-term functional outcome and ablative margin while showing that this technique can achieve 100% local tumor control rate without re-ablation. Another limitation is the retrospective character of this study. So far there is no prospective data on the combination of TAE and ablation in RCCs.

In conclusion, physicians should consider the combination of TAE and RFA in the therapy of patients ineligible for surgery with larger and/or mixed or central stage 1 RCCs.

Conflict of Interest

The authors declare that they have no conflict of interest.

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